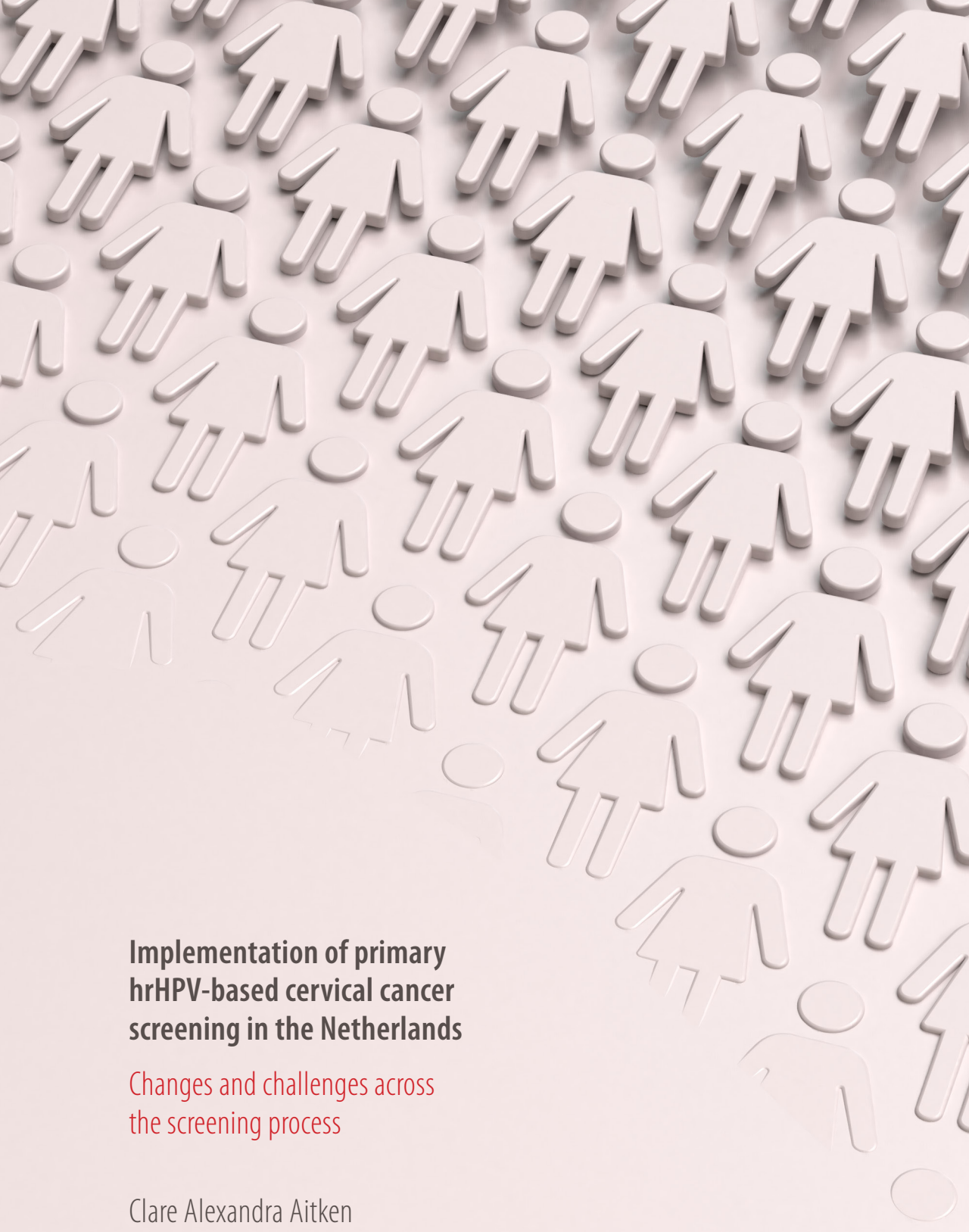

Implementation of primary hrHPV-based cervical cancer screening in the Netherlands

Changes and challenges across the screening process

Clare Alexandra Aitken

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Changes and challenges across the screening process

Invoering van primaire hrHPV-gebaseerde baarmoederhalskankerscreening in Nederland: veranderingen en uitdagingen in het screeningproces

Thesis

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Clare Alexandra Aitken
born in Canberra, Australia

Erasmus University Rotterdam

Doctoral Committee:

Promotors:	Prof. dr. H.J. de Koning
	Prof. dr. F.J. van Kemenade
Other members:	Prof. dr. B.W. Koes
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Copromotor:	dr. I.M.C.M. de Kok

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Introduction

Chapter 1

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]

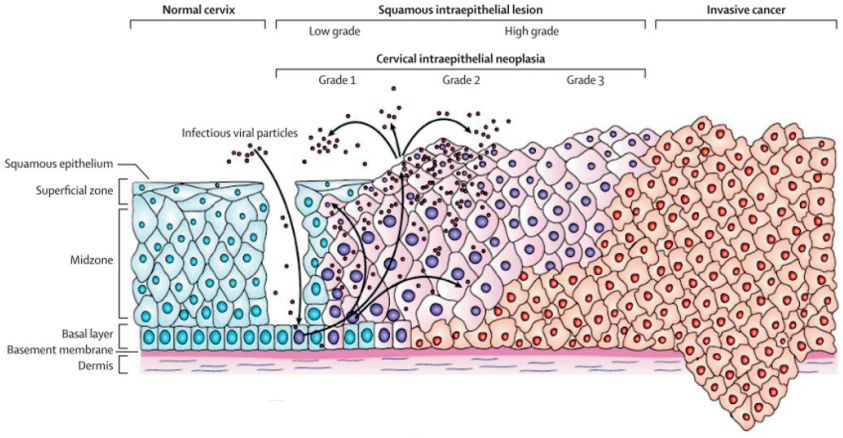

Figure 1: *Progression of disease from hrHPV infection to cervical cancer. Image modified from Crosbie et al.*[7]

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.

