

**Vaccination and Screening for the Prevention of Cervical Cancer:  
Health Effects and Cost-effectiveness**

**Vaccinatie en screening voor de preventie van baarmoederhalskanker:  
Gezondheidseffecten en kosteneffectiviteit**

**Inge Martina Cornelia Maria de Kok**

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**Vaccinatie en screening voor de preventie van baarmoederhalskanker:  
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## **Promotiecommissie**

### **Promotor:**

Prof.dr. J.D.F. Habbema

### **Overige leden:**

Prof.dr. P. J.E. Bindels

Prof.dr. Th.J.M. Helmerhorst

Prof.dr. C.J.L.M. Meijer

### **Copromotor:**

Dr. M. van Ballegooijen

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CHAPTER 1

**Introduction**



## 1.1 | Epidemiology of cervical cancer over the world

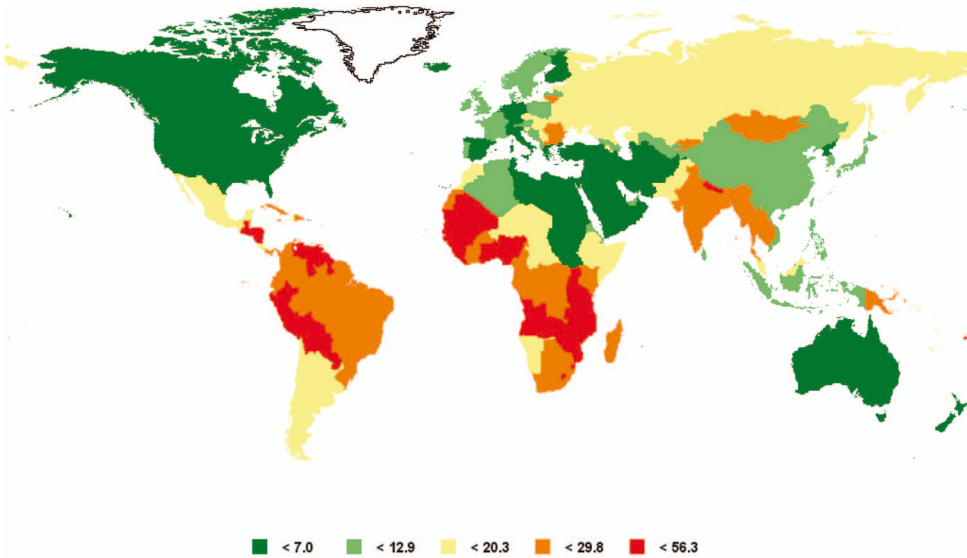
Cancer of the cervix uteri is the third most common cancer among women worldwide, with an estimated 529,000 new cases and 274,000 deaths in 2008.<sup>1</sup> Some 85% of the cases occur in less developed countries, where cervical cancer accounts for 15% of female cancers, with a risk before age 65 of 1.5%. In developed countries it accounts for only 3.6% of new cancers, with a cumulative risk at age 65 of 0.8% (Figure 1.1).<sup>2</sup> The top-5 highest incidence rates over the world have a World Standardised Rate (WSR) more than 23 cases per 100,000 life years. These high rates are observed, ranked from highest to lowest incidence, in 1) Eastern Africa, 2) Western Africa, 3) Southern Africa, 4) South-Central Asia, and 5) South America.<sup>1</sup> The five lowest rates with a WSR less than 7 per 100,000, when ranked from lowest to highest incidence, are found in 1) Western Asia, 2) Australia/New Zealand, 3) Northern America, 4) Northern Africa, and 5) Western Europe.<sup>1</sup>

Mortality rates are substantially lower than incidence. Worldwide, the ratio of mortality to incidence is 52%. Survival rates vary between regions, with quite good prognosis in low-risk regions, like 73% at 5 years in US registries<sup>3</sup> and 63% in Europe.<sup>4</sup> But even in developing countries, where many cases present at relatively advanced stages, survival rates are reasonable (for example, 30% in the African population of Harare, Zimbabwe<sup>4</sup>).

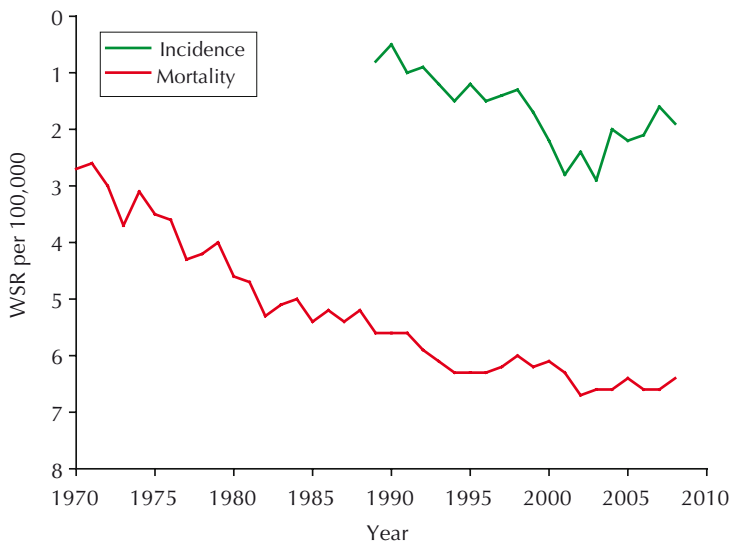
Because cervical cancer affects relatively young women, it is an important cause of lost years of life in the developing world. Yang et al.<sup>5</sup> found that it was responsible for 2.7 million (age-weighted) years of life lost (YLL) worldwide in 2000 and it is the biggest single cause of YLL from cancer in the developing world. In Latin America, the Caribbean and Eastern Europe, cervical cancer makes a greater contribution to YLL than diseases such as tuberculosis, maternal conditions or AIDS. It also makes the largest contribution to YLL from cancer in the populous regions of sub-Saharan Africa and South-Central Asia.

In the Netherlands, cervical cancer mortality has steadily declined over the last decades (Figure 1.2). The incidence, however, recently increased in the period 2001–2008 (Figure 1.2). In 2008, 699 women were diagnosed with cervical cancer and 244 women died from this disease [www.ikcnet.nl]. This was 0.3% of the total mortality in women and 1.6% of the mortality in women below the age of 50 years [www.cbs.nl]. Approximately 2% of all newly diagnosed malignant tumours in Dutch women are cancers of the uterine cervix, and 1.5% of all deaths caused by cancer in women are from cervical cancer.





**Figure 1.1** | World Standardised cervical cancer incidence by country (rate per 100,000) [Source: GLOBOCAN 2008]<sup>1</sup>



**Figure 1.2** | World Standardised incidence and mortality rates (WSR) of cervical cancer in the Netherlands, 1970–2008 [Source: Netherlands Cancer Registry]

An important factor that influences the observed trends in incidence and mortality is cervical cancer screening. The Netherlands is one of the countries with an effective screening programme.<sup>6-7</sup> As a result, the incidence and mortality in the Netherlands are internationally low; the incidence WSR was 6.1 and the mortality WSR was 1.6 per 100,000 women years in 2008 [www.ikcnet.nl]. Since randomised cervical cancer screening trials have never taken place in the Netherlands, and mortality already decreased before introduction of screening (Figure 1.2), it is uncertain to what extent the decrease in mortality is due to screening. However, several epidemiological studies observed that the widespread introduction of screening has led to decreases in the incidence and mortality from cervical cancer.<sup>8-9</sup> Based on simulation it was estimated that life expectancy will increase with 46 days if cervical cancer is totally eliminated and with 21 days if women are screened 7 times during a lifetime, with a participation rate of 80% (as it is the case in The Netherlands).<sup>10</sup> However, next to screening HPV infections and other risk factors also determine the trend in incidence of cervical cancer. Trends in mortality are also related to changes in treatment of the disease. The influences of these factors need to be explored further. This leads to the first question that will be answered in this thesis:

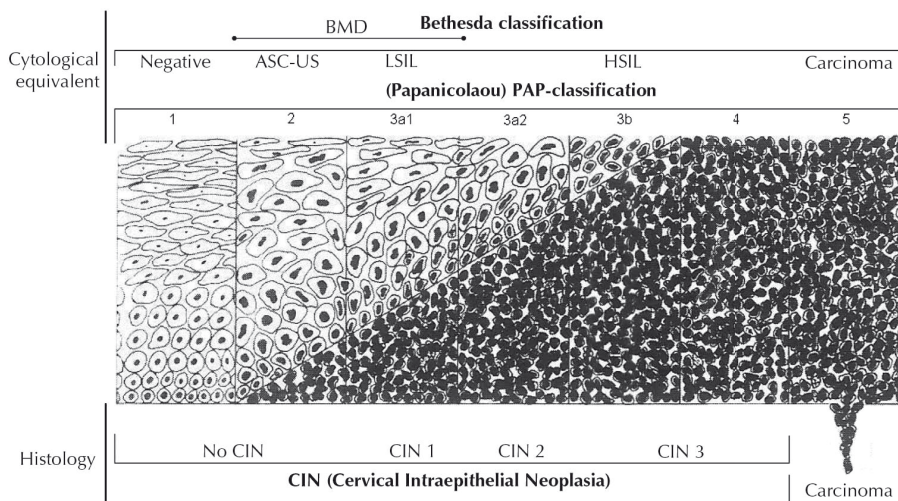
***What are the causes of the recent trend in cervical cancer in the Netherlands?***

## **1.2 | Etiology of Cervical Cancer**

Invasive carcinoma of the cervix is preceded by precursor lesions. The sequence of pathological conditions which are considered preinvasive, or premalignant, can be described in terms of increasing degree of dysplasia (Figure 1.3). These preinvasive lesions are called cervical intraepithelial neoplasia (CIN), and are histologically divided into three classes according to the thickness of epithelial layer involved in neoplastic changes; CIN 1, CIN 2 and CIN 3. Early epidemiological studies of cervical neoplasia suggested a causal relation with sexual activity. Infection with the human papillomavirus (HPV) was established to be the central cause of invasive cervical cancer.<sup>11</sup> HPVs detected within the cervix fall into two broad groups: high (or oncogenic) and low risk types. High risk types are found in >80% of CIN 2 and CIN 3 lesions,<sup>12</sup> and >99% of invasive cervical cancers.<sup>11</sup> HPV types 16 and 18 are the most important high risk types and are estimated to account for 70% of all cervical cancers worldwide.<sup>13</sup> More detailed investigations have detected about 30 HPV types in cervical samples.<sup>14</sup> However, HPVs have also been detected in a wide range (3–30%) of asymptomatic controls, indicating

that other events are required for development of neoplasia, such as viral persistence and/or altered expression of viral genes. A range of putative cofactors has been implicated in progression: HLA type, immunosuppression, sex steroid hormones, and smoking; most of these cofactors appear to influence progression to CIN 3. Approximately in 20% of women infected with high risk HPV a CIN lesion will develop within 2–4 years after acquisition of the virus.<sup>15-17</sup> The natural history includes progression to CIN 3 in 10% of CIN 1 and 20% of CIN 2 cases, whereas at least 12% of CIN 3 cases progress to invasive carcinoma.<sup>18</sup> The interval between the first manifestation of CIN 1 and the development of cervical cancer is estimated to be on average 13 years.<sup>19</sup> However, these percentages are uncertain and strongly age dependent. Still, it is clear that only a small minority of HPV infections progresses to cancer.

The causal role of HPV in all cancers of the uterine cervix has been firmly established biologically and epidemiologically. Most cancers of the vagina and anus are likewise caused by HPV, as are a fraction of cancers of the vulva, penis, oral cavity and oropharynx.<sup>20</sup> Cancer can develop if infectious particles reach the basal layer of the epithelium anywhere in the human body, where they bind to and enter into cells. If a cell is infected with HPV it leads to increasing genomic instability, accumulation of oncogene mutations, further loss of cell-growth control, and ultimately cancer.<sup>21</sup> Many people get HPV infections, but relatively few infections will lead to cancer. Thus other cofactors need to be involved, depending on the type of cancer.



**Figure 1.3** | Illustrated cytological and histological classification during the development of cervical cancer. ASC-US = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; BMD = borderline or mildly dyskaryotic.

## 1.3 | Medical Interventions to prevent cervical cancer

### 1.3.1 | Screening

#### 1.3.1.1 | Conventional Pap smear

The Papanicolaou test (also called Pap smear, Pap test, cervical smear, or smear test) is a screening test to detect preinvasive and invasive (cancerous) processes in the cervix. Preinvasive lesions can be treated, thus preventing cervical cancer. The test was invented in the 1940's by and named after the Greek doctor Georgios Papanikolaou.<sup>22</sup> In taking a Pap smear, a tool is used to gather exfoliated cells from the outer opening of the cervix of the uterus. The cells are fixated, stained and examined under a microscope to look for neoplastic abnormalities. The test aims to detect potentially pre-cancerous changes (CIN or cervical dysplasia) and early cancerous lesions, and reduce cervical cancer mortality. Even though never tested in randomised controlled trials, the Pap test has proven to be effective in reducing both morbidity and mortality from cancer of the cervix.<sup>7, 23</sup>

There are two reporting systems in current use (Figure 1.3, Table 1.1). The older Pap classification system which reports the result in five classes, and the newer Bethesda System.<sup>24</sup> According to the Pap classification abnormal results are reported as: Atypical, inflammation or uterine cells seen (Pap 2); Dysplastic, mild, moderate or severe (Pap 3); Carcinoma-in-situ (Pap 4); Suspicious for an invasive cancer (Pap 5). According to the Bethesda system abnormal results are reported as: Atypical squamous cells of undetermined significance (ASC-US); Low-grade squamous intraepithelial lesion (LSIL); High-grade squamous intraepithelial lesion (HSIL); Carcinoma.

In the Netherlands, the CISOE-A classification was introduced in 1996 to uniformly describe cytomorphological results and to increase the efficacy of the screening programme.<sup>25</sup> Briefly, the CISOE-A classification interprets smears using a rating system including information on specimen composition, inflammatory characteristics, and adequacy of the smear. The letters C (composition), I (inflammation), S (squamous), O (other and endometrium), and E (endocervical cylindrical epithelium) are used to indicate the composition and morphology of the smears. The letter A (adequacy) is used to indicate the adequacy of the smear. Squamous, columnar, and other cells are graded for the presence of dyskaryosis (dysplasia), and these values determine the interpretation of the smear. A CISOE-A classification can be translated into a Pap classification and into a Bethesda classification (Table 1.1).<sup>26</sup>

**Table 1.1** | Cytological classification applying to cervix uteri

CISOE-A	C0	S1, E1-2, O1-2	S2-3, O3, E3	S4, E4-5	S5, O4-5	S6, O6, E6	S7, E7	S8-9, O7-8, E9
<b>Pap</b>	Pap 0	Pap 1	Pap 2	Pap 3a1	Pap 3a2	Pap 3b	Pap 4	Pap 5
<b>Bethesda*</b>	Unsatisfactory for evaluation	Negative	Atrophy	ASC-H		HSIL		Squamous cell carcinoma
				ASC-US	LSIL			
				AGC	AGC favour neoplastic			

\*ASC-US atypical squamous cells of undetermined significance; ASC-H atypical squamous cells cannot exclude HSIL; AGC atypical glandular cells; LSIL low-grade squamous intraepithelial lesion; HSIL high-grade squamous intraepithelial lesion; AIS adenocarcinoma in situ.

### **1.3.1.2 | Thin layer cytology**

Since the mid-1990s, techniques based on placing the sample into a vial containing a liquid medium that preserves the cells have been increasingly used. This technique is called Liquid Based Cytology (LBC). Two of the systems are Sure-Path (TriPath Imaging) and Thin-Prep (Cytec Corp). The liquid media are primarily ethanol-based for Sure-Path and methanol-based for Thin-Prep. The sample is placed into the vial and centrifuged, processed into a cell thin-layer, stained, and examined by light microscopy. Proper sample acquisition is crucial to the accuracy of the test; a cell that is not in the sample cannot be evaluated.

Some studies report increased sensitivity for LBC compared to conventional cytology. However, a systematic review and meta-analysis showed that LBC is neither more sensitive nor more specific for detection of high-grade cervical intraepithelial neoplasia compared with the conventional Pap test.<sup>27</sup> The pooled accuracy of LBC reported is a sensitivity of 57.1% and specificity of 97.0% for not having HSIL+, compared to 55.2% and 96.7%, respectively, for conventional cytology.<sup>27</sup> LBC is more expensive than the conventional Pap test. Advantages of LBC are being suitable for HPV testing on the same material and reduced unsatisfactory specimens. However, the value for this latter advantage strongly depends on the percentage unsatisfactory specimens using the conventional Pap test, and this percentage differs between countries. For example, the United Kingdom is a country with a high 8% of the programme smears with inadequate quality for evaluation,<sup>28</sup> and with this percentage it was found that LBC is a cost-effective alternative to a conventional Pap smear.<sup>29</sup> The Netherlands is a country with a low percentage smears of inadequate quality (i.e. 1%).<sup>6</sup> In view of the different value of LBC in changing conditions, we formulated the third research question as:

***When will liquid-based cytology be a cost-effective alternative for conventional cytology in the Netherlands?***

### **1.3.1.3 | HPV screening**

The presence of HPV indicates that the person has been infected with the virus. The majority of women that get infected will successfully clear the infection within one or two years, especially at young ages. Women with an infection of prolonged duration with high-risk types (e.g. types 16, 18, 31, 45) are more likely to develop CIN, due to effects of HPV on DNA. The most widely used types of HPV tests are the Hybrid

Capture II and the Polymerase Chain Reaction tests. HPV testing is substantially more sensitive in detecting cervical neoplasia than cytology, but less specific.<sup>30</sup> HPV testing can be applied in primary cervical cancer screening, in triage of low-grade cytological abnormalities, and in follow up after treatment of cervical neoplasia.

Whether primary HPV screening is cost-effective as a primary screen test and in the follow up of low-grade cytological abnormalities depends on several parameters, such as the prevalence of HPV infections in the population, the risk of cervical cancer, the sensitivity and specificity of cytology screening, and the sensitivity and specificity of HPV screening. These parameters differ between countries. Therefore, in chapter 3.3 we will answer the fourth question:

***In which European countries is primary HPV screening preferred above primary cytology screening?***

#### **1.3.1.4 | HPV vaccination**

There are two vaccines for the prevention of primary infection with HPV on the market. Gardasil is a quadrivalent vaccine manufactured by Merck. Cervarix, a bivalent vaccine, is manufactured by GlaxoSmithKline. Both vaccines contain viruslike-particle antigens for the high risk HPV-16 and HPV-18. HPV-16/18 is estimated to be responsible for 70% of all cervical cancers worldwide.<sup>13</sup> In addition, Gardasil contains viruslike-particle antigens for low risk HPV types 6 and 11, which are responsible for about 90% of genital warts.<sup>31</sup> The viruslike-particle vaccines induce a virus-neutralizing antibody response, but pose no infectious or oncogenic risk, since they have no viral DNA core.

Several international randomized controlled trials involving approximately 50,000 young women have evaluated either the quadrivalent or the bivalent vaccine.<sup>32-39</sup> Among women not infected with the HPV types under study and who adhered to the study protocol, after 6.4 years of follow up, vaccine efficacy against CIN2+ was 100% for lesions associated with HPV-16/18 and 72% for lesions independent of HPV DNA.<sup>40</sup> Vaccination does not protect women who are already infected with HPV-16 or HPV-18 at the time of vaccination. Neither the incidence of invasive cervical cancer nor the rate of death due to cervical cancer has been assessed as a trial endpoint. Although the prevention of such outcomes in an unscreened population is of course the ultimate purpose of HPV vaccination, it would not be ethical not to offer screening as recommended in the population. The duration of immunogenicity and the need for booster vaccinations is not yet known.

In clinical trials of the quadrivalent vaccine, mild adverse events were more common in vaccine recipients than in placebo recipients. Rates of serious adverse events were not higher among recipients of either vaccine than among recipients of placebo. However, the risk for long term and rare (serious) adverse events could not be measured, due to limited duration of the trials and size of study population.

Next to cervical cancer, other cancer types are also related to HPV infections, notably cancer of the penis, vulva/vagina, anus, oral cavity and oro-pharynx.<sup>41</sup> There is no evidence to date from any clinical trial that HPV vaccination has any impact on other HPV-related cancers, but these cancers are potentially preventable. One trial showed that among women not infected with HPV16 or HPV18, the vaccine was 100% effective in preventing HPV16/18 positive grade 2–3 intraepithelial neoplasias of the vulva (VINs) and the vagina (VaINs). In the total population (i.e., including women infected with HPV16/18), the vaccine was 71% effective in preventing VIN2-3 and VaIN2-3 caused by HPV16/18 and 49% effective in preventing all VIN2-3 or VaIN2-3.<sup>36</sup>

Multiple analyses of the cost-effectiveness of vaccination against HPV have concluded that vaccination could be cost effective.<sup>42-47</sup> However, this conclusion mainly depends on the costs of the vaccine and incidence and mortality rates of cervical cancer, since this implies a limited maximum effect of HPV vaccination. The Netherlands is a country with a low cervical cancer incidence and mortality rate. Therefore, in chapter 4 we will answer the fifth question raised:

### ***Is human papillomavirus vaccination cost-effective in the Netherlands?***

## **1.4 | History of cervical cancer prevention in the Netherlands**

In the Netherlands, Pap-smear screening became widespread in the 1970's when 3 pilot screening programmes were started in the regions of Nijmegen, Rotterdam and Utrecht. Similar centrally organized programmes were soon adopted in other regions but were stopped by mid-1980's when decentralized programmes were introduced instead. Cervical cancer screening using the Pap smear test was then offered to the population in the Netherlands through an organized programme inviting all women between 35 and 54 years every 3 years. Evidence gathered in the Netherlands in the early 1990s pointed towards suboptimal performance of the screening programme, in terms of both the organization and the efficiency of screening of the target population.<sup>48-51</sup> Based on a request from the Ministry of Health for possible solutions,<sup>52</sup> new protocols and



guidelines regarding the screening and follow-up schemes, administration and financing were implemented nationally in 1996.<sup>53</sup> The screening interval was lengthened from 3 to 5 years, the age range was broadened from 35–53 to 30–60 years, and the invitational coverage was made more complete than in the old programme.<sup>49</sup> The changes have resulted in increased coverage and efficiency of the screening programme, and in a decrease of negative side effects.<sup>6</sup> However, it has been suggested that the age to initiate cervical cancer screening should even be lower, because of earlier age of sexarche. It is also argued that there is an increase in the incidence of cervical cancer in age group 30–44 years and therefore the screening age should be lowered to detect pre-invasive cervical lesions earlier. This leads to the second question that will be answered in this thesis:

***Do trends in cervical cancer warrant a change of the starting age of 30 years in the Netherlands?***

In July 2006, the Dutch National guidelines for Pathology were updated. The Netherlands Society of Pathology (NVVP), in agreement with general practitioners (NHG) and gynaecologists (NVOG), recommended an HPV DNA test in addition to the repeat Pap test six months after smears with either ASC-US or LSIL (i.e. borderline (Pap 2) or mildly (Pap 3a1) dyskaryotic (BMD) smear).<sup>54</sup> Women with a repeat BMD smear positive for hrHPV are to be referred to the gynaecologist, while those with a repeat BMD smear negative for hrHPV will get a repeat smear twelve months after the first repeat test. In the old guidelines all women with a repeat BMD+ smear were referred.

In 2009, HPV vaccination was introduced in the Dutch National Immunisation Programme (NIP) for 12-year-old girls.<sup>55-56</sup> A catch-up campaign was organised for 13- to 16-year-old girls born in 1993-1996. The advice to use the HPV DNA test as the primary screen test in the screening programme is currently under consideration of the Dutch Health Council and the advisory report will be published at the end of 2010.

## 1.5 | Methodology for calculation of health effects and costs

### 1.5.1 | Cost-effectiveness analysis

Cost-effectiveness analysis (CEAs) is the standard analytic tool supporting medical decision making concerning allocation of scarce resources. It involves estimating the incremental costs and health effects of an intervention when compared to one or more alternatives such as usual care, doing less or doing nothing.<sup>57</sup> The question such analyses seek to answer is whether the additional (health) effects of some intervention justify the associated additional costs. For the evaluation of healthcare interventions the most commonly used outcome measures are life years gained (LYG) and quality-adjusted life years (QALY) gained. CEAs can be undertaken from a number of different perspectives. The appropriate perspective depends upon the objective of the study. The broadest is the societal perspective, which incorporates all costs and health effects regardless of who incurs the costs and who obtains the effects. However, CEAs are often motivated by policy choices relevant to specific institutions. In these cases, the perspective of primary interest may be that of a care organisation, hospital, employer, health insurer, or other party. The perspective of a CEA determines which health outcomes and costs are relevant, and should be included in the analysis. When the same perspective and health outcome measures are used, interventions can be compared and ranked on the basis of their cost-effectiveness ratios (CER).

There is always much debate concerning the methods of CEA among analysts, readers, and policy-makers. The principal areas in which disagreement still persists are choice of study design, measurement and valuation of health outcomes, and the measurement of costs. Also, the application of the unrelated health care costs of postponed death, or more in general, in life years gained is one of the unresolved issues in the use of cost-effectiveness analysis. Given that one of the goals of this thesis is to explore the costs-effectiveness of cancer screening, the sixth research question we will study is:

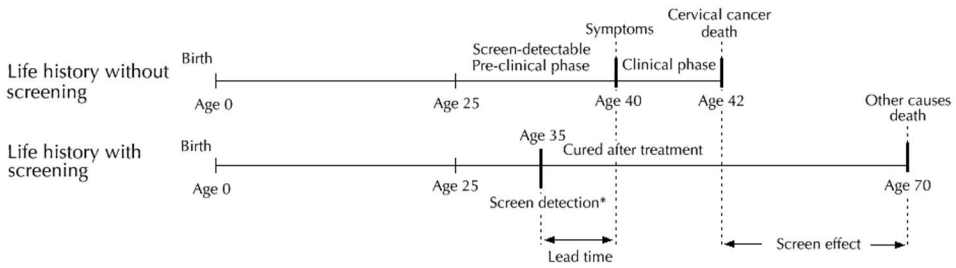
***How influential are health care costs in gained life years on the cost-effectiveness of cancer screening?***

Discounting is used in CEA to adjust future costs and health effects to their present values and volumes. While discounting in general is widely accepted in CEA, whether health and economic consequences should be discounted at the same rate raises concerns. Therefore, we will answer the seventh question in chapter 5.2:

***What are the implications of the use of differential discounting of costs and health effects for the practice of cost-effectiveness analyses?***

### 1.5.2 | The MISCAN model

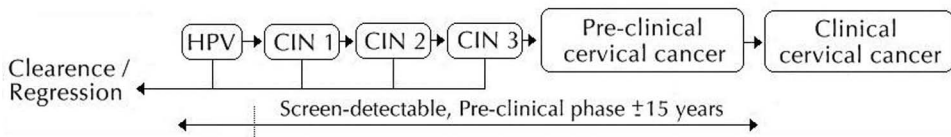
Prediction of the effects and costs of cervical cancer screening and vaccination is complex, because it involves many factors. Therefore, a computerized simulation model is indispensable to estimate interventions' current and future costs and effects. The Microsimulation Screening Analysis (MISCAN) computer simulation program<sup>58-59</sup> has been developed for building models for simulating cancer screening in a dynamic population and for subsequently applying these models to analyze and explain results of cancer screening trials, to predict and compare the (cost-) effectiveness of different screening policies, and to evaluate the monitored results of population screening programs. The program uses Monte Carlo simulation. It produces output on the effects of screening procedures, morbidity and mortality on the individual and population level. Figure 1.4 shows an example of a simulated life history which is beneficial changed by screening. In this particular example the disease starts to develop at age 25 years. Without screening, the woman develops symptoms at age 40 years and dies from cervical cancer at age 42. In case of screening a pre-invasive lesion is detected with screening at age 35, which results in a lead time (i.e. the period between screen detection and clinical detection of the disease) of 5 years. The woman is treated and cured and dies at age 70 due to another cause. In this example screening results in a gain of 28 life years.



**Figure 1.4** | Example of a screen-induced beneficial change in a life history generated by the MISCAN simulation programme

\* In this particular example earlier treatment as a result of screening leads to cure.

The calculations are based on models of the natural history of the disease (Figure 1.5) and of the impact of screening on the natural history. The approach is such that considerable flexibility exists in specifying the structure of the model and its parameters. The program consists of two parts. The DISEASE part can be used for simulating the epidemiology of the disease when no screening is taking place; it requires input on the population and on the disease process. The SCREENING part is to be used in combination with the DISEASE part. It is intended for simulation of the results and effects of a screening project. It requires input on the properties of the screening tests, the consequences of early detection by screening, and the policy (ages and intervals between screens) of the project. MISCAN models have been made and applied for cancer of the cervix, breast, colon, and prostate.<sup>10, 60-62</sup> In these models, the natural history is described by discrete tumour stages, transition probabilities between these stages, and dwelling times in each stage.



**Figure 1.5** | Schematic overview of the natural history of the disease sequence after the occurrence of an HPV infection in the MISCAN-cervix model. Women can have multiple HPV infections at one time, and can at any time acquire a new HPV infection.

## 1.6 | Contents of this thesis

The goal of this thesis is to explore the health effects and cost-effectiveness of cervical cancer screening and HPV vaccination, in the Netherlands as well as internationally. Furthermore, we address two methodological issues in cost-effectiveness analyses.

Chapter 2 addresses the first question on trends in cervical cancer; Chapter 3.1 the second question on the starting age of the screen programme; Chapter 3.2 the third question on liquid-based cytology; Chapter 3.3 the fourth question on HPV screening; Chapter 4 the fifth question on human papillomavirus vaccination; Chapter 5.1 the sixth question on health care costs in gained life years; and Chapter 5.2 the seventh question on differential discounting.



# CHAPTER 2

## **Trends in cervical cancer in the Netherlands, 1989–2006**

**Based on “Trends in cervical cancer in  
the Netherlands until 2007: Has the bottom been reached?”**

Inge M.C.M. de Kok,  
Maaïke A. van der Aa,  
Marjolein van Ballegooijen,  
Sabine Siesling,  
Henrike E. Karim-Kos,  
Folkert J. van Kemenade,  
Jan Willem W. Coebergh

On behalf of the Working Group Output of the Netherlands Cancer Registry

*Int J Cancer. 2010 Jul 12. [Epub ahead of print]*



## 2.1 | Abstract

We explored trends in incidence and mortality of cervical cancer by age, stage and morphology, and linked the observed trends to screening activities. Data was retrieved from the Netherlands Cancer Registry during 1989-2007 (incidence) and Statistics Netherlands during 1970–2007 (mortality). Trends were evaluated by calculating the estimated annual percentage change (EAPC). Joinpoint regression analysis was used to detect changes in trends. Cervical Intra-epithelial Neoplasia (CIN) detection-rates were calculated by data from 'the nation-wide network and registry of histo- and cytopathology' during 1990-2006. Total age-adjusted incidence rate (European Standardised Rate (ESR)) was 7.9 per 100,000 woman years in 2007. During 1989-1998, incidence rates decreased with an EAPC of -1.3% (95% Confidence Interval (CI) -2.2, -0.3), during 1998-2001 with -6.7% (95% CI -16.4, 4.1), and increased during 2001-2007 with 2.3% (95% CI 0.4, 4.2). Total mortality ESR was 1.9 per 100,000 woman years in 2007. Mortality rates decreased during 1970-1994 annually with -4.1% (95% CI -4.6%, -3.7%), and with -2.6% (95% CI -3.8%, -1.5%) during 1994-2007. The observed trend in total incidence is similar to the trend in squamous cell carcinomas in age group 35-54 years, suggesting that the observed trends are likely to be associated to changes in the screening programme. This is supported by the trend in CINIII detection rates. In conclusion, incidence and mortality overall decreased and levelled off. On top of that there was an extra decrease that was compensated by a following recent increase in incidence, probably resulting from reorganization of the Dutch screening programme.



## 2.2 | Introduction

In the Netherlands, over the past decades, incidence and mortality trends of cervical cancer have been steadily declining, with rates of 6.3 and 1.4 per 100,000 woman years (age-adjusted rates, standardized to the World population), respectively in 2007.<sup>63</sup> These declines can partly be described as natural declines, but are also the result of developments in the prevention and treatment of cervical cancer.<sup>7, 23</sup> Cervical cancer screening leads to the detection and treatment of Cervical Intra-epithelial Neoplasia (CIN). CIN is considered to be a pre-invasive precursor of invasive cancer and a reduction in incidence and mortality is expected because CIN management is found to be highly effective.<sup>64</sup> An additional mortality reduction is expected from the pre-clinical detection of early invasive cases which have a relatively good prognosis.<sup>65</sup>

Since the 1980s, cervical cancer screening using the Pap smear test has been offered to the population in the Netherlands through an organized programme initially inviting all women between 35 and 54 years every 3 years. The evidence gathered in the Netherlands in the early 1990s pointed towards a suboptimal performing screening programme, in terms of both the organization and the efficiency of screening of the target population.<sup>48-51</sup> Based on a request from the Ministry of Health for possible solutions,<sup>52</sup> new protocols and guidelines regarding the screening and follow-up schemes, administration and financing were implemented nationally in 1996.<sup>53</sup> A lengthening of the screening interval from 3 to 5 years was implemented in a broader target age group (30–60 instead of 35–53 years), as well as a more complete invitational coverage than in the old programme.<sup>49</sup> The changes have increased the coverage and efficiency of the screening programme, and decreased the screening-induced negative side effects.<sup>6</sup>

The key causal factor for cervical cancer is a persistent infection with the human papillomavirus (HPV) and several cofactors have been associated with HPV persistence and lesion progression, including smoking, long-term oral contraceptive use, and other sexually transmitted infections.<sup>66</sup> Studying trends in cervical cancer incidence and mortality can give information on underlying changes in HPV infections and other risk factors, or on changes in the effectiveness of cervical cancer screening, and thereby information on the likely future trends. Therefore, the aim of this study was to explore trends in incidence of and mortality from cervical cancer in the Netherlands by different age groups, stages and morphology. We will link the observed trends in incidence and mortality to the screening programme, by studying the time relation with changes in screening activities and CIN detection rates.

## 2.3 | Methods

### 2.3.1 | Data Collection

For cervical cancer incidence, including stage distribution and morphology, we used the population-based data from the nationwide Netherlands Cancer Registry (NCR), which started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres [www.ikcnet.nl]. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the nation-wide network and registry of histo- and cytopathology ('PALGA').<sup>67</sup> Additional sources are the national registry of hospital discharge, haematology departments and radiotherapy institutions. Information on patient characteristics like gender, date of birth, and tumour characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3)),<sup>68</sup> histology, stage (Tumour Lymph Node Metastasis (TNM) classification)<sup>69</sup>, grade, and primary treatment mode, are obtained routinely from the medical records. The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels.

For the present study, all patients with invasive primary epithelial cervical cancer (C53: squamous cell carcinomas (ICD-O codes 8120, 8123, 8130, 8050-8084, 8090-8094), adenocarcinomas (ICD-O codes 8144, 8262, 8480, 8481, 8482, 8490, 8380, 8310, 8441, 9110, 8140-8199, 8201-8239, 8244, 8246-8248, 8250-8559, 8561-8576) and carcinomas not otherwise specified (all other ICD-O codes in C53)) diagnosed in the period 1989–2007 in the Netherlands were included (n=13,424). They were divided into six age-groups (0-29, 30-39, 40-49, 50-59, 60-74, ≥75 years). The study period was divided into four categories: 1989–1993, 1994–1998, 1999–2003, and 2004–2007. Tumour stage was defined according to the International Federation of Gynaecology and Obstetrics ('FIGO') staging system, based on pathology information and the TNM classification. If pathology information was unknown, tumour stage was defined based on pre-treatment information.

Cervical cancer mortality data for the period 1970–2007 was obtained from Statistics Netherlands [www.cbs.nl].

The number of primary cervix uteri cytological tests and CIN grade III lesions in the Netherlands registered during the period 1990–2006 were retrieved from PALGA. From 1990 onwards all pathology laboratories were linked to this registry.<sup>67, 70</sup> PALGA identifies a woman through her birth date and the first four letters of the maiden name. This identification string enables the linkage of different tests belonging to the same

woman, and therefore also to follow individual testing histories (dates and diagnoses). As a result, we were able to count the annual number of primary cytological tests. The annual number of women diagnosed with a CINIII lesion detected by a primary cervical smear was identified by selecting all PALGA records that included pathology codes for histological defined dysplasia between 1990 and 2006. The detection rates of CIN III were calculated as the number of these lesions (numerator) per 1000 smears (denominator). To allow for follow-up, the most severe histologically confirmed diagnosis within the episode was used as the final diagnosis. An episode is defined as starting with a primary test followed by secondary tests in case this test was abnormal (at least borderline dyskaryosis) or of inadequate quality. Follow-up of secondary tests were defined as the tests made within 4 years following the primary test, unless the follow-up of this primary test had already been completed according to the Dutch guidelines (e.g. with two consecutive negative smears after borderline dyskaryotic smear, or three consecutive negative smears after histologically confirmed CIN). All other tests were seen as primary tests.

### 2.3.2 | Statistical analyses

Annual incidence and mortality rates for the period 1989-2007 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European standard population (European Standardised Rates (ESR)). Trends were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval. To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e.  $y=ax + b$  where  $y = \ln(\text{rate})$  and  $x = \text{calendar year}$ , then  $\text{EAPC} = 100 * (e^a - 1)$ ). The Joinpoint Regression Programme (version 3.3.1) from the Surveillance Research Programme of the US National Cancer Institute was used to identify changes in the trend lines during the observation periods [<http://srab.cancer.gov/joinpoint/>]. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

## 2.4 | Results

### 2.4.1 | Trends in incidence

The total incidence rate (ESR) of cervical cancer decreased from 9.1 per 100,000 woman years in 1989 to 7.9 in 2007. Joinpoint regression analysis showed that in the period 1989-1998, the total ESR decreased with an EAPC of -1.3%, 95% Confidence Interval (CI) -2.2, -0.3, followed by a more rapid, although not significant, decrease in the period 1998-2001 (EAPC -6.7%) and a subsequent increase in the period 2001-2007 (EAPC 2.3%, 95% CI 0.4, 4.2) (Figure 2.1, Table 2.1).

Over the total period, incidence rates significantly decreased in all age groups, except for age groups 20-29 and 40-49 years. The largest decrease in incidence rates in the total period was found for age group 60-64 years (EAPC -3.6%, 95% CI -5.1, -2.0) (Table 2.1), most remarkably in stage FIGO II (EAPC -6.5%, 95% CI -10.3, -2.6) (Figure 2.2). The recent increase in incidence was mainly observed in age group 35-54 years (Figure 2.3).

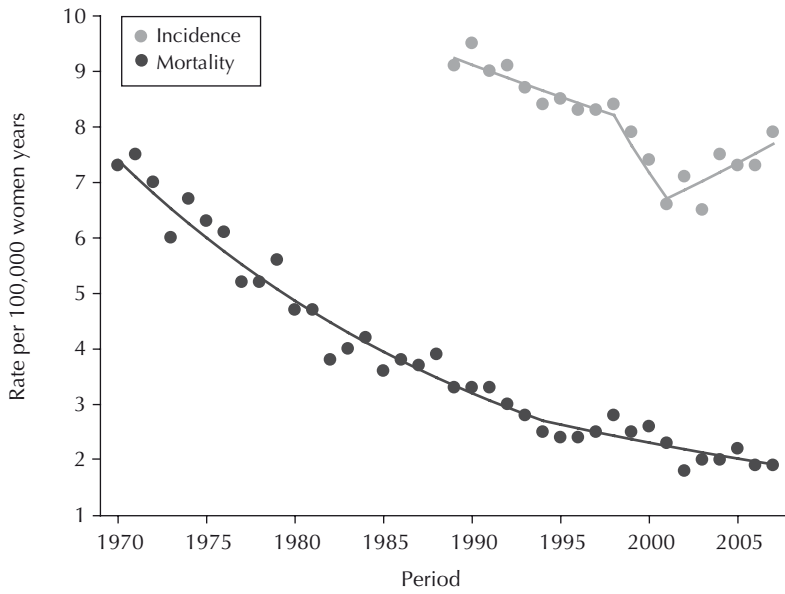
Over the total period the incidence trend in FIGO II tumours was stable, FIGO IV tumours increased and stages I and III decreased (Table 2.1). A significant decrease in FIGO I tumours was found in age groups 30-39, 60-64 and 65+ years (Figure 2.3). FIGO stage II and III tumours significantly decreased in older age groups (50+ and 60+ years, respectively). Incidence of FIGO stage IV tumours significantly increased in age group 30-39 years.

Squamous cell carcinoma (SCC) decreased during 1989-1998 (EAPC -1.3%, 95% CI -2.4, -0.2), followed by a period of more rapid (not significant) decreases during 1998-2001 (EAPC -7.3%) and increases during 2001-2007 (EAPC 2.8%, 95% CI 0.6, 4.9). The incidence of adenocarcinomas remained stable during the total period. Other cervical carcinomas or carcinomas 'Not Otherwise Specified' decreased during the total period with an EAPC of -4.1% (Table 2.1).

