General introduction

EPIDEMIOLOGY AND AETIOLOGY OF HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER

Human papillomavirus is a common sexually transmitted infection. Estimates show that a majority of sexually active women are likely to acquire an HPV infection at some time in their lives (estimates ranging from 53% to 95%, depending on assumptions).[1] HPV infections are associated with a range of both benign and malignant conditions, including genital warts and premalignant lesions and cancers of the uterine cervix, anus, vulva, vagina, penis and oropharynx. There are more than 200 HPV types that infect humans registered by the International HPV Reference Center,[2] with only some of these types being oncogenic. Twelve types of HPV (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans.[3] These types are referred to as high-risk HPV (hrHPV) in this thesis. HPV 16 and 18 are responsible for the majority of cervical cancers, in the range of 70%.[4]

While hrHPV infection is responsible for almost all cervical cancers,[5 6] not every person who is infected with hrHPV goes on to develop cervical dysplasia. HPV infects the epithelial layer of cells in the cervix.[7] Most individuals infected with hrHPV have a transient infection that clear without the need for treatment. However, if an infection is not cleared, it can cause changes to the squamous and/or glandular cells of the uterine cervix; these are persistent and transforming infections. Transforming infections can cause progression to cervical intraepithelial neoplasia (CIN; see Figure 1). Changes to the cervix can be detected by cytological or histological examination. Low-grade squamous intraepithelial neoplasia (LSIL) refers to the first stage of changes to the cervix that can be observed on cytological material. The corresponding histological diagnosis is CIN 1, with dysplasia limited to the lower third of the epithelium (Figure 1).[8] High-grade intraepithelial neoplasia (HSIL) is a more serious type of lesion, with cell changes affected more layers of the epithelium of the cervix. HSIL encompasses both CIN 2 and CIN 3 histological diagnoses, with CIN 3 is diagnosed when undifferentiated cells have replaced the full thickness of the epithelium.[8] Cervical cancer occurs when the dysplastic cells break through the basement membrane and dermis of the cervix.

The risk of persistence, or of progression to CIN or cervical cancer, is influenced by a number of factors. Firstly, the type of HPV is the most important risk factor for transformation. Infections with higher viral loads are more likely to be persistent.[9] Women who are HIV positive have an increased risk of CIN and cervical cancer than women who are HIV negative.[10] Higher parity and earlier age of first first-term pregnancy have been found to be associated with increased risk of cervical cancer.[11] Behavioural risk factors include smoking,[12 13] long-term oral contraceptive use,[13] early age of sexual initiation and higher number of lifetime sexual partners.[14]

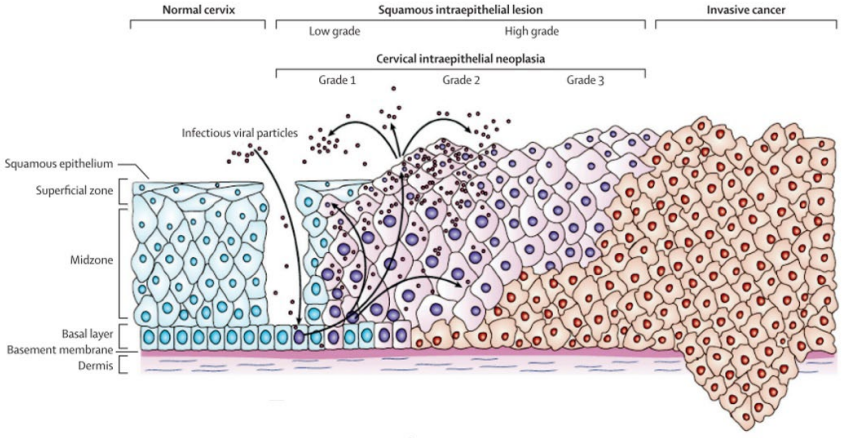

Figure 1: *Progression of disease from hrHPV infection to cervical cancer. Image modified from Crosbie et al.*[7]