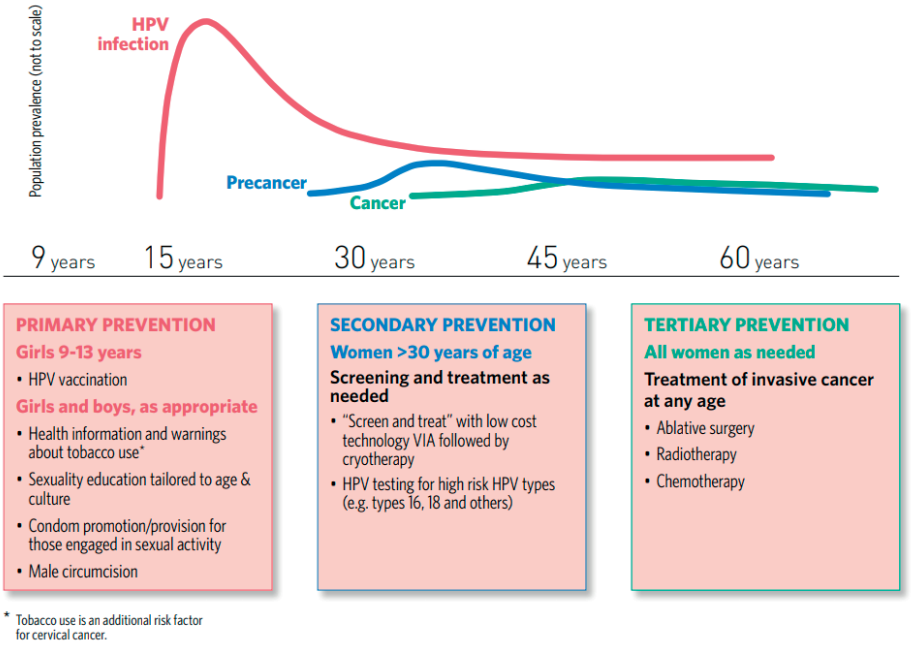

Figure 2: *Primary, secondary and tertiary cervical cancer prevention strategies and the impact by age. Image from World Health Organisation*[18]

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

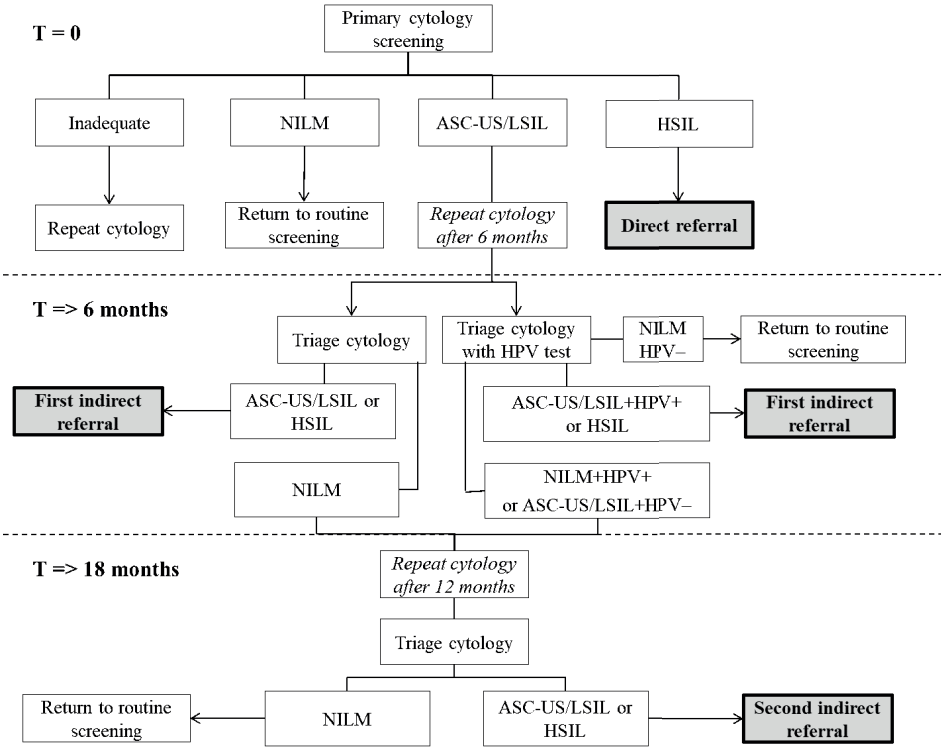

Figure 3: *Referral pathways in the Dutch Cervical Screening Programme from 1996 to 2016*
NB. Pathways including hrHPV triage were introduced later than 1996.
NILM: Negative for intraepithelial lesion or malignancy
ASC-US: Atypical squamous cells of undetermined significance
LSIL: Low-grade squamous