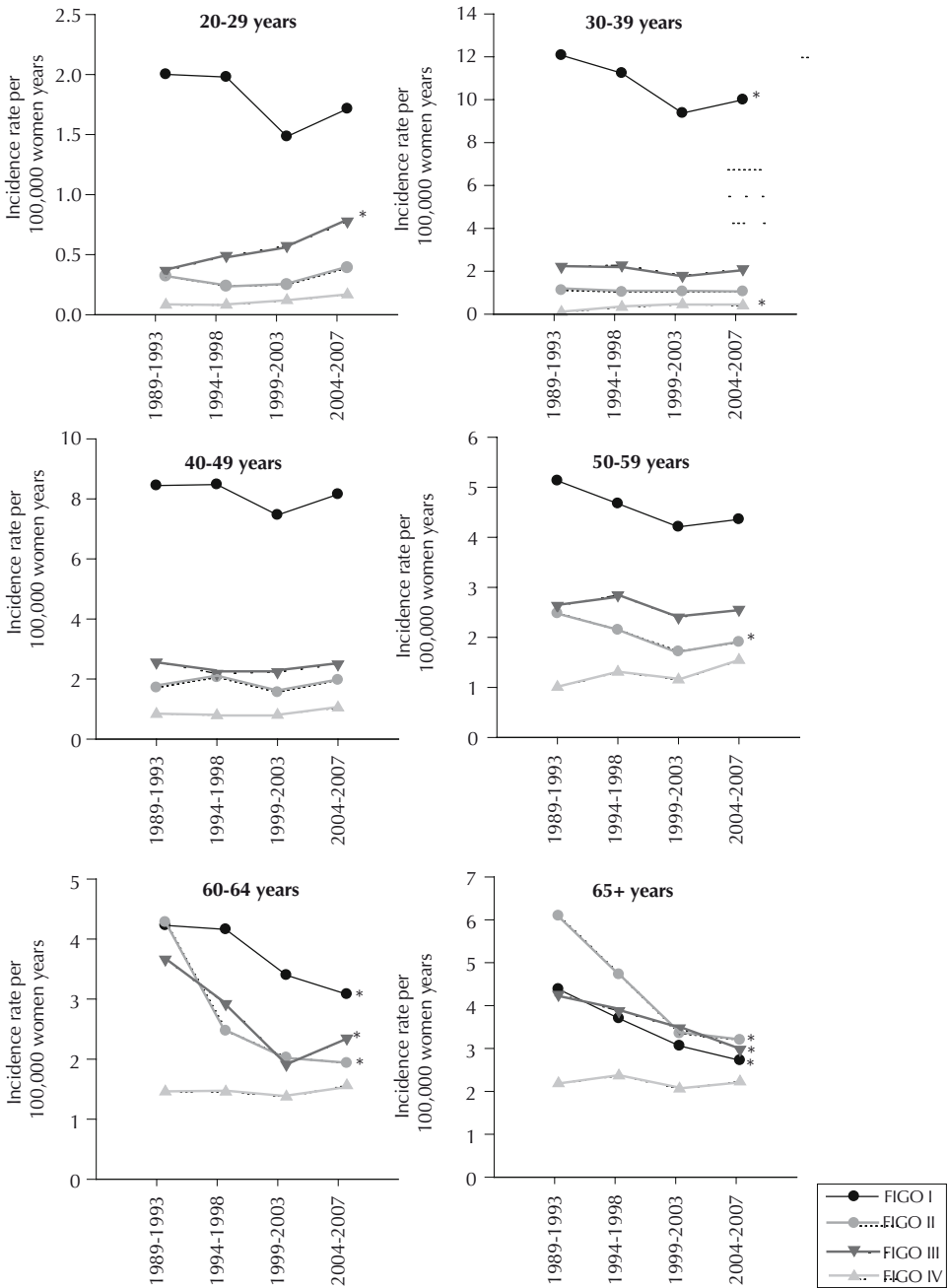
**Table 2.1** | Mean incidence rates (European Standardised Rates (ESR)) of cervical cancer in 5-year periods by age, FIGO stage and morphology in the Netherlands, 1989-2007. (NOS = Not Other Specified, EAPC = Estimated Annual Percentage Change, CI = Confidence Interval, Bold = significant trend)

	1989-93	1994-98	1999-03	2004-07	Period*	EAPC (%) (95% CI)	
Total (N=13,424)	9.1	8.4	7.1	7.5	'89-'98	<b>-1.3 (-2.2, -0.3)</b>	
					'98-'01	-6.7 (-16.4, 4.1)	
					'01-'07	<b>2.3 (0.4, 4.2)</b>	
Age groups (years)	20-29 (N=604)	2.9	2.8	2.4	3.0	'89-'07	-0.2 (-2.3, 2.0)
	30-39 (N=3,501)	16.5	15.8	13.3	14.2	'89-'00	-0.9 (-2.4, 0.6)
						'00-'03	-9.9 (-28.4, 13.2)
						'03-'07	<b>9.6 (1.9, 17.8)</b>
	40-49 (N=2,964)	14.0	13.9	12.4	13.9	'89-'07	-0.4 (-1.2, 0.4)
	50-59 (N=1,905)	11.9	11.3	9.8	10.6	'89-'05	<b>-1.8 (-2.6, -0.9)</b>
						'05-'07	14.2 (-8.3, 42.3)
60-64 (N=800)	14.8	11.7	9.0	9.3	'89-'07	<b>-3.6 (-5.1, -2.0)</b>	
65+ (N=3,581)	18.4	15.8	12.7	12.0	'89-'07	<b>-3.1 (-3.8, -2.5)</b>	
Stages	FIGO I (N=6,582)	4.5	4.3	3.6	3.8	'89-'07	<b>-1.4 (-2.2, -0.6)</b>
	FIGO II (N=2,327)	1.7	1.4	1.1	1.2	'89-'07	-2.8 (-4.1, 1.9)
	FIGO III (N=2,676)	1.7	1.6	1.4	1.5	'89-'07	<b>-1.1 (-2.1, -0.2)</b>
	FIGO IV (N=1,180)	0.6	0.7	0.6	0.8	'89-'07	<b>1.3 (0.3, 2.4)</b>
Morphology	Squamous Cell Carcinoma (N=9,947)	6.7	6.3	5.2	5.6	'89-'98	<b>-1.3 (-2.4, -0.2)</b>
						'98-'01	-7.3 (-18.2, 5.0)
						01-'07	<b>2.8 (0.6, 4.9)</b>
	Adenocarcinoma (N=2,262)	1.4	1.4	1.3	1.4	'89-'07	-0.2 (-1.1, 0.8)
NOS/Other (N=1,155)	0.9	0.7	0.6	0.5	'89-'07	<b>-4.1 (-5.6, -2.6)</b>	

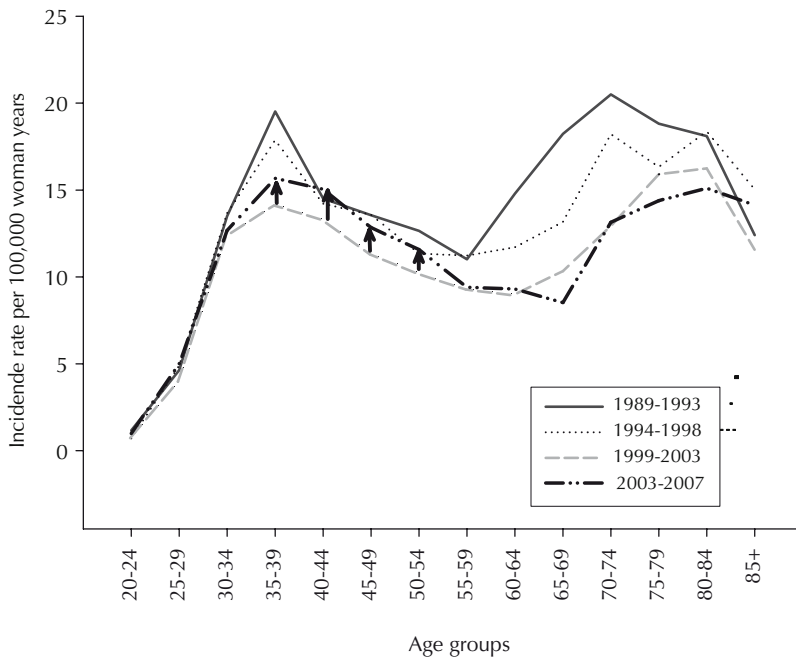
\*Period defined by joinpoint regression analysis



**Figure 2.1** | Joinpoint Regression Analysis of the total age-adjusted incidence and mortality rates (European Standardised Rates) of cervical cancer in the Netherlands, 1970/1989–2007.



**Figure 2.2** | Mean age specific incidence rates (European Standardised Rates) of cervical cancer in 5-year periods and FIGO (International Federation of Gynaecology and Obstetrics) stages in the Netherlands, 1989-2007. (\* = significant trend)



**Figure 2.3** | Mean incidence rates ((European Standardised Rates) of cervical cancer in 5-year periods by age groups in the Netherlands, 1989–2007

## 2.4.2 | Trends in mortality

The overall cervical cancer mortality rate (ESR) decreased from 7.3 per 100,000 woman years in 1970 to 1.9 in 2007. Joinpoint regression analysis showed that mortality rates decreased rapidly during 1970–1994 with an EAPC of  $-4.1\%$  (95% CI  $-4.6, -3.7$ ), and during 1994–2007 with a more moderate EAPC of  $-2.6\%$  (95% CI  $-3.8, -1.5$ ) (Figure 2.1, Table 2.2). Similar trends in mortality rates were found in age groups 40–49 years (Table 2.2). However, in age group 60–74 years mortality rates decreased more rapidly in recent years, compared to earlier periods (Table 2.2).



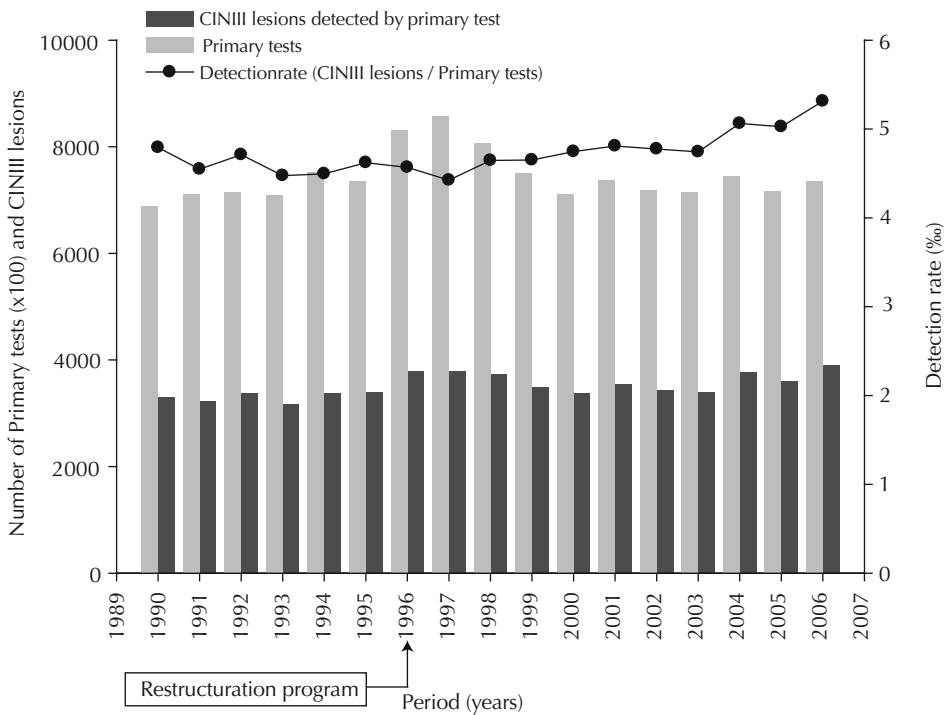
**Table 2.2** | Mortality rates (European Standardised Rates (ESR)) of cervical cancer by age groups in the Netherlands, 1970–2007. (EAPC = Estimated Annual Percentage Change, CI = Confidence Interval, n.a. = Not Applicable, Bold = significant trend)

Period	1970-73	1974-78	1979-83	1984-88	1989-93	1994-98	1999-03	2004-07	Period*	EAPC (95% CI)
Total (N=11,377)	7.0	5.9	4.6	3.8	3.1	2.5	2.2	2.0	'70-'94	<b>-4.1% (-4.6%, -3.7%)</b>
0-29 (N=120)	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	'94-'07	<b>-2.6% (-3.8%, -1.5%)</b>
30-39 (N=780)	2.6	2.0	1.8	1.8	2.2	1.7	1.7	1.5	n.a.	
40-49 (N=1,510)	9.8	7.0	4.5	3.9	3.1	2.7	2.9	2.5	'70-'07	<b>-1.2% (-1.9%, -0.6%)</b>
50-59 (N=2,188)	15.6	14.4	9.1	5.6	4.7	4.1	3.5	3.7	'70-'83	<b>-8.1% (-10.4%, -5.8%)</b>
60-74 (N=3,704)	17.5	15.4	13.7	13.2	9.1	6.4	4.8	4.5	'83-'07	<b>-1.9% (-2.9%, -0.9%)</b>
75+ (N=3,075)	26.5	22.3	19.7	17.5	16.3	14.2	13.0	10.3	'70-'89	<b>-7.3% (-8.7%, -5.9%)</b>
									'89-'07	<b>-2.0% (-3.5%, -0.4%)</b>
									'70-'96	<b>-2.3% (-3.7%, -0.8%)</b>
									'96-'07	<b>-5.8% (-6.7%, -4.8%)</b>
									'70-'07	<b>-2.4% (-2.8%, -2.0%)</b>

\*Period defined by joinpoint regression analysis.

### 2.4.3 | Trends in pre-invasive lesions

The number of CINIII lesions detected per primary cervical smear ('detection rate') was stable during the period 1990–1997 and significantly increased during 1997–2006 (Figure 2.4). During 1996–1998 the number of primary smears was relatively high, and as a result, the number of CINIII lesions detected by primary cervical smears as well. Analysing the data by different age groups showed that the most remarkable increase in number of CIN III lesions detected by primary smears in the period 1996-1998 was found in age group 30–39.



**Figure 2.4** | Number of primary cervical smears (x100), number of Cervical Intra-epithelial Neoplasia grade III (CINIII) lesions (detected by primary cytological test, showed by year of cytological test), and detection rate (%), 1990–2006.

## 2.5 | Discussion

In the Netherlands, after a period of decrease, cervical cancer incidence increased in the period 2001–2007. This increase in recent years was only seen in SCC, not in other morphologies, and in age group 35–59 years. In age group 60+ years, however, a remarkable ongoing decrease over the total period was found. Cervical cancer mortality overall decreased during 1970–2007, though more rapidly during the period 1970–1994 than 1994–2007.

Studying trends in cervical cancer incidence and mortality can give information on underlying changes in causal factors or on changes in the effectiveness of cervical cancer screening, and thereby information on the likely future trends. Studies from other European countries showed that the incidence and mortality rates of cervical cancer varied greatly throughout Europe. In most European countries incidence and mortality rates decreased over time, however, in some countries (i.e. in Eastern Europe) rates remained stable or even increased.<sup>4, 71</sup> In general, in countries where organised screening programmes have been introduced or improved, over relatively large periods of time decreases in incidence and mortality have been observed.

During the study period, cervical cancer screening with the Pap smear was the tool to prevent cervical cancer. Cytological screening is a highly efficient approach to detect SCC, but less efficient to detect adenocarcinomas.<sup>65, 72-73</sup> The observed trend in total incidence follows the trend in age group 35–54 years, and in incidence of SCC tumours, suggesting that developments in screening (aimed at 35–53 year old women before 1996) are likely to underlie the observed trends in incidence. Since the 1996 restructuring, the performance of the Dutch screening programme has improved considerably.<sup>6</sup> During the implementation period of the revised screening programme a conversion scheme for invitation was necessary to implement the longer (5 versus 3 years) interval and broader age-range. During this conversion period in 1996, 1997 and 1998, several extra birth cohorts were invited. So the overall the target population was screened more intensively, with a shorter interval between two examinations. This corresponds to an observed increased number of cervical smears and CINIII lesions during 1996–1998 (Figure 2.4). The conversion programme could explain the temporarily more rapid decrease in incidence, due to increased detection and treatment of CIN lesions. A successive period with less intensive screening (i.e. the ‘back to normal’ intensity) than resulted in a compensating increase in incidence. This explanation is supported by the fact that the age group (i.e. 30–39 years) where we saw the only significant increase in cervical

cancer incidence corresponds to the age group where we observed the most remarkable increase in detected CIN III lesions.

The results of this study support the extra benefits of a more intensive cervical cancer screening programme (i.e. decrease in incidence and mortality) than currently recommended in the Netherlands. Rebolj et al. already illustrated that the cumulative incidence rate of invasive cancer after a negative Pap smear increases from 5 per 100,000 negative smears at year 1 to 48 per 100,000 negative smears at year 6.<sup>74</sup> However, in a situation with already a low incidence rate the extra benefits in absolute terms are limited. These limited benefits have to be balanced with the extra loss of quality of life resulting from false positive screen results and overtreatment, as well as the costs, due to the extra number of programme smears in cohorts of women that are already screened. According to internationally recognised recommendations, screening with intervals from 3 to 5 years is acceptable among women with normal findings in cytological screening, and a shorter interval should be discouraged.<sup>75</sup> Also, it is known that when moving toward a more intensive policy, the incremental cost-effectiveness ratio increases because the incremental effects rapidly diminish.<sup>10</sup> A good balance between harms (i.e. loss of quality of life and costs) and benefits (i.e. life years and quality of life gained) is of great importance for a successful screening programme.

Although screening seems to determine the observed trends in incidence and mortality, this is not necessarily the only explanation. One study showed that the trend in cervical cancer incidence in the Netherlands is partly attributable to birth cohort effects, which in general implicates decreasing exposure to risk factors in successive birth cohorts.<sup>76</sup> Our study also showed (data not shown) that in all age groups the cervical cancer mortality decreases with increasing birth cohort. There is a large dip in mortality between birth cohort 1925–34 and 1935–44, due to the introduction of cervical cancer screening in the 1980's. Such a trend has been observed in other countries as well.<sup>9, 71</sup> In addition, there is a large dip in mortality in the Netherlands between birth cohorts 1915–24 and 1925–34. Also, women born in 1915–24 had a higher mortality at ages 40–50 years, compared to those born in 1905–14. This high mortality in birth cohort 1915–24 can be explained by the fact that these women were at the peak susceptible age for HPV infections (20–30 years) at the end of World War II. It is a plausible possibility that the war was associated with reduced resistance to HPV infections and, consequently, resulted in an increase in progressive infections and cervical cancer.<sup>77</sup> The trend in HPV infections, which is amongst others determined by age at first intercourse and number of sexual partners, is important to predict future trends in cervical cancer. In Finland, the rate of HPV infections in younger cohorts increased.<sup>78-79</sup> In the period 1999–2002, the

cross-sectional prevalence of high risk HPV infections in the Netherlands was estimated at 21% for age group 18–24 and 11% for age group 25–34 years,<sup>80</sup> whereas longitudinal data on HPV infections are lacking. However, due to the availability of the HPV DNA screening test,<sup>81</sup> longitudinal data on persistent HPV infections will be available in the future. The age at first intercourse in the Netherlands is decreasing; in 2005 the mean age at first intercourse was 17.3 years and 30% of the children in high school ever had sexual intercourse, compared to 17.7 years and 24%, respectively, in 1995.<sup>82</sup> The percentage of women with more than 5 sexual partners in a lifetime was 14% in 1991 compared to 37% in 2006.<sup>83</sup> These findings can result in an increase in HPV infections. Several cofactors have been associated with HPV persistence and lesion progression, including smoking, long-term oral contraceptive use, and other sexually transmitted infections.<sup>66</sup> Smoking prevalence decreased among Dutch women from 40% in the 1970s to 25% in 2007.<sup>84</sup> The prevalence of oral contraceptive increased from 27% in 1981 to 46% in 1996, and subsequently decreased to 38% in 2007 use.<sup>85</sup> Changes in registration method or completeness could in theory partly explain the observed trend in cervical cancer incidence. However, this seems unlikely since there were no changes in the method of data collection of the NCR since 1989 and the completeness of the registry is stable.<sup>86</sup>

Data showed that the trend in mortality follows the trend in incidence; in general an increase or decrease in incidence is followed by an increase or decrease in mortality one year later (Figure 2.1). So, if the recent increase in incidence continues, a significant increase in mortality could follow. Moreover, we showed a significant increased trend in FIGO IV tumours and decreased trend in FIGO I-III tumours. This might be a result from better staging due to increased use of positron emission tomography-computed tomography (PET-CT) scans.<sup>87</sup> Still, it could also be explained by a real worsening in stage with worse survival. Van der Aa et al. showed that elderly patients with higher stages were likely to receive suboptimal treatment.<sup>88</sup> Combined with the increased risk of death in elderly<sup>88</sup> and population aging one can expect an increase in mortality in the near future as well. Race and socioeconomical status have also been suggested as important prognostic factors for survival.<sup>89</sup> The percentage non-western immigrants increased in the Netherlands from 0.6% in 1972 to 6.1% in 2008 of the total population [www.cbs.nl]. On the other hand, improvements in treatment, for example the use of radiotherapy in combination with hyperthermia, appeared to have survival benefit.<sup>90</sup>

In 2009, HPV vaccination was introduced in the Dutch National Immunisation Programme. As a result, incidence of HPV infections is expected to decrease in the future. On the other hand, increased use of the more sensitive HPV DNA test may

increase detected HPV infections and, over a short period, also the detection of cervical cancer. On the longer term, however, increased early detection followed by preventive removal of preinvasive lesions should further reduce cervical cancer incidence. The Netherlands Society of Pathology (NVVP) already advocates follow-up HPV DNA testing six months after smears with either atypical squamous cells of unknown significance (ASCUS) or LSIL.<sup>54</sup> The use of the HPV test as the primary screen test in the screening programme is currently under consideration of the Dutch Health Council.

In conclusion, the overall incidence and mortality of cervical cancer decreased and levelled off in the studied period, apparently as the result from levelling off of the screen effect. On top of that, a period of rapid decrease of incidence was followed by a compensating increase, corresponding to a period of temporary increased intensity of the screening programme during the implementation period of the revised programme during 1996-1998. Next to changes in the screening programme, other underlying causes, such as an increase in HPV infections in young women, are possibly partly responsible for the observed trend. New developments, i.e. HPV vaccination and HPV DNA testing, are expected to lead to changes in future incidence and mortality. These new developments and the results of this analysis suggest that close monitoring of trends in cervical cancer incidence, mortality and prevention remains important.

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# **CHAPTER 3**

## **Screening**





## CHAPTER 3.1

# Does lowering the screening age for cervical cancer make sense?

Maaïke A. van der Aa,  
Inge M.C.M. de Kok,  
Sabine Siesling,  
Marjolein van Ballegooijen,  
Jan Willem W. Coebergh

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### 3.1.1 | Abstract

Recommendations for the age to initiate cervical cancer screening should be directed towards maximum detection of early cervical cancer. However, the screening programme should do more good than harm. The aim of this analysis was to determine whether the target age for cervical cancer screening should be lowered in view of apparent increases in new cases of invasive cancer below age 30 and in age group 30–44 years in The Netherlands. Therefore, all cervical cancer cases diagnosed between January 1, 1989 and December 31, 2003 were selected from the nationwide population based Netherlands Cancer Registry. For age group 25–39 years, incidence data were also available for 2004 and 2005. To describe trends, the estimated annual percentage of change and joinpoint analysis were used. Between ages 25 and 28 years, the absolute number of new cases of cervical cancer annually has varied between 0 and 9 per age. Significantly decreasing trends in incidence were observed for age groups 35–39 and 45–49 ( $p < 0.0001$  and  $p = 0.01$ , respectively). The annual number of deaths fluctuated with a decreasing trend for age groups 30–34 and 35–39 years ( $p = 0.01$  and  $p = 0.03$ , respectively). Because the incidence and mortality rates for cervical cancer among women younger than 30 are low and not increasing, lowering the age for cervical cancer screening is not useful at this time. Although the number of years of life gained is high for every case of cervical cancer prevented, the disadvantages of lowering the screening age would be very large and even become disproportionate compared to the potential advantages.

### 3.1.2 | Introduction

Mass screening for cervical cancer has been performed in several countries with varying success. Success depends on the coverage and intensity of the screening, such as intervals between tests, age groups covered, attendance rate, quality of laboratories, quality of follow-up after a positive test and coordination of organized and opportunistic screening.<sup>8, 91-92</sup> The objective of cervical cancer screening is to prevent the occurrence of and death from cervical cancer by detecting intraepithelial lesions (ASCUS) and treating high-grade preinvasive lesions (HSIL). However, it remains important that the screening programme should do more good than harm, as was also described by Wilson and Jungner.<sup>93</sup>

It is now well established that human papillomavirus (HPV) infection is the central causal factor in cervical cancer.<sup>11</sup> HPV is a common sexually transmitted infection, and both women and men are usually exposed to the virus after the onset of sexual intercourse. The risk of infection with HPV and also the risk of cervical cancer increase with the number of sexual partners, lower age at first sexual activity and number of sexual partners of male partners.<sup>94</sup> Additional risk indicators for cervical cancer are the number of live births, long-term use of oral contraceptives, cigarette smoking and immuno-suppression.<sup>95</sup>

The prevalence of HPV infections and, as a result, cytological abnormalities in sexually active young women is high: 80% of all women eventually have an HPV infection, with peak prevalence between ages 25 and 29.<sup>96</sup> HPV acquisition generally decreases with increasing age and HPV persistence increases with age.<sup>97</sup> The higher acquisition in younger women may be due to their higher sexual activity; the reasons for higher persistence among older patients are not clear. However, although 10% to 20% of HPV infections develop into precancerous lesions, most of these cases will clear spontaneously: the likelihood of regression of low-grade preinvasive lesions (LSIL) is 60% while the risk of progression to invasion is 1%. The likelihood that HSIL will regress is 33–40% while progression to invasion is seen in more than 12% of cases.<sup>98</sup> An observational study published in 2003 confirms that 80% of high grade dyskaryosis and dysplasia cannot be destined to progress in a woman's lifetime.<sup>99</sup> In the Netherlands, referral to the gynaecologist takes place after repeated borderline findings [atypical squamous cells of undetermined significance (ASCUS) or LSIL] or after clearly positive cytology (HSIL).

Incidence and mortality rates are low and decreasing in The Netherlands (World Standardized Rates 4.9 and 1.2 per 100,000 woman-years in 2003, respectively<sup>2, 100</sup>). Screening for cervical cancer was started in the mid 1970s within a combination of

regional programmes and opportunistic screening. In 1976, an official pilot study for cervical cancer screening was started in three regions, covering 24% of the Dutch female population. However, under political pressure, the screening programme was soon extended to other regions, reaching almost nationwide coverage around 1980. In 1988, a national screening programme was initiated for women 35–54 years, who were offered screening 7 times at 3 year intervals.<sup>101</sup> In the early 1990s, evaluation of the screening programme in the Netherlands evidently indicated a suboptimal programme, in terms of both the organization and the cost of screening the target population. In 1996, this programme was therefore revised on the basis of extensive MISCAN simulation model calculations. Since then women aged 30–60 years are offered cytological screening at six 5 year intervals.<sup>102</sup> The call-up schedule is based on birth years and therefore a woman born in 1969, for example, will be called up in 1999 as a probable, but not certain, 30-year-old at the time of the Pap smear.

Recently, it has been suggested that the age to initiate cervical cancer screening should be even lower in the Netherlands, for two reasons. Firstly, because of the increased risk of HPV-infection because of earlier sex, the incidence of cervical cancer might be rising in age group 25–29 years. Secondly, some believe that there is an increase in the incidence of cervical cancer in age group 30–44 years and therefore the screening age should be lowered to detect preinvasive cervical lesions earlier. One of the prerequisites for good screening practices is that there must not be too much harm and the screening test should be affordable. The affordability of a Pap smear is high: women do not receive too much harm from it. However, a bulk of HPV infections will be found in young women aged 25–29 when they are screened. Since most of these infections are transient, many women will be referred unnecessarily to a gynaecologist for colposcopic treatment. Recommendations for the age to initiate cervical cancer screening should therefore be directed towards maximum detection of early cervical cancer while avoiding the bulk of transient HPV infections. Since there is no database available on the incidence of HPV infections in The Netherlands, the aim of this study was to answer the question of whether the target age for cervical cancer screening should be lowered by determining (age specific) incidence and mortality rates for cervical cancer in The Netherlands.

### **3.1.3 | Material and Methods**

The Netherlands Cancer Registry (NCR) is nationwide since 1989, and therefore all cervical cancer cases diagnosed between 1 January 1989 and 31 December 2003 were

selected from this population-based cancer registry. For the age group 25–39 years, incidence data were also available for 2004 and 2005. The NCR obtains notifications from the Pathology Automated Archive (PALGA), Haematology Departments and Radiotherapy Departments of the hospitals as well as the National Registry of Hospital Discharge Diagnoses. Death certificates are not available in an identifiable form to the cancer registry because of privacy regulations. All data are obtained from patient files in the hospital and include identifying information (e.g., first letters of the name, date of birth, sex, postal code) and tumour characteristics (e.g., date of diagnosis, topography, morphology, stage). Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O), and the TNM classification is used for staging the tumours.<sup>68, 103</sup>

Although carcinoma *in situ* is registered in PALGA, it is not included in the NCR, and consequently, only newly diagnosed cases of invasive cervical cancer were included in this study.

Data on mortality from cervical cancer were derived from Statistics Netherlands (ICD-10 C53) and only available per 5 year age group.<sup>104</sup> Incidence and mortality rates per 100,000 personyears were calculated. The Estimated Annual Percentage Change (EAPC) was used as an estimate of the trend. Using calendar year as a regression variable, a regression line was fitted to the natural logarithm of the incidence rates, *i.e.*,  $y = mx + b$ , where  $y = \ln(\text{rate})$  and  $x = \text{calendar year}$ . Then  $\text{EAPC} = 100 \times (e^m - 1)$ . Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the slope of the regression line is zero, using the *t*-distribution of  $m/\text{SEm}$ . The number of degrees of freedom equals the number of calendar years minus 2. The standard error of  $m$ , *i.e.*,  $\text{SEm}$ , is obtained from the fit of the regression line. This calculation assumes that the rates increased/decreased at a constant rate over the entire period. Therefore, joinpoint regression analysis was also used to identify points that indicate a statistically significant change over time in the linear slope of the trend. In joinpoint analyses, the join points where the rate changes significantly (increase or decrease) are computed. The analysis starts with the minimum number of joinpoints, and tests whether one or more joinpoints are statistically significant and should be added to the model (up to 3 joinpoints). In the final model, each joinpoint indicates a statistically significant change in trend. Significant changes include changes in the slope of the trend. Joinpoint analyses were performed using 'Joinpoint\_' software from the Surveillance Research Program of the US National Cancer Institute.<sup>105</sup>

**Table 3.1.1** | Number and incidence rates per 100,000 person-years of cervical cancer according to age in the Netherlands, 1989–2005

Year of diagnosis	Age at diagnosis N (per 100,000)					Incidence in 5 year age groups N (per 100,000)				
	25	26	27	28	29 <sup>1</sup>	25–29	30–34	35–39	40–44 <sup>2</sup>	45–49 <sup>2</sup>
1989	1 (0.8)	4 (3.2)	6 (4.8)	5 (4.0)	11 (8.9)	27 (4.3)	78 (13.2)	105 (18.7)	77 (13.6)	64 (14.9)
1990	6 (4.7)	6 (4.7)	8 (6.3)	7 (5.5)	8 (6.4)	35 (5.5)	71 (11.9)	109 (19.3)	102 (17.5)	55 (12.5)
1991	4 (3.2)	8 (6.2)	3 (2.3)	8 (6.3)	11 (8.7)	34 (5.3)	84 (13.8)	110 (19.3)	81 (13.9)	63 (13.4)
1992	2 (1.6)	3 (2.4)	7 (5.4)	7 (5.4)	4 (3.1)	23 (3.6)	87 (14.0)	120 (20.8)	80 (14.0)	76 (14.9)
1993	1 (0.8)	7 (5.6)	3 (2.4)	8 (6.2)	12 (9.2)	31 (4.9)	93 (14.8)	118 (20.2)	77 (13.7)	70 (12.9)
1994	3 (2.3)	2 (1.6)	2 (1.6)	7 (5.5)	5 (3.9)	19 (3.0)	72 (11.3)	110 (18.5)	75 (13.3)	89 (15.8)
1995	2 (1.6)	9 (7.0)	5 (4.0)	9 (7.2)	12 (9.4)	37 (5.8)	91 (14.1)	124 (20.5)	78 (13.8)	74 (12.8)
1996	3 (2.4)	6 (4.6)	5 (3.9)	3 (2.4)	11 (8.8)	28 (4.4)	97 (15.0)	116 (18.9)	73 (12.8)	62 (10.7)
1997	0 (0.0)	6 (4.8)	2 (1.5)	8 (6.2)	15 (11.9)	31 (4.9)	90 (14.0)	103 (16.5)	86 (14.9)	84 (14.8)
1998	3 (2.7)	6 (5.0)	5 (4.0)	6 (4.6)	20 (15.5)	40 (6.5)	89 (13.9)	96 (15.2)	93 (15.9)	77 (13.8)
1999	3 (2.9)	7 (6.2)	3 (2.5)	5 (4.0)	15 (11.5)	33 (5.5)	92 (14.6)	105 (16.5)	93 (15.6)	73 (13.1)
2000	1 (1.0)	0 (0.0)	2 (1.8)	4 (3.3)	6 (4.7)	12 (2.3)	93 (15.4)	100 (15.7)	72 (11.9)	64 (11.4)
2001	0 (0.0)	2 (2.0)	9 (8.4)	3 (2.6)	11 (9.0)	24 (4.6)	74 (11.8)	101 (15.2)	69 (11.2)	58 (10.2)
2002	3 (3.1)	1 (1.0)	6 (5.8)	5 (4.6)	12 (10.4)	26 (5.2)	70 (11.2)	79 (12.3)	85 (13.6)	66 (11.5)
2003	0 (0.0)	1 (1.0)	3 (3.0)	3 (2.9)	12 (11.1)	16 (3.7)	66 (11.0)	71 (11.1)	86 (13.6)	61 (10.5)
2004	3 (3.1)	4 (4.1)	6 (6.1)	5 (5.0)	9 (8.7)	27 (5.4)	75 (12.4)	96 (14.8)	–	–
2005	1 (1.0)	6 (6.1)	4 (4.1)	4 (4.1)	13 (13)	28 (5.7)	71 (12.3)	88 (13.6)	–	–
EAPC	-1.4%	-3.8%	1.2%	-2.7%	3.6%	2.0%	-0.7%	-3.1%	-0.9%	-2.0%
<b>p-value</b>	0.635	0.260	0.658	0.072	0.102	0.862	0.226	<0.001	0.195	0.012

<sup>1</sup>The column of age 29 is white because the incidence rates may be biased by women who were diagnosed by participation in the screening programme.

<sup>2</sup>2004 and 2005 no data available for this age category.

### 3.1.4 | Results

#### 3.1.4.1 | Incidence

The incidence of cervical cancer appears to increase from age 29 onwards (Table 3.1.1). Before age 29, the absolute number of cases of cervical cancer varies annually between 0 and 9 per age year. Because of the small numbers, incidence varied markedly between different years of diagnosis, with potential decreases for ages 25, 26 and 28 years. In age group 25–29, the small increase was mainly based on the incidence among 29-year-old women. No significant rises in the incidence rates of cervical cancer were found. However, significantly decreasing trends were seen for age groups 35–39 and 45–49 ( $p < 0.0001$  and  $p = 0.01$ , respectively). With joinpoint analyses, we were not able to find any significant changes in trends over time.

#### 3.1.4.2 | Mortality

The annual numbers fluctuate across the years, with a decreasing trend for age groups 30–34 and 35–39 years ( $p = 0.01$  and  $p = 0.04$ , respectively) (Table 3.1.2). Significant rises in the incidence rates of cervical cancer could not be found. However, compared to all other age groups, age group 25–29 was the only group with a (non-significant) increasing trend. We were not able to detect any significant changes in the trends.

**Table 3.1.2** | Mortality from cervical cancer according to age group per 100,000 person-years in the Netherlands, 1989–2006

Year of diagnosis	Mortality in 5 year age groups, N (per 100,000)				
	25–29	30–34	35–39	40–44	45–49
1989	3 (0.5)	12 (2.0)	18 (3.2)	16 (2.8)	13 (3.0)
1990	4 (0.6)	10 (1.7)	17 (3.0)	15 (2.6)	16 (3.6)
1991	5 (0.8)	15 (2.5)	15 (2.6)	22 (3.8)	16 (3.4)
1992	4 (0.6)	6 (1.0)	18 (3.1)	15 (2.6)	17 (3.3)
1993	4 (0.6)	10 (1.6)	9 (1.5)	16 (2.8)	15 (2.8)
1994	1 (0.2)	7 (1.1)	17 (2.9)	15 (2.7)	12 (2.1)
1995	1 (0.2)	4 (0.6)	13 (2.2)	15 (2.7)	17 (2.9)
1996	2 (0.3)	7 (1.1)	14 (2.3)	9 (1.6)	19 (3.3)
1997	4 (0.6)	8 (1.2)	13 (2.1)	16 (2.8)	17 (3.0)
1998	0 (0.0)	6 (0.9)	14 (2.2)	14 (2.4)	21 (3.8)
1999	1 (0.2)	7 (1.1)	19 (3.0)	14 (2.4)	21 (3.8)
2000	4 (0.7)	9 (1.4)	11 (1.7)	21 (3.5)	28 (5.0)
2001	3 (0.6)	12 (1.9)	23 (3.5)	10 (1.6)	18 (3.2)
2002	4 (0.8)	5 (0.8)	11 (1.7)	9 (1.4)	16 (2.8)
2003	4 (0.8)	3 (0.5)	10 (1.5)	16 (2.5)	14 (2.4)
2004	0 (0.0)	4 (0.7)	17 (2.6)	17 (2.6)	11 (1.9)
2005	3 (0.6)	8 (1.4)	12 (1.9)	15 (2.3)	14 (2.3)
2006	2 (0.4)	3 (0.5)	10 (1.5)	13 (2.0)	16 (2.6)
EAPC	1.9%	-5.1%	-2.6%	-2.1%	-1.5%
p-value	0.495	0.010	0.032	0.075	0.163

### 3.1.5 | Discussion

Incidence of and mortality from cervical cancer in younger age groups excluded from the screening programme are very low. Mortality increased in age group 25–29 years but not significantly and mortality in this age group continues to be very low. The incidence among women 29-year-old, which is higher than the incidence for ages 25–28 separately, can be explained by the call-up schedule and the reorganization of the screening programme. The incidence for women 29-year-old started to rise in 1996, together with the lowering of the screening age from 35 to 30 years. It is known that the incidence of cancer increases after first onset of screening activities, because prevalent cases will be detected then. Also, because the call-up schedule is based on birth years



a woman will be called up as a probable, but not certain, 30-year old at the time of the Pap smear. If we adjust for this phenomenon by considering all women who were actually 29 years old at the time of diagnosis but were going to be 30 years old in the year of diagnosis as 30 at diagnosis, the increase in 29-year-old women becomes a non-significant decrease (EAPC, -4.2%;  $p = 0.1$ ).

Harm and affordability are important issues in policy making, and lowering the screening age will have both psychological and financial effects. In 2004 there were 97,000 25-year-old women in The Netherlands. The mean attendance rate in The Netherlands was 68% for age group 30–34 years (2003).<sup>106</sup> Projecting this attendance rate to 25-year-old women means that 64,000 25-year old women would have been screened if the target age of the screening programme was 25–60 years. In The Netherlands, the frequency of abnormal smears among 30-year-old women was 3.9%  $\geq$  LSIL in 2003.<sup>107</sup> A study from the United States found that 4% of women aged 25–29 years have HSIL or higher or to have repeated borderline findings, which means that about 2,560 women (4% of 64,000) will be referred to a gynaecologist for colposcopic evaluation in The Netherlands.<sup>108</sup> In addition to the anxiety associated with undergoing a colposcopic examination, false-positive results may cause persistent anxiety for many years. On the other hand, a negative screening test result may reinforce an unhealthy lifestyle.<sup>109</sup> Also, there is the problem of overtreatment; many women undergo conisation or loop electrosurgical excision procedure (LEEP) for a CIN that may otherwise go into regression because of its transient nature, especially in young women. Although the side effects of these treatment procedures are minimal, they should be avoided when not necessary.<sup>110</sup> Another potential adverse effect of false-positive results is the expenses of follow-up diagnostic procedures.

In contrast to The Netherlands, an increase in the incidence of cervical cancer in young women was seen in other countries. In Finland, a recent increase in the incidence of cervical cancer was revealed among young women,<sup>111</sup> which is underpinned by the historical increase in HPV rates.<sup>78</sup> There have been no changes in organised screening or diagnostics as such. However, the average number of sexual partners for Finnish women increased and the average age at first intercourse of these women decreased.<sup>112</sup> Also, tobacco smoking has increased substantially among young Finnish women during the 1980s.<sup>113</sup> The findings of the Finnish study are in agreement with those of other reports that there have been significantly increased detection rates of preinvasive disease in the younger age groups during recent decades.<sup>114-115</sup> A study from Iceland confirms an increasing rate of preinvasive and invasive disease among younger women and indicates the benefit of starting organised screening at 2–3 year intervals soon after age 20.<sup>116</sup>

They further state that in well-organised screening, overtreatment of young women with low-grade lesions can easily be avoided. Almost the same conclusions are drawn by a study from the United Kingdom in which it was concluded that invasive cancer rates in women aged 20–24 and 25–29 are low, but have not fallen and remain higher than in 1974. Carcinoma in situ rates have increased in women aged 20–24 and 25–29 years. In addition, the authors state that giving accurate information about low-grade lesions, together with promoting healthy lifestyles and safer sex, empowers young women to look after their sexual health.