Of all the malignancies that hrHPV infections are associated with, cervical cancer has by far the highest global burden in terms of cancer incidence and mortality. Worldwide in 2018, cervical cancer had the third highest incidence (age standardised rate: 24.7 per 100,000 women) and mortality (age standardised rate: 12.6 per 100,000 women) of all cancer types amongst women aged 25 to 74 years.[15] Low- and middle-income countries bare the greatest burden of cervical cancer incidence and mortality.[16] Incidence and mortality rates were much lower for the Netherlands (10.8 and 2.4 per 100,000 women, respectively).[15] Although these numbers are favourable, this still translates per year to approximately 735 incident cervical cancer cases and 210 cervical cancer deaths, based on an average of data from the Netherlands Cancer Registry from 2010 to 2017.[17]

INTERVENTIONS TO PREVENT hrHPV INFECTIONS AND CERVICAL DYSPLASIA

Public health interventions for the prevention and control of cervical cancer are classified by the World Health Organisation (WHO) as either primary, secondary or tertiary[18] (see Figure 2). Primary prevention strategies generally aim to reducing the incidence of new hrHPV infections. The most effective primary prevention strategy is vaccination of girls and boys against hrHPV prior to sexual debut, typically between ages 9 and 13 years. There are currently several hrHPV vaccines on the market that cover different hrHPV types, ranging from bivalent vaccines that provide protection against hrHPV 16 and 18 to nonavalent vaccines that provide protection against hrHPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. In several high-income countries, hrHPV vaccination of girls have been implemented for over a decade and reductions in the prevalence of HPV 16/18[19 20] and CIN 2+ lesions[21]

have already been shown amongst partly vaccinated cohorts. A reduction in HPV prevalence in unvaccinated, heterosexual males has also been shown,[22] suggesting that some level of cross-protection is provided to heterosexual males following the implementation of female-only vaccination programmes.[23] Other primary interventions have also been shown to be somewhat effective in reducing hrHPV infections, such as consistent condom use,[24] but results are mixed and consistent condom usage has been shown to be low.[25]

Secondary prevention strategies involve identifying women at risk of developing cervical cancer and treating lesions as appropriate. This can be achieved by screening of asymptomatic women. Treatments for cervical cancer are classified by the WHO as tertiary strategies. The remainder of this thesis will focus on secondary prevention of cervical cancer through screening.

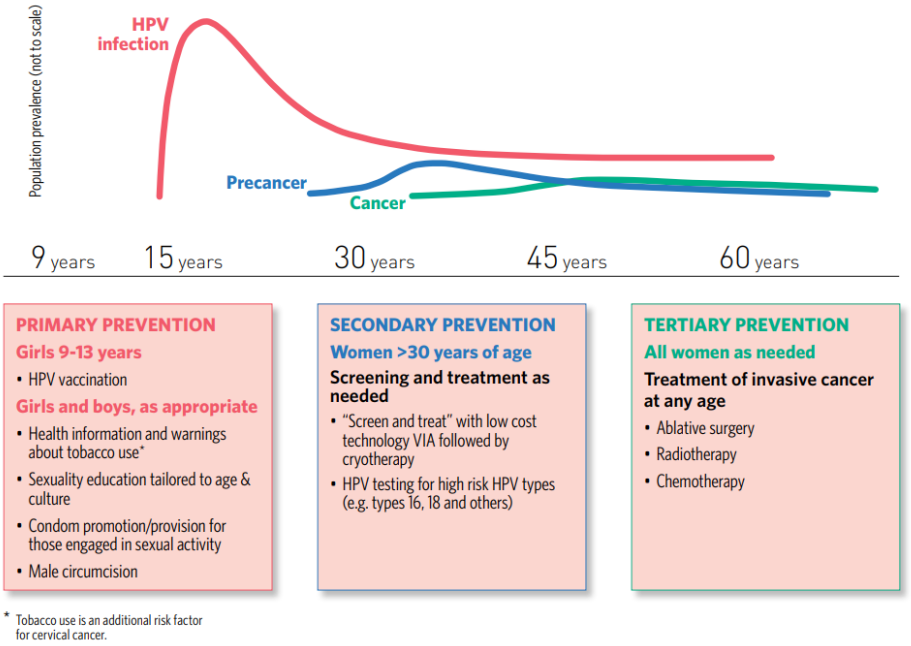

Figure 2: *Primary, secondary and tertiary cervical cancer prevention strategies and the impact by age. Image from World Health Organisation*[18]