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

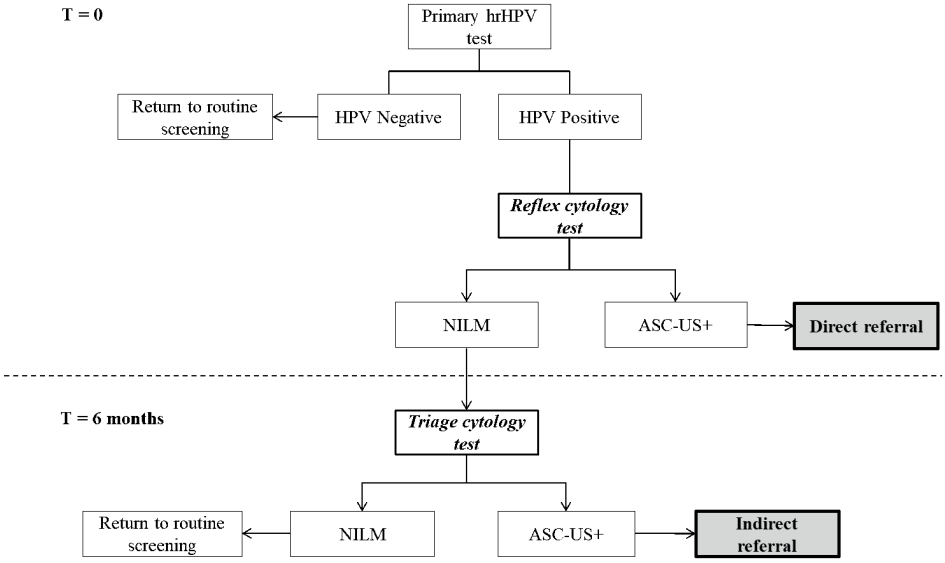

Figure 4: *Referral pathways within the Dutch Cervical Screening Programme from 2017*
NILM: Negative for intraepithelial lesion or malignancy
ASC-US+: Atypical squamous cells of undetermined significance or higher

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.

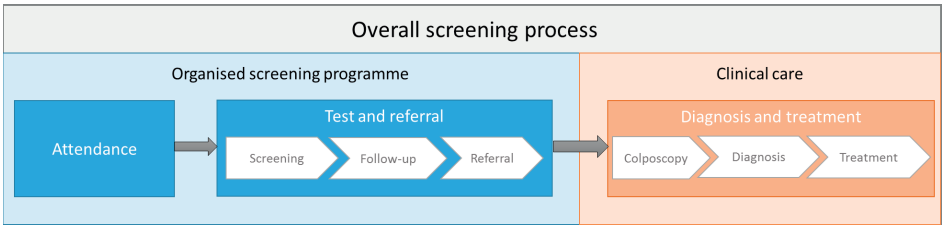

Figure 6: *Stages within cervical cancer screening programmes. Adapted from Anhang Price et al[62] and the RIVM[63]*

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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Part 2

Overall screening process

Chapter 2.1

Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study

Clare A. Aitken[1], Heleen M.E. van Agt[1], Albert. G. Siebers[2,3], Folkert J. van Kemenade[4], Hubert G.M. Niesters[5], Willem J.G. Melchers[6], Judith E.M. Vedder[3], Rob Schuurman[7,8], Adriaan J.C. van den Brule[9], Hans C. van der Linden[9], John W.J. Hinrichs[10,11], Anco Molijn[12], Klaas J. Hoogduin[12], Bettien M. van Hemel[13], Inge M.C.M de Kok[1]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam
2. PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands
3. Department of Pathology, Radboud University Medical Center
4. Department of Pathology, Erasmus MC, University Medical Center Rotterdam
5. Department of Medical Microbiology, Division of Clinical Virology, The University of Groningen, University Medical Center Groningen
6. Department of Medical Microbiology, Radboud University Medical Center
7. Facilitaire Samenwerking Bevolkingsonderzoeken
8. Department of Medical Microbiology, University Medical Center Utrecht
9. Pathologie-DNA, Jeroen Bosch Hospital
10. Symbiant Pathology Expert Centre Hoorn
11. Department of Pathology, University Medical Center Utrecht
12. NMDL-LCPL
13. Department of Pathology and Medical Biology, the University of Groningen, University Medical Center Groningen

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ABSTRACT

Background

In January 2017, the Dutch cervical cancer screening programme transitioned from cytomorphological to primary high-risk HPV DNA (hrHPV) screening, including the introduction of self-sampling, for women aged between 30 and 60 years. The Netherlands was the first country to switch to hrHPV screening at the national level. We investigated the health impact of this transition by comparing performance indicators from the new hrHPV-based programme with the previous cytology-based programme.

Methods

We obtained data from the Dutch nationwide registry of histo- and cytopathology (PALGA) for 454,573 women eligible for screening in 2017 who participated in the hrHPV-based programme between 1 January 2017 and 30 June 2018 (maximum follow-up of almost 21 months) and for 483,146 women eligible for screening in 2015 who participated in the cytology-based programme between 1 January 2015 and 31 March 2016 (maximum follow-up of 40 months). We compared indicators of participation (participation rate), referral (screen positivity; referral rate) and detection (CIN detection; number of referrals per detected CIN lesion).

Results

Participation in the hrHPV-based programme was significantly lower than in the cytology-based programme (61% vs. 64%). Screen positivity and direct referral rates were significantly higher in the hrHPV-based programme (positivity rate: 5% vs 9%; referral rate: 1% vs 3%). CIN2+ detection increased from 11 to 14 per 1,000 women screened. Overall, approximately 2.2 times more clinical irrelevant findings (i.e. ≤ CIN1) were found in the hrHPV-based programme, compared with approximately 1·3 times more clinically relevant findings (i.e. CIN2+); this difference was mostly due to a national policy change recommending colposcopy, rather than observation, of hrHPV-positive, ASC-US/LSIL results in the hrHPV-based programme.

Conclusions

This is the first time that comprehensive results of nationwide implementation of hrHPV-based screening have been reported using high-quality data with a long follow-up. We have shown that both benefits and potential harms are higher in one screening round of a well-implemented hrHPV-based screening programme than in an established cytology-based programme. Lower participation in the new hrHPV programme may be due to factors such as invitation policy changes and the phased roll-out of the new programme. Our findings add further to evidence from trials and modelling studies on the effectiveness of hrHPV-based screening.