The absence of an increase in the incidence in The Netherlands is not likely to be due to opportunistic screening in the lower age groups. In general, opportunistic screening is very low in The Netherlands, with only 33 per 1,000 women who are screened spontaneously annually in age group 20–29 years.<sup>6</sup> In The Netherlands, unfortunately, there is no linkage of the cancer registry with the cause-of-death registry. However, after 1970, there were very few uterus ‘not otherwise specified’ cases of cancer in The Netherlands and therefore the trends in mortality were affected negligibly.<sup>104</sup> Therefore, correction for this death cause certification was not required, as was in many other European countries.<sup>117-118</sup> In The Netherlands, the decrease in age at first intercourse stopped about 10 years ago.<sup>82</sup> However, the incidence of HIV and other sexually transmitted infections has been increasing, according to the latest surveillance data, and an increase in the incidence of HPV infections may therefore also be expected. Tobacco smoking, which is also a risk factor for cervical cancer,<sup>119</sup> increased among women in The Netherlands during the 1950s and 1960s and started to decrease around 1970.<sup>120</sup>

Although lowering the screening age for the whole population does not seem to improve the result of the screening programme in The Netherlands, there might be specific risk groups for cervical cancer at young age. Several studies have found more cervical abnormalities among young women in certain immigrant populations who are known to have a higher primary risk.<sup>121-122</sup> Increasing their knowledge about HPV infection might result in higher screening attendance rates.<sup>123</sup> Another risk group are prostitutes who run a higher risk of HPV infections and cervical intraepithelial lesions.<sup>124</sup> Finally, according to some studies, genital HPV infections and cervical intraepithelial lesions are more common among sexually abused than nonsexually abused girls.<sup>125</sup> However, since other studies indicate that the majority of anogenital HPV infections among children are probably the result of nonsexual horizontal transmission<sup>126</sup> and because it is so difficult to prove whether HPV infections are the result of involuntary sexual activity, it is almost impossible to classify these women as a risk group and to treat them differently in terms of offering them smears at younger age.

In conclusion, because increases in incidence and mortality rates for cervical cancer could not be found in this study or could just be attributed to earlier screening activity at age 29 since 1996, further lowering the age for cervical cancer screening is not useful at this time. Although mortality from cervical cancer is very low, the number of life-years gained is high per woman for women who are prevented from developing cervical cancer (20–40 years). However, the disadvantages of lowering the screening age in terms of ‘overtreatment and anxiety are high and seem therefore to be disproportionate. The attendance rates of the current target population should be optimized and the use of the HPV test should be increased to improve triage and management.<sup>127</sup> However, although this is not evidence based, screening at younger age might be advantageous for some high-risk groups. It seems better to focus on improving the attendance rates among high-risk groups, improving the quality of the smear and the validity of the cytological diagnosis with possibly increase in the use of the HPV test. The potential introduction of an HPV vaccine might make the question of decreasing the start age of screening irrelevant.



## CHAPTER 3.2

# **Cost-effectiveness analysis of liquid-based cytology in the Netherlands**

Esther W. de Bekker-Grob,  
Inge M.C.M. de Kok,  
Hans Bulten,  
Joost van Rosmalen,  
Judith E.M. Vedder,  
Marc Arbyn,  
Paul J.J.M. Klinkhamer,  
Bert G. Siebers,  
Marjolein van Ballegooijen

*Submitted for publication*



### 3.2.1 | Abstract

Cervical cancer screening with liquid-based cytology (LBC) has been developed as an alternative to conventional Papanicolaou (CP) smear. However, the cost-effectiveness of LBC to that of CP is questionable. We conducted a cost-effectiveness analysis comparing LBC and CP smear in cervical cancer screening based on the results of a recent and large Dutch randomized controlled trial. The MISCAN-Cervix microsimulation model and data from a recent Dutch randomised controlled trial (89,784 women included) were used to estimate the total costs and (quality-adjusted) life years ((QA)LYs) gained by screening women aged 30–60 years every 5 years with primary LBC or CP, and with cytology (LBC or CP) or human papillomavirus (HPV) testing in triage. LBC with cytology triage and CP screening with cytology triage are both dominated by screening with HPV triage. In case of HPV triage, threshold analyses showed that LBC as a primary test can be cost-effective if the extra costs per LBC-test compared to CP-test decreases from €11.7 to €3.3, if the sensitivity of LBC increases from 40–75% to 49–79%, if the quality of life for women in triage follow-up decreases from 0.994 to 0.39, or if the rate of inadequate smears after a CP-test increases from 1.1% to 16.1%. Therefore, we conclude that in a situation with a low rate of inadequate smears after a CP test, LBC is not a cost-effective alternative in cervical cancer screening.

### 3.2.2 | Introduction

The conventional Papanicolaou (Pap) test has significantly reduced cervical cancer mortality in countries with organized screening.<sup>8</sup> Nevertheless, the conventional Pap test (CP) is considered suboptimal because of the false-negative and false-positive results caused by a limited quality of sampling and preparation as well as errors in detection and interpretation. Cervical cancer screening with liquid-based cytology (LBC) has been developed as an alternative to CP in the hope of improving specimen adequacy and sensitivity in detecting cervical abnormalities.<sup>128</sup> With LBC, the cervical cells are collected with a traditional sampling device and rinsed into a vial with preservation solution rather than being smeared on a slide.<sup>129</sup>

The accuracy of LBC has been compared with CP in numerous studies, however with disparate results.<sup>27, 130-131</sup> Recently, we conducted a large cluster randomized controlled trial (RCT) (NETHCON; n =89,784 women aged 30 to 60 years participating in the national cervical screening programme; registration trialregister.nl NTR1032), which indicated that LBC does not perform better than CP in terms of relative sensitivity and positive predictive values for detection of cervical cancer precursors.<sup>132</sup> However, we showed that LBC resulted in significantly fewer unsatisfactory tests.<sup>133</sup> Another advantage of LBC to CP is that only a portion of the sample is used in LBC, so that the residual material in the vial can be used for ancillary tests such as human papillomavirus (HPV) testing in case of cytology result of atypical squamous cells of undetermined significance (ASCUS).<sup>134</sup> This may avoid i) loss to follow up between a primary cytology test and a HPV-triage test, ii) utility lost due to living in uncertainty, and iii) costs of an extra GP visit.

In this paper, we conduct a cost-effectiveness analysis comparing LBC and CP based on the results of our large RCT, and investigate to what extent the relative cost-effectiveness of LBC and CP change if a cytological test is used in the triage or if an HPV-test is used immediately after a positive cytological test result.

### **3.2.3 | Material and methods**

#### **3.2.3.1 | Randomized controlled trial**

The NETHCON trial and its outcomes have been published elsewhere.<sup>132-133</sup> In short, we conducted an RCT (n= 89,784 women aged 30 to 60 years participating in the national cervical screening programme, recruited from 246 family practices in two regions in the Netherlands; registration trialregister.nl NTR1032) to assess the diagnostic accuracy of LBC compared with CP. Two clinical laboratory sites (PAMM Laboratories Eindhoven and Radboud University Nijmegen Medical Centre, Nijmegen) participated in the trial. All family practices feeding the laboratory sites were eligible for random assignment to the experimental arm (preparation of the test using LBC) or the control arm (preparation of the test using CP). The LBC used was Thinprep® System (Hologic Corporation, Marlborough, MA). Ethical approval for this study was obtained from the Dutch Ministry of Health, Welfare and Sport.

#### **3.2.3.2 | Model description**

The costs and the effects of the screening strategies were estimated using the microsimulation screening analysis (MISCAN) model for cervical cancer.<sup>58</sup> The MISCAN-Cervix model generates a large study population with fictitious individual life histories, in which women will, at a certain rate, acquire an HPV infection and develop a pre-invasive cervical lesion and/or cervical cancer, and some will die from the disease. This simulation results in an age-specific and time-specific output of disease incidence and mortality. This fictitious population then undergoes simulated screening; this intervention will change some of the life histories. These changes constitute the effects of the intervention and are represented by the numbers of events and stages induced or prevented by the intervention; from these numbers of events we can determine the costs and quality-of-life outcomes of the intervention.

#### **3.2.3.3 | Model specifications and assumptions**

##### **3.2.3.3.1 | Demography, epidemiology and natural history**

We simulated a Dutch population at risk for cervical cancer based on demographic<sup>135</sup> and hysterectomy data.<sup>136</sup> The age distribution of the incidence of pre-invasive neoplasia that will eventually become cancer was calibrated to the age distribution of the pre-



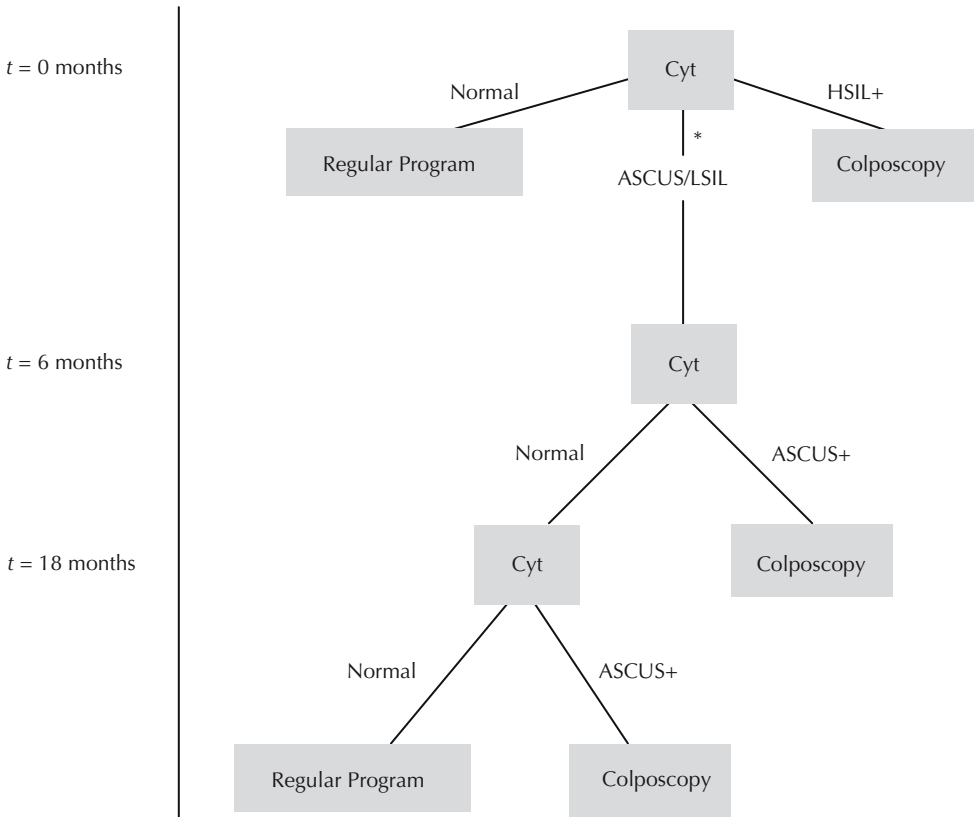
screening mortality.<sup>76</sup> The age distribution of the incidence of pre-invasive lesions that will regress before they become cancer was calibrated to the observed cervical intraepithelial neoplasia (CIN) detection rates in the Netherlands (derived from the Dutch Network and National Database for Pathology (PALGA)). The age distribution of the incidence of HPV infections that will clear before progressing to CIN was calibrated to the observed HPV prevalence.<sup>96</sup>

Disease is subdivided into seven sequential stages: HPV infection, three pre-invasive stages (CIN 1, 2 and 3) and three invasive stages (International Federation of Gynaecology and Obstetrics (FIGO)<sup>137</sup> stages 1A, 1B, and 2+). Pre-invasive stages and FIGO 1A cases can only be diagnosed by cytological screening, since no symptoms will develop, whereas stages 1B and 2+ cases can also be clinically diagnosed. An HPV-infection can only be diagnosed with an HPV test. A Weibull distribution was used to assume variation among women in the duration of the different stages. The stage-specific survival used in the model for clinical cases was age-specific and based on observed survival and on mortality to incidence ratios from the pre-screening period in the Netherlands.<sup>76</sup>

### 3.2.3.3.2 | Assumptions for screening and treatment

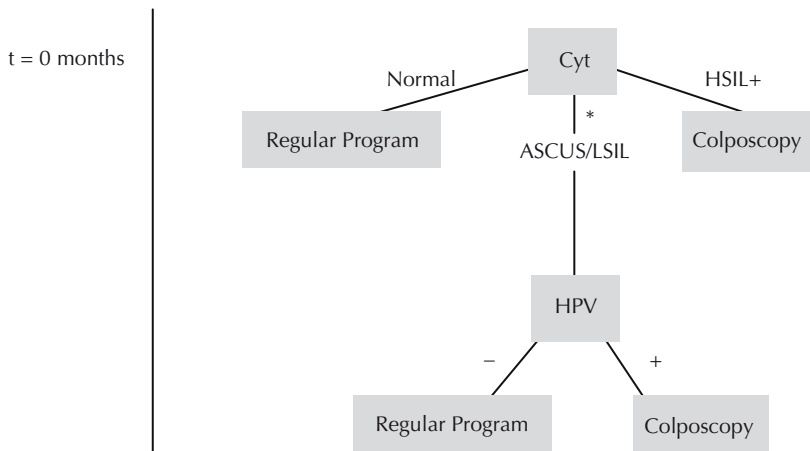
We simulated the costs and effects by screening women with CP as the primary and triage test (CP/CP) and with LBC as the primary and triage test (LBC/LBC) based on the current Dutch screening programme<sup>138</sup> (Figure 3.2.1a). To investigate to what extent the difference in cost-effectiveness between LBC and CP changes if an HPV test is used immediately after a low-grade squamous intraepithelial lesion (LSIL) or ASCUS test result, we also simulated the costs and effects by screening women with CP as the primary test and HPV triage (CP/HPV) and with LBC as the primary test and HPV triage (LBC/HPV) (so called reflex-testing)<sup>139</sup> (Figure 3.2.1b). Although other cervical screenings scenarios with primary CP and HPV triage might be more popular,<sup>140</sup> the scenario with HPV testing immediately after an ASCUS/LSIL test result contains all advantages of LBC compared to CP, and follows the literature that suggests that HPV-negative women with ASCUS should return to routine screening intervals.<sup>141</sup> We assumed that women were screened as in the current Dutch programme, that is, every 5 years from ages 30 to 60 years. The screening attendance rate was based on observed rates of women who had at least one Pap smear in the previous 5 years in the Netherlands.<sup>142</sup> We assumed that 10% of the female population never attends screening and has a threefold higher background risk for cervical cancer than the female population comprising the potential attenders.<sup>143</sup> The sensitivity of the HPV triage of ASCUS/LSIL was estimated at 94%.<sup>139</sup>

The sensitivity of CP was estimated at 40% for CIN 1, 50% for CIN 2, and 75% for CIN 3, FIGO 1A, 1B, and 2+.<sup>139</sup> The specificity of CP was assumed to be 98.5% based on the false-positive rate of Pap smears in the Dutch screening programme.



\* = 10 percent loss to follow-up both in CP/CP and in LBC/LBC

**Figure 3.2.1a** | Cervical cancer screening with CP/CP or LBC/LBC (based on recommendation of the current Dutch screening program).<sup>138</sup> Cyt = Cytological test; ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; CP = conventional Pap; LBC = liquid based cytology



\* = 10 percent loss to follow-up only in CP/HPV (in LBC/HPV women do not have to come back in case HPV triage test is required)

**Figure 3.2.1b** | Cervical cancer screening CP/HPV or LBC/HPV (based on Berkhof et al.<sup>139</sup>); i.e. a HPV-test immediately after an ASCUS/LSIL cytological test result. Cyt = Cytological test; HPV = HPV DNA test; ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; CP = conventional Pap; LBC = liquid based cytology

Based on the data from the NETHCON trial (n =89,784 women), the sensitivity and the specificity of LBC test for various (pre-)invasive cervical cancer stages were not statistically different from the conventional cytology test;<sup>132</sup> therefore we assumed that the baseline characteristics (sensitivity and specificity) of LBC and CP were similar. Based on the same data, the proportion of unsatisfactory samples was determined to be 0.33% for LBC and 1.11% for CP.<sup>133</sup>

We assumed that women with an ASCUS/LSIL test result had a repeat smear or an HPV test (depending from the screening strategy used), whereas those with an least moderately dyskaryotic test result (HSIL) were referred for colposcopy and biopsy. Detection and the associated management of pre-invasive lesions were assumed to lead to a 100% cure rate. In our assumptions, there is a loss to follow up of 10% of the women with a ASCUS/LSIL test result in all strategies,<sup>6</sup> except for the LBC/HPV strategy, where HPV testing is used as a reflex test on residual material.

### 3.2.3.3.3 | Costs and utilities

Table 3.2.1 presents the estimated costs and utilities (a *quality of life* measure between 0 (death) and 1 (perfect health)), associated with screening and treatment. Screening costs include costs of the invitational system, time and travel costs of women attending screening, costs of smear taking, cytological evaluation, and registration in PALGA. The costs of CP, diagnosis, treatment and palliative care for cervical cancer were derived from cost studies in the Netherlands.<sup>142</sup> We estimated the total costs of the LBC test €11.72 higher than the total costs of the CP test (€63.60 versus €51.88). In more detail, the material and logistic costs of LBC were respectively €7.58 and €4.25 higher than the costs of CP, whereas the personnel costs were €0.11 lower (the screening time of an LBC sample was on average 57.4 seconds shorter than the screening time of a CP sample, however, the preparation time of an LBC sample was on average 42.7 seconds longer). The costs of the HPV test were based on Rebolj et al.<sup>140</sup> (Table 3.2.1). All costs were updated to the price level of 2008. Utilities were based on Dutch data and data from other countries.<sup>76, 144</sup> In case of the LBC/HPV strategy, there is no loss of utility due to triage, whereas in the other strategies there is a small loss of utility. Also, in this LBC/HPV strategy there are no time and travel costs due to triage, which do exist in the other strategies.

### 3.2.3.4 | Cost-effectiveness analysis and sensitivity analyses

The cost-effectiveness calculations were conducted from a societal perspective. Costs and effects (i.e. numbers of screening and triage tests, screen detected neoplasms, clinical cases, disease specific deaths, and (quality-adjusted) life years (QALYs)) were discounted at an annual rate of 3% to convert future costs and health effects to the present. We determined the threshold values for LBC to be cost-effective to CP for the unit costs, the improvement in test sensitivity, the rate of inadequacy smears, and the loss of utility for women while they are in triage follow-up. We used two cost-effectiveness thresholds: i) a cost-effectiveness threshold of €20,000 per QALY gained based on earlier decisions of the Dutch government,<sup>10</sup> and ii) a cost-effectiveness threshold of €50,000 per QALY gained, which is often used in other countries.<sup>145</sup>

**Table 3.2.1** | Assumptions about the costs (price-level 2008) and the amount and duration of the utilities of different events and health states.

Screening	Unit costs, €	Utilities	
		Amount	Duration
Invitation	4.65	n.a.	n.a.
Primary test			
CP test	51.88 <sup>§</sup>	0.994	2 weeks
LBC test	63.60*	0.994	2 weeks
Triage test			
CP test	53.75 <sup>‡</sup>	0.994	1 year
LBC test	65.46 <sup>^</sup>	0.994	1 year
HPV test immediately after a ASCUS/LSIL CP test result	60.93 <sup>“</sup>	0.994	2 weeks
HPV reflex testing on residual material of an ASCUS/LSIL	33.23 <sup>†</sup>	n.a.	n.a.
LBC test result			
<b>Management after referral to gynaecologist</b>			
Diagnoses and treatment of pre-invasive stages			
False positive referral	279	0.970	1 month
CIN 1	869	0.970	0.5 year
CIN 2	1,287	0.930	1 year
CIN 3	1,507	0.930	1 year
Diagnoses and treatment of invasive cancer			
FIGO 1A	4,935	0.938	5 years
FIGO 1B	11,703	0.938	5 years
FIGO 2+	10,773	0.720	5 years
Terminal care	26,209	0.288	1 month

CIN 1 = cervical intraepithelial neoplasia grade 1; CIN 2 = CIN grade 2; CIN 3 = CIN grade 3; FIGO = International Federation of Gynecology and Obstetrics; CP = conventional Pap; LBC = liquid based cytology; ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; n.a. = not applicable

§ Includes database registration (€13.06), time and travel (€5.91), smear taking (€11.54), and cytological evaluation (€21.36).

\* Includes database registration (€13.06), time and travel (€5.91), smear taking (€11.54), and cytological evaluation (€33.08). Cytological evaluation is thus €11.72 (€33.08 vs €21.36) more expensive for LBC than for CP due to higher material (+€7.58) and logistic (+€4.25) costs, and somewhat lower personnel costs (-€0.11; screening the sample was on average 57.4 seconds per sample shorter in case of LBC, however, the preparation time of the sample was on average 42.7 seconds longer).

‡ Includes GP costs (€21.79), time and travel (€5.91), and cytological evaluation (€26.05).

^ Includes GP costs (€21.79), time and travel (€5.91), and cytological evaluation (€37.77).

“ Includes GP costs (€21.79), time and travel (€5.91), and laboratory costs (€33.23).

† Includes laboratory costs (€33.23).

## 3.2.4 | Results

### 3.2.4.1 | Effects and costs

The average effects of the CP/CP strategy and the LBC/LBC strategy per 100,000 women did not differ, except for the number of screens that were classified as unsatisfactory (see 'repeated screens' in Table 3.2.2; discount rate 0%). In the LBC/LBC strategy there were 703 unsatisfactory screens per 100,000 women compared with 2,365 in the CP/CP strategy. As a result, the LBC/LBC strategy had 0.38 fewer QALYs lost per 100,000 women than the CP/CP strategy (5,363.50 versus 5,363.88 QALYs lost), and this strategy decreased the costs for repetition of unsatisfactory tests by 63.6% (from €122,696 to €44,711). However, the total costs were higher for the LBC/LBC strategy (€23.5 million per 100,000 women) than for the CP/CP strategy (€20.9 million per 100,000 women) due to the increased costs per cytology performed; i.e. an increase of €26.0 per women during lifetime.

Comparing the CP/HPV strategy to the LBC/HPV strategy (i.e. the screening strategies which contained an HPV test immediately after an ASCUS/LSIL cytological test result) yields more differences (Table 3.2.3; discount rate 0%). Because with LBC women do not have to come back for their triage HPV test, there were 23.26 fewer QALYs lost per 100,000 women during triage (5,266.84 versus 5,290.10 QALYs lost), and less time and travel costs for women with minor cytological lesions. These advantages and the advantage of lower costs for unsatisfactory tests did not counterbalance the €2.4 million higher costs of primary testing (i.e. €15.1 million for LBC versus €12.7 million for CP) due to the higher LBC unit costs. The cost-effectiveness ratio without discounting was €96,905 per QALY gained. With discounting at 3%, the cost-effectiveness ratio was €100,726 per QALY gained.

### 3.2.4.2 | Threshold Analyses

Four parameters significantly affect how LBC compares to CP: i) unit costs; ii) test sensitivity; iii) loss of utility for women while they are in triage follow-up, and iv) rate of inadequacy smears. The first threshold analysis showed that for the parameter 'unit costs', the all-in price of LBC may be at most €3.3 more expensive than CP (i.e. the extra costs per LBC-test compared to CP-test should be decreased from €11.7 to €3.3) to make the LBC/HPV strategy more cost-effective than the CP/HPV strategy at a cost-effectiveness threshold of €20,000 per QALY gained (Figure 3.2.2; discount rate 3%). At

a cost-effectiveness threshold of €50,000 per QALY gained, the threshold all-in price per LBC may be at most €6.4 more expensive than CP (Figure 3.2.2).

**Table 3.2.2.** Estimated costs and effects for CP/CP and LBC/LBC per n=100,000 women (0% discounting).

<b>Costs and effects</b>	<b>CP/CP (No.)</b>	<b>LBC/LBC (No.)</b>
<b>Effects (DR=0%)</b>		
First primary screens	213,101	213,101
Triage screens	7,366	7,366
Repeated screens <sup>§</sup>	2,365	703
False positive	208	208
CIN1 lesions	229	229
CIN2 lesions	187	187
CIN3 lesions	609	609
SD cases of invasive ca	38	38
Clin cases of invasive ca	244	244
Deaths from cervical ca	137	137
Life-years lost	4,943	4,943
QALYs lost	5,364	5,364
QALYs lost (DR=3%)	2,770	2,770
<b>Costs (DR=0%)</b>		
Screening (including triage test)	12,824	15,408
Repeated screens <sup>§</sup>	123	45
Treatment*	7,998	7,998
Total	20,945	23,451
Total (DR=3%)	13,260	15,091

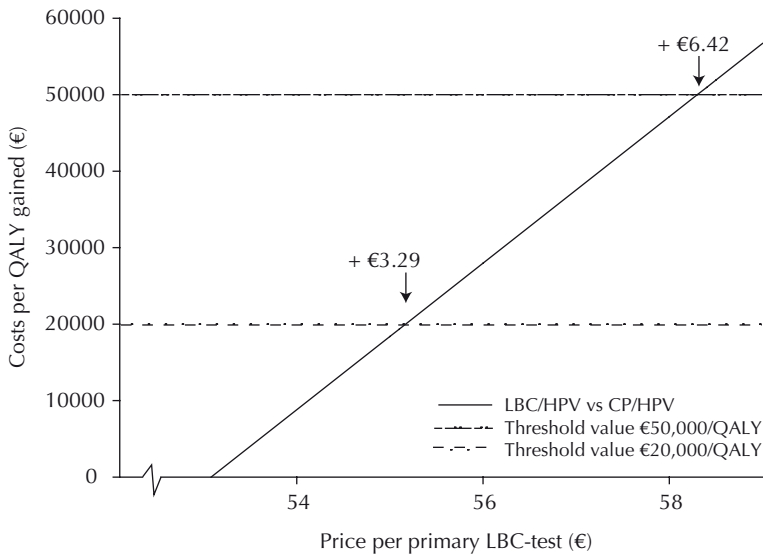
CP = conventional Pap-test; LBC = liquid based cytology; SD = screen detected; ca = cancer; clin = clinically detected; DR = discount rate; No. = numbers; k€ = 1,000 euro; § screens that were classified as unsatisfactory and had to be repeated; \* including costs of terminal care

**Table 3.2.3** | Estimated costs and effects for CP/HPV and LBC/HPV per n=100,000 women (0% discounting).

<b>Costs and effects</b>	<b>CP/HPV (No.)</b>	<b>LBC/HPV (No.)</b>
<b>Effects (DR=0%)</b>		
First primary screens	213,113	213,132
Triage screens	3,915	4,124
Repeated screens <sup>§</sup>	2,366	703
False positive	197	206
CIN1 lesions	194	205
CIN2 lesions	194	197
CIN3 lesions	585	578
SD cases of invasive ca	35	33
Clin cases of invasive ca	246	243
Deaths from cervical ca	136	135
Life-years lost	4,902	4,883
QALYs lost	5,290	5,267
QALYs lost (DR=3%)	2,738	2,723
<b>Costs (DR=0%)</b>		
	<b>CP/HPV (k€)</b>	<b>LBC/HPV (k€)</b>
Screening (including triage test)	12,668	15,065
Repeated screens <sup>§</sup>	123	45
Treatment*	7,898	7,823
Total	20,689	22,943
Total (DR=3%)	13,166	14,693

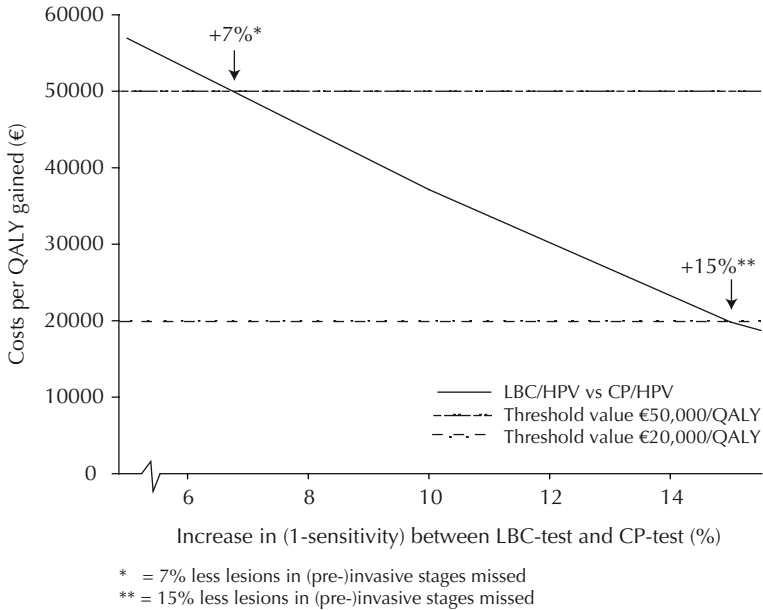
CP = conventional Pap-test; LBC = liquid based cytology; HPV = human papillomavirus; SD = screen detected; ca = cancer; clin = clinically diagnosed due to clinical symptoms; DR = discount rate; No. = numbers; k€ = 1,000 euro; § screens that were classified as unsatisfactory and had to be repeated; \* including costs of terminal care





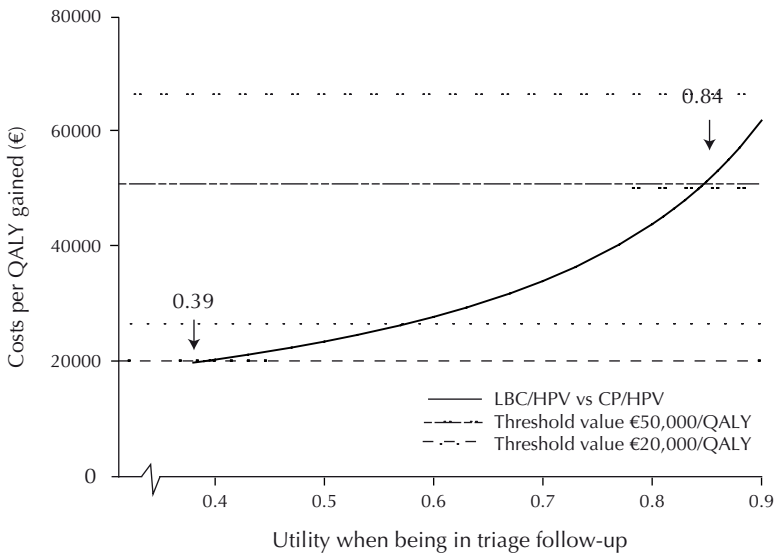
**Figure 3.2.2** | Sensitivity analysis of the impact of all-in price per primary LBC-test on the cost-effectiveness of substituting the screening strategy CP/HPV by the screening strategy LBC/HPV (costs and effects discounted at 3%). The intersections between the horizontal lines (i.e. the acceptability thresholds) and the LBC/HPV vs CP/HPV line represent the threshold price per primary LBC-test compared to primary CP-test (€51.88) at which the cost-effectiveness of the screening strategy LBC/HPV would correspond to the acceptability threshold. QALY = quality-adjusted life-year; CP = conventional Pap test; LBC = liquid based cytology; HPV = human papillomavirus

The second threshold analysis showed, assuming equal increments in terms of percentage, that at a cost-effectiveness threshold of €20,000 per QALY gained, the sensitivity of the LBC test for each different disease stage should increase by 15% (i.e. the sensitivity of the LBC test should be increased from 40–75% to 49–79%) to make LBC a cost-effective alternative to CP (Figure 3.2.3). At a cost-effectiveness threshold of €50,000 per QALY gained, the sensitivity values of LBC-test should be increased from 40–75% to 44–77%.



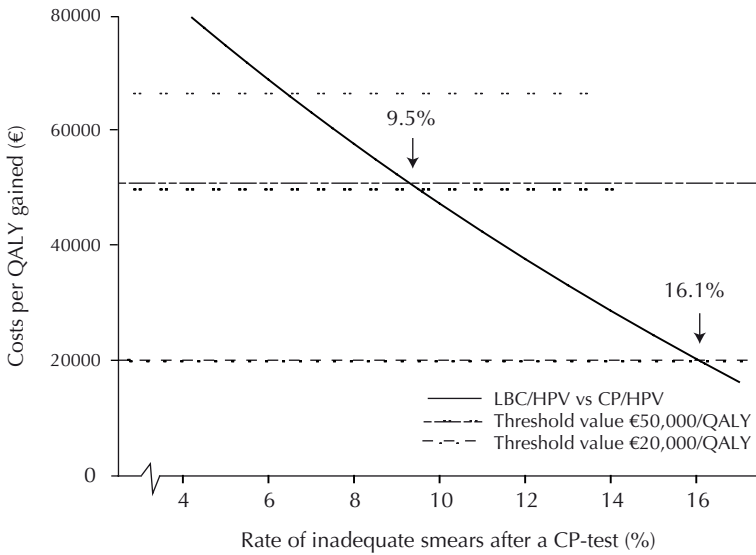
**Figure 3.2.3** | Sensitivity analysis of the impact of differences sensitivity between LBC-test and CP-test on the cost-effectiveness of substituting the screening strategy ‘CP with HPV-testing in the triage’ by the screening strategy ‘LBC with HPV-testing in the triage’ (costs and effects discounted at 3%). The intersections between the horizontal lines (i.e. the acceptability thresholds) and the LBC/HPV vs CP/HPV line represent the threshold increase in sensitivity of LBC-test compared to CP-test at which the cost-effectiveness of the screening strategy LBC/HPV would correspond to the acceptability threshold. QALY = quality-adjusted life-year; CP = conventional Pap test; LBC = liquid based cytology; HPV = human papillomavirus.

The third threshold analysis showed that the loss of utility (i.e. quality of life) for women while they are in triage follow-up should be decreased from 0.994 to 0.39 (i.e. a 61% reduction in quality of life) to make LBC cost-effectiveness to CP (Figure 3.2.4). At a cost-effectiveness threshold of €50,000 per QALY gained, the threshold amount of utility for women while they are in triage follow-up is 0.84.



**Figure 3.2.4** | Sensitivity analysis of the impact of amount of utility due to triage test two weeks after CP-test on the cost-effectiveness of substituting the screening strategy CP/HPV by the screening strategy LBC/ HPV (costs and effects discounted at 3%). The intersections between the horizontal lines (i.e. the acceptability thresholds) and the LBC/HPV vs CP/HPV line represent the threshold amount of utility for women while they are in triage follow-up at which the cost-effectiveness of the screening strategy LBC/HPV would correspond to the acceptability threshold. QALY = quality-adjusted life-year; CP = conventional Pap test; LBC = liquid based cytology; HPV = human papillomavirus

The final threshold analysis showed that for the parameter ‘inadequacy smears’, the rate of inadequate smears of CP should be 16.1% to make the LBC/HPV strategy more cost-effective than the CP/HPV strategy at a cost-effectiveness threshold of €20,000 per QALY gained (Figure 3.2.5; discount rate 3%). At a cost-effectiveness threshold of €50,000 per QALY gained, the threshold rate of inadequate smears of CP was 9.5% (Figure 3.2.5).



**Figure 3.2.5** | Sensitivity analysis of the impact of rate of inadequate smears after a CP test on the cost-effectiveness of substituting the screening strategy CP/HPV by the screening strategy LBC/HPV (costs and effects discounted at 3%). The intersections between the horizontal lines (i.e. the acceptability thresholds) and the LBC/HPV vs CP/HPV line represent the threshold rate of inadequate smears after a CP-test at which the cost-effectiveness of the screening strategy LBC/HPV would correspond to the acceptability threshold. QALY = quality-adjusted life-year; CP = conventional Pap test; LBC = liquid based cytology; HPV = human papillomavirus

### 3.2.5 | Discussion

LBC with cytology triage and CP screening with cytology triage are both dominated by screening with HPV triage. In case a HPV based triage (i.e. HPV reflex testing on the residual LBC material of an ASCUS/LSIL test result) was followed, LBC gained slightly more QALYs than CP, and less time and travel costs. However, these advantages of LBC did not counterbalance the higher LBC unit costs. Using a discount rate of 3%, threshold analyses showed that LBC can correspond to an acceptability threshold of €20,000 per QALY gained if the extra costs per LBC-test compared to CP-test decreases from €11.7 to €3.3, if the sensitivity of LBC for each stage of disease increases from 40–75%

to 49–79%, if the utility for women while they are in triage follow-up decreases from 0.994 to 0.39, or if the rate of inadequacy smears after a CP-test increases from 1.1% to 16.1%.

Our finding that LBC was not a cost-effective alternative to CP is consistent with the results of several previous studies.<sup>146-147</sup> However, some studies had contrary results; Karnon et al.<sup>29</sup> and Neville and Quinn<sup>148</sup> concluded that LBC was a cost-effective alternative to a conventional Pap smear. In contrast to our study, they assumed that the sensitivity values of LBC were more favourable than the sensitivity values of CP. We based our data on a large RCT,<sup>132</sup> which showed that the accuracy of LBC and CP in the Netherlands was comparable; probably caused by the high quality standards of conventional screening in the Netherlands. However, findings of the NETHCON trial were in agreement with a meta-analysis including high-quality studies from three continents.<sup>27</sup> Although LBC caused fewer inadequate smears than CP, this had a small benefit in the Dutch situation where CP had already a low rate of inadequate smears of 1.11%. It should be remarked that in British studies, favourable conclusions were driven by the high rate on inadequate CP (from over 11%) which were reduced to <2% in LBC.<sup>149-150</sup>

Most of the data used in the MISCAN model (e.g. costs, demographic data, CIN detection rates, screening attendance rate, age of screening, and frequency of screening) were based on Dutch data. As some of the data may differ in other countries, the external generalisability of this study (outside of the Netherlands) may be questionable at first sight. However, looking in more detail the conclusion 'LBC is not a cost-effective alternative in cervical cancer screening in a situation with a low rate of inadequate smears after a Pap test' is quite robust if input values from other countries are used. For example, in the Netherlands, the frequency of screening is relatively low compared to other countries. If the frequency of screening is assumed to be higher this would lead to better health outcomes for both arms equally. However, the gap between LBC and conventional screening regarding the total costs will be (much) larger. As a result, the difference in cost-effectiveness may be even more favourable for the conventional arm. Changing demographic data, CIN detection rates, or age of screening will have a similar effect for both screening arms; i.e. the conclusion remains the same. Only if the difference in costs between LBC and conventional testing will be much smaller and/or the lost to follow-up between conventional screening and the HPV-test in triage will increase substantially, LBC can be a cost-effective alternative in cervical cancer screening in a situation with a low rate of inadequate smears after a Pap test.

The cost-effectiveness acceptability threshold of €20,000 per QALY gained for the Netherlands<sup>10</sup> is relatively low compared with the €50,000 per QALY gained threshold often used for other countries.<sup>145</sup> As a result, interventions are more often considered not cost-effective in the Netherlands. As we have shown, to achieve a cost-effectiveness ratio of €50,000 per QALY gained, the price per LBC test would still have to be decreased considerably.

LBC was already incorporated in the Dutch national guidelines<sup>138</sup> and executed in several institutions, although the cost-effectiveness of LBC was not determined. Our results showed that the cost-effectiveness is not an important argument to substitute CP by LBC. However, there are more criteria to take into account in a decision to implement LBC. For example, cytotechnologists may prefer LBC because samples are easier to read, and for computer automated screening (not implemented routinely in the Netherlands) LBC may be preferred.

The costs of LBC were relatively high compared to the costs of CP. The large difference in costs is caused by material, logistic as well as personnel costs. Further automation of LBC might lead to mass production and cost reduction. Research is needed to find out how much costs can decrease due to automation.

Although we conducted several sensitivity analyses, a limitation of our study was the uncertainty of test characteristics and costs. Another limitation was that we did not investigate the cost-effectiveness of LBC in case of computer automated screening. Further research is therefore recommended.

In conclusion, in a situation with a low rate of inadequate smears of CP like the Netherlands, LBC can only become a cost-effective alternative if the LBC test is at most €3.3 more expensive than the CP test, if the sensitivity of LBC increases substantially, if the quality of life for women who have to come back for HPV triage testing becomes equal to living with advanced cancer, or if screening with CP results in more than 16% inadequate smears.

## CHAPTER 3.3

# **Cost-effectiveness of primary hpv screening compared to primary cytology screening for cervical cancer in Europe**

Inge M.C.M. de Kok,  
Joost van Rosmalen,  
Peter Sasieni,  
Joakim Dillner,  
Thomas Iftner,  
Marjolein van Ballegooijen

*Submitted for publication*



### 3.3.1 | Abstract

**Background:** In recent years it has been confirmed from longitudinal studies that HPV tests have higher sensitivity than cytology for detecting clinically relevant cervical neoplasia. However, its specificity is lower. We will investigate whether and under which circumstances based on different European countries, HPV screening is preferred over cytology. We also calculate the preferred number of examinations per lifetime in different European countries.

**Methods:** For 6 different European scenarios, 1,539 screening policies are compared using the microsimulation model MISCAN. We determined the optimal screening strategy in terms of incremental cost-effectiveness ratios.

**Findings:** Primary HPV screening is the preferred primary test over the age of 30 in many scenarios. Primary cytology screening is preferred in scenarios with low costs of cytology or high prevalence of HPV in combination with high costs of HPV testing.