Screening for cervical cancer

The goal of cervical cancer screening programmes is to reduce morbidity and mortality from cervical cancer within the population. In order to reach this goal, programmes are designed to detect clinically significant premalignant lesions or early-stage cancers of the uterine cervix, and refer women with these lesions for treatment prior to progression to invasive cervical cancer. For the purposes of monitoring and evaluation, clinically significant

lesions are either defined as CIN 2+ or CIN 3+, as the likelihood of these lesions persisting or progressing are higher than the likelihood of these lesions regressing (Table 1).[26 27]

Table 1: *Suggested likelihoods of regression, persistence and progression of CIN lesions. Adapted from Arbyn et al.[26] and Östör[27]*

Lesion grade	Regression	Persistence	Progression to CIN 3	Progression to invasive cancer
CIN 1	60%	30%	10%	1%
CIN 2	40%	40%	20%	5%
CIN 3	33%	<55%	–	>12%

Screening can either be organised or opportunistic. An organised cervical cancer screening programme is characterised by the following qualities:[28-30]

- A defined programme structure driven by policies that specify the target population, method and interval for screening and the screening pathway;
- A population-based register that can be used to identify and invite women in the target population;
- A team that are responsible for the management of the programme; and
- Adequate quality control and assurance systems at all levels of the programme, that allow for monitoring and evaluation.

Juxtaposed to this, opportunistic screening involves *ad hoc* testing of women, rather than participation following invitation through a structured call-recall system.[29 30] The European Guidelines for Quality Assurance for Cervical Cancer Screening recommend population-based, organised programmes are implemented and discourage opportunistic screening.[26]

Prior to the implementation of organised cancer screening programmes, trials are usually conducted to estimate the impact of screening on morbidity and mortality and whether the benefit of screening outweigh the risks on a population level. Trials of cytology-based cervical cancer screening were not conducted prior to implementation, so there are no trial estimates available for the impact of cervical cancer screening on the incidence of, and mortality from, cervical cancer. However, results from observational studies conducted in Europe suggest that organised cervical cancer screening programmes are associated with reduced mortality from cervical cancer.[31]

While all cervical cancer screening programmes have the same goal, the combination of different factors used to define a programme, such as test type, screening interval, start and end age and triage algorithms, differs widely between countries. How a particular country or region decides which combination of strategies to use depends on the priorities, available budgets, capacity and infrastructure as well as different acceptability of risk.

THE DUTCH CERVICAL CANCER SCREENING PROGRAMME

History of screening in the Netherlands

Organised cervical cancer screening began in the Netherlands in 1976 with a wide-spread pilot of cytology screening. Nationwide screening began in the 1980's, offering cytology-based screening to women aged 35 to 53 years every three years.[32] Over time, the age range and screening interval were changed based on cost-effectiveness research, with screening of women aged 30 to 60 years every five years becoming the standard protocol.[33] Several changes were implemented over the years to the cytology-based screening programme including the introduction of liquid-based cytology[34-36] and hrHPV co-testing for women who were triaged.[37] By 2016, most screening was conducted using either SurePath and ThinPrep liquid-based cytology mediums and 84% of triaged women were co-tested for hrHPV at their control cytology six months after