BACKGROUND

Primary hrHPV DNA screening, evaluated in clinical trials, has been shown to be more effective and cost-effective than cytology screening for the detection of pre-malignant and malignant cervical lesions.[1,2] Following advice from the Dutch Health Council[3] and a feasibility study by the Dutch National Institute for Public Health and the Environment (RIVM),[4] primary high-risk HPV (hrHPV) screening replaced cytology screening in the Dutch national cervical cancer screening programme in January 2017. Each of the five regional screening organisations implemented hrHPV-based screening sequentially during the first quarter of 2017 and by April 2017, the national implementation was complete. Women can choose either to have a cervical smear taken by their general practitioner (GP) or to use a self-sampling kit.[5] Laboratory testing of screening programme samples is performed in five dedicated screening laboratories.

As part of the initial feasibility study, modelling analysis was conducted assessing the costs and effects of implementing primary hrHPV-based screening in the Netherlands.[4] Recent modelling estimated that nationwide implementation of primary hrHPV-based screening was expected to reduce cervical cancer diagnoses by 13% and related deaths by 15% compared with cytology-based screening, while also reducing overall programme costs.[6]

The success of a screening programme depends on the implementation of well-defined protocols and guidelines.[7] Screening programmes should be regularly monitored using high-quality data for quality assurance, to evaluate effectiveness and to identify potential harms.[8] Although results from the implementation of primary hrHPV screening in Italy and Turkey have been published,[9,10] these data lack robust results on detection of CIN lesions and do not compare the performance of hrHPV screening with cytology-based screening. Results from the Italian programme were also limited to a number of regions. Comprehensive results from the implementation of a nationwide hrHPV screening programme have yet to be published.

Data from the nationwide network and registry of histo- and cytopathology (PALGA) has enabled regular, high-quality monitoring of organised cervical cancer screening in the Netherlands for many years. This comprehensive dataset has national coverage[11] enabling us to assess the impact of cervical cancer screening programme policies on a national level. In order to evaluate the performance of the new primary hrHPV-based screening programme, we aimed to compared outcomes of the first year of the new programme with outcomes of the previous cytology-based cervical cancer screening programme.

METHODS

The cytology-based Dutch cervical screening programme

Until the end of 2016, the Dutch cervical cancer screening programme used cytology as the primary screening test. Women were invited to make an appointment for screening with their GP every five years from ages 30 to 60. Women could choose to opt-out of screening either temporarily (in the case of pregnancy, illness or other short-term reason) or indefinitely (in the case of hysterectomy or non-medical reasons such as conscientious objection).

There were various referral pathways in the cytology-based programme, depending on the result of primary cytology screening (Figure 1a). Direct referrals for colposcopy were given to women with high-grade cervical cytological abnormalities (high-grade squamous intraepithelial lesion (HSIL)) at primary screening. If women had low-grade cervical cytological abnormalities (atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL)) at primary screening, they were advised to make an appointment with their GP after six months for a follow-up smear. For women advised to have a follow-up cytology at six months, hrHPV triage was used in some cases, depending on the policy of the laboratory performing the test. Referral advice was given to women at the six month screening who had the following result: a) ASC-US or higher (when no hrHPV triage was performed) or, in the case of hrHPV triage, b) ASC-US/LSIL and hrHPV-positive or c) HSIL. Further repeat testing at 18 months was advised for women with cytology negative for intraepithelial lesion or malignancy (NILM) when no hrHPV triage was used or for NILM, hrHPV-positive results or ASC-US/LSIL, hrHPV negative results. When hrHPV triage testing at six months was used, women were referred back for routine screening if they were hrHPV-negative and cytology negative. All women with ASC-US+ cytology at 18 months were referred.

The hrHPV-based Dutch cervical screening programme

Primary hrHPV screening was implemented in the Netherlands on 1 January 2017 (Figure 1b), replacing the cytology-based programme. Women are invited to participate by their regional screening organisation every five years between the ages of 30 and 60, with some exceptions based on hrHPV positivity in the previous screening round; women with a negative hrHPV test result at age 40 or 50 are invited for screening after ten years instead of five and women who test hrHPV-positive at age 60 are invited for final screening at age 65. Women who do not wish to have a cervical sample taken at their GP can request a self-sampling kit. If requested at primary invitation, women were sent the self-sampling kit approximately four months after the initial invitation letter. Non-responders received a reminder letter four months after the initial invitation, which also contained information about how to request the self-sampling kit. Women who

requested the self-sampling kit after this reminder received it immediately. Reflex cytology was immediately performed on hrHPV-positive GP-collected samples. As cytology on self-sampled cervicovaginal material is unreliable,[12,13] women with an hrHPV-positive result on self-sampling were invited to have a cytological smear taken by their GP.

The referral algorithm in the hrHPV-based programme was simplified. HrHPV-positive women with cytological abnormalities (i.e. ASC-US or worse) were referred for colposcopy, while hrHPV-positive women with normal cytology were invited for repeat cytology testing after six months.