**Interpretation:** Primary HPV screening over the age of 30 is cost-effective in most European countries.



### 3.3.2 | Introduction

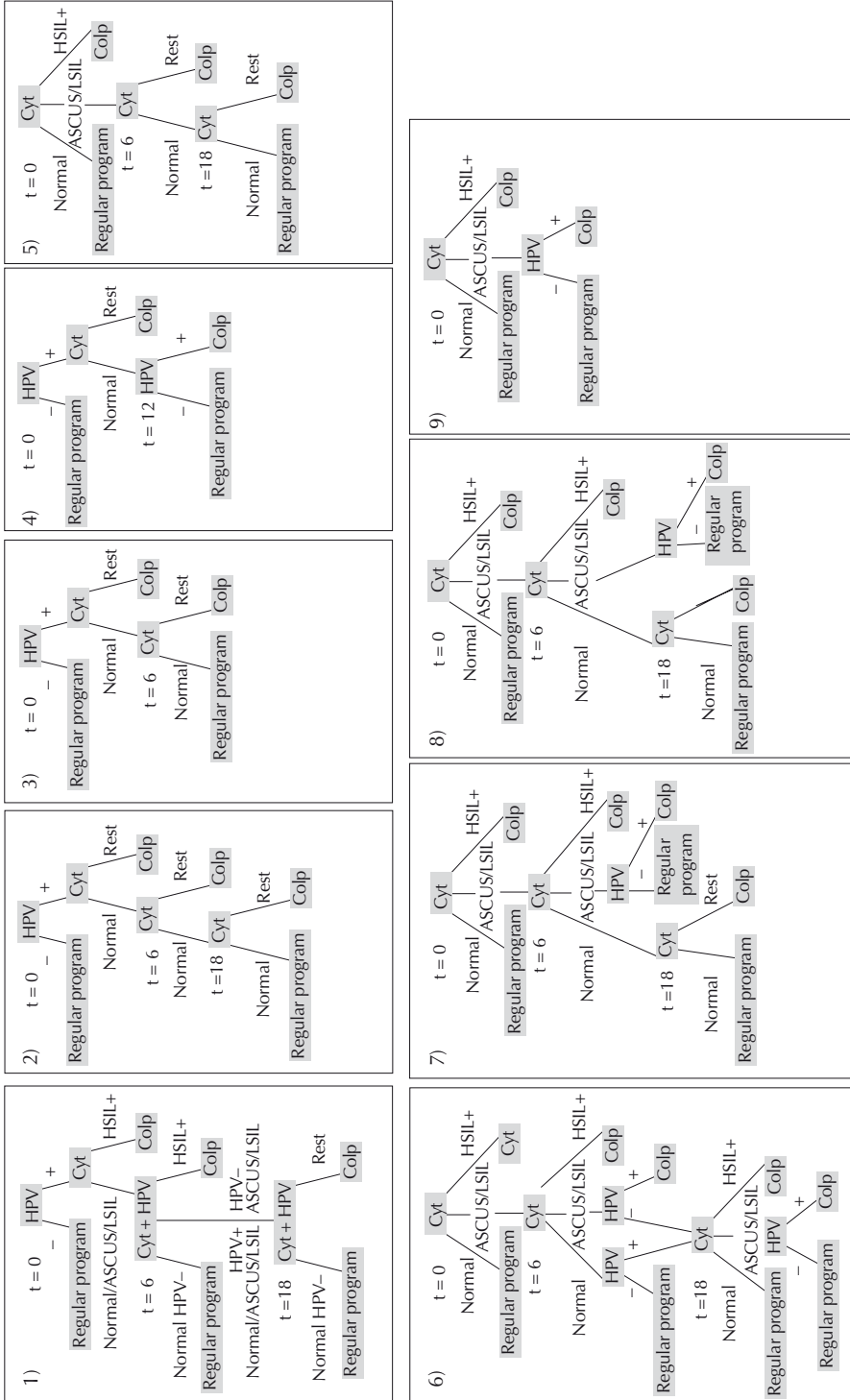
Cytological screening has reduced the incidence of cervical cancer predominantly in countries with organised screening,<sup>4, 151</sup> but there are still annually almost 60,000 incident cases and 30,000 deaths from the disease in Europe.<sup>152</sup> Vaccination against the human papillomavirus (HPV) is, or will be, introduced in many European countries,<sup>153</sup> however, women who are already sexually active are not eligible to be vaccinated. In these women, cervical cancer screening remains the primary preventative strategy, and screening in unvaccinated women indeed will go on for several decades. Cytology has limited reproducibility,<sup>154</sup> and meta-analyses and pooled analyses, both of cross sectional studies, have established that HPV tests have higher sensitivity than cytology for detecting high grade cervical intraepithelial lesions (CIN).<sup>30, 127</sup> Moreover, more recent studies have shown that combined HPV and cytology testing has high negative predictive values for not having high grade CIN in the next screening round.<sup>155-157</sup> As a result, joint European data suggested that screening intervals could safely be lengthened to six years among women with a negative result on an HPV test, which could compensate for the increased referral rate resulting from HPV based screening strategies.<sup>158</sup> In view of these results screening guidelines must be reconsidered to possibly improve cervical cancer outcomes, and thereby enhance the cost-effectiveness of cervical cancer prevention.

Previous cost-effectiveness analyses done for cervical cancer screening in Europe showed that efficient screening policies for cervical cancer can be characterized by an average screening age of about 50 years.<sup>10</sup> We expect, however, that different epidemiologic and screening characteristics lead to different advised number of Pap smears offered per woman, age range to be screened, and time period between the scheduled number of examinations.

Different country characteristics can lead to different preferred primary and triage screen test. Addressing unvaccinated cohorts of women, we will investigate under which circumstances based on different European countries, which test, cytology or HPV screening is preferred over cytology screening from a cost-effectiveness perspective. In addition, we calculate the optimal number of screening rounds per lifetime in different European scenarios, compared to different cost-effectiveness thresholds. We varied HPV and cytology triage schedules, screening age range and intervals between strategies, and cervical cancer risk, HPV prevalence, previous screening, test characteristics of cytological and HPV testing and costs per test between scenarios.

### 3.3.3 | Material and methods

We considered only two primary tests, but we included nine different screening test-strategies: one with primary cytology and cytology triage, four with primary HPV testing and cytology or a combination of cytology and HPV triage, and four with primary cytology with HPV or a combination of HPV and cytology triage (Figure 3.3.1). The test-strategies are based on strategies proposed in the literature. Although in this article we will not focus on exploring different triage strategies, we still included so many alternatives to make sure that we did compare primary cytology combined with optimal triage with primary HPV screening combined with optimal triage. The details of the 9 test strategies considered are as follows (Figure 3.3.1): 1) Primary HPV screening with immediate cytology triage for HPV positive tests and a combination of cytology and HPV triage after 6 and 18 months;<sup>30</sup> 2) Primary HPV screening with immediate cytology triage for HPV positive tests and cytology triage after 6 and 18 months<sup>159</sup>; 3) Primary HPV screening with immediate cytology triage for HPV positive tests and cytology triage after 6 months (adjusted<sup>159</sup>); 4) Primary HPV screening with immediate cytology triage for HPV positive tests and HPV triage after 12 months<sup>160</sup>; 5) Primary cytological testing with repeat cytology for borderline/mildly abnormal smears after 6 and 18 months<sup>6</sup>; 6) Primary cytological testing with repeat cytology for borderline/mildly abnormal smears and HPV testing after 6 and 18 months<sup>138</sup>; 7) Primary cytological testing with repeat cytology for borderline/mildly abnormal smears after 6 and 18 months and immediate HPV testing for borderline/mildly abnormal repeat smears after 6 months<sup>140</sup>; 8) Primary cytological testing with repeat cytology for borderline/mildly abnormal smears after 6 and 18 months and HPV testing after 12 months for borderline/mildly abnormal repeat smears after 6 months<sup>140</sup>; and 9) Primary cytology screening with immediate HPV testing for borderline/mildly abnormal smears.<sup>159</sup>



**Figure 3.3.1** | Screening scenarios evaluated in the cost-effectiveness analysis. Cyt = conventional cytology, HPV = HPV testing, t = time in months, Colp = Colposcopy, ASCUS = Atypical Squamous Cells of Undetermined Significance, LSIL = Low-grade Squamous Intraepithelial Lesion, HSIL = High-grade Squamous Intraepithelial Lesion.

### 3.3.3.1 | The model

Costs and effects of the different screening strategies were estimated using the micro-simulation screening analysis (MISCAN) model.<sup>58</sup> The MISCAN model generates a large study population with fictitious individual life histories, in which women will, at a certain rate, acquire an HPV infection and develop a preinvasive cervical lesion and cervical cancer, and some will die from the disease. Infections can also be cleared or produce CIN that will regress. Women can acquire multiple infections during life, with each its own natural history. This results in an age-specific and time-specific output of disease incidence and mortality. This fictitious population then undergoes simulated screening. The intervention will change some of the life histories. These changes constitute the effects of the intervention and are represented by the numbers of events and stages induced or prevented by the intervention that are linked with their specific costs and quality-of-life outcomes.

### 3.3.3.2 | Model specifications: demography, epidemiology, and natural history

The base model was based on the Dutch population, assuming that age distributions of CIN and cancer, demographic and hysterectomy data are comparable in the rest of Europe. The population at risk for cervical cancer was simulated based on demographic<sup>161</sup> and hysterectomy data.<sup>136</sup> The age distribution of the incidence of preinvasive neoplasia that will eventually become cancer was calibrated to the age distribution of the prescreening mortality; the latter distribution was corrected for cohort effects based on an age – period – cohort analysis.<sup>76</sup> The age distribution of the incidence of preinvasive lesions that will regress before they become cancer was calibrated to the observed cervical intraepithelial neoplasia (CIN) detection rates in the Netherlands (derived from the Dutch Network and National Database for Pathology [PALGA]) for the period 1997 – 2001. The age distribution of the incidence of HPV infections that will clear before progressing to CIN was calibrated to the observed HPV prevalence.<sup>96</sup>

Disease is subdivided into seven sequential stages: high risk HPV infection (low risk HPV infections are not simulated in the model), three pre-invasive stages (CIN 1, 2, and 3), and three invasive stages (FIGO [International Federation of Gynecology and Obstetrics] stages 1A, 1B, and 2+). Pre-invasive stages and FIGO 1A cases can only be diagnosed by screening, since no symptoms will develop, whereas stage 1B and 2+ cases can also be clinically diagnosed. The disease is usually not progressive; in the model, most HPV infections will clear without ever resulting in neoplasia, and lesions

in the pre-invasive stages can regress naturally. In the pre-invasive stages (CIN 1, 2, and 3), a high risk HPV infection may or may not be present, though the CIN 3 stage can only develop if a high risk HPV infection is present; if no high-risk HPV infection is present, the lesion will always regress. In the invasive stages, all women are assumed to be HPV infected. A woman can develop multiple HPV infections and neoplasias in her lifetime, and multiple infections and neoplasias can exist at the same time. A Weibull probability distribution was used to assume variations among women in the duration of the different stages. The inputs on stage-specific survival in clinical cases are age-specific and are based on observed survival data and on Dutch mortality-to-incidence ratios from the pre-screening period in the Netherlands,<sup>76</sup> assuming that stage-specific survival is comparable in the rest of Europe.

The model presented is a population model that simulates the life histories of 8 million women born from 1939 to 1992. Women born before 1939 are too old to attend screening after 2009, and women born after 1992 are eligible for HPV vaccination. Because of the expected lower cancer risk for vaccinated women, a separate screening strategy will have to be determined for vaccinated cohorts in the future. The simulated screening policies were assumed to start in 2009 and to continue until all simulated women have completed their screening programs. Most European countries already had a screening program before 2009. Screening practices before 2009 will influence the effectiveness of the screening program after 2009; therefore, we considered all simulated situations with and without this practice. Information on the screening activities before 2009 was obtained from the Dutch National Pathology Database, assuming that the European variation in screening activities will not influence the effectiveness of the screening program after 2009.

Based on mortality levels in different European countries we assumed three different background risks, i.e., the risk of dying of cervical cancer in a situation without screening, of cervical cancer-related mortality; 5.0, 7.5 and 10 per 100,000 deaths per women year. In case of past screening practices, the eventual mortality rates of invasive cervical cancer simulated in 2009 were 2.0, 3.0 or 4.0 per 100,000 life years in case of a background risk of 5.0, 7.5 or 10 per 100,000 women years, respectively. For our analyses, we assumed that the lifetime background risk of developing cervical cancer (or its progressive precursors) was proportional to the estimated relative level of cervical cancer mortality for each birth cohort. The relative risks per birth cohort were derived from an age-period-cohort analysis.<sup>162</sup> Furthermore, we assumed that there was a fixed ratio in each birth cohort between the lifetime risks of pre-invasive disease that will spontaneously regress and pre-invasive disease that will progress to cervical cancer.

### 3.3.3.3 | Assumptions for screening and treatment

We assumed that 10% of the population never attends screening and has a 3 times higher background risk for cervical cancer than the 90% potential attenders (e.g. the high-risk stratum and the low-risk stratum).<sup>143</sup> The attendance rate of the potential attenders from 2009 onward was assumed to be 80% for all primary screenings; in the model, follow-up screenings and referrals for colposcopy are always attended.

The assumptions for screening are presented in Table 3.3.1. Many parameters in Table 3.3.1 are varied to account for differences between countries. The sensitivity of the HPV test was estimated at 95% for a high-risk HPV infection. Because uncertainty exists about the sensitivity of the HPV test we also assumed a sensitivity of 90% (see '*Cost-effectiveness and sensitivity analyses*'). The sensitivity of the Pap smear (i.e., the probability of scoring at least Pap 2) for different disease stages was assumed to be 40% for CIN 1, 50% for CIN 2, and 75% for CIN 3 +.<sup>163</sup> For countries with lower sensitivity of the Pap smear we assumed sensitivities 32%, 40% and 60%, respectively. Because several screening strategies distinguish between a Pap 2/3a1 smear and a smear that is greater than Pap 3a1, the probability of scoring greater than Pap 3a1 also needs to be specified for each stage. The sensitivity of testing for at least moderate dyskaryosis (i.e. the probability of scoring more than Pap 3a1) is assumed to be 4% for CIN 1, 19% for CIN 2, 47% for CIN 3, and 49% for cervical cancer. In case of lower sensitivity of the Pap smear we assumed a sensitivity of 3%, 15% and 38%, respectively. The specificity of the Pap test is estimated to be 98.5%, based on the false-positive rate of Pap smears in the Dutch screening programme. The specificity of the HPV test for HPV infections is assumed to be 100%. However, the prevalence of HPV in women with CIN 1 or less also determines the effect of HPV screening. In situations with a higher background risk, the increase in the risk of getting infected with HPV is proportional to the increase in the risk of getting cervical cancer. Since the absolute risk of getting an HPV infection with CIN 1 or less is higher than the absolute risk of getting an HPV infection with CIN 1 or more, the increase in the risk of getting an HPV infection is higher than the increase in the risk of getting cervical cancer. As a result, the prevalence of HPV is determined by the background risk as follows: 6% for background risk 5.0 per 100,000, 8% for background risk 7.5 per 100,000 and 10% for background risk 10.0 per 100,000. In addition, in case of a scenario with a higher prevalence we multiplied the number of triage tests with a factor 2.

Detection and the associated management of pre-invasive lesions were assumed to lead to a 100% cure rate. For screen-detected invasive cancers, the survival was

modelled as a reduction in the risk of dying of cervical cancer compared with that of dying of clinically diagnosed cancer; in the model, screen-detection of an invasive cancer results in a reduction of the risk of dying of cervical cancer of either 80% (FIGO 1A), 60% (FIGO 1B), or 20% (FIGO 2+).

**Table 3.3.1** | Varied parameters in the analysis

Parameter	Values	
Background incidence	5.0 / 7.5 / 10 per 100,000	
Past screening	Yes / No	
Sensitivity cytology	Sensitivity (probability of at least Pap 2) for CIN 1	40% / 32%
	Sensitivity (probability of at least Pap 2) for CIN 2+	50% / 40%
	Sensitivity (probability of at least Pap 2) for CIN 3+	75% / 60%
	Probability of at least Pap 3a2 for CIN 1	4% / 3%
	Probability of at least Pap 3a2 for CIN 2	19% / 15%
	Probability of at least Pap 3a2 for CIN 3+	47% / 38%
Specificity cytology (for neoplasia)	97% / 98.5%	
Sensitivity HPV screening (for high risk HPV infection)	90% / 95%	
Prevalence of HPV in $\leq$ CIN1*	low / high	
Laboratory costs HPV screening	€21.36 / €33.23	
Total cost cytology	€25.94 / €51.88	
Threshold value	€20,000 / €30,000 /	
	€50,000 per QALY gained	

\* Depends also on background risk. In addition, in case a country has a high prevalence we multiplied the number of false positive women with a factor 2. So, in case background risk = 5 per 100,000 prevalence is 6% / 3%; background risk = 7.5 per 100,000 prevalence is 8% / 4%; background risk = 10 per 100,000 prevalence is 10% / 5%.

### 3.3.3.4 | Assumptions for costs and utilities

The costs and utilities used in the analysis are presented in Table 3.3.2. Screening costs include the invitational system, time and travel costs, costs of smear taking, costs of cytologic evaluation, and costs of registration in the pathology database. The costs of screening, diagnosis, and treatment procedures for detected pre-invasive lesions, of primary treatment of invasive cervical cancer and of treatment and palliative care for advanced cervical cancer were derived from cost studies in the Netherlands<sup>142</sup> To consider differences in screening costs across Europe the total costs of cytology were divided by two. In the model, a small (psychological) loss of the quality of life is assumed

**Table 3.3.2** | Assumptions on costs, amount and duration of lost utility for different events and health states (costs are given in 2008 prices)

	Costs (€)	Utilities lost	
		Amount	Duration
<b>Invitation</b>	4.65	0	-
<b>Cytology primary</b>			
Laboratory costs, primary test	21.36*		
Organisation	11.02		
GP costs, primary test	11.54	0.006	2 weeks
Time/travel	5.90		
Programme costs	2.04		
Total	25.94 / 51.88		
<b>Cytology repeat</b>			
GP costs, repeat test	21.79		
Laboratory costs, repeat test	26.04	0.006	Time since the last test*
Time/Travel	5.90		
<b>HPV-test primary</b>			
Laboratory costs, primary test	33.23 / 21.36		
Organisation	11.02		
GP costs, primary test	11.54	0.006	2 weeks
Time/Travel	5.90		
Programme costs	2.04		
<b>HPV-test repeat</b>			
GP costs, repeat test	21.79		
Laboratory costs, repeat test	33.23	0.006	Time since the last test
Time/Travel	5.90		
<b>Diagnoses and treatment pre-invasive stages</b>			
False positive	279	0.005	0.5 year
CIN1	869	0.03	0.5 year
CIN2	1,287	0.07	1 year
CIN3	1,507	0.07	1 year
<b>Diagnoses and treatment invasive cancer</b>			
FIGO 1A	4,935	0.062	5 years
FIGO 1B	11,703	0.062	5 years
FIGO 2+ (screen-detected)	11,535	0.28	5 years
FIGO 2+ (clinically detected)	10,773	0.28	5 years
Terminal care	26,209	0.712	1 month

\*The time since the last test can be two weeks (if a woman is invited for a repeat test immediately after a positive primary test), six months, or 12 months.



for attending a screening and for attending follow-up screenings after a positive primary screening. Larger losses of the quality of life are assumed for receiving treatment and for having a terminal stage of cervical cancer. Utilities were based on (inter)nationally published data.<sup>43, 76, 144</sup>

### 3.3.3.5 | Cost-effectiveness and sensitivity analyses

In our analyses, we varied the ages at which screening takes place. We considered all screening policies with starting ages of 25, 27, 30 or 32 that comprise at least 3 and at most 10 screenings and that have an interval of at least 3 years and at most 10 years; policies that include screenings over the age of 70 were not simulated. For scenario F) (Table 3.3.3), we also considered policies that comprise 11 to 20 screenings, with an interval between 1 and 10 years. For each of the 9 screening strategies, we simulated all screening policies described above (i.e. 171 policies); in total, 1,539 policies were simulated for 6 different scenarios (Table 3.3.3). The scenarios were based on differences in characteristics observed between European countries. The Netherlands would for example fit scenario A), Italy scenario B), Germany scenario C), Finland scenario D), Denmark scenario E), and Romania Scenario F).

In the results, the costs and effects of screening are accounted for until all simulated women have died. The total costs consist of the costs for the invitations, the primary and follow-up screenings, the treatment of pre-invasive and invasive lesions, and terminal care. The effects are presented in terms of the numbers of life years gained (LYsG) and QALYs gained by screening for cervical cancer. The number of LYsG is calculated as the difference in total years lived by the population between the situation in which the screening programme is implemented and the situation in which no screening occurs after 2009. To determine the number of QALYs gained (or lost) by screening, we first compute the total number of QALYs as the number of years lived by the population minus the utility loss associated with attending screening, receiving treatment, and having a terminal stage of cervical cancer. The number of QALYs gained is then given by the total number of QALYs for the situation in which the screening programme is implemented, minus the total number of QALYs in the situation in which no screening occurs after 2009. The costs-effectiveness calculations are conducted from the adjusted societal perspective (productivity losses due to illness and death were not counted). To convert future costs and health effects to the present, both costs and effects (life years and utility losses) were discounted towards the year 2009 at a rate of 3%.

**Table 3.3.3** | Plausible combination of parameters for six different scenarios (A to F). R=Background Risk, =  $P_{HPV}$  = Prevalence of HPV,  $SP_{Cyt}$ = Specificity of cytology,  $S_{Cyt}$  = Sensitivity of cytology, noscr = no past screening,  $\epsilon_{Cyt}$  = costs of cytology

Parameter	Possibilities	A) R↓	B) R↔, ↑P <sub>HPV</sub>	C) R↔, S <sub>Cyt</sub> ↓, SP <sub>Cyt</sub> ↓	D) R↓, SP <sub>Cyt</sub> ↓	E) R↑, ↑P <sub>HPV</sub>	F) R↑, noscr, S <sub>Cyt</sub> ↓, SP <sub>Cyt</sub> ↓, $\epsilon_{Cyt}$ ↓
Past Screening	Yes   No	Yes	Yes	Yes	Yes	Yes	No
Background risk without screening	5.0 7.5 10.0 per 100,000	5.0	7.5	7.5	5.0	10.0	10.0
Prevalence of HPV	Low   High*	Low (3%)	High (8%)	Low (4%)	Low (3%)	High (10%)	Low (5%)
Sensitivity Cytology	60% 75%‡	75%	75%	60%	75%	75%	60%
Specificity Cytology	97% 98.5%	98.5%	98.5%	97%	97%	98.5%	97%
Costs Cytology (Total, including organisation costs)	€26 €52	€52	€52	€52	€52	€52	€26
Costs HPV test (laboratory costs) †	€21 €33	€21 / €33	€21 / €33	€21 / €33	€21 / €33	€21 / €33	€21 / €33
Sensitivity HPV test +	90% 95%	90% / 95%	90% / 95%	90% / 95%	90% / 95%	90% / 95%	90% / 95%

\* The prevalence for countries with background risk 5.0 per 100,000 is 97%, with 7.5 per 100,000 it is 96% and with 10.0 per 100,000 it is 95%. In case a country has a high prevalence we multiplied the number of false positive women with a factor 2.

‡ Sensitivity for all CIN stages (Table 1) was varied with the same rate (i.e. 60%:75%), CIN3+ was given as example

† Both possibilities are analysed becomes these parameters are uncertain.

Since the costs and the sensitivity of the HPV test are uncertain, we also calculated the cost-effectiveness of all 1,539 policies with lower costs of the HPV test (i.e. equal laboratory costs for HPV testing as for cytology screening) and lower sensitivity (90% instead of 95%).

### 3.3.4 | Results

For the six different scenarios that reflect different possible situations in Europe, there were predicted costs and QALYs gained for 1,539 simulated screening strategies (Table 3.3.3). Strategies that were more costly and less effective than other strategies were ruled out as non-efficient by simple dominance. Strategies that were more costly and less effective than a combination of other strategies were ruled out as non-efficient by extended dominance.

To show what the influence of the different characteristics of the scenarios (A to F) is on the results of screening, we showed the undiscounted results of three screening strategies (Table 3.3.4). The strategies are 1) primary cytology with cytology triage, 2) primary HPV screening (sensitivity 90%) with two times cytology triage, and 3) primary HPV screening (sensitivity 95%) with two times cytology triage. Based on the recommended European Union screening guidelines,<sup>164</sup> all women were screened starting at age 30 and with an interval of 5 years until age 60 years. The number of triage screens increase with background risk and, more clearly, with a lower specificity of primary cytology or – in case of primary HPV screening – with a higher prevalence of HPV (Table 3.3.4). The number of CIN2/3 lesions, cancer cases and deaths from cervical cancer increase with background risk for all screening strategies. In case the primary test is less sensitive, the number of CIN2/3 lesions decrease and the number of cancers and deaths increase (Table 3.3.4).

**Table 3.3.4** | Undiscounted results of 1) Primary cytology with cytology triage, 2) Primary HPV screening with two times cytology triage (sensitivity of HPV screening 90%), and 3) Primary HPV screening with two times cytology triage (sensitivity of HPV screening 95%). Women are screened seven times during a lifetime, starting at age 30, and with a 5-year interval. Results per 100,000 life years. R=Background Risk,  $P_{HPV}$  = Prevalence of HPV,  $SP_{Cyt}$  = Specificity of cytology,  $S_{Cyt}$  = Sensitivity of cytology, noscr = no past screening,  $\epsilon_{Cyt}$  = costs of cytology

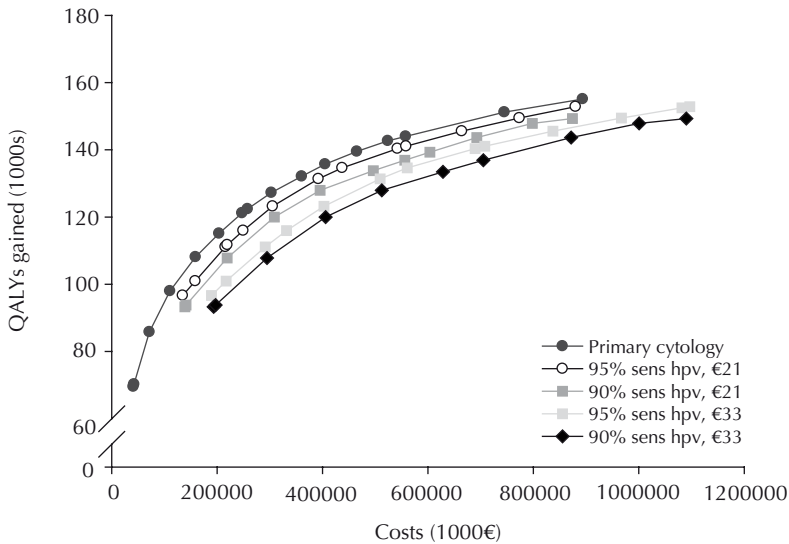
Scenario	# First primary screens	# Triage screens	# CIN2/3 lesions	# Cancer cases	# Deaths from cervical cancer
<b>Primary cytology with cytology triage</b>					
A) R↓	5,704.28	190.99	15.98	5.65	2.60
B) R↔, ↑P <sub>HPV</sub>	5,707.97	205.59	23.87	8.45	3.88
C) R↔, S <sub>Cyt</sub> ↓, SP <sub>Cyt</sub> ↓	5,703.45	352.46	21.05	9.59	4.38
D) R↓, SP <sub>Cyt</sub> ↓	5,704.28	345.75	15.98	5.65	2.60
E) R↑, ↑P <sub>HPV</sub>	5,710.02	220.58	31.65	11.18	5.17
F) R↑, noscr, S <sub>Cyt</sub> ↓, SP <sub>Cyt</sub> ↓, $\epsilon_{Cyt}$ ↓	5,692.39	362.81	33.61	15.86	7.21
<b>Primary HPV screening with two times cytology triage, sensitivity of HPV screening 90%</b>					
A) R↓	5,705.80	274.95	16.64	5.30	2.46
B) R↔, ↑P <sub>HPV</sub>	5,711.26	759.60	24.93	7.93	3.66
C) R↔, S <sub>Cyt</sub> ↓, SP <sub>Cyt</sub> ↓	5,707.75	415.67	24.46	8.62	3.94
D) R↓, SP <sub>Cyt</sub> ↓	5,705.80	274.95	16.64	5.30	2.46
E) R↑, ↑P <sub>HPV</sub>	5,713.40	1,003.19	33.25	10.45	4.90
F) R↑, noscr, S <sub>Cyt</sub> ↓, SP <sub>Cyt</sub> ↓, $\epsilon_{Cyt}$ ↓	5,699.30	561.40	39.60	14.20	6.44

Scenario	# First primary screens	# Triage screens	# CIN2/3 lesions	# Cancer cases	# Deaths from cervical cancer
<b>Primary HPV screening with two times cytology triage, sensitivity of HPV screening 95%</b>					
A) R↓	5,706.22	289.22	17.08	5.21	2.42
B) R↔, ↑P <sub>HPV</sub>	5,711.88	800.39	25.59	7.79	3.60
C) R↔, S <sub>cyt</sub> ↓, SP <sub>cyt</sub> ↓	5,708.38	437.25	25.17	8.46	3.87
D) R↓, SP <sub>cyt</sub> ↓	5,706.22	289.22	17.08	5.21	2.42
E) RT, ↑P <sub>HPV</sub>	5,714.23	1,056.07	34.07	10.27	4.83
F) RT, noscr, S <sub>cyt</sub> ↓, SP <sub>cyt</sub> ↓, € <sub>cyt</sub> ↓	5,700.19	589.76	40.71	13.94	6.32

Primary HPV screening was preferred over primary cytology screening in most scenarios considered (Table 3.3.5). In scenarios B) and E), the two scenarios with high prevalence of HPV, primary cytology screening was preferred only if also higher costs for HPV screening were assumed. In scenario F), the scenario with low costs for cytology, primary cytology was preferred, notwithstanding the lower sensitivity and specificity that accompanied the lower costs. We found that this result was not related to the higher background risk of scenario F, but only to the low costs of cytology. Figure 3.3.2A shows the efficient frontier of scenario F for primary cytology screening and for primary HPV screening. It shows how primary HPV screening is dominated by primary cytology screening, regardless of the considered HPV sensitivity and costs. Figure 3.3.2B shows for scenario F the steep increase in incremental cost-effectiveness ratios (ICERs) to gain a few QALYs if the more effective but also more costly primary HPV screening is applied. It shows that there are no strategies that prefer primary HPV screening below the threshold of €50,000 per QALY gained.

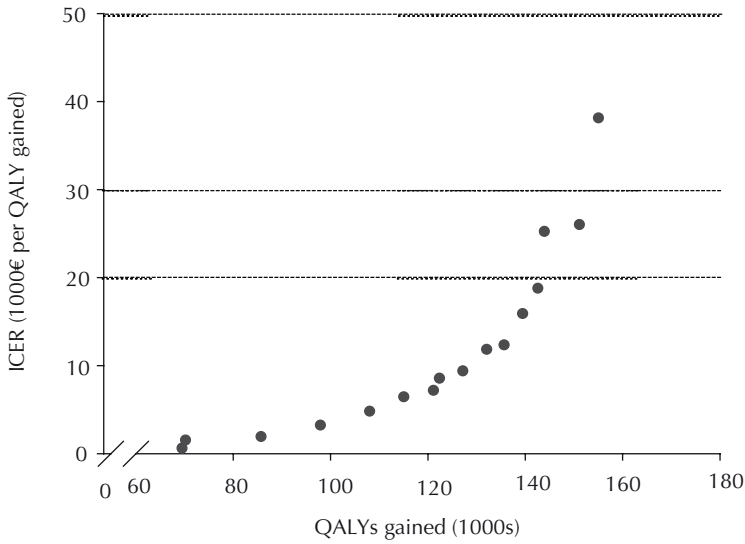
**Table 3.3.5** | Preferred primary test at a threshold between €20,000 and €50,000 per QALY gained, where the sensitivity of HPV screening is 90% or 95%, and laboratory costs of the HPV test are €21 or €33. R=Background Risk,  $P_{\text{HPV}}$  = Prevalence of HPV,  $SP_{\text{cyt}}$  = Specificity of cytology,  $S_{\text{cyt}}$  = Sensitivity of cytology, noscr = no past screening,  $\epsilon_{\text{cyt}}$  = costs of cytology

Scenario	90%, €21	95%, €21	90%, €33	95%, €33
A) R↓	HPV	HPV	HPV	HPV
B) R↔, ↑ $P_{\text{HPV}}$	HPV	HPV	CYT	CYT
C) R↔, $S_{\text{cyt}}$ ↓, $SP_{\text{cyt}}$ ↓	HPV	HPV	HPV	HPV
D) R↓, $SP_{\text{cyt}}$ ↓	HPV	HPV	HPV	HPV
E) R↑, ↑ $P_{\text{HPV}}$	HPV	HPV	CYT	CYT
F) R↑, noscr, $S_{\text{cyt}}$ ↓, $SP_{\text{cyt}}$ ↓, $\epsilon_{\text{cyt}}$ ↓	CYT	CYT	CYT	CYT



**Figure 3.3.2A** | Representation of the simulated efficient frontiers of scenario F, when assuming only primary cytology screening or only primary HPV screening. In case of primary HPV screening we assumed 1) 95% sensitivity €21 laboratory costs for HPV screening, or 2) 90% sensitivity €21 laboratory costs for HPV screening, or 3) 95% sensitivity €33 laboratory costs for HPV screening, or 4) 90% sensitivity €33 laboratory costs for HPV screening,. Each mark represents an efficient programme with different screening ages. Costs in thousands of Euros and effects in thousands of quality adjusted life years (QALYs) gained, 3% discount rate for costs and effects

The number of examinations during a woman's lifetime of the efficient policies mainly depends on the background risk of the considered scenario and on the cost-effectiveness threshold applied (Table 3.3.6A). In scenario A) and D) (low background risk and with past screening) three examinations during a lifetime are cost-efficient at a threshold of €20,000 per QALY gained, and five at a threshold of €50,000 per QALY gained. On the other hand, in scenario F) (high background risk and no past screening) 13 examinations during a lifetime are costs-efficient at a threshold of €20,000 per QALY gained, and 20 at the €50,000 threshold. The age range increased from age 30–46 years for policies with three examinations during a lifetime to age 27–65 years for those with 20 scheduled examinations (Table 3.3.6B). The interval between two examinations ranged from eight to three years.



**Figure 3.3.2B** | Incremental cost-effectiveness ratio (ICER) in thousands of Euros per quality adjusted life years (QALYs) gained and effects in thousands of QALYs gained of the simulated efficient frontiers of scenario F (primary cytology with HPV triage). Each mark represents an efficient programme with different screening ages. Costs and effects are discounted at 3% per year. Dotted lines represent €20,000, €30,000 and €50,000 per QALY gained threshold.



**Table 3.3.6A** | Number of screening round per threshold (20k = €20,000 per QALY gained, 30k = €30,000 per QALY gained, 50k = €50,000 per QALY gained), where the sensitivity of HPV screening is 90% or 95%, and laboratory costs of the HPV test are €21 or €33. R=Background Risk, =  $P_{HPV}$  = Prevalence of HPV,  $SP_{cyt}$  = Specificity of cytology,  $S_{cyt}$  = Sensitivity of cytology, noscr = no past screening,  $\epsilon_{cyt}$  = costs of cytology

Scenario	90%, €21			95%, €21			90%, €33			95%, €33		
	20k	30k	50k	20k	30k	50k	20k	30k	50k	20k	30k	50k
A) R↓	3	4	5	3	4	5	3	3	3	3	3	4
B) R↔, ↑ $P_{HPV}$	3	5	7	4	5	7	5	6	8	5	6	8
C) R↔, $S_{cyt}$ ↓, $SP_{cyt}$ ↓	4	5	8	4	5	7	3	5	6	4	5	7
D) R↓, $SP_{cyt}$ ↓	3	4	5	3	4	5	3	4	5	3	4	5
E) R↑, ↑ $P_{HPV}$	5	7	10	5	7	9	6	7	10	6	7	10
F) R↑, noscr, $S_{cyt}$ ↓, $SP_{cyt}$ ↓, $\epsilon_{cyt}$ ↓	13	17	20	13	17	20	13	17	20	13	17	20

**Table 3.3.6B** | Age ranges of the screening programme per threshold (20k = €20,000 per QALY gained, 30k = €30,000 per QALY gained, 50k = €50,000 per QALY gained), where the sensitivity of HPV screening is 90% or 95%, and laboratory costs of the HPV test are €21 or €33. R=Background Risk,  $P_{HPV}$  = Prevalence of HPV,  $SP_{cyt}$  = Specificity of cytology,  $S_{cyt}$  = Sensitivity of cytology, noscr = no past screening,  $\epsilon_{cyt}$  = costs of cytology

Scenario	90%, €21			95%, €21			90%, €33			95%, €33		
	20k	30k	50k	20k	30k	50k	20k	30k	50k	20k	30k	50k
A) R↓	30-46	30-54	30-58	30-46	30-54	30-62	30-46	30-46	30-54	30-46	30-46	30-54
B) R↔, ↑ $P_{HPV}$	32-46	32-56	30-66	32-56	30-58	30-66	30-50	30-55	30-65	30-50	30-55	30-65
C) R↔, $S_{cyt}$ ↓, $SP_{cyt}$ ↓	32-53	30-58	30-65	32-56	30-58	30-66	32-46	30-58	30-65	30-54	30-58	30-66
D) R↓, $SP_{cyt}$ ↓	30-46	30-54	30-58	30-46	30-54	30-65	30-46	30-46	30-58	30-46	30-46	30-54
E) R↑, ↑ $P_{HPV}$	32-53	30-58	30-65	32-56	30-58	30-66	30-55	30-60	30-66	30-55	30-60	30-66
F) R↑, noscr, $S_{cyt}$ ↓, $SP_{cyt}$ ↓, $\epsilon_{cyt}$ ↓	30-66	30-62	27-65	30-66	30-62	27-65	30-66	30-62	27-65	30-66	30-62	27-65

### 3.3.5 | Discussion

We showed that primary HPV screening is preferred in many of the scenarios that would correspond to the cervical cancer screening situation of European countries. However, for countries with high prevalence of HPV and high costs for the HPV test, primary cytology screening is preferred over primary HPV testing. This finding indicates that it is important to organise primary HPV screening in such a manner that the costs of the test are low. This can be achieved by concentrating the large numbers of HPV DNA tests in large laboratories, in order to achieve economy-of-scale effects (i.e., the costs per test are lower if more test are analysed). Primary cytological screening is also preferred in countries with low costs of cytology screening. Additionally, we found that for countries with high prevalence of HPV, low sensitivity of cytology, and high costs for cytology, primary HPV screening is preferred over primary cytology testing. Nevertheless, the costs of cytology normally are low in countries with less valid cytology tests, which indicates primary cytology. Countries with a high risk of cervical cancer or a high cost-effectiveness threshold are recommended to screen more intensively (i.e. begin at a younger age, end at an older age, and have a shorter interval between the scheduled examinations) than countries with a low cervical cancer risk or a low cost-effectiveness threshold.

We analysed four different triage schedules with primary HPV and five schedules with primary cytology. The triage schedules slightly varied between the strategies. In most scenarios primary HPV testing with only cytology triage for HPV positive tests was the preferred strategy. However, with low sensitivity of (repeat) cytology (scenario C), it was preferred to add HPV-testing to repeat cytology after a positive primary HPV test. In case primary cytology screening was preferred over primary HPV screening, HPV triage was efficient. Cytological testing with repeat cytology was never an efficient triage schedule.

Other published cost-effectiveness analyses on HPV screening evaluated the combination of Pap and HPV testing as primary screening and some studies evaluated HPV testing alone as the primary test. The publications provided costs and effect estimates, and ICER versus Pap screening programmes with 1-,2-, 3-, 5-year interval. The publications differ in many respects: they investigated different screening strategies in terms of the applied tests or test combinations, screening intervals, and target ages. The studies also differ in the methodological approach (type of model, analytic time horizon, and the perspective of the analysis, cost calculations, etc.). As a result, the conclusions are heterogeneous: there are three analyses in favour of primary HPV screening in a

conventional cytology setting,<sup>139, 165-166</sup> one analysis is in favour in a LBC setting but against it in a conventional cytology setting,<sup>167</sup> one in favour of it in a conventional setting but against it in a LBC setting<sup>168</sup> and one against it in a conventional setting.<sup>144</sup>

A limitation of our analysis is that strategies were not permitted to differ by age group. HPV DNA screening is not acceptable as a screen test before the age of 30.<sup>169</sup> It was also shown from a cost-effectiveness point of view that primary cytology screening is preferred under the age of 30 and primary HPV testing at and over the age of 30.<sup>170</sup> The only cost-effective policy we found with screening under the age of 30 was with primary cytology screening (Table 3.3.6B).

The present cost-effectiveness estimates are obtained for a model that aimed to be representative of cervical cancer screening in the Netherlands. By varying epidemiologic (i.e. background risk and past screening) and screening characteristics (i.e. test sensitivity, specificity and costs) we adapted the model to different country situations. However, in addition to the level of cervical cancer incidence, the pattern of age-specific incidence differs between countries. The peak age-specific incidence in the Netherlands without screening occurs at a young age (approximately at age 45)<sup>49</sup>, however, in some other countries the peak age-specific incidence occurs at an older age.<sup>171</sup> In that case there will be a shift to an on older age for the estimated optimal screening starting age, and/or to lengthening of the screening interval. Also, demographic characteristics were not varied, what could lead to changes in the choice of the most efficient screening scenario. Especially life expectancy will influence the ending age, for example, if the mean age at death in other counties is at a younger age compared to the Netherlands, the optimal stopping age for screening will move downward and cost-effectiveness will be less favourable due to less life years gained.

We assumed that 10% of the population never attends screening and has a 3 times higher background risk for cervical cancer than the 90% potential attenders (e.g. the high-risk stratum and the low-risk stratum), based on international data when mass screening for cervical cancer started.<sup>143</sup> If this 'healthy screening selection' is not applicable (anymore), we could have underestimated the effect of screening, and thus also the cost-effectiveness. The preferred number of examinations during a lifetime at a certain threshold would than become higher.