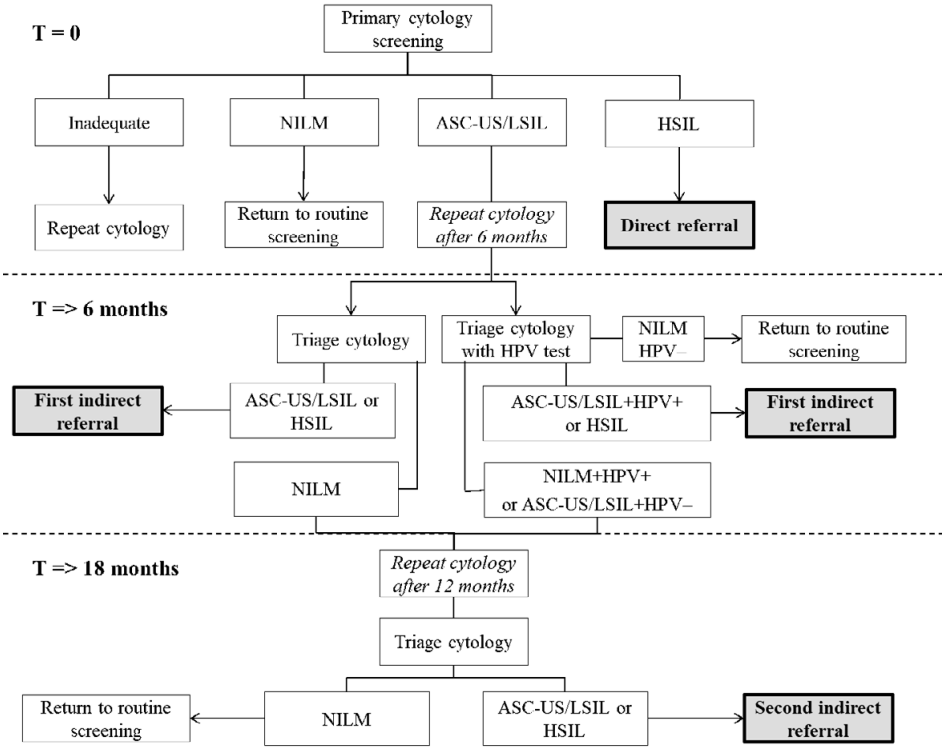

Figure 3: *Referral pathways in the Dutch Cervical Screening Programme from 1996 to 2016*
NB. Pathways including hrHPV triage were introduced later than 1996.
NILM: Negative for intraepithelial lesion or malignancy
ASC-US: Atypical squamous cells of undetermined significance
LSIL: Low-grade squamous

primary screening.[38] The referral and triage algorithm for the cytology-based screening programme can be found in Figure 3.

Transition to hrHPV-based screening

In 2017, the Netherlands became the first country in the world to introduce a nationwide hrHPV-based cervical cancer screening programme. The switch to hrHPV-based screening was based on advice from the Dutch Health Council, published in 2011.[39] HrHPV screening has been shown to provide better protection against cervical cancer, due to higher sensitivity for CIN 2+ lesions,[40] thus making it a suitable alternative to primary cytology-based screening. Primary hrHPV-based screening had been extensively studied in the Netherlands, with various studies and trials conducted to assess the performance of hrHPV testing in the Dutch screening-eligible population. The POBASCAM trial found that, compared to cytology-based screening, primary hrHPV-based screening resulted in earlier detection of CIN 3+ lesions,[41] better protection against CIN 3+ lesions in subsequent screening rounds[42] and found that a negative hrHPV primary screening result was followed by a lower cumulative risk of CIN 3+ lesions over 14 years.[43] These findings supported the implementation of primary hrHPV-based screening in the Netherlands, with an extension of the screening interval for hrHPV negative women at age 40 and 50 years. Results from POBASCAM were also in line with other international trials.[44] The possibility of including self-sampling in a hrHPV-based programme was also studied, with the IMPROVE trial showing that the self-sampling was non-inferior to clinician-collected sampling in terms of CIN 2+ sensitivity and specificity.[45]

Prior to implementation of the programme, cost-effectiveness analysis found that, in comparison to the cytology-based programme, hrHPV-based screening would be 13–15% more effective and would reduce costs of both the screening programme (approximately 35% lower) and the total societal costs of screening, including diagnostic and treatment costs (approximately 20% lower).[46]

Transition to HPV-based cervical cancer screening involved the following changes to the test and triage parameters of the screening programme:

- Use of hrHPV tests as the primary screening test;
- The introduction of hrHPV self-sampling as a possible screening modality;
- Cytology triage after hrHPV positive screening; and,
- Reduced number of screening rounds by extending screening intervals to 10 years for women who test hrHPV-negative at age 40 and 50 years.

The triage and referral algorithm was also modified, with women with hrHPV positive, ASC-US or higher screen results being directly referred for colposcopy (Figure 4).