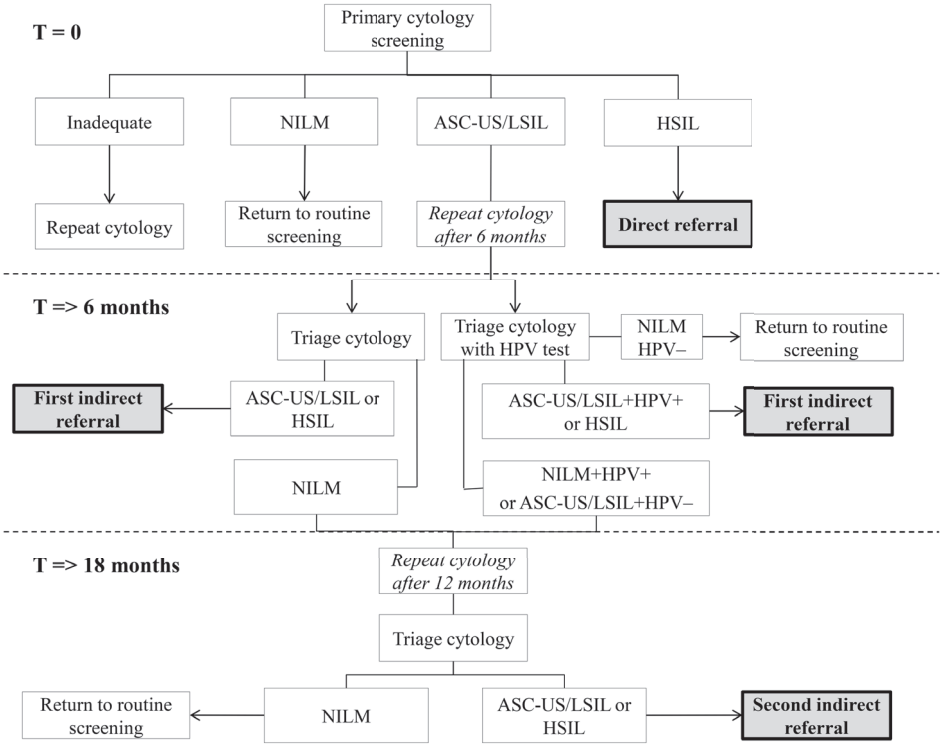

***Figure 1a**: Screening protocol cytology-based screening programme*
NILM: Negative for intraepithelial lesion or malignancy
ASC-US: Atypical squamous cells of undetermined significance
LSIL: Low-grade squamous intraepithelial lesion
HSIL: High-grade squamous intraepithelial lesion

Organisational and policy differences between the two programmes

In the Netherlands, there are five regional screening organisations responsibility for the implementation of the screening 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

Overall screening process

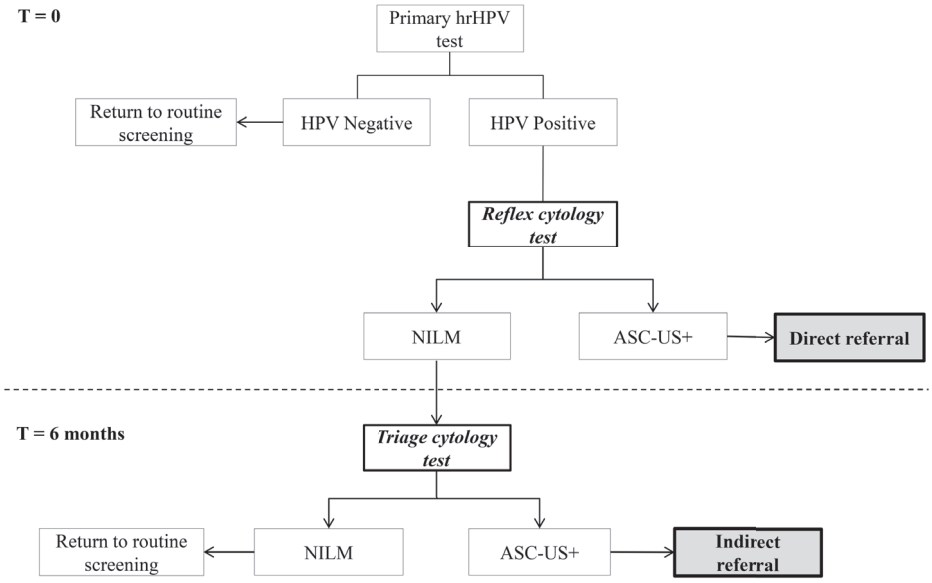

***Figure 1b**: Screening protocol HPV-based screening programme*
NILM: Negative for intraepithelial lesion or malignancy
ASC-US: Atypical squamous cells of undetermined significance
LSIL: Low-grade squamous intraepithelial lesion

invited after their birthday in the year they were eligible for invitation. In the cytology-based programme, invitations were sent by the regional screening organisation, GP 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. The number of laboratories responsible for analysing primary screens from the programme was reduced from approximately 40 in the cytology-based programme to five in the hrHPV-based programme (one per region).

hrHPV test in the new programme

Clinician-collected samples were 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) was used for self-sampling. The self-collected brushes were sent to the laboratories by regular mail. The brush of the self-sampling device was transferred into 20ml of ThinPrep medium prior to hrHPV testing. All laboratories used the Cobas® 4800 HPV test (Roche Diagnostics, Alameda CA, USA) to test the clinician-collected- and self-samples. 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 was also tested for the presence of human cells by amplification of the human beta-globin gene. The clinical performance of the Cobas® 4800 system has been validated using Dutch samples,[14] and the Evalyn® Brush was compared with lavage self-sampling in a Dutch population and found to have equivalent performance.[15] All tests used in the hrHPV-based programme were selected through a tendering process.

Study design and data source

This study is a longitudinal, retrospective population-based cohort study. We obtained results of primary screening tests and any associated follow-up from the Dutch nationwide registry of histo- and cytopathology (PALGA) for two cohorts. The cytology cohort consisted of women who participated in the cytology-based screening programme between 1 January 2015 and 31 March 2016 (maximum follow-up of 40 months). The hrHPV cohort consisted of women who participated between 1 January 2017 and 30 June 2018 in the hrHPV screening programme (maximum follow-up of almost 21 months). An inclusion period of 18 months was used for the hrHPV cohort to compensate for the phased implementation of the new programme (see Additional file 1).