The use of QALYs as an outcome measure in cost-effectiveness modelling is recommended by the panel of cost-effectiveness in health and medicine,<sup>172</sup> but reliable quantification of quality of life aspects of screening and cervical cancer is still problematic. Our analyses have shown that the optimal screening strategy is primary HPV screening with cytology triage in many situations. This finding, however, is sensitive to the loss of

utility associated with a triage episode (until referral to screening or colposcopy) after a positive HPV test. We found for the Dutch situation that if the utility loss associated with follow-up screenings was the equivalent of 7 days of life instead of 2 day of life per year spent in triage, primary cytological screening with HPV triage would be more cost-effective than primary HPV testing <sup>173</sup>. Still, the conclusion that primary HPV screening is cost-effective in many European scenarios remains if we calculate the costs per life year gained, instead of QALY gained.

In conclusion, we have conducted an extensive simulation study to evaluate the cost-effectiveness of a variety of cervical cancer screening strategies and to determine the optimal testing strategy in different scenarios that are exemplary for countries or regions in Europe. Primary HPV screening is preferred in many scenarios. Primary cytology screening is preferred in countries with low costs of cytology or high prevalence of HPV in combination with high costs per HPV test.



## **CHAPTER 4**

# **Human Papillomavirus vaccination**





# CHAPTER 4.1

## **Cost-effectiveness analysis of Human Papillomavirus vaccination in the Netherlands**

Inge M.C.M. de Kok,  
Marjolein van Ballegooijen,  
J. Dik F. Habbema

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### 4.1.1 | Abstract

**Background:** In the Netherlands, low cervical cancer incidence and mortality rates might limit the cost-effectiveness of vaccination against the human papillomavirus (HPV). We examined the effect on cervical cancer incidence and mortality of adding HPV vaccination to the current Dutch cervical cancer screening situation and calculated the cost-effectiveness.

**Methods:** Costs and effects were estimated under favorable assumptions (ie, that HPV vaccination provides lifelong protection against 70% of all cervical cancers, has no side effects, and is administered to all women regardless of their risk of cervical cancer) by using the microsimulation screening analysis (MISCAN) model. The impact of changes in the price of vaccination, number of booster vaccinations, vaccination attendance rate, vaccination efficacy, cervical cancer incidence level, and quality-of-life assumptions were investigated in sensitivity analyses.

**Results:** Using the current price of €118 per vaccine dose and with discounting of costs and effects at an annual rate of 3%, adding HPV vaccination to the current Dutch screening situation had a cost-effectiveness ratio of €53,500 per quality-adjusted life year (QALY) gained. The threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to an acceptability threshold of €20,000 per QALY gained was €40. With the addition of one or more (up to four) booster vaccinations during a lifetime, this threshold price decreased to €33 for one booster (to €16 for four boosters). With a doubling of the cervical cancer incidence level, the cost-effectiveness ratio was €24,400 per QALY gained and the maximum price per dose at threshold of €20,000 was €97. All threshold prices were lower under less favorable effectiveness assumptions.

**Conclusion:** In the Netherlands, HPV vaccination is not cost-effective even under favorable assumptions. To become cost-effective, the vaccine price would have to be decreased considerably, depending on the effectiveness of the vaccine.

## 4.1.2 | Introduction

Multiple analyses of the cost-effectiveness of vaccination against the human papillomavirus (HPV) have concluded that vaccination should be cost effective.<sup>42-47</sup> However, this conclusion mainly depends on the incidence and mortality rates of cervical cancer. Low incidence and mortality implies a limited maximum effect of HPV vaccination.

The low cervical cancer incidence and mortality in the Netherlands is associated with an efficient national screening program, in which women are invited to have a free Pap smear every 5 years from age 30 to 60 years.<sup>6</sup> Cervical cancer mortality in the Netherlands has steadily declined over the last five decades, and in 2005, it was 1.6 per 100,000 woman-years [World Standardized Rate (WSR)<sup>162</sup>]. This rate is lower than the WSR of 2.5 per 100,000 woman-years in the United States in the period 2001-2005 and 1.9 per 100,000 woman-years in the United Kingdom in 2005.<sup>3-4</sup>

This study explores the cost-effectiveness of adding HPV vaccination to the current screening situation in the Netherlands. Earlier decisions by the Dutch government on the cervical cancer screening program were based on cost-effectiveness analyses that used a cost-effectiveness acceptability threshold of €20,000 per quality-adjusted life year (QALY) gained,<sup>10</sup> that is, an intervention with a cost-effectiveness ratio above €20,000 per QALY gained was not considered acceptable. We used this threshold in this analysis; in addition, we explored a threshold of €50,000 per QALY gained. For comparison with other cost-effectiveness analyses, the main analyses were performed under the favorable assumptions for vaccination, i.e., that vaccination provides lifelong protection against 70% of all cervical cancers, has no side effects, and is administered to all women regardless of their risk of cervical cancer. Given that the price per vaccine dose for a vaccination program is negotiable, we performed a threshold analysis to determine the unit price per vaccine dose that would result in an acceptable cost-effectiveness ratio under these assumptions. Because uncertainty exists about the duration and strength of protection afforded by HPV vaccination, we performed a sensitivity analysis in which we varied the lifetime number of vaccinations as well as the vaccine's efficacy rate. Finally, for maximum generalizability of the results, we examined the cost-effectiveness of HPV vaccination in situations in which the cervical cancer incidence differs from that in the Netherlands.

### 4.1.3 | Material and methods

Costs and effects were estimated using the microsimulation screening analysis (MISCAN) model.<sup>58</sup> The MISCAN model generates a large study population with fictitious individual life histories, in which women will, at a certain rate, acquire an HPV infection and develop a pre-invasive cervical lesion and/or cervical cancer, and some will die from the disease. This simulation results in an age-specific and time-specific output of disease incidence and mortality. This fictitious population then undergoes simulated screening and/or vaccination; these interventions will change some of the life histories. These changes constitute the effects of the intervention and are represented by the numbers of events and stages induced or prevented by the intervention that are linked with its costs and quality-of-life outcomes.

#### 4.1.3.1 | Model Specifications and Assumptions

##### 4.1.3.1.1 | Demography, epidemiology and natural history

We simulated a Dutch population at risk for cervical cancer based on demographic<sup>174</sup> and hysterectomy<sup>136</sup> data. The age distribution of the incidence of preinvasive neoplasia that will eventually become cancer was calibrated to the age distribution of the pre-screening mortality; the latter distribution was corrected for cohort effects based on an age-period-cohort analysis.<sup>76</sup> The age distribution of the incidence of preinvasive lesions that will regress before they become cancer was calibrated to the observed cervical intraepithelial neoplasia (CIN) detection rates in the Netherlands (derived from the Dutch Network and National Database for Pathology [PALGA]) for the period 1997–2001. The age distribution of the incidence of HPV infections that will clear before progressing to CIN was calibrated to the observed HPV prevalence.<sup>96</sup>

Disease was subdivided into seven sequential stages: HPV infection, three preinvasive stages (CIN grades I, II, and III), and three invasive stages (International Federation of Gynecology and Obstetrics [FIGO] stages IA, IB and II+).<sup>137</sup> The first disease stage-HPV infection (without neoplasia) – cannot be diagnosed because screening is performed with cytology and not with an HPV test; preinvasive stages and FIGO IA cases can only be diagnosed by screening and not clinically because stage IA is asymptomatic, whereas stage IB and II+ cases can be diagnosed by screening as well as clinically. A Weibull distribution was used to assume variation among women in the duration of the different stages. The stage-specific survival used in the model for clinical cases (ie, cases diagnosed based on symptoms as opposed to screen detection) was age

specific and based on observed survival and on Dutch mortality-to-incidence ratios from the prescreening period in the Netherlands.<sup>76</sup>

#### 4.1.3.1.2 | Assumptions regarding screening, vaccination, and treatment

We assumed that women were screened as currently occurs in the Dutch program, i.e., every 5 years from age 30 to 60 years. The screening attendance rate was based on the observed rates from PALGA for women who had at least one Pap smear in the previous 5 years.<sup>142</sup> We assumed that 10% of the population would never attend screening and would have a threefold higher background risk for cervical cancer than the 90% of the population comprising the potential attenders.<sup>143</sup> The sensitivity of the smear for different disease stages was estimated at 50% for CIN I, 65% for CIN II, 80% for CIN III, 85% for pre-clinical invasive stages IA and IB, and 90% for preclinical invasive stage II+.<sup>163</sup> Specificity of the test was assumed to be 98.5%, based on the false-positive rate of Pap smears in the Dutch screening program. We assumed that women with a borderline test result (atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion) had a repeat smear and those with a positive test result (high-grade squamous intraepithelial lesion) were referred for colposcopy and biopsy. Detection (and the associated management of preinvasive lesions) was assumed to lead to a 100% cure rate. For screen-detected invasive cancers, survival was modeled as a reduction in the risk of dying from cervical cancer compared with that of dying from clinically diagnosed cancer.

We assumed that the first HPV vaccination (comprising three doses) was at age 12 years. The vaccination participation rate was assumed to be 85% with no selection with regard to the risk of cervical cancer. For additional vaccinations (comprising one dose each) during a lifetime, we assumed that only women who received the first vaccinations were invited and that the participation rate was 100%. We assumed that the first round of three vaccinations conferred lifelong immunity. Vaccine efficacy was estimated to be 70% against cancer, 35% against preinvasive lesions, and 1.5% against HPV infections; these estimates were based on the prevalence of HPV types 16 and 18 in cancers, the weighted mean of the prevalence of HPV types 16 and 18 in CIN I, CIN II, and CIN III lesions worldwide, and the prevalence of HPV types 16 and 18 in women with normal cytology.<sup>13, 35, 96</sup>

#### 4.1.3.1.3 | Costs and utilities

Table 4.1.1 presents the estimated costs and utilities associated with vaccination, screening, and treatment. Screening costs include costs of the invitational system,

time and travel costs for women attending screening, costs of smear taking, costs of cytological evaluation, and costs of registration in PALGA. Vaccination costs include costs of the invitational system; time, travel, and administrative costs for women attending vaccination; and the cost of the vaccine dose itself<sup>175</sup>. The costs of screening, diagnosis, and treatment procedures for detected preinvasive lesions, of primary treatment of invasive cervical cancer, and of treatment and palliative care for advanced cervical cancer were derived from a cost study conducted in the Netherlands.<sup>142</sup> Utilities were based on Dutch data and data from other countries.<sup>43, 76, 144</sup>

#### **4.1.3.1.4 | Model**

The model we present is a cohort model. For this cohort analysis, we used the cervical cancer risk level for Dutch women born after 1940.<sup>76</sup> On the basis of Dutch mortality data, we assumed that women born after 1940 have a lower risk of cervical cancer than women born before 1940.<sup>162</sup> The incidence rate of invasive cervical cancer simulated without the current screening program was 12.3 per 100,000 life years (lifetime risk = 1.0%), and the mortality rate was 4.9 per 100,000 life years (lifetime risk = 0.4%). The incidence rate of invasive cervical cancer simulated under the current screening program was 6.1 per 100,000 life years (lifetime risk = 0.5%), and the mortality rate was 2.1 per 100,000 life years (lifetime risk = 0.2%).

#### **4.1.3.2 | Cost-effectiveness and Sensitivity Analyses**

The results account for the simulated effects and costs until all simulated women have died. The effects are presented as numbers of clinical cases, screen-detected cancers, disease-specific deaths, life years lost, and QALYs lost to cervical cancer. Costs were calculated by multiplying the unit costs linked to specific events (ie, invitations, tests, vaccinations, detection of preinvasive lesions, cancer diagnosis, and deaths) by the numbers of those events. The same methodology was applied to calculate utilities. The cost-effectiveness calculations were conducted from a societal perspective. The costs and effects calculations were made for screening plus vaccination versus screening alone. Costs and effects were discounted at an annual rate of 3% to convert future costs and health effects to their value at the point in time when all women were 12 years old.

**Table 4.1.1** | Assumptions about the costs, and the amount and duration of the utilities of different events and health states\*

Effect	Costs per effect (€)	Utilities	
		Amount	Duration
<b>Vaccination</b>			
Initial vaccination (three doses)		0.995	3 weeks
Vaccine material†	354.00		
Time and travel costs	9.42		
Administration	18.00		
Organization‡	22.50		
Booster vaccination (one dose)		0.995	1 week
Vaccine material†	118.00		
Time and travel costs	5.60		
Administration	6.00		
Organization‡	7.50		
<b>Screening</b>			
Primary test§	53.64	0.994	2 weeks
Costs of surveillance test	51.00	0.994	1 year
<b>Treatment</b>			
Diagnoses and treatment of preinvasive stages			
False-positive	265.00	0.995	0.5 year
CINI	825.00	0.970	0.5 year
CINII	1,221.00	0.930	0.5 year
CINIII	1,430.00	0.930	0.5 year
Diagnoses and treatment of invasive cancer			
FIGO IA	4,683.00	0.940	5.5 years
FIGO IB	11,105.00	0.940	5.5 years
FIGO II+	10,223.00	0.823	5.5 years
Terminal care	24,870.00	0.288	1 month

\* CINI = cervical intraepithelial neoplasia grade 1; CINII = cervical intraepithelial neoplasia grade 2; CINIII = cervical intraepithelial neoplasia grade 3; FIGO = International Federation of Gynecology and Obstetrics. †Includes injection fluid and needle. ‡Includes invitation and database registration. §Includes invitation, time and travel, smear taking, cytologic evaluation, and database registration.

In sensitivity analyses, we examined the impact on cost-effectiveness of varying the unit price of vaccination, the need for booster vaccinations to keep up lifelong vaccine protection, the attendance rate to vaccination, the efficacy of vaccination, and the utilities. We varied the background cervical cancer risk level (in other words, the

4.1

incidence level of cervical cancer in situations in which no screening exists) to allow our results to be compared with those of other cost-effectiveness analyses for situations with different cervical cancer incidence and mortality levels. For example, when we doubled the background risk, the incidence in the situation with screening (which we did not change and continued to use as the comparator situation) also doubled. For each sensitivity analysis, we calculated the cost-effectiveness ratio with the assumed vaccination costs and the threshold price per dose for vaccination to be cost effective with an acceptability threshold of €20,000 per QALY gained. As an alternative, we also used an acceptability threshold of €50,000 per QALY gained, in keeping with cost-effectiveness policies in other countries.<sup>145</sup> To evaluate the impact of quality-of-life estimates on the cost-effectiveness ratio and threshold price, we calculated the cost-effectiveness ratio and threshold prices under unfavorable quality-of-life assumptions for vaccination (ie, disutilities of vaccination doubled, and disutilities of the other health states halved) and under favorable quality-of-life assumptions for vaccination (ie, disutilities of vaccination halved, and disutilities of the other health states doubled).

Finally, we specifically adjusted our assumptions regarding the cervical cancer risk level and costs of vaccination to match those in cost-effectiveness analyses for other countries.

## **4.1.4 | Results**

### **4.1.4.1 | Analysis Under Favorable Assumptions**

Table 4.1.2 presents the undiscounted effects and costs per 100,000 simulated women. Adding one vaccination (of three doses) with lifelong effectiveness to the current screening program in the Netherlands prevented 36% of the CINII and CINIII lesions detected by screening alone (850 lesions), 60% of the cervical cancers diagnosed (240 cancers), and 61% of the deaths from cervical cancer (100 deaths). There were 60% fewer life years lost (2470 life years) and 61% fewer QALYs lost (2680 QALYs). Based on the over-the-counter price per vaccine dose, the total costs increased by 64%, from €42.4 million per 100,000 women to €69.5 million per 100,000 women, which is an increase of €272 per woman during her lifetime.

Table 4.1.3 shows the total costs and effects before and after discounting. The cost-effectiveness ratios with discounting at 0% were €11,000 per life year gained and



€10,100 per QALY gained and with discounting at 3%, €59,700 per life year gained and €53,500 per QALY gained.

**Table 4.1.2** | Estimated costs and effects of adding HPV16/18 vaccination to the current screening program in the Netherlands (under favorable assumptions) compared with the costs and effects of the current screening program\*

Costs and effects	Screening only	Vaccination plus screening	Vaccination plus screening compared with screening only, No. (%)
<b>Effects, No.</b>			
First primary screens	84,810	84,846	36 (0.04)
Follow-up primary screens	380,780	380,752	-28 (-0.01)
Triage screens	19,010	18,140	-870 (-5)
First rounds of three vaccinations	N/A	84,220	84,220 (100)
Screen-detected CINII or CINIII lesions	2370	1520	-850 (-36)
Screen-detected cases of invasive cancer	86	33	-53 (-61)
Clinically detected cases of invasive cancer	410	170	-240 (-60)
Deaths from cervical cancer	170	70	-100 (-61)
Life years lost	4130	1660	-2470 (-60)
QALYs lost	4390	1710	-2680 (-61)
<b>Costs, €</b>			
Screening testing (including triage test)	28,850,710	28,808,950	-41,760 (-0.14)
Vaccination	N/A	34,018,710	34,018,710 (100)
Treatment of preinvasive lesions	4,308,520	3,039,290	-1,269,230 (-29)
Treatment of (advanced) cancer <sup>†</sup>	9,192,210	3,659,530	-5,532,680 (-60)
<b>Total</b>	<b>42,351,430</b>	<b>69,526,470</b>	<b>27,175,040 (64)</b>

\*Based on 100,000 simulated women followed from birth to death; no discounting. CINII = cervical intraepithelial neoplasia grade 2; CINIII = cervical intraepithelial neoplasia grade 3; QALYs = quality-adjusted life years. †Includes costs of terminal care.

**Table 4.1.3** | Cost-effectiveness of adding HPV16/18 vaccination to the current screening program in the Netherlands (under favorable assumptions), compared with the current screening program only\*

Costs per effect	Vaccination plus screening compared with screening alone	
	0% discounting	3% discounting
Total costs, €	27,175,000	22,153,400
Total LYs gained	2470	370
Total QALYs gained	2680	410
Costs/LY gained, €	11,000	59,700
Costs/QALY gained, €	10,100	53,500

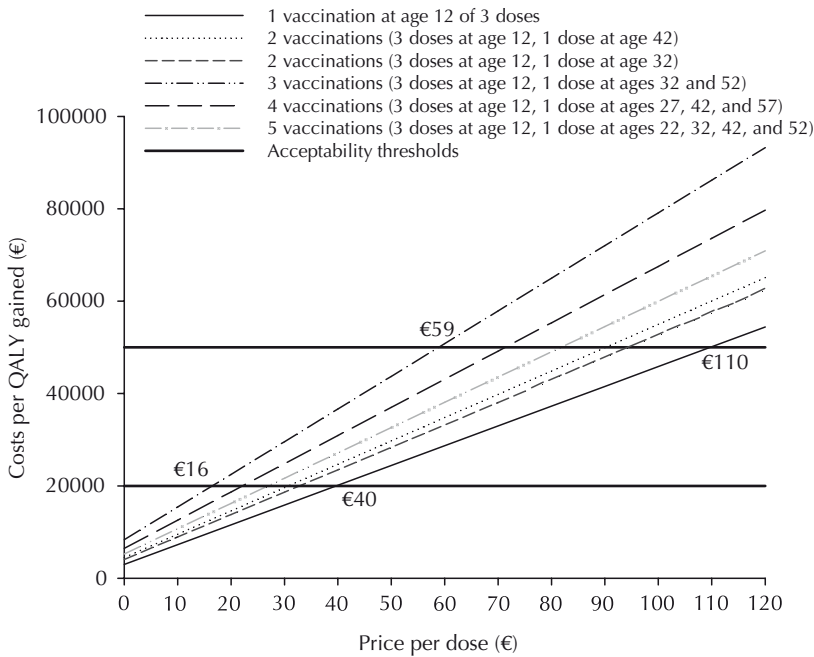
\*Based on 100,000 simulated women, followed from birth to death; costs and effects discounted at 0% and 3%. Costs are rounded to the nearest € 100. LY = life year, QALY = quality-adjusted life year.

#### 4.1.4.2 | Threshold Vaccine Price and Sensitivity Analysis

The threshold price per vaccine dose at which the cost-effectiveness of HPV vaccination would be €20,000 per QALY gained was €40 under favorable assumptions. Adding one or more booster vaccinations during a lifetime decreased the threshold price per vaccine dose to €33 for one booster and to €16 for four boosters (Figure 4.1.1, Table 4.1.4). At a cost-effectiveness threshold of €50,000 per QALY gained, the threshold price per vaccine dose was €110 and decreased to €95 with one booster vaccination and to €59 with four booster vaccinations (Figure 4.1.1, Table 4.1.4).

The cost-effectiveness ratio of adding HPV vaccination to the current situation varied with the underlying incidence of cervical cancer. For a situation in which the incidence of cervical cancer was 50% of that in the Netherlands, as, for example, is the case in Finland [WSR in 2005: 3.3 per 100,000 woman-years<sup>4</sup>], the cost-effectiveness ratio of adding HPV vaccination was €105,600 per QALY gained and the maximum price per dose was €14 at a threshold of €20,000 per QALY gained and €50 at a threshold of €50,000 per QALY gained. If, on the other hand, the incidence under the screening program was twice as high as that in the Netherlands, as, for example, is the case in Denmark [WSR in 2003: 10.8 per 100,000 woman-years<sup>4</sup>], the cost-effectiveness ratio of adding HPV vaccination was €24,400, and the maximum prices per dose at thresholds of €20,000 and €50,000 per QALY gained were €97 and €241, respectively (Figure 4.1.2, Table 4.1.4). At a fourfold higher incidence level, as, for example, is the case in Brazil [WSR in 2002 = 23.4 per 100,000 woman-years<sup>176</sup>], the cost-effectiveness ratio was €10,900 per QALY gained. For an eightfold higher incidence level, as, for

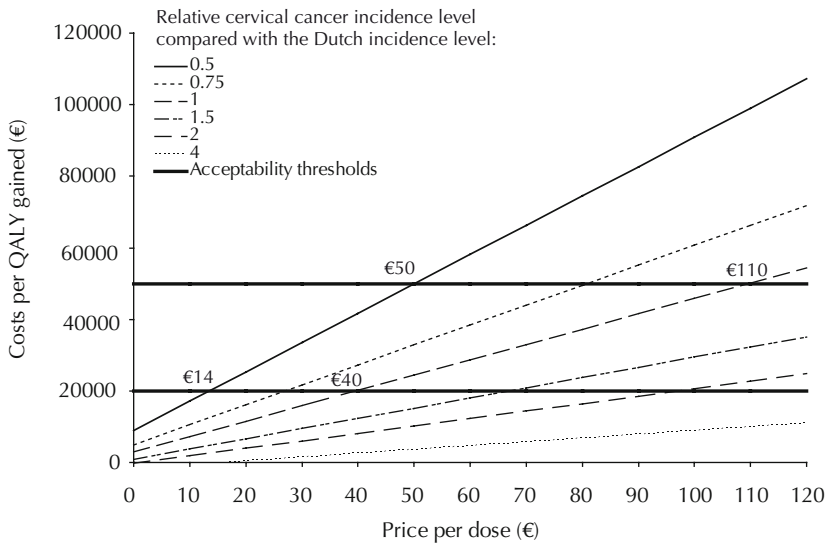
example, is the case in Zimbabwe [WSR in 2002 = 52.1 per 100,000 woman-years<sup>176</sup>], the cost-effectiveness ratio was €4,100 per QALY gained.



**Figure 4.1.1** | Sensitivity analysis of the impact of the number of vaccinations during a lifetime and of differences in price per vaccine dose on the cost-effectiveness of adding HPV16/18 vaccination to the current screening program in the Netherlands compared with the current screening program only (costs and effects discounted at 3%). The intersections between the horizontal lines (ie, the acceptability thresholds) and the other lines represent the threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to the acceptability threshold. QALY = quality-adjusted life year

Another parameter that had considerable impact on the cost-effectiveness of adding HPV vaccination to the current screening situation was the efficacy of the vaccination for preventing cervical cancer. For example, an absolute increase of 20 percentage points in vaccination efficacy (from 70% to 90%) decreased the cost-effectiveness ratio to €39,600, whereas an absolute decrease of 20 percentage points in efficacy (from 70% to 50%) increased the cost-effectiveness ratio to €76,000. At the €20,000 threshold, the corresponding threshold prices for a 20% points increase and a 20% points decrease in

efficacy were €58 and €24, respectively (Table 4.1.4). Furthermore, varying the utilities (ie, disutilities of vaccination halved or doubled, and disutilities of the other health states halved or doubled) increased the cost-effectiveness ratio to €60,400 under the least favorable quality-of-life assumptions for vaccination, and decreased the ratio to €46,000 under the most favorable quality-of-life assumptions for vaccination. At the €20,000 threshold, the corresponding threshold prices for the least and most favorable assumptions were €34 and €47, respectively (Table 4.1.4). The vaccination attendance rate had an impact on the costs and effects of vaccination but only negligible effects on the cost-effectiveness ratio and the threshold price of vaccination (Table 4.1.4).



**Figure 4.1.2** | Sensitivity analysis of the impact of variation in the relative incidence of cervical cancer compared with the Dutch incidence level and of differences in price per vaccine dose on the cost-effectiveness of adding HPV16/18 vaccination (assuming lifelong protection) to the current screening situation compared with the current screening program only (costs and effects discounted at 3%). The intersections between the horizontal lines (ie, the acceptability thresholds) and the other lines represent the threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to the acceptability threshold. QALY = quality-adjusted life year.

Another parameter that had considerable impact on the cost-effectiveness of adding HPV vaccination to the current screening situation was the efficacy of the vaccination for preventing cervical cancer. For example, an absolute increase of 20 percentage points in vaccination efficacy (from 70% to 90%) decreased the cost-effectiveness ratio to €39,600, whereas an absolute decrease of 20 percentage points in efficacy (from 70% to 50%) increased the cost-effectiveness ratio to €76,000. At the €20,000 threshold, the corresponding threshold prices for a 20% points increase and a 20% points decrease in efficacy were €58 and €24, respectively (Table 4.1.4). Furthermore, varying the utilities (ie, disutilities of vaccination halved or doubled, and disutilities of the other health states halved or doubled) increased the cost-effectiveness ratio to €60,400 under the least favorable quality-of-life assumptions for vaccination, and decreased the ratio to €46,000 under the most favorable quality-of-life assumptions for vaccination. At the €20,000 threshold, the corresponding threshold prices for the least and most favorable assumptions were €34 and €47, respectively (Table 4.1.4). The vaccination attendance rate had an impact on the costs and effects of vaccination but only negligible effects on the cost-effectiveness ratio and the threshold price of vaccination (Table 4.1.4).

To examine whether HPV vaccination could become cost-effective in the Dutch context, we evaluated HPV vaccination under a combination of favorable assumptions regarding the efficacy and effectiveness of the vaccination program. For comparison, we also calculated the cost-effectiveness ratio and threshold price per dose vaccine under much less favorable assumptions, i.e., five vaccinations (four boosters after the initial round) during a lifetime to maintain lifelong protection, 50% attendance rate (assuming that the 10% of the persistent nonattenders for screening, who were assumed to have a threefold higher risk of cervical cancer than the attenders, will not attend vaccination), and 50% efficacy of the vaccine on cervical cancer. Under these combined assumptions we found that adding HPV vaccination to the current screening situation in the Netherlands had a cost-effectiveness ratio of €362,100 per QALY gained. In this situation, the price per vaccine dose would have to be –€8 to achieve a cost-effectiveness ratio of €20,000 per QALY gained (€3 to achieve a cost-effectiveness ratio of €50,000 per QALY gained). In other words, even if the price per vaccine dose would be €0, vaccination would still not be cost-effective.

**Table 4.1.4** | Sensitivity analyses of the undiscounted costs and number of QALYs gained per 100,000 simulated women of the cost-effectiveness of adding HPV16/18 vaccination (assuming lifelong protection) to the current screening program in the Netherlands compared with the current screening program only and of the threshold price per vaccine dose to be cost effective considering a cost-effectiveness threshold value of €20,000 or €50,000 per QALY gained\*

Assumption	Undiscounted costs, 1000 €	Undiscounted no. of QALYs gained	Discounted CER <sup>†</sup> , €	Price per vaccine dose to be cost effective, €
				At €20,000/ QALY gained threshold
				At €50,000/ QALY gained threshold
<b>Number of vaccinations during a lifetime</b>				
1 (age 12, three doses)	27,175	2680	53,500	40
2 (age 12, three doses; age 42, one dose)	38,722	2680	61,300	33
2 (age 12, three doses; age 32, one dose)	38,722	2680	64,100	31
3 (age 12, three doses; ages 32 and 52, one dose)	50,269	2680	69,800	27
4 (age 12, three doses; ages 27, 42, and 57, one dose)	61,815	2680	78,500	22
5 (age 12, three doses; ages 22, 32, 42, and 52, one dose)	73,362	2680	91,800	16
<b>Vaccination attendance rate, %</b>				
50	15,994	1580	53,600	40
85	27,175	2680	53,500	40
100	32,104	3100	54,400	39
<b>Vaccination efficacy against cervical cancer, %</b>				
50	29,142	1950	76,000	24
70	27,175	2680	53,500	40
90	25,197	3520	39,600	58

Assumption	Undiscounted costs, 1000 €	Undiscounted no. of QALYs gained	Discounted CER <sup>†</sup> , €	Price per vaccine dose to be cost effective, €
				At €20,000/ QALY gained threshold
				At €50,000/ QALY gained threshold
<b>Cervical cancer incidence, fold change relative to the Dutch incidence rate in the model</b>				
0.5	30,053	1450	105,600	14
0.75	28,590	2100	70,700	27
1 <sup>‡</sup>	27,175	2680	53,500	40
1.5	24,291	4020	34,600	67
2	21,196	5510	24,400	97
4	9679	10,680	10,900	203
6	-1324	15,580	6400	304
8	-11,785	20,170	4100	399
<b>Assumed amount of utilities lost</b>				
Least favorable assumptions for vaccination	27,175	2540	60,400	34
Most favorable assumptions for vaccination	27,175	2920	46,000	47

\* QALYs = quality-adjusted life years; CER = cost-effectiveness ratio. †In costs per QALY gained, with costs and effects discounted at an annual rate of 3%. ‡ Incidence rate = 6.1 per 100,000 life years.

In the Netherlands costs and effects are sometimes discounted at 4% and 1.5%, respectively, per year. Applying these rates in this analysis would reduce the costs for HPV vaccination from €53,500 to €19,700 per QALY gained

In Table 4.1.5 we compare our results for HPV vaccination added to screening with published cost-effectiveness ratios from other countries. After adjusting for the incidence risk ratio for the specific study compared with that in the Netherlands (in our model) and for the costs of vaccination in the specific study, the cost-effectiveness ratio from this analysis was similar to other cost-effectiveness ratios. For example, Goldie et al.<sup>43</sup> estimated that the cost-effectiveness ratio of HPV16/18 vaccination that was 90% effective would be US\$24,300 (or €16,300) per QALY gained, assuming vaccination costs of US\$393 (or €264) for the first vaccination round (compared with €404 in this study) and an incidence risk ratio of cervical cancer 1.7 times higher than that in our study (0.86% vs 0.5%). When we adjusted our model for these differences, the cost-effectiveness ratio of HPV vaccination was €18,300 per QALY gained. This analysis suggests that other than differences in vaccination costs, differences in risk level explain to a large extent the differences in cost-effectiveness ratios.

**Table 4.1.5** | Published cost-effectiveness ratios (CERs) of vaccination added to the current situation (costs per quality-adjusted life year gained) from other countries compared with the cost-effectiveness ratio from this analysis adjusted for the incidence risk ratio of the specific study and the costs of vaccination in the specific study\*

Country	Incidence risk ratio	Costs of vaccination, €		Published CER, €	Adjusted CER <sup>†</sup> , €
		Costs of vaccine	Program costs		
Netherlands	1.0	354	50	53,500	53,500
Israel <sup>177</sup>	0.5	242	46	54,700	74,000
United Kingdom <sup>178</sup>	1.4	296	13	26,600	25,200
Canada <sup>179</sup>	1.6	257	Not reported	19,900	19,200
United States <sup>43</sup>	1.7	202	62	16,300	18,300
United States <sup>47</sup>	1.4 <sup>‡</sup>	270	66	29,300	29,100
Mexico <sup>180</sup>	3.8	176	0	2,000	3,000

\* Costs of vaccination and published CERs are converted to Euros, using exchange rates as of August 21, 2008 (€1 = US \$1.4894, GBP 0.7933, CAD 1.5561, MXN 15.0302). <sup>†</sup>Adjusted for incidence risk ratio (column 2) and costs of vaccine and program costs (columns 3 and 4, respectively). <sup>‡</sup>Because the incidence of cervical cancer in the situation in which vaccination was applied was not published, we used the incidence of cervical cancer in the United States as reported for for 2001–2005,<sup>3</sup> which was 8.4 per 100,000 woman-years.



### 4.1.5 | Discussion

In this study we calculated the cost-effectiveness of adding HPV vaccination to the current screening situation in the Netherlands. Adding vaccination under the favorable assumptions that it would provide lifelong protection against 70% of all cervical cancers, have no side effects, and would be given to all women regardless of their risk of cervical cancer had a cost-effectiveness ratio of €53,500 per QALY gained. This cost-effectiveness ratio is considerably higher than the cost-effectiveness threshold of €20,000 per QALY gained. In this favorable situation (in which only one vaccination round of three doses is required for a 100% lifelong protection against HPV 16/18-related cervical cancer), to achieve a cost-effectiveness ratio of €20,000 per QALY gained, the price per initial vaccination must be approximately €40 per dose. With one additional booster vaccination for lifelong protection, the price per initial vaccination must be €33 per dose and with four booster vaccinations, €16 per dose. All of these threshold prices were lower under less favorable effectiveness assumptions and were considerably less than the current over-the-counter per-dose price of €118 in the Netherlands. Furthermore, our study revealed that the cervical cancer incidence and mortality level in the context in which the vaccination was applied had a substantial impact on these results.

The long term efficacy and effectiveness of a national HPV vaccination program is uncertain. To examine whether HPV vaccination could become cost-effective in the Dutch context, we evaluated HPV vaccination under a combination of favorable assumptions. However, almost all cost-effectiveness analyses of HPV vaccination have used these same favorable assumptions, which has resulted in an optimistic bias, to which we are, to some extent, contributing. Thus, for comparison, we also calculated the cost-effectiveness ratio and threshold price per dose vaccine under much less favorable assumptions, i.e., five vaccinations (four boosters after the initial round) during a lifetime to maintain lifelong protection, 50% attendance rate (assuming that the 10% of the persistent nonattenders for screening, who were assumed to have a threefold higher risk of cervical cancer than the attenders, will not attend vaccination), and 50% efficacy of the vaccine on cervical cancer incidence. Under these combined assumptions we found that adding vaccination to the current screening situation in the Netherlands had a cost-effectiveness ratio of €362,100 per QALY gained. In this situation, the price per dose vaccine would have to be -€8 to achieve a cost-effectiveness ratio of €20,000 per QALY gained (€3 to achieve a cost-effectiveness ratio of €50,000 per QALY gained). In other words, even if the price per vaccine dose would be €0, vaccination would still not be cost-effective.

Previous cost-effectiveness analyses of HPV vaccination that compared screening plus vaccination versus screening only<sup>42-47, 178-180</sup> produced lower cost-effectiveness ratios than the one produced in this study. We showed that this difference could be explained (to a large extent) by differences in the incidence of cervical cancer in the situation in which vaccination was applied. For example, when the incidence level under the current screening program was doubled or halved in our model, the cost-effectiveness ratio of vaccination plus screening compared with screening only was more than halved and almost doubled, respectively (Table 4.1.4). In most of the other cost-effectiveness analyses (except for that conducted in Israel), the incidence of cervical cancer was higher than in our study for the Dutch situation.

Another explanation for the variation among published cost-effectiveness ratios is differences in the costs of vaccination. The assumed total cost of vaccination in the Netherlands was approximately 1.5 times higher than the assumed cost of vaccination in the studies from other countries. One reason for this difference is that in the Dutch situation, additional costs for the initial vaccination of three doses excluding the price of the vaccine itself (eg, costs of invitations, administration of the vaccine, and time and travel costs for the women) were estimated at €49.92, whereas estimates of these additional costs in other studies ranged from €0 in Mexico<sup>180</sup> to €46 in Israel.<sup>177</sup> The studies from the United States assumed higher additional costs (€62 and €66).<sup>43, 47</sup> However, the main reason for differences in vaccination costs is that the over-the-counter price of the vaccine itself in the Netherlands was assumed to be €354 (for three doses) compared with the lowest price of €176<sup>180</sup> and the highest price of €296<sup>178</sup> in other studies. We accounted for this discrepancy by varying the unit price of vaccination in the sensitivity analysis.

The acceptability of the cost-effectiveness ratio of HPV vaccination also varies depending on the acceptability threshold that is used. The cost-effectiveness acceptability threshold of €20,000 per QALY gained for the Netherlands [which was used for cost-effectiveness analyses of screening in the Netherlands<sup>10</sup>] is relatively low compared with the €50,000-per-QALY-gained-threshold often used for other countries.<sup>145</sup> As a result, interventions are often considered not cost-effective (ie, the cost-effectiveness ratio is higher than the threshold). As we have shown, to achieve a cost-effectiveness ratio of €50,000 per QALY gained (under the assumption of lifelong protection), the over-the-counter price per vaccine dose had to decrease only slightly (from €118 to €110) for the Dutch situation (Table 4.1.4).

We have also shown that the number of booster vaccinations (which are required to maintain lifelong protection against cervical cancer) has an impact on the cost-

effectiveness ratio. However, the efficacy of HPV vaccination is related to other uncertain factors. For example, there is evidence the HPV vaccine can cross protect against HPV 31 and HPV 45, which are closely related to HPV 16 and HPV 18, respectively.<sup>35</sup> In addition, other oncogenic HPV types may fill the biological niche that remains after the elimination of HPV 16/18 infections and as a result cause more cervical cancer than they do in the absence of vaccination. Furthermore, a proportion of 12-year-old girls may have already been exposed to HPV16/18 at the time of vaccination,<sup>181</sup> such exposure is important because the effectiveness of the vaccine is lower if HPV16/18 is present in the person who is vaccinated.<sup>182</sup> As a result of these uncertain factors, the protection offered by vaccination against HPV 16/18 may be larger, but is probably smaller, than initially anticipated. We showed that variation in HPV vaccination efficacy had a considerable impact on the cost-effectiveness ratio of HPV vaccination.

To our knowledge, no data are available on the relationship between participation in vaccination and the risk for cervical cancer. In our base case analysis we assumed that all simulated women, regardless of their risk of cervical cancer, received HPV vaccination at the initial or the booster vaccination rounds. However, a pilot study in the United Kingdom showed that the uptake of HPV vaccination was lower among girls from less affluent backgrounds and minority groups, who often have a higher cervical cancer risk.<sup>183</sup> Because screening is selectively used by women who are at lower risk of cervical cancer,<sup>143</sup> it is also plausible that HPV vaccination attendance (especially at the booster rounds, which are given to adults) will also be selective to some extent, which would decrease the cost-effectiveness of vaccination.

Another factor with an uncertain effect on the cost-effectiveness ratio of HPV vaccination is immigration. Evidence from Centers for Disease Control and Prevention indicates that the relatively higher incidence and mortality rates of cervical cancer in the United States compared with the Netherlands are due to immigration of foreign-born women into the United States, many of whom have not been screened for this disease in their country of origin.<sup>184</sup> Given that the application of vaccination is limited to younger ages, which excludes women who immigrate as adults, the effect of vaccination is only applied to a lower risk population of women raised in the US. These latter women may even be at lower risk than women in the Netherlands, due to the more intensive screening in the United States. As a result, the effectiveness, and therefore also the cost-effectiveness, of HPV vaccination estimated for the US female population will probably be less favorable than for the Dutch women.

This study has two limitations. First, because we did not model viral transmission, the impact of factors such as herd (or community) immunity was underestimated. Herd

immunity would have affected at most 15% of the simulated women because we assumed that 85% of the women were vaccinated and that vaccine protection is lifelong. Second, we did not take into account the impact of vaccination on other HPV-related diseases, such as genital warts and other HPV-related cancer types. To our knowledge, there is no evidence to date from any clinical trials that HPV vaccination has any impact on other HPV-related cancers. One trial showed that among women not infected with HPV16 or HPV18, the quadrivalent vaccine against HPV types 16/18/45/11 was 100% effective in preventing vulval intraepithelial neoplasias (VINs) grade 2–3 and vaginal intraepithelial neoplasias (VaINs) grade 2–3 that were positive for HPV16/18. In the total population (ie, including women infected with HPV16/18), the quadrivalent vaccine was 71% effective in preventing VIN2-3 and VaIN2-3 caused by HPV16/18 and 49% effective in preventing all VIN2-3 or VaIN2-3.<sup>36</sup> Chesson et al.<sup>185</sup> and Kim et al.<sup>47</sup> estimated that including the effect of the bivalent HPV vaccination against HPV types 16 and 18 on other HPV-related cancers will decrease the cost-effectiveness ratio of vaccination by 25% or 30%, respectively. Another HPV-related disease we did not take into account is genital warts. Results so far show that the quadrivalent vaccine is 51% effective for the prevention of genital warts associated with any type of HPV.<sup>34</sup> However, any gain in quality of life due to the prevention of genital warts is expected to be relatively small, given their short duration and non-lethality. Savings due to the prevention of warts will also be limited. For example, in the Netherlands, the estimated annual savings if all genital warts were prevented is €375,000 [assuming 1,500 cases<sup>186</sup> and €250 per case<sup>187</sup>], whereas the estimated annual savings due to the prevention of cervical cancers is approximately €3,500,000 [assuming 600 cases,<sup>188</sup> €8,500 per case,<sup>142</sup> and that 70% of the cases are prevented].