In addition to the recommended changes, there was a consolidation of pathology laboratories that perform testing of primary screening samples from approximately 40

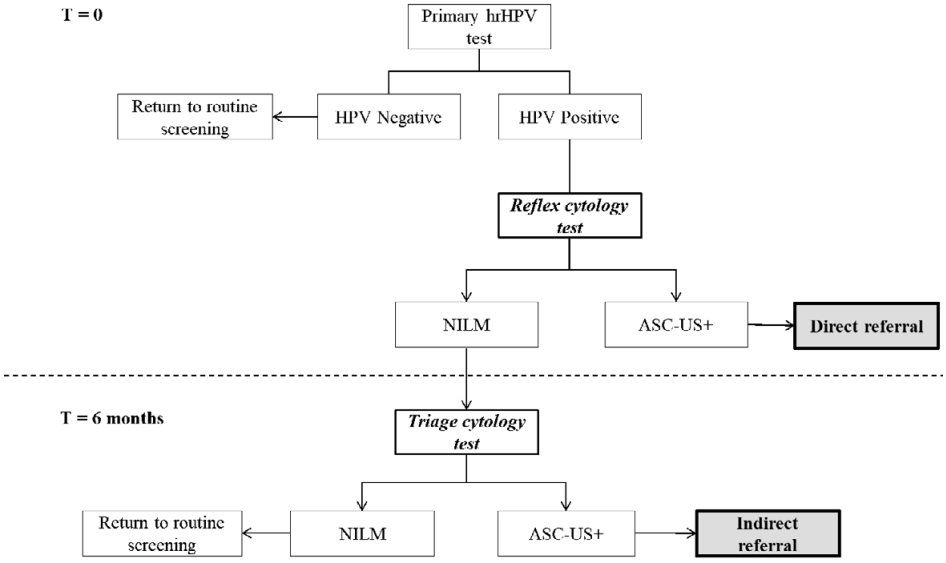

Figure 4: *Referral pathways within the Dutch Cervical Screening Programme from 2017*
NILM: Negative for intraepithelial lesion or malignancy
ASC-US+: Atypical squamous cells of undetermined significance or higher

labs in the old cytology-based programme to five labs in the new hrHPV-based screening programme. There were several reasons for the reduction in the number of laboratories, including maintaining the quality of cytology interpretation. Consolidation of the processing of screening programme tests was also more efficient in terms of costs due to economies of scale. The implementation of the hrHPV-based programme provided an appropriate moment to consolidate these services to one laboratory per screening organisation (there are five screening organisations across the country; see Figure 5).

Starting in January 2017, these changes were gradually rolled out by screening region over the first quarter of 2017. By April 2017, all screening regions were sending invitations in the new programme. With the change from cytology-based to hrHPV-based screening, the policy for inviting women was changed, with the regional screening organisations sending all invitations in a standard manner; women were all invited after their birthday in the year they were eligible for invitation. In the cytology-based programme, invitations were either sent by the regional screening organisation, general practices or using a combined approach. The timing of the invitation also varied depending on which organisation sent the invitation; some invitations were sent at the start of the year that women would become eligible to participate and some were sent after the women's birthdate.

Primary HPV screening and self-testing

Women invited for screening in the Dutch programme are able to choose between having a sample taken by their GP or by requesting a self-sampling device using their digital identification number (*DigiD*), which is linked to their social security number (*burgerservicenumber*, BSN). All tests within the new screening programme were selected via a tendering process run by the Dutch Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu*, RIVM).

Clinician-collected samples are collected in 20mL ThinPrep medium (Hologic, Marlborough, United States), transported and stored at room temperature until processed in the laboratory. The Evalyn® Brush (Rovers Medical Devices, Oss, the Netherlands) is used for self-sampling. The self-collected brushes are sent to the laboratories by regular mail. The brush of the self-sampling device is transferred into 20mL of ThinPrep medium prior to hrHPV testing. All laboratories used the Cobas® 4800 HPV test (Roche Molecular Systems, Inc, Branchburg, NJ, USA). The Cobas® 4800 HPV test is a CE in vitro diagnostic (IVD) certified kit (for clinician-collected cervical scraps only) for use in combination with the Cobas® 4800 system for nucleic acid extraction, PCR setup, real-time PCR amplification and result analysis. As part of the assay procedure, each sample is also tested for the presence of human cells by amplification of the human beta-globin gene.

Reflex cytology is performed on hrHPV positive clinician-collected samples. For hrHPV positive self-samples, women are contacted and asked to make an appointment with their GP for reflex cytology. The results of reflex cytology determine whether a woman is directly referred for colposcopy or invited to return for a repeat cytology test six months after primary screening.