All pathology laboratories in the Netherlands are linked to PALGA.[11] Identification of women is based on their birthdate and up to the first eight letters of their surname (maiden name is used for married women) and allows linkage of tests belonging to the same woman, enabling individual screening histories to be followed. For all primary and follow-up tests, the corresponding advice codes were analysed. Age was defined as the woman's age at the time of the primary screening test, classified into five-year age groups. Given differences in invitation policies between the two programmes, slightly different age ranges have been used for the hrHPV cohort and the cytology cohort (see Additional file 1).

Data analysis

To compare the performance of the hrHPV-based screening programme with the cytology-based screening programme, we calculated indicators in three categories: *participation* (participation rate), *referral* (screen positivity rate, positive cytology among screen positive women, referral rate from primary screening (direct referral), referral rate from follow-up smear (indirect referral) and total referral rate (direct and indirect referrals combined)) and *detection* (findings after referral per 1,000 screened women, number of positive screen test results/number of referrals for colposcopy per detected CIN2+ or CIN3+ lesion).

The participation rate was defined by the number of primary screening tests divided by the number of women eligible for screening. The number of eligible women was estimated from the number of women in the Dutch population who would reach screening

age in 2015 or 2017 (i.e. aged 29, 34, etc.) on 1 January 2015 for the cytology cohort and on 1 January 2017 for the hrHPV cohort. This data was obtained from Statistics Netherlands[16] and adjusted for the risk of having their cervix removed by hysterectomy.[17]

Referrals were identified based on advice codes recorded in PALGA and could be direct or indirect (see Additional file 1). Overdiagnosis and false positive screening results are recognised harms of screening.[18] Screen positivity and referrals can lead to psychological distress[19,20] and colposcopy itself can result in physical symptoms.[21] As such, we considered screen positivity and referral to be proxies for potential harms. To estimate the harms-benefits ratio of screening, we calculated the number of screen positives and number of referrals per detected CIN2+ and CIN3+ case. Detailed information about data definitions can be found in Additional file 1.

All analyses were performed using IBM SPSS Statistics 24. Chi-squared tests were performed to compare differences between proportions. *p* values of 0.05 or less were statistically significant.

RESULTS

Participation

A total of 454,573 women eligible for screening invitation in 2017 participated in the hrHPV-based programme between 1 January 2017 and 30 June 2018 and 483,146 women eligible for screening invitation in 2015 participated in the cytology-based programme between 1 January 2015 and 31 March 2016. Women ranged in age from 29 to 61 years.

Figure 2 shows that the overall participation rate in 2017 in the hrHPV-based programme was significantly lower than in the cytology-based screening programme in 2015 (64% in 2015 compared with 61% in 2017; $p < 0.001$). The participation rate in the hrHPV-based programme was lower in all age groups. The biggest difference was found in age group 45-49 years (68% in 2015 compared with 63% in 2017; $p < 0.001$). Differences in participation rates were statistically significant for all age groups ($p < 0.001$).

The percentage of inadequate cytology smears recorded at primary screening as a proportion of all primary screening reduced from 1.6% in 2015 to 0.1% in 2017 ($p < 0.001$).

Of all women participating in the hrHPV-based programme, 8% used the self-sampling kit (i.e. 36,295 self-sampled compared with 418,278 clinician-collected) (Figure 3).

Referral

Figure 4 shows that the proportion of women with a positive screen test was significantly higher in the hrHPV-based programme than in the cytology-based programme

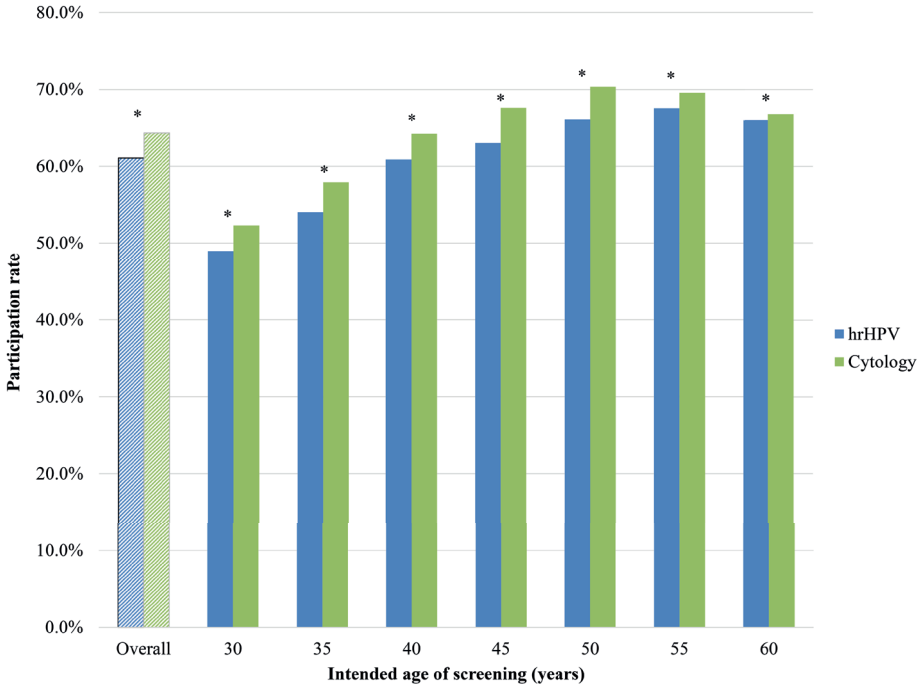

***Figure 2**: Participation rate in hrHPV-based screening (2017) and in cytology-based screening (2015) by age.* 454,573 women participated in hrHPV-based screening programme and 483,146 women participated in the cytology-based screening programme. NB. Please refer to Additional file 1 for a comprehensive explanation of age group criteria.

* Pearson's chi-square test significantly different between test types ($p < 0.001$).