Although the HPV vaccine has not been available long enough to evaluate its long-term side effects, it is safe over the short term, with only a small number of adverse events registered in women aged 15–26 years.<sup>189</sup> However, most countries intend to vaccinate 12-year-old girls, and vaccine safety and/or efficacy has not yet been tested in this age group. Thereby, depending on the population, cervical cancer is a relatively rare disease (for the Netherlands, 1 death case will be prevented per 1000 vaccinated girls). As a result, also rare adverse events due to vaccination will influence the risk-benefit ratio of vaccination. Therefore, future studies on the adverse effects among vaccinated 12-year-old girls are important, primarily for safety, but also for cost-effectiveness estimates.

Because of the scarcity of resources, trade-offs are often necessary in medical decision making. Gafni and Birch<sup>190</sup> have addressed the value of threshold cost-effectiveness ratios in decision making. They argued that decision-makers need information about

the opportunity costs of a policy decision (ie, the next best alternative that must be given up as a result of the decision) to improve efficient resource allocation.<sup>190</sup> Opportunity costs are the health outcomes that are achievable with other interventions that were not undertaken because these resources were committed to the intervention under consideration.<sup>191</sup> In our analysis, the opportunity costs of HPV vaccination are preventing 100 deaths, or 2500 life years, for a price tag of €27 million.

The consequences of discounting future costs and effects on the cost-effectiveness ratio can be substantial, especially when the intervention involves current costs and future effects (ie, the time between current costs and future effects is rather long), as it typically is with prevention. In 2006, the Dutch Health Care Insurance Board ('College voor Zorgverzekeringen') recommended that costs and effects were to be discounted at 4% and 1.5%, respectively, per year.<sup>192</sup> In this analysis, applying these rates would reduce the costs for HPV vaccination from €53,500 to €19,700 per QALY gained. However, in 1996, when policy decisions were being made about cervical cancer screening in the Netherlands, both costs and effects were to be discounted at 4%.<sup>193</sup> Because these new cost-effectiveness criteria (ie, 4% for costs and 1.5% for effects) would also favor the cost-effectiveness ratio of cervical cancer screening, we need to reconsider optimal screening (ie, screen ages, interval between screen tests, and frequency) and compare the health effects gained due to allocating more resources to screening to the health effects gained due to adding vaccination to the Dutch screening program. Such an analysis should include the design of an optimal combination of HPV vaccination and screening, including combinations of vaccination with different levels of cytological and HPV screening for the Dutch situation.

In conclusion, many uncertainties still exist about the effects of HPV vaccination on HPV-related diseases. Our cost-effectiveness analysis shows that in the Netherlands, a country with low cervical cancer incidence and mortality, HPV vaccination is not cost-effective (even under as-yet unproven favorable assumptions). To become cost-effective, the vaccine price would have to be decreased considerably, depending on the effectiveness of the vaccine.

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## CHAPTER 4.2

# **Would the effect of HPV vaccination on non-cervical HPV-positive cancers make the difference for its cost-effectiveness?**

Inge M.C.M. de Kok,  
J. Dik F. Habbema,  
Joost van Rosmalen,  
Marjolein van Ballegooijen

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### 4.2.1 | Abstract

Besides cervical cancer, the human papillomavirus (HPV) is found in other cancers and may be preventable with HPV vaccination. However, these other cancers are often not accounted for in cost-effectiveness analyses of HPV vaccination. This study estimates the potential maximum effect on the cost-effectiveness ratio (CER) of HPV vaccination of preventing non-cervical HPV-positive cancers.

For the Dutch situation, a mathematical equation was used to estimate the maximum impact if all cancer cases of the penis, vulva/vagina, anus, oral cavity and oro-pharynx with HPV16/18 are prevented, in terms of number of life years gained, savings and improvement in the CER of vaccination. For other countries and for future developments, we show how the impact on the CER varies depending on the incidence of cervical/non-cervical HPV 16/18-related cancers, vaccine costs, and clinical costs.

For the Netherlands, compared to if the vaccine is only effective against cervical cancer, if the other HPV16/18-positive cancers are prevented in women only, the effect is estimated at a 14% increase in life years gained, an 18% increase in savings, and a 13% decrease in the CER. If vaccination prevents HPV-positive cancers in both men and women, these figures increase to 25%, 26% and 21%, respectively. In conclusion, if HPV vaccination fully prevents all non-cervical HPV-positive cancers, this would substantially increase its cost-effectiveness. The impact of vaccination varies depending on the incidence of cervical/non-cervical HPV-positive cancers 16/18, the vaccine costs, and clinical costs. Observed combinations of these parameters show a decrease in the CER of between 10% and 31%.



## 4.2.2 | Introduction

Cervical cancer is the most important human papillomavirus (HPV) – related cancer worldwide. In the Netherlands, the incidence and mortality trends of cervical cancer have been steadily declining with rates of 6.3 and 1.4 per 100,000 woman years (age-adjusted rates, standardized to the world population), respectively, in 2007.<sup>63</sup> However, HPV infections are also found in other cancer types, notably cancer of the penis, vulva/vagina, anus, oral cavity and oro-pharynx.<sup>41</sup> Since we are able to vaccinate against HPV types 16 and 18, a part of these cancers is potentially preventable. The possible effect of vaccination on non-cervical HPV-positive cancers has generally not been accounted for in cost-effectiveness analyses of HPV vaccination.<sup>42-46</sup> This is valid, since estimates of the effect of vaccination on the incidence of non-cervical HPV-positive cancers, except for vulval and vaginal lesions,<sup>36</sup> are not yet evidence based. On the other hand, Chesson et al.<sup>185</sup> and Kim et al.<sup>47</sup> estimated that including the effect of vaccinating 12-year-old girls on non-cervical HPV-positive cancers will decrease the cost-effectiveness ratio (CER) by 25% or 18-30%, respectively; thus, the effect of HPV vaccination on these cancers might be substantial.

To estimate the costs and effects of HPV vaccination microsimulation models are generally used, which simulate individual event histories for an idealized population of interest.<sup>194</sup> Microsimulation is flexible but complex and not always necessary. Compared to the simulation of screening, the simulation of HPV vaccination is sometimes much simpler, depending on the assumptions made. For analyses that evaluate the effect of waning or combining vaccination with a variety of screening strategies, a (micro-) simulation approach is indicated. For herd immunity, a dynamic model is required. However, when the assumed effect of vaccination is a certain percentage reduction in incidence and mortality a more direct epidemiological approach, using a mathematical equation, is sufficient.

We used such a direct approach to estimate the potential maximum effect on the CER of HPV vaccination of preventing non-cervical HPV-positive cancers. Since we wanted to estimate the maximum effect of preventing these cancers, the analyses were performed under the favorable assumption that 100% of the female population is vaccinated against HPV types 16 and 18. We assumed that men are not vaccinated. So, in case the vaccine prevents cancers in women only we assumed 0% herd immunity, in case it also prevents cancers in men we assumed 100% herd immunity. The effects concern the number of life years gained (LYsG) and savings due to preventing treatment costs. Subsequently, in the Dutch situation we calculated the decrease of the CER of

HPV vaccination as a result of these effects. The characteristics that influence the relative effect of preventing also non-cervical HPV-positive cancers, differ between countries. For example, cervical cancer burden differs between countries, amongst others due to variation in cervical cancer screening.<sup>71, 195</sup> Therefore, we show for other countries and for future developments how the impact on the CER varies depending on the incidence of cervical and non-cervical HPV16/18-positive cancers, the vaccine costs, and the costs of clinical healthcare.

### **4.2.3 | Material and methods**

To calculate the number of LYsG due to preventing HPV16/18-positive cancers, the number of life years lost due to these cancers was estimated using data from the Netherlands Cancer Registry (NCR). The NCR contains nationwide data on all cancer types in the Netherlands since 1989 and is more than 95% complete.<sup>196</sup> The present study includes patients with cancer of the cervix, penis, vulva/vagina, anus, oral cavity and oro-pharynx. We used the number of incident cancer cases and the number of deaths by cancer type and gender in the period 1999–2003. Incidence and mortality rates were calculated using the population size, stratified by gender, in the period 1999-2003.<sup>197</sup> Rates are given as the number of cases per 100,000 persons (men or women, followed from birth till death) (Table 4.2.1). However, because for this period no data were available on oro-pharynx cancers, but only on total pharynx cancer, the sub-group of oro-pharynx cancer rates were calculated by multiplying pharynx cancer rates by the gender-specific proportions of oro-pharynx cancer (54% in males and 67% in females), based on the NCR data over earlier periods.<sup>198</sup> Per cancer site, the preventable proportion was estimated as the HPV 16/18-related proportion described in a published review, based on worldwide data (Table 4.2.1).<sup>41</sup> The mean number of LYsG per prevented cancer death was calculated as the life expectancy at the mean age at cancer death in 1999-2003, separately for men and women (Table 4.2.1).<sup>197</sup>

To calculate the medical savings due to preventing treatment costs of HPV16/18-positive cancers (Table 4.2.1), the healthcare costs for treatment per cancer case were estimated using ‘diagnosis treatment combinations’ (DBC).<sup>199-200</sup> The DBC system was introduced in the Netherlands for the registration and reimbursement of hospital and medical specialist care. The fixed prices for reimbursement per DBC were based on information about unit costs of healthcare services and the average number of healthcare services applied per cancer treatment. To calculate the savings due to preventing costs of

Cancer with HPV16/18 deaths (Table 4.2.1), the costs per cancer death were estimated as the average costs in the last year of life at the mean age at death per cancer site. These costs were based on health insurance, home care, nursing homes, and mortality data.<sup>201-202</sup>

The number of LYsG due to preventing HPV16/18-positive cancers (Table 4.2.2) were calculated for a cohort of 100,000 persons (men only, women only, or both genders, followed from birth till death) as the number of Cancer with HPV16/18 deaths times the mean number of LYsG per prevented cancer death. The savings due to preventing HPV16/18-positive cancers (Table 4.2.2) were calculated for a cohort of 100,000 persons (men only, women only, or both genders) as the number of HPV16/18-positive cancers times the costs per cancer case, and the number of Cancer with HPV16/18 deaths times the costs per cancer death (Table 4.2.2). The number of LYsG and the cost savings were discounted at a rate of 3% towards 12 years of age (since, in the Netherlands, vaccination is advised at that age).

The proportional decrease in the total costs of vaccination, as a result of increased savings due to preventing the non-cervical HPV-positive cancers, was calculated as (the extra savings per 100,000 persons) / (costs of vaccination per 100,000 persons – savings due to the prevention of cervical cancer). For the Dutch situation, the undiscounted costs of vaccination per 100,000 women were estimated at €40,000,000, based on the assumption that all women are vaccinated at age 12 at a cost of €400 for three doses.<sup>203</sup> The undiscounted costs of vaccination per 100,000 persons (both genders) were estimated at €20,000,000, assuming that all women are vaccinated at age 12 at a cost of €400 for three doses,<sup>203</sup> and that 50%<sup>204</sup> of the cohort are women (eg 50,000 persons). The decrease in the CER of HPV vaccination due to preventing non-cervical HPV-positive cancers was calculated using the proportional increase in number of LYsG and the proportional decrease in total costs.

It is possible to use the data from the Dutch situation to calculate the proportional change in the CER in other countries. The differences between countries in the impact of including the effect on non-cervical HPV-positive cancers on the CER mainly depend on four variables. These are the incidence/mortality of cervical cancer, the incidence/mortality of non-cervical HPV-positive cancers, the clinical costs level, and the vaccination costs. Using these variables, the proportional change in CER for other countries, if the vaccine is effective in both genders, can be estimated as

$$1 - \frac{WST_{cc}LYG_{cc}/5.1}{WSR_{cc}LYG_{cc}/5.1 + WSR_{nc}LYG_{nc}/6.2} \left( 1 - \frac{WSR_{nc}S_{nc}/6.2}{50,000CoV/CCL - WSR_{cc}S_{cc}/5.1} \right)$$

or in case the vaccine is effective in women only

$$1 - \frac{WSRT_{cc}LYG_{cc}/5.1}{WSR_{cc}LYG_{cc}/5.1 + WSR_{nc}LYG_{nc}/6.2} \left( 1 - \frac{WSR_{nc}S_{nc}/5.7}{100,000CoV/CCL - WSR_{cc}S_{cc}/5.1} \right)$$

in which CoV is the costs of vaccination in Euros per woman, WSR<sub>cc</sub> is the world standardized incidence rate of cervical cancer, WSR<sub>nc</sub> is the world standardized incidence rate of non-cervical cancer, CCL is the relative clinical costs level compared to the Dutch clinical costs (Dutch level = 1), S<sub>cc</sub> is the savings of preventing cervical cancer in the Dutch situation, S<sub>nc</sub> is the savings of preventing non-cervical cancer in the Dutch situation, LYG<sub>cc</sub> is the life years gained by preventing cervical cancer in the Dutch situation, and LYG<sub>nc</sub> is the life years gained by preventing non-cervical cancer in the Dutch situations. The derivation of the equation is given in the appendix. The values of the LYG and savings in the Dutch situation are given in Table 4.2.2. We used the Dutch cervical cancer incidence (world standardized rate (WSR) of 5.1 per 100,000 (rate in 2003)<sup>63</sup>), and the Dutch non-cervical cancer incidence (WSR of 6.2 or 5.7 per 100,000, if effective in both genders or in women only, respectively). The coefficients in this formula are based on a cohort of 100,000 persons. In the case that the vaccine is effective in both genders 50% of the cohort is female, in the case that effectiveness is in women only then 100% of the cohort is female.

In sensitivity analyses, we calculated the proportional decrease of the CER with different values for these variables. In these analyses, the Dutch clinical costs level was multiplied by a factor between 0.1 and 3, based on the mean health expenditure levels per capita worldwide.<sup>205</sup> In the same analyses, the vaccine costs were varied between €100 and €500 for three initial doses, the cervical cancer incidence (WSR) was varied between 2.5 and 50 per 100,000 women years, and the non-cervical cancer with HPV incidence WSR between 0.5 and 36 per 100,000 person years, based on incidence levels

worldwide.<sup>41, 176, 206</sup> The range in non-cervical cancer with HPV incidence is wide, because it was calculated as the two extreme situations that all individual HPV-positive cancers have the lowest or the highest incidence levels observed worldwide. We also estimated the proportional decrease of the CER for scenarios based on the situation in Finland, Denmark, the United Kingdom (UK) and the United States (US). We calculated the world standardized incidence rates based on the number of incident HPV-positive cancers and the population size in each of these countries.<sup>3, 207-211</sup> We assumed that the age distributions for the cancer incidence and the life tables were similar to those in the Netherlands. For the US, Finland and Denmark, the sub-group of oro-pharynx cancer rates were calculated by multiplying pharynx cancer rates by 54% in males and 67% in women, based on the Dutch NCR data. Also, we assumed the same anal cancer crude incidence rate in Finland and Denmark as in the Netherlands. Vulvar/vaginal cancer incidence data in Finland and Denmark are the data of cancer of 'other female genital organs', excluding cancer of the cervix uteri, corpus uteri, uterus and ovary. The clinical costs level and vaccination costs were based on published cost-effectiveness analyses,<sup>47, 178, 185</sup> or, in case no cost-effectiveness analyses were published, they were assumed to be the same as in the Netherlands.

## 4.2.4 | Results

### 4.2.4.1 | Basic data

Table 4.2.1 shows the data for the different cancer sites with HPV in the Netherlands. Anal cancer occurs more often in women than in men (53 vs. 39 per 100,000 persons, followed from birth till death). Oro-pharyngeal and oral cancer occurs more often in men than in women (78 vs. 42 and 362 vs. 274 per 100,000 persons, respectively). For anal, oral and oro-pharyngeal cancer, women were slightly older at diagnosis and at death than men. The proportion of cancer cases attributable to HPV16/18 ranged from 3% for oral cancer to 70% for cervical cancer and 83% for anal cancer.

The estimated medical costs per case for treatment ranged from €4,000 for penile cancer to €8,000 for cervical and vulvar/vaginal cancer. Costs associated with a cancer death ranged from €16,600 for vulvar/vaginal cancer to €19,600 for cervical, oral and oro-pharyngeal cancer.

**Table 4.2.1** | Summary data on HPV-positive cancers in the Netherlands (1999–2003) for women (W) and men (M).

		Cervix	Penis	Vulva/ Vagina	Anus	Oral cavity	Oro- pharynx
Lifetime incidence per 100,000 persons	W	547	-	246	53	274	42
	M	-	75	-	39	362	78
Mortality per 100,000 persons	W	196	-	91	12	80	21
	M	-	16	-	11	104	41
Mean age at diagnosis (years)	W	52	-	71	65	64	60 <sup>a</sup>
	M	-	68	-	63	60	60 <sup>a</sup>
Mean age at death (years)	W	64	-	77	74	70	66 <sup>a</sup>
	M	-	70	-	67	64	63 <sup>a</sup>
Mean number of Life Years Gained per prevented case	W	21	-	10	13	16	19
	M	-	12	-	14	17	17
Proportion attributable to HPV16/18		70%	25%	32%	83%	3%	11%
Costs of care per incident case		€ 8,000	€ 4,000	€ 8,000	€ 5,000	€ 6,000	€ 6,000
Costs of care per death case	W	€ 19,600	-	€ 16,600	€ 18,800	€ 19,500	€ 19,500
	M	-	€ 19,500	-	€ 19,500	€ 19,600	€ 19,600

<sup>a</sup>Mean age at diagnosis and mean age at death are for all pharyngeal cancer (data for the sub-site oro-pharyngeal cancer are not available).

#### 4.2.4.2 | Life years gained

If vaccination prevents non-cervical HPV16/18-positive cancers in women only, the number of LYsG will increase by 21% compared to if only cervical cancer is prevented (from 1,421 to 1,712 per 100,000 persons, Table 4.2.2). If cancers are prevented in both men and women, this percentage increases to 35%. If the effects are discounted at a rate of 3% per year, these percentages become 14% and 25%, for prevention in only women and in both men and women, respectively.

**Table 4.2.2** | Life years gained (LYsG) and savings by cancer site, in case HPV16/18-positive cancers are eliminated in women only (W), in men only (M), or in both women and men (Both), per 100,000 persons followed from birth till death.

		Cervix	Penis	Vulva/ Vagina	Anus	Oral cavity	Oro-pharynx	Total	Total, excluding cervix
Mean number of LYsG per 100,000 persons, undiscounted	W	2,812	-	317	138	37	85	3,388	576
	M	-	57	-	145	56	165	422	422
	Both	1,421	28	160	141	46	124	1,921	500
Mean number of LYsG per 100,000 persons, discounted at 3% per year to age 12 years	W	915	-	65	31	9	22	1,042	127
	M	-	13	-	38	15	43	109	109
	Both	462	7	33	34	12	32	580	118
Total savings per 100,000 persons, undiscounted (1000 €)	W	5,707	-	1,071	378	90	136	7,382	1,674
	M	-	156	-	349	133	296	934	934
	Both	2,883	77	541	364	111	189	4,165	1,282
Total savings per 100,000 persons, Discounted at 3% per year to age 12 years (1000 €)	W	1,765	-	192	79	19	29	2,084	319
	M	-	32	-	80	32	71	215	215
	Both	892	16	97	68	21	31	1,124	232

### 4.2.4.3 | Medical savings and total costs

If as a result of vaccination, non-cervical HPV16/18-positive cancers are prevented in women only, the savings due to the avoidance of cancer treatment will increase by 29% compared to the savings from preventing cervical cancer only (from €5,707,000 to €1,674,000 per 100,000 women, Table 4.2.2). If non-cervical HPV16/18-positive cancers are prevented in men and women, this percentage increases to 44%. After discounting at a rate of 3% per year, the savings will increase by 18% and 26%, for prevention in only women and in both men and women, respectively. Given these increased savings, the decrease in discounted total costs if the vaccine is effective in women only is  $319,000 / ((100,000 * €400) - 1,765,000) * 100\% = 0.8\%$  (Table 4.2.2). If the vaccine is effective in both men and women, the decrease in total costs is  $232,000 / ((50,000 * €400) - 892,000) * 100\% = 1.2\%$ .

### 4.2.4.4 | Impact on the CER

For the Netherlands, taking the effects of preventing non-cervical HPV16/18-positive cancers into account will, depending on whether these cancers are prevented in only women or in both men and women, increase the number of LYsG by 14% or 25% and decrease the total costs of vaccination by 0.8% or 1.2%, respectively. As a result, the total CER will decrease by  $1 - ((1 - 0.008) / (1 + 0.14)) * 100\% = 13\%$  if all HPV16/18-positive cancers are prevented in women compared to if only cervical cancer is prevented. If cancers are prevented in both men and women, the CER will decrease by 21%.

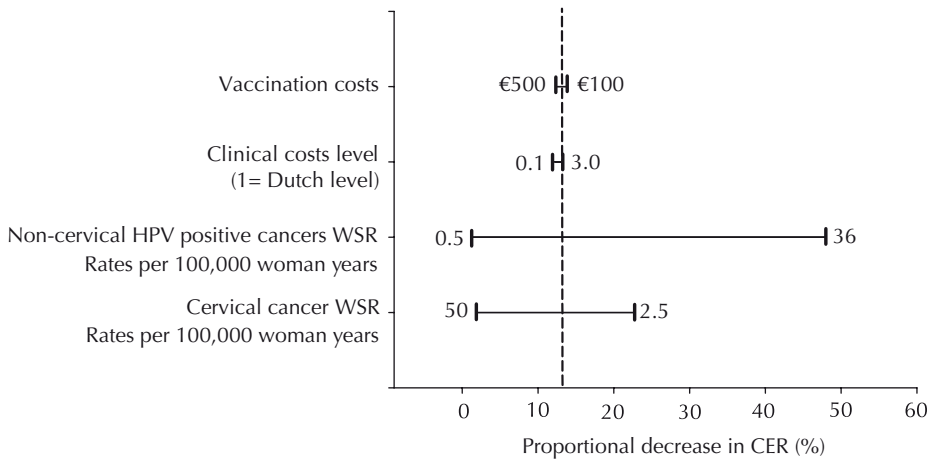
Figure 4.2.1 and Table 4.2.3 show the decrease of the CER at different levels of cervical cancer incidence, non-cervical cancer incidence, different vaccine prices (price for three initial doses) and clinical costs levels (1 = Dutch clinical costs level). Of the four variables, the variation in the incidence of non-cervical HPV-positive cancers has the largest influence and the clinical costs level has the smallest influence on the decrease in the CER (Figure 4.2.1). Multi-way variation of the four parameters shows a decrease in the CER between 0% and 114% (Table 4.2.3). However, the scenarios with the maximum and minimum effect are a combination of low cervical cancer incidence with high non-cervical cancer incidence and vice versa (scenarios 2 and 3), which are unlikely scenarios. Plausible combinations (scenarios 1, 4-9) show a decrease in the CER between 3% and 14% if the vaccine is effective in women only (Table 4.2.3). If it is effective in both genders the decrease may vary between 4% and 31%.



**Table 4.2.3** | Multi-way sensitivity analysis of the decrease in the cost-effectiveness ratio (CER) of HPV vaccination when preventing HPV-related cancers at different levels of A) cervical cancer incidence, World Standardized Rate (WSR, per 100,000 women years), B) non-cervical HPV-positive cancers incidence (WSR per 100,000 person years), C) clinical costs levels (1 = Dutch clinical costs level) and D) vaccine prices (price for three initial doses), if HPV infections are prevented in women only or in both men and women (costs and effects are discounted at 3%).

Scenario	A) Cervical cancer WSR	B1) Non-cervical HPV. positive cancers WSR, women only	B2) Non-cervical HPV. positive cancers WSR, both genders	C) Clinical costs level	D) Vaccination costs (€)	Decrease in CER if effective in women (%)	Decrease in CER if effective in both (%)
1 Base Case (Dutch situation)	5.1	5.7	6.2	1	400	-13%	-21%
2 A) ↑, B) ↓, C) ↑, D) ↓ <sup>a</sup>	50	0.5	0.5	3	100	0%	0%
3 A) ↓, B) ↑, C) ↑, D) ↓ <sup>a</sup>	2.5	36	36	3	100	-78%	-114% <sup>b</sup>
4 A) ↓, B) ↓, C) ↑, D) ↑ <sup>a</sup>	2.5	0.5	0.5	3	500	-3%	-4%
5 A) ↑, B) ↑, C) ↓, D) ↓ <sup>a</sup>	50	36	36	0.1	100	-9%	-17%
6 Scenario based on United Kingdom	6.2	5.5	6.4	2	300	-11%	-22%
7 Scenario based on United States	5.3	5.9	7.7	3	300	-14%	-31%
8 Scenario based on Denmark	16.3	5.6	6.9	1	400	-5%	-10%
9 Scenario based on Finland	3.2	4.4	4.2	1	400	-15%	-23%

<sup>a</sup> ↓ = smallest value considered, ↑ = largest value considered (see Fig. 4.2.1 for the extremes considered). Scenarios 2 and 3 are the contrasting (in terms of influence on the CER) but not necessarily realistic combinations, and scenarios 4 and 5 the two contrasting realistic combinations of the extreme parameter values. <sup>b</sup> i.e. Cost saving



**Figure 4.2.1** | One-way sensitivity analysis of the decrease in the cost-effectiveness ratio of HPV vaccination when preventing HPV-related cancers at extreme values of cervical cancer incidence, of non-cervical HPV-positive cancers incidence, for the clinical costs level and for the vaccine price (price for three initial doses), if HPV infections are prevented in women only (costs and effects are discounted at 3%). Dashed line is the base case result. (WSR = World Standardized Rate, CER = cost-effectiveness ratio)

## 4.2.5 | Discussion

Taking full prevention of non-cervical HPV16/18-positive cancers into account substantially decreases the CER of vaccinating 12-year-old girls. If costs and effects are discounted at a rate of 3%, this maximum approach yields a decrease of 21% for the Dutch situation. However, the CER of HPV vaccination in the Netherlands, without accounting for the effect on the non-cervical HPV-positive cancers, is estimated at €53,500 per Quality Adjusted Life Year (QALY) gained.<sup>203</sup> Thus, even if the effect on all HPV-positive cancers is taken into account, HPV vaccination would still not be cost-effective considering the Dutch cost-effectiveness threshold of €20,000 per QALY gained. The Dutch threshold is, however, very low. If we would consider the threshold of £30,000 per QALY gained (approximately €36,000) the National Institute for Health and Clinical Excellence (NICE) stated as acceptable, HPV vaccination would be just above the cost-effectiveness threshold if the effect on all HPV-positive cancers is taken into account. Moreover, the estimated CER of €53,500 was based the 2009 over-the-counter

price in the Netherlands of approximately €400 for three doses. Currently the price of the vaccine already significantly decreased as the result of negotiations, and the price may even drop further. This means that vaccination is more likely to be cost-effective.

The results for various levels of cancer incidence, clinical costs and vaccination costs show that the decrease can differ in other countries. Several cost-effectiveness analyses of vaccination against HPV, without accounting for the effect on the non-cervical HPV-positive cancers, have been published.<sup>42-46</sup> For example, Kulasingam et al.<sup>178</sup> found that vaccination with screening, compared to screening alone, was associated with an incremental cost-effectiveness ratio of €26,600 per QALY gained.<sup>203</sup> Compared to the Dutch situation, they assumed lower vaccination costs (€309)<sup>203</sup> and two times higher cancer treatment costs. If the effect on non-cervical HPV-positive cancers in women only is taken into account, the cost-effectiveness ratio decreases by 11% (Table 4.2.3) to €23,700 per QALY gained.

We assumed a lifelong 100% protection of the vaccine against HPV16/18-positive cancers. Trials to evaluate the effect of HPV vaccination on cervical cancer show protection of the vaccine against HPV16/18-related pre-invasive lesions of 98%, in HPV16/18 naive women.<sup>33</sup> Although the effect of the vaccine against invasive cervical cancer can tentatively be estimated from the effect against pre-invasive lesions, it is not yet established. In addition, the duration of the protection is still unknown. A lower or shorter effectiveness in preventing cervical cancer would substantially increase the CER, either by a decreased number of life years gained, or by the addition of the costs of booster vaccinations. In both cases, assuming that the efficacy of the prevention of non-cervical HPV-positive cancers follows that of cervical cancer, the relative impact on the CER of preventing these cancers would basically not change.

There is some evidence of cross-protection of the vaccine against HPV 31 and HPV 45, which are closely related to HPV 16 and 18, respectively.<sup>35</sup> On the other hand, there is a possibility that other oncogenic HPV types will eventually fill the biologic niche left behind after the elimination of HPV types 16 and 18. In both cases, the relative impact on the CER of preventing non-cervical HPV-positive cancers could change, if HPV types 31/45 (or the types that fill the niche) have a different prevalence in non-cervical HPV-positive cancers than in cervical cancer. It is reported that the prevalence of HPV types 31/45 is comparable for cervical and penile cancer, but less prevalent in the other non-cervical HPV-positive cancers.<sup>212-217</sup> Thus, the relative impact on the CER of preventing non-cervical cancers could be somewhat smaller in case of cross-protection.

In addition to the uncertainty about the effectiveness of the vaccine against cervical cancer, the effectiveness may be less in preventing non-cervical HPV16/18-

positive cancers than in preventing cervical cancers. The effect of HPV vaccination on non-cervical HPV-positive cancers is not known. Nevertheless, one trial showed that in women not infected with HPV-16/18, the vaccine was 100% effective in preventing HPV16/18 positive vulval/vaginal intraepithelial neoplasias grade 2–3.<sup>36</sup> Moreover, compared to cervical cancer, HPV is less prevalent in these cancers. This could indicate that HPV infection is not a necessary condition for these cancer cases in which HPV was found<sup>41</sup> and, therefore that these HPV-positive cancers could not be prevented as effectively by HPV vaccination. A lower effectiveness against the non-cervical HPV-positive cancers compared to the effect against cervical cancer would result in a smaller decrease of the CER.

The effect of vaccination is maximal if HPV-positive cancers are prevented in both men and women. In the best case, the protection in men would totally result from herd immunity. Nevertheless, since it is unlikely that all women will be vaccinated, and since men may have sex with men, it is also unlikely that all men will be protected due to reduced transmission. In case the effect of the vaccine in men required the vaccination of boys, the presented costs of the vaccination program would approximately double. If both men and women are vaccinated, the proportional decrease in CER as a result of the effect against all HPV-positive cancers is still 21%.

We estimated costs per LYG and not costs per QALY gained. By lack of evidence-based utility data for the relatively rare cancers described in the present study, we could have assumed similar disability weights for the non-cervical HPV-positive cancers as for cervical cancer. This would however lead to approximately the same proportional decrease in the CER of HPV vaccination. On the other hand, some analyses of the cost-effectiveness of HPV vaccination include the impact of vaccination on the quality of life and costs due to the prevention of non-lethal HPV-related diseases, such as genital warts and cervical intraepithelial neoplasia. For these analyses, our resulting proportional effect on the CE of vaccination of including other cancers is slightly overestimated. The reason is that the proportional decrease in the CER due to the prevention of non-cervical HPV related cancers in that case would be smaller, since the relative extra benefits of preventing these cancers would be smaller. The impact on the quality-of-life of different HPV-related diseases needs further investigation.

We computed the influence of differences in the cervical and non-cervical HPV-positive cancers background level. In this way, we show the impact of preventing non-cervical HPV-positive cancers in different countries, similar to the scenarios based on the situation in Finland, Denmark, the UK and the US. In the present calculations, demographic data, age distributions of cancer incidence, and cancer survival data

from the Netherlands were used. Variation in these inputs would influence the results. However, since differences in these data would generally affect the prevention of cervical cancer in roughly the same way as for non-cervical cancers, the influence regarding the relative impact of preventing non-cervical cancers on the CER would be limited. The proportion of cancers that is HPV 16 or 18 positive was estimated from the global burden of HPV-positive cancers,<sup>41</sup> and was assumed to be equal in all countries. However, these proportions may vary between countries.<sup>41</sup> The effect of a lower or higher proportion would have the same effect on the CER as a lower or higher background incidence of non-cervical HPV-positive cancers, of which the effect is shown in Figure 4.2.1 and Table 4.2.3.

We examined the effect of adding HPV vaccination to the cervical cancer screening situation. We did not consider the costs of screening. The effects of the screening programme do differ only slightly between the situation with vaccination and the situation without vaccination. Therefore, the costs and effects of the screening programme are almost identical in both situations and will not affect the cost-effectiveness ratio of HPV vaccination. The only small effect that we have underestimated is the fact that in the situation with vaccination less CIN lesions are detected by screening, compared to the situation without vaccination. As a result, the treatment costs for CIN would decrease and the cost-effectiveness ratio of HPV vaccination in case the vaccine will only prevent cervical cancer would be slightly smaller. As a result, the proportional decrease in case the vaccine will prevent all HPV related cancers would be smaller as well. However, this effect will be limited. We showed that without discounting the total costs of HPV vaccination decrease with 1.8% due to preventing CIN2/3 lesions.<sup>203</sup> With discounting this effect would even be smaller, since treatment costs for CIN lesions occur later in time than the costs of vaccination.

Finally, the Dutch Health Care Insurance Board ('College voor Zorgverzekeringen') recommended in 2006 that costs and effects were to be discounted at 4% and 1.5%, respectively, per year.<sup>192</sup> In this analysis, applying these rates to the Dutch situation would result in a 15% instead of a 13% decrease in the CER, if vaccination prevents HPV-positive cancers in women only. If vaccination prevents cancers in men also, this figure is 24% instead of 21%.

In conclusion, this study shows how a simple calculation can be used to estimate the potential improvement of the cost-effectiveness ratio of HPV vaccination by including the effect of preventing non-cervical HPV-positive cancers. Results are based on the assumption that all cancers attributed to HPV16/18 are prevented lifelong. With this hypothesis, the effect for the Netherlands is estimated at a 21% decrease.

For other countries, the impact depends on the incidence of cervical and non-cervical HPV 16/18-related cancer, the vaccine costs and the clinical healthcare price level. The actual effect of HPV vaccination on non-cervical HPV-positive cancers can only be revealed by follow-up of HPV-vaccinated populations.

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### 4.2.6 | Appendix: Derivation of the equation

The equation to estimate the proportional change in the cost-effectiveness ratio if the vaccine is effective in both men and women in other countries can be derived as follows:

$$1 - \text{CER with other cancers} / \text{CER without other cancers} =$$

$$1 - \frac{\text{costs with other cancers}}{\text{effects with other cancers}} / \frac{\text{costs without other cancers}}{\text{effects without other cancers}} =$$

$$1 - \frac{\text{costs of vaccination} - \text{savings with other cancers}}{\text{effects with other cancers}} / \frac{\text{costs of vaccination} - \text{savings without other cancers}}{\text{effects without other cancers}} =$$

$$1 - \frac{50,000\text{CoV} - \text{WSR}_{cc}S_{cc}\text{CCL}/5.1 - \text{WSR}_{nc}S_{nc}/6.2}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1 + \text{WSR}_{nc}\text{LYG}_{nc}/6.2} / \frac{50,000\text{CoV} - \text{WSR}_{cc}S_{cc}/5.1}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1}$$

$$1 - \frac{\text{WSR}_{cc}\text{LYG}_{cc}/5.1}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1 + \text{WSR}_{nc}\text{LYG}_{nc}/6.2} \frac{50,000\text{CoV} - \text{WSR}_{cc}S_{cc}\text{CCL}/5.1 - \text{WSR}_{nc}S_{nc}/6.2}{50,000\text{CoV} - \text{WSR}_{cc}S_{cc}/5.1}$$

$$1 - \frac{WSRT_{cc}LYG_{cc}/5.1}{WSR_{cc}LYG_{cc}/5.1 + WSR_{nc}LYG_{nc}/6.2} \left( 1 - \frac{WSR_{nc}S_{nc}CCL/6.2}{50,000CoL - WSR_{cc}S_{cc}CCL/5.1} \right) =$$

$$1 - \frac{WSRT_{cc}LYG_{cc}/5.1}{WSR_{cc}LYG_{cc}/5.1 + WSR_{nc}LYG_{nc}/6.2} \left( 1 - \frac{WSR_{nc}S_{nc}/6.2}{50,000CoV/CCL - WSR_{cc}S_{cc}/5.1} \right)$$

, in which CoV is the costs of vaccination in Euros per woman, WSR<sub>cc</sub> is the world standardized incidence rate of cervical cancer, WSR<sub>nc</sub> is the world standardized incidence rate of non-cervical cancer, CCL is the relative clinical costs level compared to the Dutch clinical costs (Dutch level = 1), S<sub>cc</sub> is the savings of preventing cervical cancer in the Dutch situation, S<sub>nc</sub> is the savings of preventing non-cervical cancer in the Dutch situation, LYG<sub>cc</sub> is the life years gained by preventing cervical cancer in the Dutch situation, and LYG<sub>nc</sub> is the life years gained by preventing non-cervical cancer in the Dutch situations.

The equation for the case in which the vaccine is effective in women only can be derived in the same way.





## **CHAPTER 5**

# **Methodological issues in cost-effectiveness analyses**



# CHAPTER 5.1

## **The impact of healthcare costs in gained life years on the cost-effectiveness of cancer screening**

Inge M.C.M. de Kok,  
Johan J. Polder,  
Marjolein van Ballegooijen,  
Louise-Maria Berkers,  
Willem Jan Meerding,  
Matejka Rebolj,  
J. Dik F. Habbema

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### 5.1.1 | Abstract

It is under debate whether health care costs related to death and in life years gained (LYsG) due to life saving interventions should be included in economic evaluations. We estimated the impact of including these costs on cost-effectiveness of cancer screening. We obtained health insurance, home care, nursing homes, and mortality data for 2.1 million inhabitants in the Netherlands in 1998-1999. Costs related to death were approximated by the health care costs in the last year of life (LastYL), by cause and age of death. Costs in LYsG were estimated by calculating the health care costs in any life year. We calculated the change in cost-effectiveness ratios (CER's) if unrelated health care costs in the LastYL or in LYsG would be included. Costs in the LastYL were on average 33% higher for persons dying from cancer than from any cause. Including costs in LYsG increased the CER by €4,040 in women, and by €4,100 in men. Of these, €660 in women, and €890 in men, were costs in the LastYL. Including unrelated health care costs in the LastYL or in LYsG will change the comparative cost-effectiveness of health care programs. The CER's of cancer screening programmes will clearly increase, with approximately €4,000. However, because of the favourable CER's, including unrelated health care costs will in general have limited policy implications.

## 5.1.2 | Introduction

Cancer screening induces both costs and savings.<sup>218</sup> Savings occur due to avoided treatment of advanced disease and palliative care, whereas the costs increase because of screening activities and because more cases of (preinvasive) neoplasia will be found than in the situation without screening.

Cost-effectiveness analysis, the standard analytic tool supporting medical decision making, involves estimating the costs and effects of an intervention compared with an alternative, e.g. the care that would be given if the intervention was not used at all, or with a different intensity of the intervention under investigation, such as less frequent screening.<sup>219</sup> One of the most persistent unresolved issues in the use of cost-effectiveness analysis is the application of the health care costs related to postponed death, or more in general, of unrelated health care costs in life years gained.<sup>220</sup> It is increasingly argued that economic evaluations should include these costs to be consistent,<sup>221</sup> since life years gained due to spending unrelated health care costs are generally included. However, the most common practice is to include medical cost for illnesses related to the intervention, and to ignore increases in medical expenditures due to other illnesses that arise during the life years gained. A particular kind of unrelated health care costs in life years gained are medical costs related to death from another cause.<sup>222</sup> Since increasing life expectancy due to preventive interventions simply postpones the costs related to death, it is believed that not considering these costs would overestimate the savings in health care costs.<sup>223</sup> Future unrelated health care costs might be large enough to raise the cost-effectiveness ratio to such a degree that the ranking of alternative interventions can be changed, which constitutes important information to policymakers. The impact is greatest when the intervention primarily extends life, such as is the case with cancer screening.<sup>224</sup>

We considered both: 1) including the health care costs related to postponed death, regardless of its cause, and 2) more in general of including the unrelated health care costs in life years gained. As a proxy of costs related to death, we studied the health care costs in the last year of life, discerning between deaths caused by a specific cancer (focusing on cancers for which screening is recommended or at least under discussion) from deaths due to any cause. We also investigated the health care costs in the life years gained and how they depend on age. Finally, to understand the potential impact, we calculated the increase these costs would make on the estimated cost-effectiveness ratio.

### 5.1.3 | Material and methods

We obtained health insurance data for 1998 and 1999 for a sample of 2.1 million inhabitants, representing 13.4% of the whole Dutch population in 1999. The study group is representative for the Dutch population regarding age, gender and cause of death.<sup>201</sup> Of the study population, 66.5% was insured by social health insurance and 33.5% by private health insurance, which was in line with the corresponding distribution in the general population in 1999 (63.5% vs 36.5% insured by social and private health insurance, respectively).<sup>225</sup> Both insurance schemes covered a similar package of health care services. The health services we included were the expenses for physicians, primary care, hospitals, drugs and related services. We also included expenditures on nursing homes and home care. A detailed description of the health services included, the study group and the cost calculation and projection is presented elsewhere.<sup>201</sup>

The data on nursing homes and home care was linked with health insurance data at individual level, using birth date, sex and zip code. The registration of home care was complete. The nursing homes registry covered 65% of the users of nursing home care. Since the coverage appeared to be non-selective, we adjusted the average nursing home costs in our study population, using a correction factor depending on coverage per geographical area (on average: 100/65).

Subsequently, to obtain date and cause of death, the data of the health insurance companies was linked with mortality data from Statistics Netherlands, using birth date, sex, and zip code. In the final analysis, we distinguished between costs of survivors (N = 2,093,748) and decedents (N = 14,839), the latter stratified by cause of death. All individuals who entered or dropped out the study population in 1998 or 1999, for example due to a change in their insurance scheme, or individuals who died in 1998, were excluded from the study. Also, individuals who died in 2000 were excluded, because part of their health expenditures in 1999 could include costs related to death.