Classification of cytology tests within the programme

Since 1996, cytology smears in the Netherlands have been classified according to the CISOE-A system.[47] This system requires pathologists to grade cytological findings on six domains to describe composition and morphology of the cytology slide: **C**omposition, **I**nflammation, **S**quamous, **O**ther and endometrium, **E**ndocervical cylindrical epithelium and **A**dequacy. This information is then used to provide advice about potential follow-up screening or referral from the programme, and can be used to inform gynaecologists about the origin and severity of dysplasia upon referral. Implementation of the CISOE-A system led to a reduction in borderline smears,[47] and consequently a reduction in the number of screens with repeat advice.[48] The CISOE-A system can be converted to alternative grading systems, such as the Bethesda and Pap classification systems. The concordance between these systems is summarised in Table 2.

Table 2: *Concordance between CISOE-A, Pap and Bethesda grading systems. Adapted from Oncoline*[49]

CISOE-A	Papanicolaou (Pap)	Bethesda 2001
C0	Pap 0	Inadequate
S1, O1-2*, E1-2#	Pap 1	Negative for intraepithelial lesion or malignancy (NILM) *# E2: no endocervical cells* ** O2: atrophy*
S2-3, O3	Pap 2	Atypical squamous cells of undetermined significance (ASC-US)
E3	Pap 2	Atypical glandular cells (AGC), endocervical origin
E4-5	Pap 3a1	AGC, endocervical origin *(E4 low grade, E5 intermediate grade)*
S4	Pap 3a1	Low-grade squamous intraepithelial lesion (LSIL)
S5	Pap 3a2	High-grade squamous intraepithelial lesion (HSIL)
O4-5	Pap 3a2	AGC, endometrial origin
E6, O6	Pap 3b	AGC, E6 high grade neoplasia
S6	Pap 3b	HSIL (*ASC-H)
E7	Pap 4	Adenocarcinoma in situ (AIS). *(Used interchangeable with E6)*
S7	Pap 4	Carcinoma in situ *(Used interchangeable with S6)*
S9, O7-9, E9	Pap 5	Invasive carcinoma
S1, E1-5, O1-3 in combination with EX 15	Pap 3a2	Atypical squamous cells, HSIL cannot be ruled out (ASC-H)

Diagnosis and treatment of CIN following referral

Once referred from screening, women undergo colposcopy and possibly receive diagnostic or therapeutic interventions. Biopsies can be taken from the transformation zone, taking one or more samples to be analysed for a histological diagnosis. While there are multiple options for treatment of CIN lesions including excisional, destructive and medicinal interventions, large loop excision of the transformation zone (LLETZ) is most commonly used in the Netherlands. There are two main treatment strategies for women referred for colposcopy: expectant management or see-and-treat management. Women under expectant management receive diagnostic biopsy at the initial colposcopy. The results of the initial biopsy and visual inspection of the cervix help direct the management plan for the patient. In see-and-treat management, women are provided curative treatment as part of the initial colposcopy. See-and-treatment management can provide several potential benefits, including reducing loss to follow up, convenience for women and lower costs. However, the higher risks of overtreatment mean that the use of see-and-treat management should be limited to women with both high-grade cytology and high-grade colposcopic image.[50]

Consensus-based guidelines for the diagnosis and treatment of CIN following referral have been developed by experts in the field and are authorised by Dutch Professional

Associations for Obstetrics and Gynaecology, Pathology and Medical Microbiology, in cooperation with the Dutch Professional Association for General Practitioners and the Dutch Patient Federation. These guidelines were updated in 2015 and provide guidance to medical practitioners about prevention, screening, diagnosis and treatment of CIN and other HPV-associated lesions of the female genital tract (adenocarcinoma in situ and vaginal intraepithelial neoplasia).[51] The guidelines provide the following advice about the treatment of CIN lesions:

- In principle, **CIN 1 lesions** should not be treated. In the case of persistent low-grade cytology outside of reproductive age, treatment options may be discussed with the patient.
- For **CIN 2 lesions**, individual assessment is required, particularly in younger women, weighting up the risks and benefits of treatment. If treatment is offered, LLETZ is recommended.
- **CIN 3 lesions** should always be treated. Women with high-grade cytology (moderate dyskaryosis/dysplasia or worse) and colposcopy are eligible for see-and-treat management. LLETZ is the recommended treatment modality.