(increased from 5% in 2015 to 9% in 2017; $p < 0.001$). Related to this, we found that the proportion of women referred to the gynaecologist also significantly increased (from 1% in the cytology-based programme to 3% in the hrHPV-based programme; $p < 0.001$). The increase in screen positive tests and in the referral rate were largest in women aged 30-34 years, where the proportion of positive screen tests increased from 9% in the cytology-based programme to 21% in the hrHPV-based programme ($p < 0.001$) and the referral rate increased from 3% to 8% ($p < 0.001$).

In the hrHPV-based programme, we found a significantly higher hrHPV positivity rate in clinician-collected than in self-collected samples (9.2% vs 7.6%; $p < 0.001$). In addition, amongst hrHPV-positive women, more women had a cytological abnormality after self-sampling than clinician-collected sampling (37.2% vs 32.2%; $p < 0.001$) (Figure 3).

Detection

Figure 5 shows per 1,000 women screened, the total number of referrals (both direct and indirect) to the gynaecologist and the number of CIN2+ lesions detected after referral.

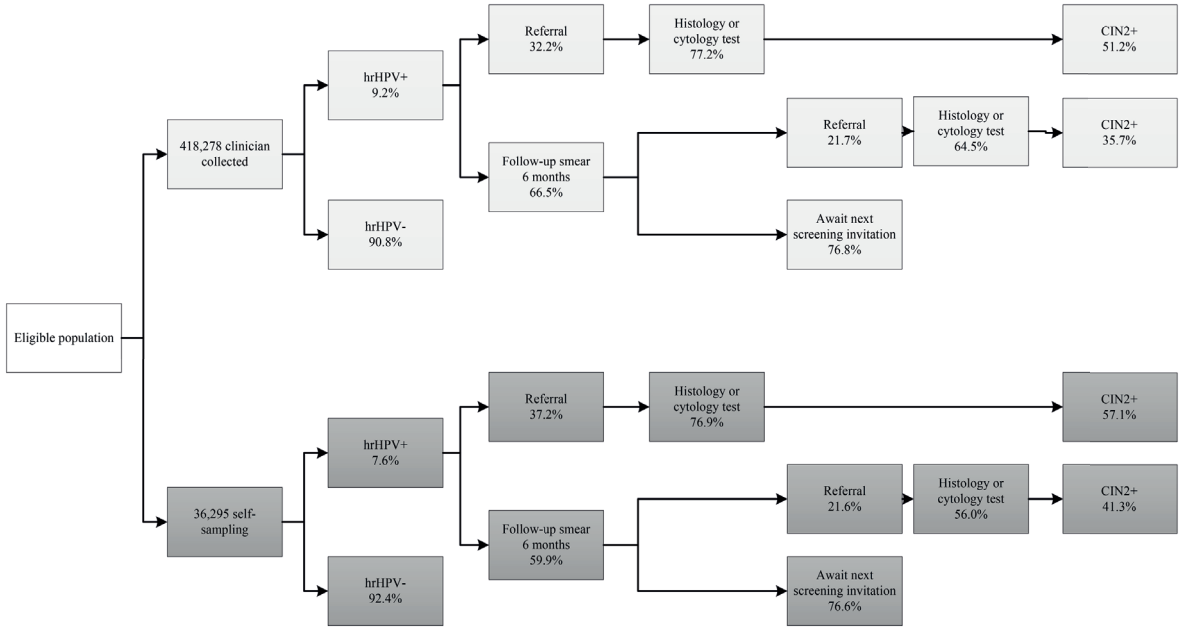

***Figure 3**: Flowchart of participation, referral and detection within the new hrHPV-based screening programme, 2017 cohort.*

Pearson's chi-square test significantly different for hrHPV positivity, direct referral rates and follow-up smear ($p < 0.001$) and CIN2+ detection rates from direct referral ($p = 0.002$) between clinician-collected and self-sampling.

Pearson's chi-square test not significantly different for proportions of histology or cytology tests (from direct referral; $p = 0.805$, from indirect referral; $p = 0.042$), indirect referral rate ($p = 0.974$), proportions with recommendation to await next screening invitation ($p = 0.884$), CIN2+ detection rates from indirect referral ($p = 0.319$) between clinician-collected and self-sampling.

NB. Sum of advice after screening will not be 100% due to a proportion of screens with repeat cytology due to inadequate cytology quality or loss to follow-up (self-sampling arm only). Cytology was assessed in 90.1% of hrHPV positive cases in the self-sampling arm. Repeat cytology because of inadequate cytology quality after a positive screen result was recommended in 1.3% of clinician-collected cases and 1.6% of self-sampling cases with cytology (1.3% of self-sampling cases had other recommendations). Repeat cytology because of inadequate cytology quality in a follow-up smear at 6 months was recommended in 1.5% of clinician-collected cases and 1.8% of self-sampling cases.

The number of referrals increased from 20 to 39 per 1,000 women screened, and the CIN2+ detection rate increased from 11 to 14 per 1,000 women screened ($p < 0.001$). Overall, the referral rate doubled and the CIN2+ detection rate increased by 34% ($p < 0.001$). For the youngest age group, the referral rate increased by 92% ($p < 0.001$) and the CIN2+ detection rate by 30% ($p < 0.001$).