#### 5.1.3.1 | Health care cost in the last year of life

The costs before dying were approximated by the healthcare costs in the last year of life. For decedents in 1999 we calculated health expenditures in the 365 days prior to death. For privately insured decedents we had information on the date of death and total health care expenditure for the individual years 1998 and 1999, as well as the exact health expenditures during the last year of life. For individuals with a social health

insurance scheme we had information on the date of death and the total health care expenditure for the separate years 1998 and 1999, but not the exact health expenditures during the last year of life. We therefore interpolated the cost in the last year of life for individuals with social health insurance. Since health expenditure is increasing within the last year of life, we used a non-linear interpolation method. We divided the privately insured population into twelve groups according to their month of death in 1999, and for each group calculated the fraction of the 1998 expenditure that belonged to the last year of life. Since the month of death of the decedents with social insurance schemes was known, we could use these fractions to estimate the share of their individual 1998 expenditure that belonged to the last year of life. We calculated the costs in the last year of life under the assumption that the distribution of the costs over the last years of life (not the level of those costs) is comparable for both groups of insurance.

We calculated the 95% confidence intervals for health care costs in the last year of life based on a lognormal distribution. This was not possible for the costs of nursing homes, because for this cost category only average figures on group level were available (by age, gender and cause-of-death). The costs before dying were stratified by age, gender and cause of death. We stratified the causes of death into five types of cancer that are potentially preventable due to screening (lung, colon, prostate, breast, and cervical cancer), all cancer, and all causes (Figure 5.1.1). Due to the small number of decedents in the younger age groups we used an asymmetric age structure: 0–44 years, 45–54 years, 55–64 years, and from then on 5-year categories ending with the category 95 years and older (Figure 5.1.2).

### 5.1.3.2 | Health care costs in life years gained

We calculated the average health care costs in the life years gained, by gender and age category at which deaths is prevented. To do so, we first calculated the average annual health care costs by age and gender, using costs in ‘survivors’ (Figure 5.1.3). In this way, these annual costs were cleared from the costs in the last year of life. Second, we summated these annual health care costs for each specific expected life year gained. The expected number of life years gained for individuals whose death is prevented (postponed) by screening were estimated by age at which death is prevented and gender, using life tables for the Dutch population.<sup>226</sup> Third, we added up the costs in the expected life years gained in survivors and the costs in the last year of life.

### 5.1.3.3 | Increase in costs per life years gained

We calculated the increase in costs per life year gained when taking into account both the unrelated health care costs of dying (Table 5.1.1) and the unrelated health care costs during life years gained (Table 5.1.2), by gender and age at which death is prevented (postponed), undiscounted and discounted (costs and life years gained by 3% towards age 50, assuming screening starts at that age). To do so, we divided the calculated health care costs in the substituting last year of life and the health care costs in life years gained, respectively, by the average number of life years gained.

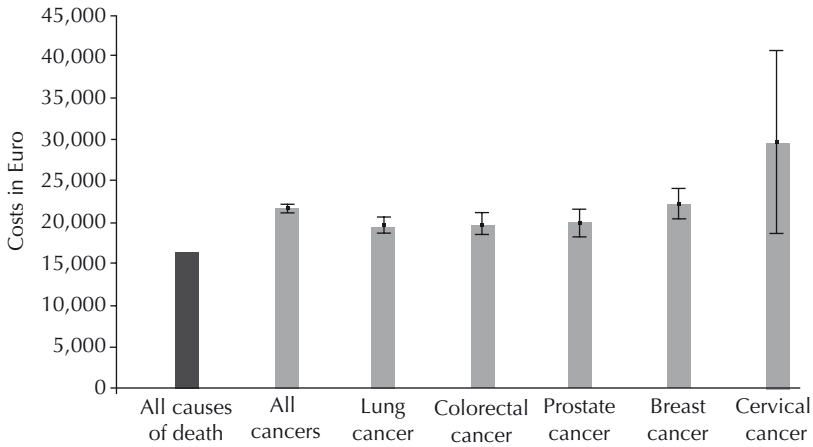
As an example, we calculated the impact of the above estimated extra costs per life year gained on the cost-effectiveness ratio of breast cancer screening, assuming that the mean age at breast cancer death (68 years<sup>227</sup>) is the average age at which death is prevented by breast cancer screening in our population. We used evidence from literature on cost-effectiveness of breast cancer screening without accounting for the here evaluated unrelated health care costs.<sup>228</sup> Included in this cost-effectiveness analysis were costs of screening, and the costs of diagnostics, primary treatment, follow up, and palliative care of breast cancer. The effect of screening was estimated by the difference in number of life years lost due to breast cancer with and without screening. Costs and effects were adjusted with a 3% annual discount rate.

All costs and cost-effectiveness ratios were indexed according to the price level of 2008 using the consumer price index.

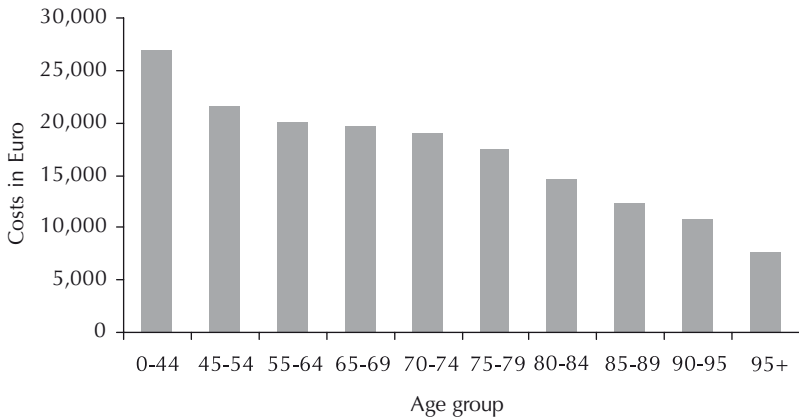
## 5.1.4 | Results

The health care costs in the last year of life were significantly higher for individuals who died from cancer than for those who died from any cause (€21,700 vs. €16,300) (Figure 5.1.1). The costs in individuals who died of cervical cancer were the highest (€29,700), partly explained by the fact that cervical cancer patients die at a relative younger age. Nevertheless, the difference with dying from other cancers was not significant due to the small number of cervical cancer death cases. Considering all causes of death, health care costs in the last year of life decreased with age (€26,800 in age-group 0–44 to €7,500 in age-group 95+) (Figure 5.1.2). The average yearly health care costs increased with age (€800 in age-group 0–44 to €4,600 in age-group 95+) (Figure 5.1.3).



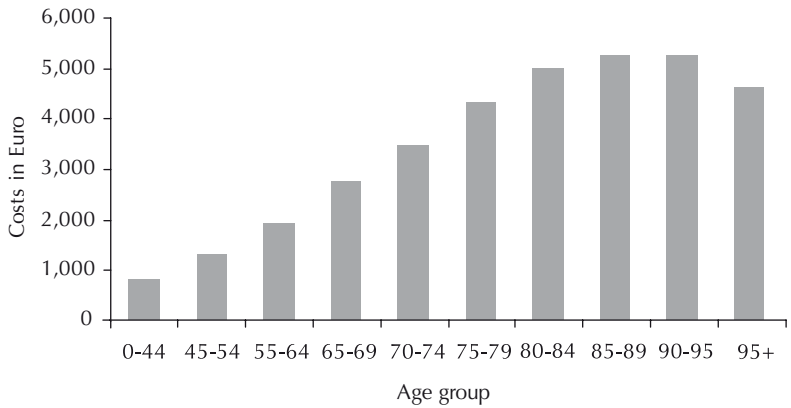


**Figure 5.1.1** | Mean (95% Confidence Intervals) health care costs in the last year of life, by cause of death (excluding nursing home care).



**Figure 5.1.2** | Mean health care costs in the last year of life by age group, all causes of death.

5.1



**Figure 5.1.3** | Mean health care costs per life year, by age group.

Table 5.1.1 shows the increase in costs per life year gained if unrelated health care costs in the postponed last year of life are taken into account. After discounting, costs per life year gained increase for men on average by €680, and for women by €480. This increase increases with age at which death is prevented, despite the fact that the costs in the last year of life decrease with age (Figure 5.1.2). The reason is that the number of life years gained, the denominator in the equation, decrease with age.

**Table 5.1.1** | Increase in costs per life year gained when taking into account health care costs in the postponed last year of life, by sex and age at which death is prevented (discounted at 0% and 3%).

Age at prevented death	0% discounting		3% discounting	
	Men	Women	Men	Women
50–54	€ 600	€ 460	€ 500	€ 360
55–59	€ 710	€ 540	€ 630	€ 450
60–64	€ 880	€ 650	€ 700	€ 500
65–69	€ 1,100	€ 790	€ 800	€ 550
70–74	€ 1,360	€ 980	€ 890	€ 610
Mean	€ 890	€ 660	€ 680	€ 480

Table 5.1.2 shows the increase in costs per life year gained when unrelated health care costs in life years gained are taken into account. After discounting, costs per life year

gained increase for men on average by €4,100, for women by €4,000. This increase becomes larger with age at which death is prevented, because the yearly health care costs increase with age (Figure 5.1.3).

The effect of discounting on the increase in costs per life years gained is limited, because both costs, as well as life years gained, are discounted at the same rate (3% per year).

The impact overall depends on the cost-effectiveness ratio before the adjustment. For breast cancer screening in the Netherlands, for example, this ratio was estimated at approximately €2,700 per life year gained (UK£1515,- in 2002).<sup>228</sup> If health care costs unrelated to the prevented breast cancer in the life years gained are taken into account, the cost-effectiveness ratio would increase to approximately €7,300 per life year gained, which means an increase of 171%. If only the unrelated health care costs in the postponed last year of life are taken into account, the cost-effectiveness ratio would increase to approximately €3,200 per life year gained, which is an increase of 20%. The effect would have been smaller if screening prevented death at younger ages, while a larger increase would occur if age at prevented death would have been higher.

**Table 5.1.2** | Increase in costs per life year gained when taking into account unrelated health care costs in life years gained, by sex and age at which death is prevented (discounted at 0% and 3%).

Age at prevented death	0% discounting		3% discounting	
	Men	Women	Men	Women
50–54	€ 3,280	€ 3,370	€ 3,120	€ 3,190
55–59	€ 3,650	€ 3,710	€ 4,150	€ 3,880
60–64	€ 4,140	€ 4,140	€ 4,040	€ 4,400
65–69	€ 4,750	€ 4,640	€ 4,640	€ 4,580
70–74	€ 5,370	€ 5,150	€ 5,170	€ 5,070
Mean	€ 4,110	€ 4,100	€ 4,100	€ 4,040

### 5.1.5 | Discussion

We demonstrated that the health care costs in the last year of life are higher than the mean yearly health care costs and that the former costs decrease with age, whereas the latter increase with age. The costs in the last year of life are higher for individuals who die from cancer than for those who die from any cause. If we take medical costs in the

postponed last year of life into account, costs per life year gained increase between €360 and €890, depending on age and gender. These higher costs occur because in traditional cost-effectiveness calculations the savings of prevented cure and care are overestimated, since the costs of dying are only postponed rather than avoided. If, instead, we take unrelated health care costs in all life years gained into account, the costs per life year gained increase between €3,100 and €5,200. This effect increases with age at which death is prevented by screening.

The specification of which costs to include in the analysis depends on the perspective of the economic evaluation.<sup>219</sup> Unrelated health care costs in gained life years need to be included from the health services' perspective. From the societal perspective, however, all costs and effects resulted from the intervention need to be considered. Therefore, if medical costs in life years gained are included in the evaluation, non-medical costs in life years gained and productivity gains should also be included. However, because of practical concerns, e.g. lack of data, and unresolved theoretical issues surrounding the inclusion of costs in added life years, researchers often do not include these costs. Thereby, researchers can choose to neglect unrelated health care costs in gained life years, since the guidelines for economic evaluations are not explicit on the inclusion of these costs. Since costs related to death can be regarded as a correction of the savings, because they are not prevented but only postponed by prevention,<sup>223</sup> they can be included from the health services' perspective, as well as from the societal perspective.

The impact of including the unrelated health care costs in the last year of life was limited, because prevention of cancer death on average replaces a rather expensive last year of life of relatively young individuals with a less costly last year of life at a higher age. The fact that the last year of life of individuals who die of cancer is relatively expensive was also found by studies from the United States<sup>229-231</sup> and from Australia.<sup>232</sup> That unrelated health care costs in the last year of life are higher for cancer patients than for other decedents can be explained by intensive and more expensive treatment. Furthermore the group of other decedents includes a substantial fraction of 'sudden death', among others by myocardial infarctions, strokes and accidents.<sup>233</sup> Given the higher costs of cancer deaths and because health care costs related to death decrease with age, simply shifting the costs related to a prevented cancer death to the future will underestimate the total costs of the intervention. Discounting of future costs reduces the impact on the cost-effectiveness ratio of including the postponed costs even further. On the other hand, if age-related disutility during added life years is considered, the impact on the cost-effectiveness ratio (costs per Quality Adjusted Life Year gained) would

increase, since added life years are lived at older ages, and the quality of these life years is relatively less.

Since the cost-effectiveness ratio of cancer screening increases when unrelated health care costs in the postponed last year of life or in all life years gained are taken into account, including these costs in the cost-effectiveness analyses may have impact on the policy decisions about a particular screening program, also because the optimal (from a cost-effective point of view) screen policy may change. On the other hand, if these costs are included for e.g. the current breast cancer screening program in the Netherlands, the costs per life year gained still are acceptable according the Dutch threshold value of about €20,000 per quality adjusted life year gained. The cost-effectiveness ratio (without including costs in the last year of life or in life years gained) of other cancer screening programmes in the Netherlands, such as cervical cancer screening (€9,500 per life year gained<sup>142</sup>), and Faecal Occult Blood Test based colorectal cancer screening (€15,000 per life year gained<sup>234</sup>), also remain under the acceptability threshold. The increase in cost-effectiveness ratio for colorectal cancer screening will be higher than the increase in cost-effectiveness ratio for cervical cancer screening, because the average age at which death is prevented is higher for colorectal cancer screening than for cervical cancer screening (Table 5.1.1, 5.1.2).

By including unrelated health care costs in the last year of life, as well as in life years gained, the cost-effectiveness ratio of prevention of lethal illnesses can become less favourable compared to prevention of non-lethal illnesses. Vaccination during childhood against, for example, mumps and rubella, prevents a lot of severe disabilities, but in developed countries individuals rarely die of those diseases in absence of vaccination. As a consequence, there are no health care costs related to postponed death or in life years gained in this situation. Therefore the cost-effectiveness ratio of prevention of these non-lethal illnesses will not change.

Bonneux et al.<sup>235</sup> showed that elimination of fatal diseases, such as cancer, significantly increases the life time expected health care costs. They found that elimination of cancer will increase the health care costs with €2,300 (£912 in 1988) and €3,000 (£1,190 in 1988) per life year gained for men and women, respectively. The difference between these results and our estimated increase in costs per life year gained when taking into account health care costs in life years gained, is explained by the fact that health care costs have increased in the last twenty years.<sup>236</sup>

In de meantime, when cost-effectiveness analyses are used for policy decisions it is important that any type of costs are either consistently excluded or consistently included.<sup>237</sup>

### 5.1.5.1 | Strengths and weaknesses

A strength of our study is that we linked health care costs to the official mortality register on the individual level, and were therefore able to analyse cost differences per cause of death. Also, we included all medical care costs, whereas most other studies focus on hospital care only. Thereby, due to the fact that the government heavily regulates the Dutch health care system, the claims on the health insurance are very comparable to the actual health care costs, which makes the estimation of the medical costs reliable.

A potential weakness is that we used average annual health care expenditures as an estimate of the yearly health care costs of individuals whose cancer death is prevented by cancer screening, whereas individuals whose cancer death is prevented may tend to have a more active health care seeking pattern. Also, there is some evidence that individuals diagnosed with cancer have an increased risk of other diseases due to the fact that the risk factor that played a role in the development of cancer can cause other diseases as well.<sup>238-239</sup> The symptoms or illnesses that generate the possible higher expenses in individuals whose cancer death is prevented are not directly related to the illness for which death was prevented, and are therefore considered as unrelated health care costs. As a consequence, the assumption that these individuals have average annual unrelated health care expenditures, may have led to a slight underestimation of the increase in costs per life year gained.

Finally, as we mentioned before, it is argued that for an evaluation from a societal perspective non-medical costs and benefits in life years gained, i.e. productivity gains, paid pensions and non-health related quality of life, need to be included in economic evaluations.<sup>240</sup> We did not take into account these issues, since they go beyond the scope of this study, but should be studied in the continuing debate on costs and benefits of prevention.

In conclusion, taking the unrelated health care costs in the postponed last year of life or during all life years gained into account in cost-effectiveness analyses will change the relative cost-effectiveness of health care programs and may influence priority settings. The cost-effectiveness ratios of cancer screening programmes will clearly increase, with approximately €4,000. However, because of the favourable cost-effectiveness ratios, including unrelated health care costs in life years gained will in general have limited policy implications.

### Acknowledgements

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## CHAPTER 5.2

# **Practical implications of differential discounting in cost-effectiveness analyses with varying numbers of cohorts**

James O'Mahony,  
Inge M.C.M. de Kok,  
Joost van Rosmalen,  
J. Dik F. Habbema,  
Werner Brouwer,  
Marjolein van Ballegooijen,

*Value Health. 2010 [In press]*



## 5.2.1 | Abstract

**Objective:** To call attention to the influence of the number of birth-cohorts used in cost-effectiveness analysis (CEA) models on incremental cost-effectiveness ratios (ICERs) under differential discounting.

**Methods:** The consequences of increasing the number of birth-cohorts are demonstrated using a CEA of cervical cancer prevention as an example. The cost-effectiveness of vaccinating 12 year old girls against the Human Papillomavirus is estimated with the MISCAN model for 1, 10, 20 and 30 birth-cohorts. Costs and health effects are discounted with equal rates of 4% and alternatively with differential rates of 4% and 1.5% respectively. The effects of increasing the number of cohorts are shown by comparing the ICERs under equal and differential discounting.

**Results:** The ICER decreases as the number of cohorts increases under differential discounting, but not under equal discounting.

**Conclusions:** The variation of ICERs with the number of cohorts under differential discounting prompts questions regarding the appropriate specification of CEA models and interpretation of their results. In particular, it raises concerns that arbitrary variation in study specification leads to arbitrary variation in results. Such variations could lead to erroneous policy decisions. These findings are relevant to CEA guidance authorities, CEA practitioners and decision makers. Our results do not imply a problem with differential discounting per se, yet they highlight the need for practical guidance for its use.



## 5.2.2 | Introduction

### 5.2.2.1 | Debate over Differential Discounting

Discounting is used in cost-effectiveness analysis (CEA) to adjust future costs and health effects to their present values and volumes. This adjustment is to account for the positive time preference for goods, including health.<sup>241</sup> While discounting in general is widely accepted in CEA and other forms of economic analysis,<sup>242</sup> whether discount rates for costs and effects should be equal has been debated extensively within health economics.<sup>242-249</sup> Equal discount rates for costs and effects are most commonly used.<sup>250</sup> Equal discounting is supported by a number of arguments, the most important of which are Weinstein and Stason's consistency thesis, Keeler and Cretin's postponing paradox and the tradability of health argument.<sup>243-244, 251</sup> Increasingly however, differential discounting is advocated, whereby health effects are discounted at a different (typically lower) rate than costs.<sup>242, 246-247, 249, 252</sup> Previous arguments for differential discounting were primarily based on the anticipation of an increasing societal value of health as income grows.<sup>247, 252-253</sup> Recent work has shown, more generally, that differential discounting is justified if the cost-effectiveness threshold is anticipated to change, where the threshold may be defined with reference to either the consumption value of health or the cost-effectiveness of displaced interventions at the margin in the context of fixed health care budgets.<sup>254</sup>

Currently, only small number of CEA authorities recommend differential discounting.<sup>255</sup> The Dutch Health Care Insurance Board (College voor Zorgverzekeringen [CVZ]) revised its recommended rates in 2006, from equal rates of 4% to differential rates of 4% and 1.5% for costs and health effects respectively.<sup>192, 252</sup> Belgium also recently adopted differential discounting at rates of 3% and 1.5% for costs and effects respectively.<sup>256</sup> The National Institute for Health and Clinical Excellence (NICE) in England and Wales used differential discounting from its inception with rates of 6% and 1.5% for costs and effects respectively, but reverted to equal discounting at 3.5% in 2004.<sup>247, 257</sup>

#### 5.2.2.2 | Modelling and Decision Rules in Cost-Effectiveness Analysis

Modelling is widely used in cost-effectiveness analysis of healthcare interventions.<sup>258</sup> Modelling can be used both to extrapolate outcomes beyond trial follow-up periods and to simulate interventions that have not or cannot be assessed using

controlled trials.<sup>241, 259-260</sup> CEA models most commonly only simulate one cohort of individuals.<sup>261</sup> A multiple-cohort modelling approach is more appropriate in some cases, such as where risk factors change over time, leading to cohort effects; where the effects of a disease are dynamic, such as in infectious diseases; or, where both prevalent and incident cohorts need to be considered.<sup>194, 261-263</sup>

Decision making using CEA relies on comparisons between analyses to determine which interventions are cost-effective. In theory, interventions can be ranked by their incremental cost-effectiveness ratios (ICERs) and accepted in order of cost-effectiveness until the budget constraint is reached.<sup>264</sup> In practice, it is more typical to accept interventions with ICERs below a given threshold as cost-effective.<sup>244</sup> Both decision rules compare interventions' ICERs, either directly in the case of the ranking rule, or indirectly through the threshold.

### **5.2.2.3 | Overview**

We compare the results of single-cohort and multiple-cohort CEAs of the same intervention to quantify the consequences of alternative numbers of cohorts (henceforth CEA specification) under differential discounting. We show, using a CEA of vaccination against the Human Papillomavirus (HPV) as an illustrative example, that the ICER falls as more cohorts are included in the analysis under differential discounting, but remains constant under equal discounting. Recent work by Hoyle and Anderson also notes that increasing the number of cohorts reduces ICERS under differential discounting.<sup>261</sup> We address this particular issue in greater depth and consider its significance for CEA practice and healthcare decision making. In this paper, we take no normative stance for or against differential discounting, however, we consider its consequences from the perspective of equal discounting being the policy norm in most countries to date. Most previous studies of differential discounting have addressed its theoretical merits; our study adds to the literature by explicitly considering the practical consequences of differential discounting for decision making using CEA.

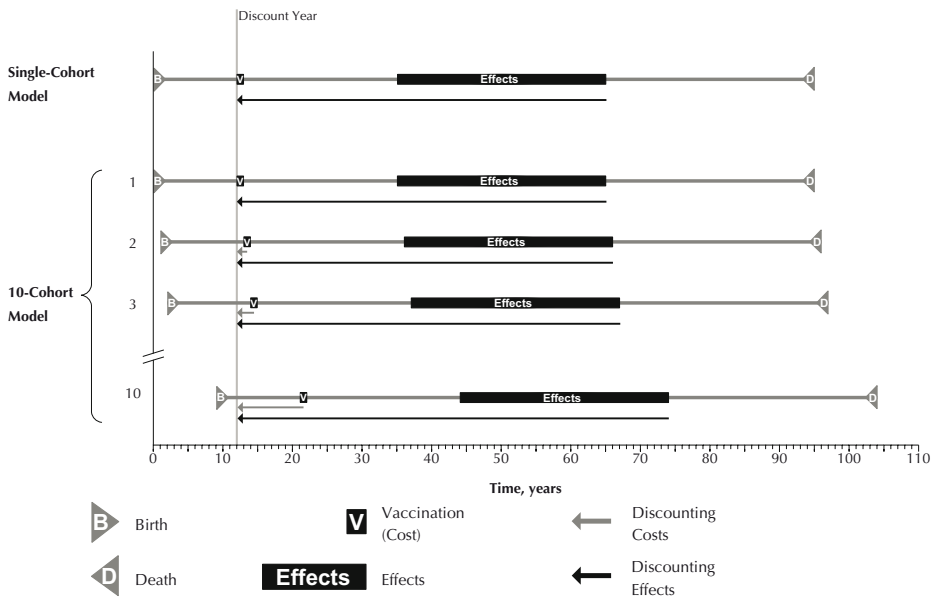
### **5.2.3 | Material and Methods**

We examine how an intervention's ICER changes as the number of cohorts in a CEA model increases. We use the example of the MISCAN microsimulation screening analysis model of HPV vaccination in the Netherlands used in a recently published

CEA.<sup>203</sup> Further detail of the model specification and assumptions can be found in that publication. The model simulates the individual life histories of one or more birth-year cohorts of women, who, in the absence of either screening or vaccination, acquire a HPV infection at a certain rate, some develop a pre-invasive lesion and/or cancer, of whom a proportion die from the disease. This results in an age and calendar time-specific output of disease incidence and mortality. The simulation is repeated, now including screening both with and without vaccination. Screening is simulated as the current Dutch programme: 7 screens between the ages of 30–60 at 5 year intervals. Vaccination is administered at age 12. These interventions change some of the life histories, either by preventing disease or detecting and treating it earlier, resulting in improved health states, longer life and reduced treatment costs. Treatment costs and quality of life adjustments are then applied to these consequences to estimate the intervention's treatment cost savings and quality-adjusted life year (QALY) gains. The difference between the total net discounted costs and health effects of screening alone and screening and vaccination combined is used to calculate the incremental cost-effectiveness of HPV vaccination.

A number of additional simplifying assumptions are made in the present study: the undiscounted costs and effects are the same for every cohort; no booster vaccination is required; and, there are no start-up or fixed programme costs. A large number of women (1 billion) are simulated in each model to minimise differences due to random error. Each cohort in the multi-cohort models contains an equal proportion of the total number of individuals.

The ICER of HPV vaccination from a single-cohort analysis is compared to ICERs from analyses with 10, 20 and 30 cohorts. The analyses differ only in the number of cohorts used; all else is held constant. Each cohort is defined by its birth year and each receives the vaccination one year after the preceding cohort. Figure 5.2.1 depicts a single-cohort and a 10-cohort model. Costs and effects are discounted by 4% and 1.5% respectively and also by a common rate of 4%. Costs and effects are discounted to the year the first cohort is vaccinated.



**Figure 5.2.1** | Comparison of discounting of cost and effects between a single-cohort model and a multi-cohort model with 10-cohorts.

### 5.2.4 | Results

Table 5.2.1 presents the results of the single and multi-cohort models under equal and differential discounting. The table reports the discounted incremental costs and effects and the corresponding ICERs in each of the models and discount rate assumptions. The table also reports the ICERs of the multi-cohort models as a percentage of that of the single-cohort model.

The ICERs are significantly lower under differential discounting compared to equal discounting. This is due to the lower discounting of health effects; consequently the discounted effects are larger while the discounted costs remain the same, resulting in lower ICERs.

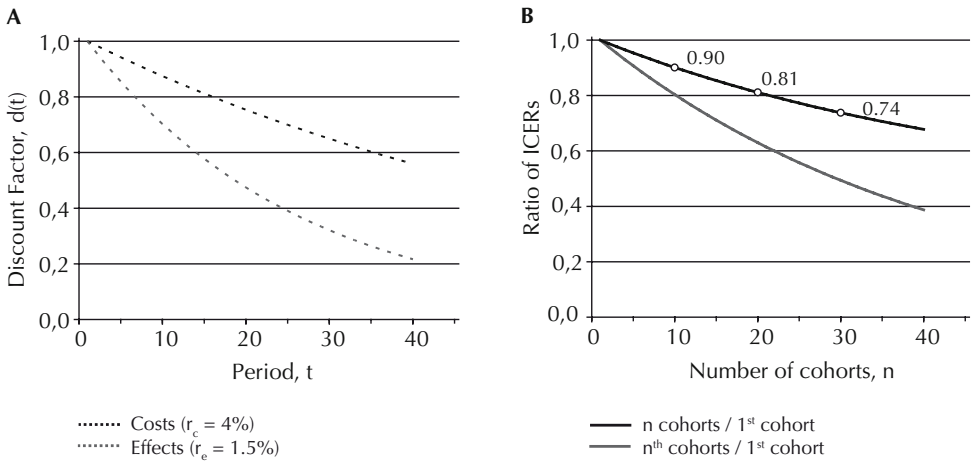
**Table 5.2.1** | Incremental costs, incremental health effects, ICER of adding vaccination against the Human Papillomavirus 16/18 to the current screening programme in the Netherlands, a comparison of a single cohort and multiple cohort models with 10, 20 and 30 cohorts under equal discounting of 4% for costs and effects and differential discounting of 4% and 1.5% for costs and effects respectively.

	Equal Discount rates: 4% & 4%			Differential discount rates: 4% & 1.5%				
	Single Cohort	10 Cohorts	20 Cohorts	30 Cohorts	Single Cohort	10 Cohorts	20 Cohorts	30 Cohorts
Incremental costs, €M	324,423	273,662	229,268	194,470	324,423	273,662	229,268	194,470
Incremental effects, QALYs (000s)	3,190	2,690	2,254	1,912	10,839	10,146	9,444	8,809
ICER, €/QALY	101,700	101,700	101,700	101,700	29,900	27,000	24,300	22,100
Ratio of ICERs, multiple/single cohort	reference	100%	100%	100%	reference	90%	81%	74%

QALY=quality-adjusted life-year; ICER= incremental cost-effectiveness ratio.

The important result, however, is the variation in ICERs between models with different numbers of cohorts. The ICERs do not vary significantly with the number of cohorts under equal discounting; the small differences in costs and effects are due to random variation in the simulation model. Conversely, with differential discounting the ICERs are considerably lower in the multi-cohort models and fall as the number of cohorts increases. The magnitude of the differences is large: the 10-cohort model has an ICER that is approximately 90% of the single-cohort model's ratio; the 30-cohort model has an ICER that is approximately 74% of the single-cohort model's ratio.

Panel A of Figure 5.2.2 shows the annual discount factors for the current Dutch discount rates for cost and effects of 4% and 1.5 % respectively, where  $t=1$  is the discount year. The grey line in panel B shows the ratios of ICERs of the  $n^{\text{th}}$  future cohort relative to the 1<sup>st</sup> cohort at the discount year, where each cohort is  $n-1$  years from the discount year and undiscounted costs and effects are equal for all cohorts. This line is also the ratio of the discount factors shown in panel A. The black line in panel B represents the ratio of ICERs of a multi-cohort model with  $n$  cohorts relative to a model of a single cohort at the discount year, with the points labelled for models with  $n = 10, 20$  and  $30$  cohorts.



**Figure 5.2.2** | (A) Annual discount factors over time under discount rates of 4% and 1.5% for costs and effects respectively; (B) ratio of ICERs of the  $n^{\text{th}}$  single cohort relative to the 1<sup>st</sup> single cohort at the discount year and the ratio of ICERs of a multi cohort model with  $n$  cohorts relative to the 1<sup>st</sup> single cohort under simplifying assumptions

## 5.2.5 | Discussion

### 5.2.5.1 | Explanation

Our results are easily explained by considering the differences between equal and differential discounting. Under equal discounting, varying the length of time between the discount year and the intervention (and its effects) does not influence the ICER, because although the present value of costs and effects change, they vary proportionately. It is in this respect that Lipscomb et al. describe CEA as “time neutral” under equal discounting.<sup>265</sup> CEA is not “time neutral” under differential discounting. Increasing the length of time between the intervention and the discount year causes the present value of effects to fall less than proportionally to the reduction in the present value of costs, resulting in a lower ICER. Consequently, both shifting a single cohort to a later period relative to the discount year and adding later cohorts to a CEA will not cause the ICER to fall under equal discounting, but will under differential discounting. Our analysis demonstrates the second of these two effects.

We have highlighted the consequences of a lower discount rate on health effects, which is appropriate if the threshold is growing, as the discount differential should approximate the annual growth rate of the threshold.<sup>254</sup> However, the threshold may not necessarily grow over time, even with an expanding health care budget, but may be static or fall.<sup>266</sup> A falling threshold would imply a larger discount rate for health than costs,<sup>267</sup> resulting in increasing ICERs as more cohorts are included.

### 5.2.5.2 | Relevance for Practice and Policy

The analysis shows how the number of cohorts used in CEA can influence ICERs. To understand the practical significance of this result we have to consider current CEA practice. The current understanding of appropriate CEA model specification most likely does not account for the influence of varying numbers of cohorts. Consequently, without clear guidance on the matter, CEA practitioners are likely to continue specifying studies with the minimum number of cohorts they consider necessary; because interventions differ in their modelling requirements, this will continue to result in the variety of models specifications evident in reviews of modelling methodologies.<sup>194, 268-269</sup>

The concern is that arbitrary variation in CEA specifications leads to results which, in part, vary arbitrarily too. A related concern is that CEAs may be deliberately specified with large numbers of cohorts or large lags between the discount year and the start of the intervention to achieve low ICERs. We have focused on the issue of multiple cohorts

rather than unnecessarily long lags between the discount year and implementation because the latter is more easily recognisable as inappropriate manipulation of the CEA. Such arbitrary or strategically chosen variations can compromise comparability between studies. As a result CEAs, may not be adequately reflecting the policy choices they are intended to inform. These concerns are compounded by the probable lack of awareness among decision makers of the influence of CEA specifications on results. Decision makers may well continue comparing ICERs directly, without taking the different model specifications into account or checking whether they adequately reflect the relevant policy choice. Such direct comparisons could lead to incorrect policy choices, whereby an intervention is deemed cost-effective as it has a lower ICER than the threshold or an alternative intervention, but where this result is due to arbitrarily or strategically chosen differences in the CEA specification, rather than the intervention's actual implementation and inherent characteristics.

Naturally, these concerns lead to a consideration of how to avoid or reduce arbitrary variations between studies. For instance, one could prescribe a base-case specification that imposes a standard number of cohorts for all CEAs. However, given the wide variation of both the characteristics and implementation of interventions, a standardised CEA specification may not adequately reflect these differences and thus result in meaningless comparisons. Therefore, if standardisation is not possible, it is not yet clear how or if CEA practice can be adapted to avoid arbitrary variation between studies. Consequently, CEAs should be evaluated on an informed, case by case basis. Accordingly, it is appropriate to demand a clear justification of the CEA specification from the CEA practitioner.

These questions of how to specify and interpret CEAs relate to doubts about the appropriateness of current CEA decision rules. A number of authors have indicated that ICERs are inappropriate for determining the optimal timing of interventions.<sup>242, 270-272</sup> Counter-intuitive results arise under both equal and differential discounting. For example, decision makers choosing the period of implementation with the lowest ICER will prefer to (infinitely) postpone implementation under differential discounting (the postponing paradox),<sup>243</sup> whereas, unrealistically, they should be indifferent between immediate implementation or infinite postponement under equal discounting. While both these results are difficult to defend, it is the postponing paradox that has generated debate in the literature. The postponing paradox has been dismissed as irrelevant to actual policy choices.<sup>246</sup> Indeed, when using a threshold based decision rule, any postponement will not be infinite, but until the ICER falls below the threshold.



While the relevance of the postponing paradox to actual policy choices is disputed, our results show that interventions modelled with a greater proportion of their implementation in the future are advantaged by lower ICERs. In this context, Cohen's questioning of the appropriateness of current decision rules to health care services that exhaust their budgets annually without saving a surplus may be relevant.<sup>271</sup> He commented that using CEA to compare interventions over multiple periods implies that cohorts compete for resources that are fungible across periods, whereas it might be more appropriate to use CEA to compare cohorts competing for resources within periods. Consequently, the debate over differential discounting and the implications for comparisons between studies may prompt a broader reconsideration of policy decision rules and the economic evaluation of healthcare

### 5.2.5.3 | Recommendations for CEA Practice

The aim of this study is to promote awareness of the effects of alternative CEA specifications under differential discounting among CEA practitioners and decision makers. We hope CEA advisory bodies will recognise the significance of the findings presented here and reflect it in their guidance, for example: (i) by requiring a justification of the CEA's specification; (ii) by providing guidance to decision makers regarding the influence of the number of cohorts included. Such clarity is important, as confusion regarding the validity of comparisons between analyses can only serve to damage CEA's credibility with decision makers and others. Note that the issues raised in this paper should not be interpreted as arguments against differential discounting; rather they should be understood as a call for greater understanding of its practical implications. CEA authorities considering adopting differential discounting should consider these practical implications in addition to the theoretical arguments. CEA practitioners and decision makers in countries already using differential discounting would benefit from recognising its implications to ensure best practice and correct policy choices.

### 5.2.5.4 | Limitations and Further Research

We emphasise that this paper does not provide a complete discussion of the methodological implications of differential discounting. Such a discussion would require a detailed review of the underlying theoretical basis for comparing interventions across different time periods with a changing threshold, which is beyond the scope of this study. This remains an important area for future research and debate; see Claxton et

al.<sup>254</sup> for further discussion. However, this paper does call attention to some important practical issues related to differential discounting that both analysts and policy makers need to be aware of when using and comparing the results of cost-effectiveness analyses in practice.

# CHAPTER 6

## **Discussion**



In this thesis we studied the health effects and cost-effectiveness of cervical cancer screening and HPV vaccination, in the Netherlands as well as internationally. We also addressed two methodological issues in cost-effectiveness analyses. In this final chapter we will first answer and discuss the research questions formulated in chapter 1, based on the results described in this thesis. Next, we will discuss future directions for cervical cancer prevention. Finally, we will formulate conclusions and recommendations.

## **6.1 | Answers to research questions**

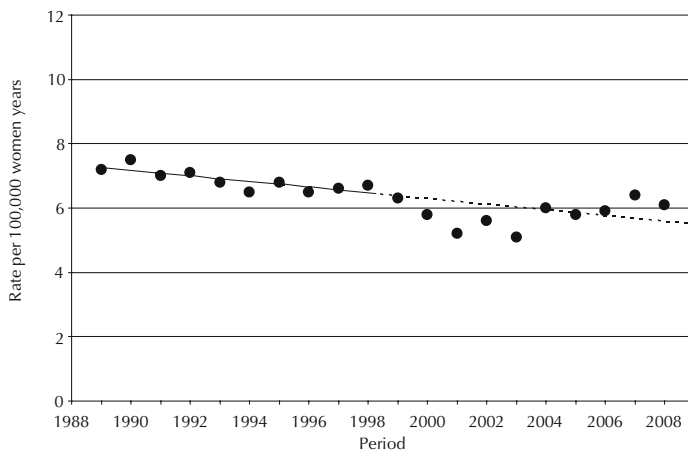
### **6.1.1 | What are the causes of the recent trends in cervical cancer in the Netherlands?**

In the Netherlands, after a period of decrease, cervical cancer incidence increased in the period 2001–2007. A possible explanation lies in a period of more frequent screening due to restructuration of the Dutch national screening programme in 1996, when the screening interval was lengthened from 3 to 5 years.

We showed that the increase in incidence is possibly a compensating increase after a period of rapid decrease of incidence between 1998 and 2001. This period of rapid decrease corresponded to a period of temporary increased intensity of the screening programme in the implementation period of the revisions of the programme between 1996 and 1998. The increase was only seen in squamous cell carcinomas (SCC), not in other morphologies, and in age group 35–59 years. This supports the hypotheses of the effect of screening since cytological screening is effective in detecting SCC and its precursors, but less in detecting other morphologies. In addition, the affected age group corresponds to the screening age group in the Netherlands (i.e. 30–60 years).

Figure 6.1 shows the trend if, without changes in the screen programme, the ongoing trend before 1998 had continued. So, if a past period of more intensive screening is the main cause for the (compensating) increase in incidence, we expect the increase to stop after 2006. Instead of a continuing decrease as presented by the trend line in figure 6.1, it is more likely that the trend in incidence will level off as a result from levelling off of the screen effect. If the increase continues there probably is another important factor that plays a role. One possibility is an increase in the cervical cancer background risk due to changes in HPV infections and other risk factors. The age at first intercourse in

the Netherlands is decreasing,<sup>82</sup> and the percentage of women with more than 5 sexual partners in a lifetime increased from 14% in 1991 to 37% in 2006.<sup>83</sup> These sexual habits can result in an increase in HPV infection rate. Longitudinal data on HPV infections are lacking, but with the increased use of HPV testing in the general population, these data will become available in the future. This can give a lot of information on the expected trend in cervical cancer in the future. Finally, another possibility is that the effect of a longer screening interval as implemented in 1996, even with a broader age range, is less favourable than anticipated.



**Figure 6.1** | Total age-adjusted incidence rates (European Standardised Rates) of cervical cancer in the Netherlands, 1989–2008. Line represents the trend line for the period 1989–1998.

Cervical cancer mortality overall decreased during 1970–2007, though more rapidly during the period 1970–1994 than 1994–2007. Meanwhile, the trend in mortality follows the trend in incidence: data show that an increase or decrease in incidence is followed by an increase or decrease in mortality one year later. Indeed, Dutch mortality increased, although not significant. If the recent increase in incidence would continue, a significant increase in mortality is to be expected.

Based on these findings, it seems that a more intensive cervical cancer screening programme with shorter intervals is favourable. However, the benefits have to be balanced with the extra loss of quality of life resulting from false positive screen results

and overtreatment, as well as the costs, due to the extra number of programme smears in cohorts of women that are already screened.

### **6.1.2 | Do trends in cervical cancer warrant a change of the starting age of 30 years in the Netherlands?**

No increase in incidence and mortality rates for cervical cancer below age 30 could be found, so this gives no reason to lower the starting age for cervical cancer screening.

Over the last decades the number of cervical cancer cases and deaths under the age of 30 years is stable and low; <20 cases and <5 death per year.<sup>63</sup> We also did not see an increase in mortality in age group 30-34 years. This, however, does not prove that the background risk in young women did not increase, since there was also an increase in screening in this age group. But it does also not give a reason to lower the starting age.