The 2015 guidelines provided more stringent advice about the treatment of CIN 2 lesions than in the previous version of the guidelines.[52] For women who wish to become pregnant, the harms of excisional treatments of pre-malignant lesions, including increased risk of pre-term birth, premature rupture of the membranes, low birth weight, and perinatal mortality,[53-56] may outweigh the benefits of treatment of CIN 2 lesions.

Governance of the Dutch Cervical Cancer Screening Programme

The RIVM has responsibility for the governance and coordination of the national screening programme. The RIVM also provides all communication materials for the screening programme and is responsible for managing the monitoring and evaluation of the programme. In practice, monitoring and evaluation of the programme is conducted by independent researchers at external organisations. Regional screening organisations are responsible for the implementation of the screening programme in practice, including sending invitations to eligible women and communicating results with them. Over the years, the number of regional screening organisations have been consolidated from 12 organisations to five (Figure 5).

Monitoring and evaluation of the Programme

Monitoring provides regular oversight and feedback about performance of the screening programme to stakeholders, based on a pre-specified list of indicators using routinely collected data.[58] Evaluation serves a different purpose, using in-depth analysis on particular research questions to provide information about impact and effectiveness

Figure 5: *Regional screening organisations in the Netherlands. Image from Bevolkingsonderzoek Nederland*[57]

of programme- or policy changes.[59] Both monitoring and evaluation are needed for ensuring quality and safety in the screening programme. Monitoring and evaluation are commonly used in health services research to manage the quality and performance of health services, to identify areas for improvement and as a signalling tool for programme managers and policy makers when performance of a health service is not as optimal as it should be.

Data required for monitoring and evaluation

For effective monitoring and evaluation, high quality, timely and accessible data is required.[60] The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA Foundation) has provided data for monitoring and evaluation of the Dutch cervical screening programme for more than 20 years. PALGA has complete coverage of all pathology laboratories in the Netherlands and compiles information from all cytological and histological examinations into a centralised databank.[61] Monitoring of the programme is partly conducted using an extract of all cervical cytology and histology records from PALGA This extract is processed using a SAS program that has been specifically developed for the purposes of monitoring and evaluation (PALEBA).

Screening histories from individual women can be followed in PALEBA thanks to a pseudonymised personal identifier. This personal identifier is created using the eight letters of a woman's surname and their date of birth. For more detailed evaluation questions, other data sources are available for linkage with PALEBA, including information about cancer diagnoses from the Netherlands Cancer Registry, information about invitations from the regional screening organisations and information about socio-economic variables from Statistics Netherlands. In the hrHPV-based screening programme, monitoring is also conducted using data extracts from ScreenIT, an ICT system which records all invitations, reminders and participation (amongst other information). The use of these datasets, including data from PALGA, is subject to approval of the data owners.

SCREENING AS A PROCESS

Cervical cancer screening programmes operate as a process,[62] involving the women invited for screening, screening organisations, the RIVM and clinical care providers, including GPs (and in some practices, physician assistants), pathologists, cytotechnicians and gynaecologists (see Figure 6). From the perspective of the organisations involved, the delineation of responsibilities and funding is clear; the RIVM and regional screening organisations are responsible for the first half of the screening process (blue section Figure 6) and at the point of referral, screening transitions to clinical care, with the management of care becoming the responsibility of the gynaecologists and costs being covered by health insurance companies (orange section Figure 6).

However, from the perspective of women participating in screening, the process of screening involves a continuous course of care, moving from the care of the GP to specialist care if required, without division between what is managed and funded by different parties. Without a national screening programme, many women who are referred to the gynaecologist would not have ended up in clinical care. Understanding outcomes for women across all stages of the screening programme is necessary to get a complete view of performance and cost-effectiveness of the programme.

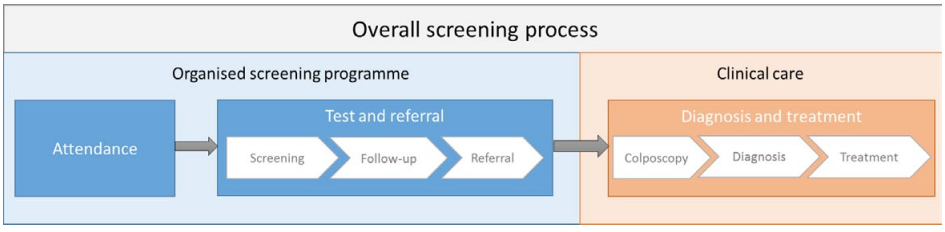

Figure 6: *Stages within cervical cancer screening programmes. Adapted from Anhang Price et al[62] and the RIVM[63]*

AIMS OF THIS THESIS

This thesis aims to evaluate the Dutch cervical cancer screening programme as a whole (**Part 2**), as well as each stage of the screening process: attendance (**Part 3**), test and referral (**Part 4**) and clinical care (**Part 5**). In particular, this thesis will focus on the transition from cytology-based screening to hrHPV-based screening. The thesis aims to answer the following questions:

Part 2: Overall screening process

Following the initial implementation of the programme and monitoring of the overall process of screening, specific questions were raised about aspects of the new programme that were not performing as expected or were not optimal. Specifically, it was critical to understand if the programme was performing as expected and how the new screening programme performed in comparison to the old cytology-based screening programme.

1. *What was the impact of implementation of the hrHPV-based screening programme on short-time programme indicators? (**Chapter 2.1**)*

Cost-effectiveness analyses that was performed prior to the implementation of the new programme found that hrHPV-based screening was more cost-effective than cytology-based screening. However, these estimates were based on assumptions from the literature. With information from the new programme now available, it was of interest whether the hrHPV-based programme was still considered more cost-effective than cytology-based screening.

2. *Is the new hrHPV programme still considered to be more cost-effective than the cytology-based screening when using the results of the first year of the hrHPV-based screening programme to calculate cost-effectiveness? (**Chapter 2.2**)*

Part 3: Attendance

Short-term monitoring of the new hrHPV-based programme found that participation in the new programme was lower than the old cytology-based programme. This was unexpected, especially given the availability of self-sampling. It is unclear if the new programme was reaching a different population group than the old cytology-based programme. Furthermore, the centralisation of the invitation system meant that changes were made to which organisations could send out invitations.

3. *What factors (both personal and organisational) are related to attendance, and which factors are related to the drop in attendance rates between the old and new screening programmes? (**Chapter 3**)*

Part 4: Test and referral

Test

In the new hrHPV-based screening programme, all cytology slides that are examined by cytotechnicians and pathologists are hrHPV positive. Previous research has indicated that, when the professional reading the slide is aware of its hrHPV status, there is a upward bias in the rating of the slide. Whether this was likely to happen in the Dutch setting was unknown.

4. *Are ratings of cytology slides by cytotechnicians influenced by the knowledge of hrHPV status? (**Chapter 4.1**)*

Referral

Given the high number of unnecessary referrals from the new hrHPV-based screening programme, optimisation of the triage algorithm may be required to minimise potential harms from unnecessary referrals. Any new triage algorithm would need to reduce these referrals with little to no impact on cervical cancer incidence and mortality and be easy to implement within the current laboratory procedures.

5. *What are the options for optimising the triage algorithm of the hrHPV-based screening programme within the current parameters of the programme? (**Chapter 4.2**)*

Atypical glandular cells (AGC) are a rare but high-risk cytological abnormality. Evidence suggests that women with AGC are at higher risk of cervical and other gynaecological cancers. In the old-cytology-based programme, depending on the severity of the abnormality, some women with AGC smears were advised to have repeat cytology rather than a direct referral. The risk of a cancer diagnosis in these groups has not been investigated previously using Dutch data.

6. *What is the risk of cervical and other gynaecological cancers following AGC on cervical cytology and is this higher than the risk following squamous cell abnormalities of comparable severity? (**Chapter 4.3**)*

Part 5: Diagnosis and treatment

Despite the fact that women are referred as a direct consequence of the screening programme and the risks associated with overtreatment following cervical screening, there is little evidence about adherence to the published CIN treatment guidelines. If there are gaps between the guidelines and current clinician practice, these could be used to identify areas for potential improvement.

7. *What are the trends in CIN management and treatment following referral following the Dutch cervical cancer screening programme, and are these trends in line with the clinical guidelines? (**Chapter 5**)*

The final part of this thesis (**Part 6**) will summarise the findings from **Parts 2 to 5** as well as propose potential changes to the Dutch cervical cancer screening programme (***Chapter 6.2***). Potential improvements to the monitoring and evaluation of the programme by improving quantification of harms of the screening process are also discussed (***Chapter 6.1***).

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