The dilemma with screening in young women is that the detection rate of harmless preinvasive lesions is high. This results in overtreatment and anxiety. This is particularly true when women are primarily screened with the HPV DNA test, because many young women are infected with harmless HPV infections. So, it is hard to keep a good balance between the harms and benefits of cervical cancer screening in young women. Changes in background risk or prevention can already lead to imbalance. This means that close monitoring of cervical cancer in the young age groups remains important and that screen ages need to be reconsidered periodically.

### **6.1.3 | When will liquid-based cytology be a cost-effective alternative for conventional cytology in the Netherlands?**

In the Dutch situation, liquid-based cytology is not cost-effective. It can only become cost-effective if it is at most €3.30 (instead of €11.70) more expensive than the conventional Pap test, if its sensitivity increases with 15%, if the quality of life for women while being in triage (period with repeat testing) is extremely poor, or if screening with conventional cytology results in more than 16% inadequate smears.

A large Dutch randomized controlled trial that evaluated the performance of liquid-based cytology (LBC) indicated that LBC does not perform better than conventional pap (CP) screening in terms of relative sensitivity and positive predictive values for detection

of cervical cancer precursors.<sup>132</sup> We showed that one way to compensate for the higher costs of LBC would be a 15% higher sensitivity (i.e. 15% less lesions in (pre-)invasive stages are missed). Although LBC produced fewer inadequate smears than CP,<sup>132</sup> this had only a small benefit in the Dutch situation where CP already had a low rate of inadequate smears (1%).<sup>6</sup> We found that LBC would become a cost-effective alternative if CP resulted in 16% inadequate smears. The advantage that with LBC triage HPV tests can be performed on the same material does have a favourable influence on its cost-effectiveness. The reason is the loss in quality of life in the period of repeat testing after a positive CP. However this impact is small, and the loss of quality life for women who need a repeat smear for the HPV test after a positive CP test needs to be extremely high (i.e. equal to living with advanced cancer) to compensate for the higher costs of LBC. LBC €11.70 more expensive than CP, due to higher material, logistic and personnel costs. We showed that given the small advantages for LBC compared to CP, LBC should be at most €3.30 more expensive than CP to become cost-effective. If we would also consider primary HPV screening the conclusion on the cost-effectiveness of cytology screening would be different (See answer question 6.1.4).

LBC was already allowed according to the Dutch national programme guidelines and is currently used in several institutions.<sup>138</sup> It was introduced without evidence for its cost-effectiveness. So apparently there are other arguments than cost-effectiveness to substitute CP by LBC. One argument, for example, is that the majority of cytotechnologists prefer LBC because samples are easier to read. One could question how to incorporate this issue in a cost-effectiveness analysis. It is in fact related to feasibility, and questions to what extent conventional cytology will remain a realistic alternative.

The development of technologies to evaluate cervical smears fortunately does not stop. One technology that has been under development for some decades now is automated image analysis. This involves the translation of a cervical smear into a computerised image, which is then analysed by the computer to identify areas on slides with cells likely to be abnormal. The most abnormal views are selected in a file for review. The location of these views on the slide is automatically recorded to facilitate an additional review with the microscope. The current automated systems only work in conjunction with LBC, so if we want to use computer automated screening in the future, LBC is necessary. However, the value of automated screening, and how to integrate them in the screening protocol, is still under evaluation. So far the evidence suggests that automated image analysis is equivalent in test performance to manual screening.<sup>273</sup> The older systems with CP also were not associated with improved test performance.

### 6.1.4 | In which European countries is primary HPV screening preferred above primary cytology screening?

Primary HPV screening is cost-effective in most European countries, but is only recommended in women over the age of 30 years, because of the high prevalence of harmless HPV infections in young women. Primary cytology screening is preferred in countries with low costs of cytology or high prevalence of HPV in combination with high costs per HPV test.

The benefits and risks of HPV testing compared with cytological screening depend both on the primary tests and on the subsequent triage procedures. Our analyses have shown that the optimal screening strategy is primary HPV screening with cytology triage in many situations. A disadvantage of primary HPV screening is however, that HPV testing is associated with increased burden and costs due to follow up of women detected with harmless infections and treatment of lesions of which many would have regressed. As a result, the cost-effectiveness results are sensitive to the loss of utility associated with a triage episode. We found that if the utility loss associated a half year of triage was 7 instead of 2 days (as we assumed), primary cytological screening can become more cost-effective than primary HPV testing.

The disadvantage of primary HPV screening of detecting many harmless HPV infections is much more pronounced in young women. These infections usually clear spontaneously, so their detection carries a risk of too many psychological distress, colposcopies, and over-treatment. Thus, it is essential that HPV testing-based screening is introduced in women older than 30 years of age, within an organised programme with ongoing process performance evaluation rather than in an opportunistic setting. Whether this is feasible is a question that has to be answered for each country separately. If not, HPV screening might not be the best option. For women aged 35 or more, the HPV positivity rate is generally much lower than for younger women and the potential value of HPV DNA testing as a substitute of cytology in this group is substantially better than for younger women.<sup>274</sup>

The key public health challenge is to find a short triage procedure for women who test positive for HPV at primary screening, with few referrals that is still safe. In our analysis cytology was the follow up test, sometimes in combination with HPV testing. However, their smears could be genotyped. Genotyping in HPV positive women can distinguish HPV16 and HPV18 infections that seem to warrant more aggressive clinical management than other hrHPV types. So, using HPV genotyping may increase the specificity of HPV DNA testing thereby reducing referrals for colposcopies and



treatment. However, it increases the number of triage tests, since women with other HPV types than HPV16 and 18 are staying in triage. The value of genotyping is currently under evaluation in several ongoing trials.<sup>275</sup>

A major problem of the current cervical screening programmes still is lack of attendance. Non-participating women are at increased risk of cervical cancer independent from not being protected by screening. Offering self sampling to non-attendees of cervicovaginal material for HPV DNA screening has been suggested as a way of increasing screening coverage. Large cohort studies showed that high risk HPV testing on self collected cervicovaginal samples had good sensitivity for cervical intraepithelial neoplasia (CIN) 2+ and that it is a feasible and effective method of increasing coverage in a screening programme. The coverage indeed increased due to the self-test. A disadvantage of the self test can be that women will not attend regular screening anymore and wait for the self-test, while it is not yet known whether the self test is as good as the screentest used in the organised programme.

### 6.1.5 | Is human papillomavirus vaccination cost-effective in the Netherlands?

In countries with a low cervical cancer incidence and mortality like the Netherlands, HPV vaccination is not cost-effective if the 'over-the-counter' vaccine price in 2009 (approximately €360) has to be paid.

We also analysed the impact on the effects, costs and cost-effectiveness ratio (CER) of vaccination if the effect of HPV vaccination on other HPV related cancers is included. For the Netherlands, if the other HPV16/18-related cancers are maximally prevented in women, the effect is estimated at a 14% increase in life years gained, an 18% increase in savings, and thus a 13% decrease in the CER. If vaccination prevents HPV-related cancers in both men and women, these figures increase to 25%, 26% and 21%, respectively. However, the CER of HPV vaccination in the Netherlands, without accounting for the effect on the non-cervical HPV-related cancers, is under favourable assumptions estimated at approximately €50,000 per Quality Adjusted Life Year (QALY) gained. Thus, even if the effect on all HPV-related cancers is taken into account, HPV vaccination at the considered over the counter price would still not be cost-effective considering the Dutch cost-effectiveness threshold of €20,000 per QALY gained.

Meanwhile, the price per dose as negotiated for the Swedish national vaccination programme has been as low as €22 for the bivalent and €33 for the quadrivalent vaccine.<sup>276</sup> This price is lower than the estimated threshold price per vaccine dose to be cost effective considering a cost-effectiveness threshold value of €20,000. Only if

4 additional boosters are necessary to maintain lifelong protection, or if the cervical cancer risk is half the risk in the Netherlands, the price per dose should be lower than €22 for vaccination to be cost-effective. The price of vaccines may even drop further. This means that vaccination will be cost-effective in most countries. The only reasons left not to vaccinate one could think of are negative effects of vaccination that are not completely ruled out (yet), like a possible negative impact on screening participation<sup>183</sup> and long term negative side effects on health.

For the effectiveness of vaccination, an important issue is herd immunity. Herd immunity implies a reduced exposure to HPV in the population and therefore determines the effects of vaccination in unvaccinated women and, if relevant, in vaccinated women after the effectiveness of vaccination waned. So, additional prevention of cervical cancer via herd immunity induces extra effects without extra costs. The CER will be affected most favourably with participation rates that have the highest impact via herd immunity. This is typically not the situation with high participation rates and long lasting efficacy, when almost all women are already protected directly through vaccination. But it is also not necessarily the situation with low participation rates, when there is little herd immunity. The extra effect of herd immunity will be highest at some intermediate participation level. Taira et al.<sup>46</sup> found that this was the case at a participation rate of about 50%.<sup>46</sup> We did not include herd immunity in our analysis, while participation to vaccination in the Netherlands is currently about 50%. The estimate for the herd immunity effect depends on estimates for sexual behaviour, viral transmissibility, infection-induced resistance against re-infection, and lengths of transmissible infection. All these estimates have a considerable range of uncertainty and sensitivity analyses are important here.

### **6.1.6 | How influential are health care costs in gained life years on the cost-effectiveness of cancer screening?**

If all health care costs in gained life years are taken into account, compared to considering only the costs related to the disease targeted by the intervention, the cost-effectiveness ratios of cancer screening programmes will clearly increase, with approximately €4,000 per life year gained. If only health care costs in the postponed last year of life are additionally taken into account, the cost-effectiveness ratios of cancer screening programmes increase with approximately €700 per life year gained for men and €500 per life year gained for women.

Taking the unrelated health care costs in life years gained into account in cost-effectiveness analyses will change the relative cost-effectiveness of health care programs and may influence priority settings. For example, the cost-effectiveness ratio (CER) of prevention of lethal illnesses can become less favourable compared to prevention of non-lethal illnesses. This is because there are no health care costs related to postponed death or in life years gained if we prevent non-lethal illnesses. Therefore the CER of prevention of these non-lethal illnesses will not change. Also, because costs are dependent of age, the ranking of CERs can change according to the age groups most affected by the interventions. In theory, the specification of which costs to include in the analysis depends on the perspective of the economic evaluation.<sup>219</sup> Nevertheless, there is a longstanding controversy about whether future resource use includes costs for diseases unrelated to the intervention in question, which occur during added years of life. Adherents argue that insofar as health care expenditures rise when people live longer, the true costs of the intervention exceeds the simple expenditures for treatment. According to the alternative view, however, health care is but one of the many costs of living longer: If medical costs in life years gained are included in the evaluation, non-medical costs in life years gained and productivity gains should also be included. In addition to this difference of opinion, there are particular difficulties (e.g. lack of data) in including costs for unrelated illness in added years of life. Therefore, and for consistency among cost-effectiveness analyses, researchers often do not include these costs at least in base case calculations.

### **6.1.7 | What are the implications of the use of differential discounting of costs and health effects for the practice of cost-effectiveness analyses?**

Under unequal discounting, the incremental cost-effectiveness ratio of an intervention decreases as the time between the discount year and the year of the intervention increases. So, the use of unequal discount rates for costs and effects leads to confusing and incomparable cost-effectiveness results. This is not the case under the use of equal discount rates.

We showed that under differential discounting the incremental cost-effectiveness ratio (ICER) of an intervention decreases as the number of cohorts in the analyses increases (i.e. the time between the discount year and the year of the intervention increases). We also showed that this is not the case under equal discounting. The variation of ICERs with the number of cohorts under differential discounting prompts questions

regarding the appropriate number of cohorts for cost-effectiveness analyses (CEA) and interpretation of their results. In particular, it raises concerns that arbitrary variation in study specification leads to arbitrary variation in results. Such variations could lead to erroneous policy decisions.

These concerns lead to a consideration of how to avoid or reduce arbitrary variations between studies. A standardised CEA specification may not adequately reflect the wide variation of the characteristics of interventions. Thereby, there are often no criteria to assign a particular methodological assumption as the right one. Currently, CEA advisory bodies do not reflect the significance of the findings presented here in their guidance. Therefore, it is not yet clear how (or if) CEA practice can be adapted to avoid arbitrary variation between studies when using differential discount rates.

Finally, interventions can be ranked by their ICERs and accepted in order of cost-effectiveness until the budget constraint is reached.<sup>264</sup> In practice, it is more typical to accept interventions with ICERs below a given threshold as cost-effective.<sup>244</sup> Since with the use of differential discount rates all ICERs become more favourable, it is the question whether the cost-effectiveness threshold needs to be changed. If the threshold will not be lowered, more interventions will turn out to be cost-effective considering the threshold. As a result, more resources will be needed to afford these interventions.

## **6.2 | The future of cervical cancer prevention**

As long as there is no perfect instrument to prevent cervical cancer, the prevention of cervical cancer is still under development. Although many countries already have an ongoing screening programme and/or vaccination programme, there are still a lot of countries without any method of cervical cancer prevention. In addition, these are often the countries with the highest burden of disease. Not only due to the lack of prevention, but also because these are typically countries with a high cervical cancer risk. For these countries it is important that in the future some way of cervical cancer prevention will be available. For the western countries, such as the Netherlands, new and better preventative methods are also still under development. Some of these interventions were discussed in this thesis. In continuation, several important issues need to be solved in the coming years:

### 6.2.1 | Screening of vaccinated girls

As routine cervical cancer vaccination is taken into account in several countries, vaccinated women will be invited to attend cervical cancer screening in the near future. To reduce overdiagnosis and inefficient screening guidelines in vaccinated women, the screening guidelines need to be changed for the vaccinated groups in the population. Guidelines may differ in which test is used (HPV-DNA test, conventional cytology screening, and/or thin layer cytology) and at what ages women are screened. We need to know what, from a cost-effectiveness point of view, the optimal screening policy for cervical cancer is in unvaccinated versus vaccinated women.

Another issue will be the differentiation between unvaccinated and vaccinated women in the invited for vaccination cohorts, instead of the differentiation between 'for vaccination invited' and 'not for vaccination invited' cohorts. If there is a good registration of vaccinated women, one might consider a different screening programme for vaccinated women than for unvaccinated women. It is, however, the question whether this is feasible and ethical to do.

### 6.2.2 | Vaccination of boys

Male HPV infection is an important concern, both for the disease burden in men and for the risk of transmission to women. HPV is associated with a variety of cancers in men, including anal cancer and a subset of penile and oral cancers. Other HPV-related diseases of clinical importance in men include condylomata acuminata (genital warts) and recurrent respiratory papillomatosis. The protective efficacy of HPV vaccination in men has not yet been fully established. However, there may be a rationale for vaccinating boys. The cost-effectiveness of vaccination of boys needs to be examined. Moreover, if the price per dose will become as low as negotiated for the Swedish national vaccination programme (€22 for the bivalent and €33 for the quadrivalent vaccine) vaccination of boys might be cost-effective. On the other hand, if the participation rate in girls is high, the effect of herd immunity will be high in boys as well, and the additional effect of vaccinating boys might be limited.

### 6.2.3 | Estimating costs and effects of new screening strategies

In the discussion of the chapters and of this thesis we have mentioned some new screening strategies that have been developed, but were not evaluated in this thesis. For

example, cervical smears can be genotyped, self sampling tests can be used for HPV DNA screening and a cervical smear can be translated into a computerised image for automated image analysis. In the future, we need to estimate whether these interventions are effective and costs-effective strategies to prevent cervical cancer.

#### **6.2.4 | Monitoring**

In the Netherlands, several new strategies were implemented to prevent cervical cancer. First, new screening protocols and guidelines were implemented in 1996, which still have consequences for the current cervical cancer incidence and mortality rates. Second, HPV vaccination was introduced in the Dutch National Immunisation Programme in 2009. Third, HPV tests for the follow up of cytological positive women are increasingly used. Fourth, primary HPV screening will possibly be introduced. In addition, we showed that cervical cancer incidence increased recently. So the prevention of cervical cancer is a dynamic process. Therefore, monitoring of cervical cancer remains important in the future.

### **6.3 | Conclusions**

- In the Netherlands, cervical cancer prevention programmes are successful and the disease is not a major public health problem anymore in terms of incidence and mortality.
- In recent years, an increase in cervical cancer incidence was seen, after a period of sharp decrease in incidence.
- In a country with high quality of conventional cytology, with few inadequate smears, liquid based cytology can only become a cost-effective alternative if the costs are reduced considerably.
- Primary HPV screening over the age of 30 is cost-effective in most European situations. Only in situations where the prevalence of HPV infections and the costs of the HPV test are high, primary cytology screening with HPV triage is recommended.
- The application of differential discount rates in cost-effectiveness analyses is not obvious and has major consequences for cost-effectiveness results of preventive interventions.
- Monitoring of cervical cancer incidence and mortality remains important.

## 6.4 | Recommendations

- Cervical cancer incidence should be monitored closely
- Primary HPV screening can be implemented in the Netherlands. Samples should be evaluated in large laboratories for good quality assurance and low costs.
- Primary HPV screening should be only considered over the age of 30 years, in countries with a low prevalence of HPV infections.
- In the Netherlands, liquid based cytology should not have a higher reimbursement rate than conventional cytology.
- It should be evaluated what the optimal screening program in vaccinated women will be.
- Guidelines for the implementation of differential discount rates should be developed





## Summary

Cancer of the cervix uteri is the third most common cancer among women worldwide. The incidence and mortality in the Netherlands, however, are very low, partly because of an effective screening programme. Next to the well-known conventional Pap smear, other medical interventions are available and have been developed more recently to prevent death from cervical cancer. This is, amongst others, liquid-based cytology, HPV DNA screening, and HPV vaccination. This thesis presents health effects and cost-effectiveness of cervical cancer screening and HPV vaccination, in the Netherlands as well as internationally.

In the Netherlands, cervical cancer mortality has steadily declined over the last decades, while cervical cancer incidence recently increased after a period of decrease. In **Chapter 2** we explored the possible causes of the recent observed trends in cervical cancer in the Netherlands. To do so, we analysed the incidence and mortality by age, stage and morphology, and linked the observed trends to screening activities. We found that a possible explanation for the increase in incidence lies in a period of intensive screening during the transition period of the Dutch national screening programme from a 3 to a 5 years interval starting in 1996.

## Screening

In **chapter 3** we explore three different issues related to the cervical cancer screening programme. We first determined in **chapter 3.1** whether trends in cervical cancer warrant a change of the starting age of the screening programme. We found no increase in incidence and mortality rates for cervical cancer in the age groups under age 30. Therefore we concluded that the cancer trends give no reason to lower the starting age for cervical cancer screening.

Furthermore, in **chapter 3.2** we found that liquid-based cytology (LBC) is not a cost-effective alternative for conventional Pap screening, in the current Dutch screening situation. Advantages of LBC are 1) suitability for HPV testing on the same material and 2) reduced rate of unsatisfactory specimens. Given these advantages, we found that LBC (only in combination with HPV testing as follow up test) will become a cost-effective alternative in the Netherlands if the price decreases, if the sensitivity of the test increases, if the loss of quality of life for women while being in triage is extremely high, or if screening with conventional cytology results in more inadequate smears. So,

in a country with high quality of conventional cytology with less inadequate smears as the Netherlands, implementation of LBC can only be advised if the costs are reduced considerably.

Finally, we explored in which European countries primary HPV screening should be preferred above primary cytology screening in **chapter 3.3**. We found that primary HPV screening with sole cytology triage, or cytology and HPV triage, are the best strategies for many European countries. Primary cytology screening with a single HPV test in triage is preferred in countries with low costs of cytology and/or a high HPV infection rate. Primary HPV screening is never recommended in women under the age of 30 years. Furthermore, we showed that countries with a high risk of cervical cancer or a high cost-effectiveness threshold are recommended to screen more intensive than countries with a low cervical cancer risk or a low cost-effectiveness threshold.

## Vaccination

The cost-effectiveness of vaccination against HPV depends on the costs of the vaccine and incidence and mortality rates of cervical cancer. The Netherlands is a country with a low cervical cancer incidence and mortality rate. In 2009, the 'over-the-counter' vaccine price was €360 for three doses. In **chapter 4** we explored the cost-effectiveness of HPV vaccination in the Dutch situation. We found that vaccination is not cost-effective in the Netherlands, given the price that in 2009 had to be paid. Even if the effect on all HPV-related cancers (i.e. cancer of the penis, vulva/vagina, anus, oral cavity and oro-pharynx) was taken into account, HPV vaccination would still not be cost-effective considering the Dutch cost-effectiveness threshold of €20,000 per QALY gained. Currently the price of the vaccine already significantly decreased as the result of negotiations (for example €22 per dose in the Swedish national vaccination programme) and the price may even drop further. This means that anno 2011 vaccination will be cost-effective in most countries.

## Methodological issues

There is always much debate concerning the methods of cost-effectiveness analyses among analysts, readers, and policy-makers. In **chapter 5** we discussed two areas in which disagreement still persists. We first discussed in **chapter 5.1** the issue of the

application of the unrelated health care costs in life years gained by exploring how influential health care costs in gained life years are on the cost-effectiveness of cancer screening. We found that the cost-effectiveness ratios of cancer screening programmes will significantly increase. However, because of the favourable cost-effectiveness ratios of cancer screening programmes, this will in general have limited policy implications. Nevertheless, it may influence priority settings.

The second issue we discussed was the use different discount rates for costs and effects. In **chapter 5.2** we showed that the use of unequal discount rates leads to confusing and incomparable cost-effectiveness results. More specific, we showed that the incremental cost-effectiveness ratio of an intervention decreases as the number of cohorts in the analyses increases, which is not the case under equal discounting. Currently, cost-effectiveness analysis advisory bodies do not reflect the significance of these findings in their guidance.

## Conclusions

- In the Netherlands, cervical cancer prevention programmes are successful and the disease is not a major public health problem anymore in terms of incidence and mortality.
- In recent years, an increase in cervical cancer incidence was seen, after a period of sharp decrease in incidence.
- In a country with high quality of conventional cytology, with few inadequate smears, liquid based cytology can only become a cost-effective alternative if the costs are reduced considerably.
- Primary HPV screening over the age of 30 is cost-effective in most European situations. Only in situations where the prevalence of HPV infections and the costs of the HPV test are high, primary cytology screening with HPV triage is recommended.
- The application of differential discount rates for costs and effects in cost-effectiveness analyses is not obvious and has major consequences for cost-effectiveness results of preventive interventions.

## **Recommendations**

- Cervical cancer incidence should also in the future be monitored closely
- Primary HPV screening can be implemented in the Netherlands. Samples should be evaluated in large laboratories for good quality assurance and low costs.
- Primary HPV screening should be only considered over the age of 30 years.
- In the Netherlands, liquid based cytology should not have a higher reimbursement rate than conventional cytology.
- It should be evaluated what the optimal screening program in vaccinated women will be.
- Guidelines for the implementation of differential discount rates should be developed

# Samenvatting

Baarmoederhalskanker is de derde meest voorkomende kanker bij vrouwen wereldwijd. In Nederland zijn de incidentie en mortaliteit echter erg laag, mede door een effectief screeningsprogramma. Naast de bekende conventionele Pap-test zijn er de laatste jaren andere interventies om sterfte aan baarmoederhalskanker te voorkomen beschikbaar gekomen. Dit zijn onder andere dunnelaag cytologie, HPV DNA screening, en HPV vaccinatie. Dit proefschrift beschrijft de gezondheidseffecten en kosteneffectiviteit van baarmoederhalskankerscreening en HPV vaccinatie, zowel in Nederland als internationaal.

De sterfte aan baarmoederhalskanker is in Nederland de laatste decennia gestaag gedaald, terwijl de incidentie recentelijk gestegen is na een lange periode van daling. In **Hoofdstuk 2** hebben we de mogelijke oorzaken van de recentelijk in Nederland geobserveerde trends in baarmoederhalskanker onderzocht. Dit is gedaan door de incidentie en mortaliteit te analyseren naar leeftijd, stadium en morfologie van de tumor, en we hebben de geobserveerde trends gekoppeld aan de screeningsactiviteiten. We vonden dat de recente stijging in incidentie mogelijk verklaard kan worden door een periode van geïntensiverde screening tijdens de overgangsfase van het oude naar het nieuwe screeningsprogramma in 1996, toen overgegaan werd van een 3- naar een 5-jaars interval.

## Screening

In **hoofdstuk 3** hebben we drie verschillende onderwerpen gerelateerd aan het baarmoederhalskanker screeningsprogramma onderzocht. Eerst hebben we in **hoofdstuk 3.1** bepaald of de trends in baarmoederhalskanker wijzen op een aanpassing van de eerste screenleeftijd in het screeningsprogramma. We zagen geen stijging in baarmoederhalskankerincidentie en -mortaliteit in de leeftijdsgroepen onder de leeftijd van 30 jaar. We concludeerden daarom dat de kankertrends geen aanleiding geven om de screenleeftijd te verlagen.

In **hoofdstuk 3.2** hebben we vervolgens aangetoond dat in de huidige Nederlandse screening situatie, dunnelaag cytologie ('liquid-based cytology' (LBC)) geen kosteneffectief alternatief is voor de conventionele Pap-test. Voordelen van LBC zijn 1) men kan op hetzelfde materiaal een HPV bepaling uitvoeren en 2) minder uitstrijkjes zijn onbeoordeelbaar. Gegeven deze voordelen, vonden we dat LBC (in combinatie met

de HPV test als vervolgttest) in Nederland een kosteneffectief alternatief is als de prijs van LBC daalt, als de sensitiviteit van de test stijgt, als het verlies aan kwaliteit van leven voor vrouwen die in het vervolgttraject zitten extreem hoog is, of als de conventionele Pap-test resulteert in meer onbeoordeelbare uitstrijkjes. Dus, in een land waar de conventionele Pap-screening van hoge kwaliteit is met weinig onbeoordeelbare uitstrijkjes zoals in Nederland, wordt de invoering van LBC alleen geadviseerd als de kosten ervan sterk gereduceerd worden.

Als laatste hebben we in **hoofdstuk 3.3** onderzocht in welke Europese landen primaire HPV screening de voorkeur heeft boven primaire cytologische screening. We vonden dat in de meeste Europese landen primaire HPV screening met enkel cytologische vervolgttesten, of met zowel cytologische als HPV vervolgttesten, de beste strategieën zijn. In landen met lage kosten voor cytologische screening en/of een hoge HPV infectiedruk heeft primaire cytologische screening met één enkele HPV vervolgttest de voorkeur. Primaire HPV screening wordt nooit aanbevolen voor vrouwen onder de leeftijd van 30 jaar. Verder hebben we nog aangetoond dat er in landen met een hoog risico op baarmoederhalskanker of landen met een hoge kosteneffectiviteitsgrens meer intensieve screening aanbevolen kan worden dan in landen met een laag risico of een lage kosteneffectiviteitsgrens.

## Vaccinatie

De kosteneffectiviteit van de vaccinatie tegen HPV hangt af van de prijs van het vaccin en van de baarmoederhalskankerincidentie en -sterfte. Nederland is een land met een lage baarmoederhalskankerincidentie en -sterfte. In 2009 was de 'over-the-counter' vaccin prijs €360 voor drie doses. In **hoofdstuk 4** hebben we de kosteneffectiviteit van HPV vaccinatie in de Nederlandse situatie onderzocht. We vonden dat vaccinatie voor de prijs die in 2009 betaald moest worden niet kosteneffectief is in Nederland. Zelfs als het effect van vaccinatie op alle HPV-gerelateerde kankers (i.e. kanker van de penis, vulva/vagina, anus, mondholte en oropharynx) werd meegenomen was HPV vaccinatie nog niet kosteneffectief bij het gebruik van de Nederlandse kosteneffectiviteitsgrens van €20,000 per gewonnen QALY. Momenteel is de prijs van het vaccin al significant gedaald als gevolg van onderhandelingen (in het Zweedse nationale vaccinatieprogramma is er bijvoorbeeld €22 per dosis betaald) en de prijs kan zelfs nog verder dalen. Dit betekent dat vaccinatie anno 2011 in de meeste landen kosteneffectief zal zijn.

## Methodologische kwesties

Er bestaat bij onderzoekers, lezers en beleidsmakers altijd veel discussie over de methodiek van kosteneffectiviteitsanalyses. In **hoofdstuk 5** hebben we twee onderwerpen besproken waar de meningen nog steeds over verdeeld zijn. We hebben in **hoofdstuk 5.1** het meenemen van niet-gerelateerde gezondheidszorgkosten die gemaakt worden tijdens de gewonnen levensjaren besproken, door uit te zoeken welke invloed deze kosten hebben op de kosteneffectiviteit van kankerscreening. We vonden dat door het meenemen van deze kosten de kosteneffectiviteitsratio's van kankerscreening programma's significant stijgen. Echter, door de gunstige kosteneffectiviteitsratio's van de kankerscreening programma's heeft deze stijging weinig gevolgen. Het meenemen van de extra kosten kan echter wel tot gevolg hebben dat bepaald interventies een lagere prioritering krijgen dan andere interventies.

De tweede kwestie die we bediscussieerd hebben is het gebruik van ongelijke disconteringsvoeten voor kosten en effecten. In **hoofdstuk 5.2** hebben we aangetoond dat het gebruik van ongelijke disconteringsvoeten kan leiden tot verwarrende en onvergelykbare kosteneffectiviteit resultaten. We hebben laten zien dat de incrementele kosteneffectiviteitsratio van een interventie daalt als het aantal cohorten in de analyse stijgt, en dat dit niet het geval is bij het gebruik van gelijke disconteringsvoeten. Op dit moment erkennen organen die adviseren over het doen van kosteneffectiviteitsanalyses en over de kosteneffectiviteit van interventies nog niet de significantie van deze gevolgen in hun richtlijnen.

## Conclusies

- Baarmoederhalskanker preventie is succesvol in Nederland. De ziekte is geen groot volksgezondheidsprobleem meer wanneer we kijken naar de incidentie en mortaliteit.
- De laatste jaren was er in Nederland een stijging in baarmoederhalskankerincidentie, na een periode waarin we een sterke daling in incidentie zagen.
- In een land met conventionele Pap-screening van hoge kwaliteit en met weinig onbeoordeelbare uitstrijkjes, zal dunnelaag cytologie alleen een kosteneffectief alternatief zijn wanneer de kosten ervan sterk gereduceerd worden.
- In de meeste Europese landen is primaire HPV screening kosteneffectief voor vrouwen boven de 30 jaar. Alleen in landen waar de prevalentie van HPV infecties

en de kosten van de HPV test hoog zijn, of waar de kosten van cytologische screening laag zijn, wordt primaire cytologische screening aanbevolen met een HPV vervolgtest.

- De toepassing van ongelijke disconteervoeten voor kosten en effecten in kosteneffectiviteitsanalyses is onduidelijk en heeft grote gevolgen voor de kosteneffectiviteit van preventieve interventies.

## **Aanbevelingen**

- Baarmoederhalskankerincidentie moet ook in de toekomst goed gemonitord worden
- Primaire HPV screening kan in Nederland ingevoerd worden. Uitstrijkjes moeten geëvalueerd worden in grote laboratoria om de kwaliteit te borgen en de kosten te drukken.
- Primaire HPV screening moet alleen ingevoerd worden voor vrouwen boven de 30 jaar.
- In Nederland moet dunnelaag cytologie geen hogere vergoeding krijgen dan conventionele cytologie.
- Er moet nagegaan worden wat het optimale screeningsprogramma voor gevaccineerde vrouwen is.
- Er moeten richtlijnen komen voor het gebruik van ongelijke disconteringsvoeten.



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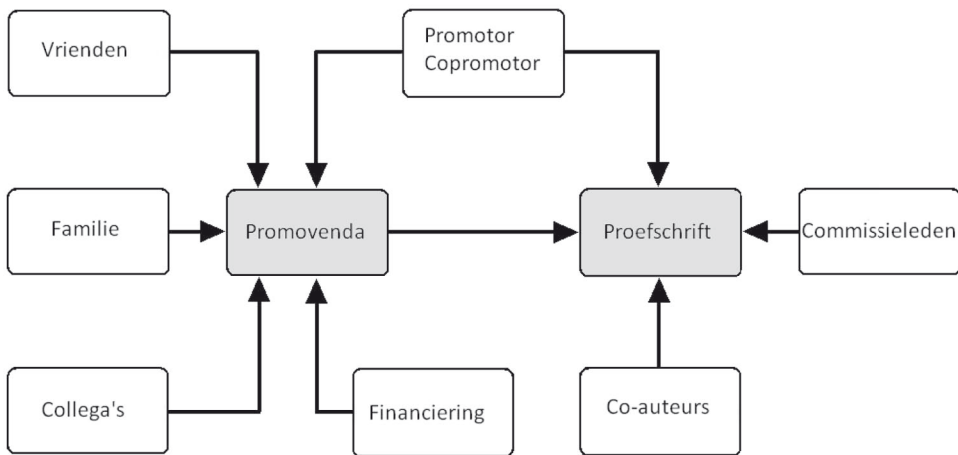
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**Figuur 1** | Model van de invloed van verschillende categorieën van personen op de totstandkoming van een proefschrift.

Maar zoals ik de afgelopen jaren heb geleerd is een model zelden de correcte afspiegeling van de werkelijkheid. Er zijn altijd gevallen, in dit geval personen, die niet exact in het model passen. Zo zijn er verschillende collega's die ook vriend of co-auteur zijn, familieleden die tevens als vriend worden beschouwd, en vrienden die familie geworden zijn... Ondanks dat het tegenwoordig maatschappelijk minder verantwoord is mensen in hokjes te stoppen wil ik toch graag per categorie een aantal personen specifiek bedanken:

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# PhD Portfolio Summary

## Summary of PhD training and teaching activities

Name PhD student: Inge M.C.M. de Kok      PhD period: 2007–2010  
 Erasmus MC Department: Public Health      Promotor: Prof.dr. J.D.F. Habbema  
    Supervisor: Dr. M. van Ballegooijen

1. PhD training	Year	Workload (ECTS)
<b>Research skills</b>		
Master of Public Health, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2007-2010	62.3
<b>General academic skills</b>		
Didactic course 'Didactiek op maat', Erasmus MC Desiderius school	2009	0.4
<b>Presentations</b>		
Presentations at the department of Public health	2008	0.6
International conferences	2008-2010	4.1
National conferences	2008-2009	1.8
<b>Conferences</b>		
Congres Infertiliteit, Gynaecologie en Obstetrie	2007	0.1
EUropean Research Organisation on Genital Infection and Neoplasia	2007-2010	2.1
European advanced Course in Cervical Pathology	2008	1
HPV in Human Pathology Congress	2008-2009	1.4
Werkgroep Epidemiologisch Onderzoek Nederland	2008	0.6
Society for Medical Decision Making	2009	0.7
International Cancer Screening Network	2010	0.7
<b>Seminars/ Symposia</b>		
Attending seminars of the department of Public Health	2007-2010	3.6
9e symposium Stichting Baarmoederhals-kankerpreventie Oost: 'HPV, het begin of het einde?', Arnhem	2007	0.2
Facing a new era of cervical cancer prevention, Amsterdam	2008	0.3

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**Seminars/ Symposia** (*continued*)

Netspar Symposium: 'Living longer in good health', Rotterdam	2008	0.2
Cancer screening: trials and modeling to guide public health policies, Rotterdam	2009	0.2
Evidentie en beslissen in de gezondheidszorg: Stand van wetenschap en praktijk, Rotterdam	2010	0.2

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**2. Teaching activities**

Lecturing: NIHES course 'Maternal and Child health' (HS09)	2009	0.2
Lecturing and supervising: Curriculum medical students, 4th year, Theme 4.2: the population as a patient, Erasmus MC, Rotterdam.	2009-2010	1.4

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# Curriculum Vitae

Inge de Kok was born on November 5, 1982 in Waalwijk, the Netherlands. In 2001, she completed her secondary education (VWO) at the Dr. Mollercollege in Waalwijk. From 2001-2007 she studied at the Radboud University Nijmegen. After being excluded for studying 'Medicine' (due to numerus clausus) she started studying 'Biology' in 2001. In 2002 she started studying 'Biomedical Sciences' and obtained a Master's degree in 'Epidemiology' in 2007. As a part of this study she did several research projects which resulted in international papers. In 2005-2006 she studied trends in colorectal cancer at the 'National University of Singapore'. In 2006 she examined the influence of socioeconomic status in childhood on cancer incidence in adult life, and in 2007 she studied whether the starting age for the cervical cancer screening programme in the Netherlands needed to be lowered. Both studies were done at the department of Public Health of the Erasmus MC, Rotterdam. In March 2007 she started working as a researcher at the same department, where she carried out the research presented in this thesis. During this period, she also enrolled in the Master of Science programme at the Netherlands Institute for Health Sciences, and obtained her Master of Public Health in 2010. Currently, she is still working at the department of Public Health.

Inge is married to Gerben Driesprong.

Inge de Kok werd geboren op 5 november 1982 te Waalwijk, Nederland. In 2001 behaalde ze haar atheneumdiploma aan het Dr. Mollercollege in Waalwijk. Vervolgens startte zij met studeren aan de Radboud Universiteit in Nijmegen. Na uitgeloot te zijn voor de studie 'Geneeskunde' begon zij in 2001 aan de studie 'Biologie'. In 2002 begon zij met de studie 'Biomedische wetenschappen' en behaalde in 2007 haar Master diploma 'Epidemiologie'. Tijdens haar studie deed ze verschillende onderzoeksprojecten welke resulteerde in artikelen in internationale tijdschriften. In 2005-2006 bestudeerde ze trends in colorectaal kanker aan de 'National University of Singapore'. In 2006 heeft ze onderzocht wat de invloed van sociaaleconomische status in de jeugd op kanker incidentie op volwassen leeftijd is en in 2007 of de leeftijd voor baarmoederhalskankerscreening omlaag zou moeten, beiden op de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC, Rotterdam. Vanaf maart 2007 was zij als onderzoeker verbonden aan deze afdeling, waar zij het onderzoek verrichtte beschreven in dit proefschrift. Gelijktijdig volgde ze de post-doctorale opleiding Public Health aan het 'Netherlands Institute for Health Sciences' en behaalde in 2010 haar Master. Na haar promotie blijft ze verbonden aan de afdeling Maatschappelijke Gezondheidszorg.

Inge is getrouwd met Gerben Driesprong.



# List of publications

1. **de Kok IMCM**, van Rosmalen J, Sasieni P, Dillner J, Iftner T, van Ballegooijen M. Cost-effectiveness of primary HPV screening compared to primary cytology screening for cervical cancer in Europe. *Submitted*
2. de Bekker-Grob EW, **de Kok IMCM**, Bulten J, van Rosmalen J, Vedder JEM, Arbyn M, Klinkhamer PJJM, Siebers AG, van Ballegooijen M. Cost-effectiveness analysis of liquid-based cytology in the Netherlands. *Submitted*
3. O'Mahony J, **de Kok IMCM**, van Rosmalen J, Habbema JDF, Brouwer W, van Ballegooijen M. Practical implications of differential discounting in cost-effectiveness analyses with varying numbers of cohorts. *Value Health. In press*
4. **de Kok IMCM**, Habbema JDF, van Rosmalen J, van Ballegooijen M. Would the effect of HPV vaccination on non-cervical HPV-positive cancers make the difference for its cost-effectiveness? *Eur J Cancer. 2010 Oct 22. Epub ahead of print*
5. **de Kok IMCM**, van der Aa MA, van Ballegooijen M, Siesling S, Karim-Kos HE, van Kemenade FJ, Coebergh JWW; On behalf of the Working Group Output of the Netherlands Cancer Registry. Trends in cervical cancer in the Netherlands until 2007: Has the bottom been reached? *Int J Cancer. 2010 Jul 12. Epub ahead of print*
6. van Ballegooijen M, **de Kok IMCM**, Habbema JDF. Ongelijke discontering van zorgkosten en -effecten: Verwarrend. [Unequal discounting of health care costs and effects causes confusion]. *Ned Tijdschr Geneeskd. 2010;154:A1970 (In Dutch)*
7. **de Kok IMCM**, van Ballegooijen M, Habbema JDF. Response Re: Cost-Effectiveness Analysis of Human Papillomavirus Vaccination in the Netherlands. *J Natl Cancer Inst 2010;102(5): 359-360.*
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10. **de Kok IMCM**, Polder JJ, Habbema JDF, Berkers LM, Meering WJ, Rebolj M, van Ballegooijen M. The impact of healthcare costs in the last year of life and in all life years gained on the cost-effectiveness of cancer screening. *Br J Cancer. 2009 Apr 21;100(8):1240-4.*
11. van der Aa MA, **de Kok IMCM**, Siesling S, van Ballegooijen M, Coebergh JWW. Geen basis voor verlaging onderste leeftijdsgrens van bevolkingsonderzoek

- op baarmoederhalskanker. [No justification for reducing the lower age limit for cervical cancer screening] *Ned Tijdschr Geneeskd.* 2009;153:B96 (In Dutch)
12. **de Kok IMCM**, Habbema JDF, Mourits MJE, Coebergh JWW, van Leeuwen FE. Vaccinatie tegen baarmoederhalskanker in het Rijksvaccinatieprogramma [Grounds for the inclusion of vaccination against cervical cancer within the National Immunisation Programme] *Ned Tijdschr Geneeskd.* 2008 Nov 29;152(48):2639-40; author reply 2640-1. (In Dutch)
  13. **de Kok IMCM**, Habbema JDF, Mourits MJE, Coebergh JWW, van Leeuwen FE. Onvoldoende gronden voor opname van vaccinatie tegen Humaan papillomavirus in het Rijksvaccinatieprogramma [Insufficient basis for the inclusion of Human papillomavirus vaccination in the National Immunisation Programme in The Netherlands] *Ned Tijdschr Geneeskd.* 2008 Sep 13;152(37):2001-4. (In Dutch)
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