Cytology or histology was performed in 77% of women directly referred to the gynaecologist in the hrHPV-based programme (Figure 3). In the remaining 23%, only colposcopy was performed after referral or women were lost to follow up. In case of indirect referrals, in 64.5% of clinician-collected or 56.0% of self-sampling ($p = 0.974$) cytology or histology was performed. The CIN2+ detection rate after cytology or histology varied across the four different groups in the hrHPV-based programme: from 35.7%

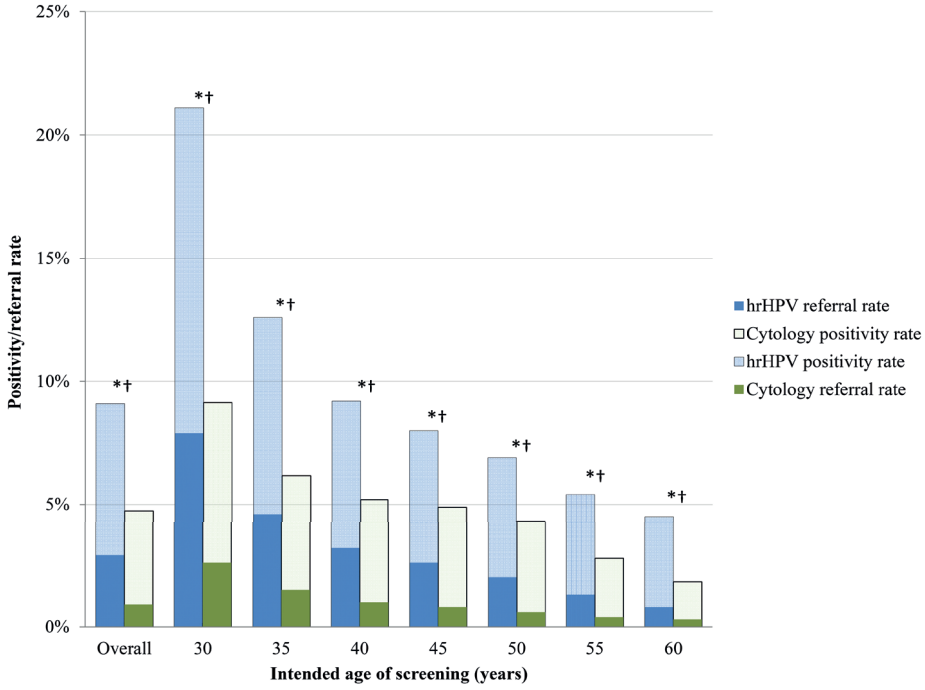

Figure 4: *Screen positivity and direct referral rates by screening programme and age.*
Cytology-based screening results are based on the 2015 screening cohort and hrHPV-based screening results are based on the 2017 screening cohort. Screen positivity in the hrHPV-based screening programme is hrHPV-positive, irrespective of reflex cytology results. 454,573 women participated in hrHPV-based screening programme and 483,146 women participated in the cytology-based screening programme. NB. Please refer to Additional file 1 for a comprehensive explanation of age group criteria.
* Pearson's chi-square test significantly different for screen positivity rates between test types ($p < 0.001$).
† Pearson's chi-square test significantly different for referral rates between test types ($p < 0.001$).

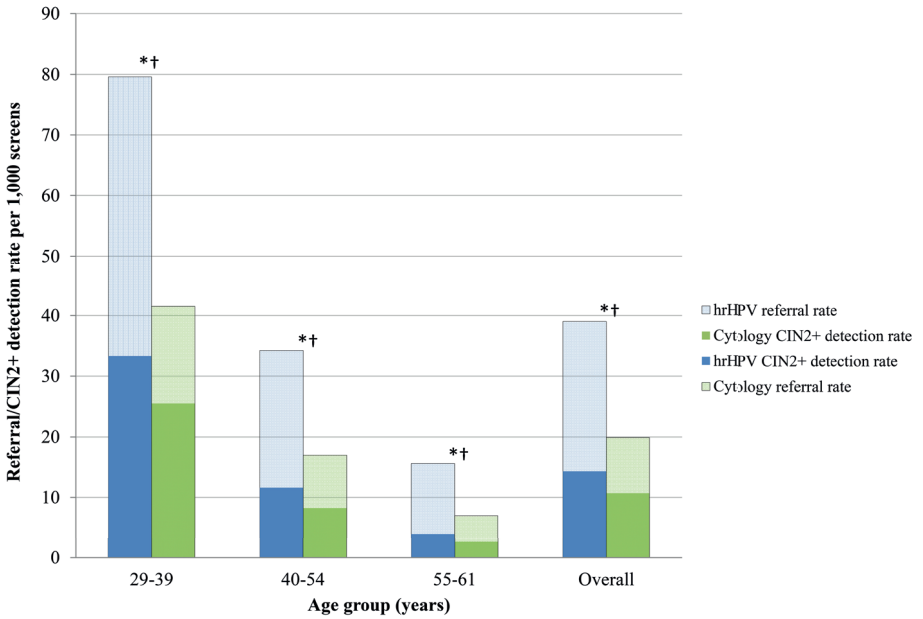

Figure 5: *Total referral and CIN2+ detection rates in all screened women by screening programme and age.* Cytology-based screening results are based on the 2015 screening cohort and hrHPV-based screening results are based on the 2017 screening cohort. 454,573 women participated in hrHPV-based screening programme and 483,146 women participated in the cytology-based screening programme. Referral rates include direct and indirect referrals. NB. Please refer to Additional file 1 for a comprehensive explanation of age group criteria.

* Pearson's chi-square test significantly different for referral rates between test types ($p < 0.001$).

† Pearson's chi-square test significantly different for CIN2+ detection rates between test types ($p < 0.001$).

in indirect referred women after a clinician collected sample to 57.1% in direct referred women after self-sampling (Figure 3).

Table 1 shows the different findings after direct and indirect referrals for the hrHPV-based and cytology-based programmes. We found that in the hrHPV-based programme after referral, approximately 2.2 times more clinically irrelevant findings were found (i.e. 'cytology only', 'no dysplasia' or CIN1), compared with approximately 1.3 times more clinically relevant findings (i.e. CIN2, CIN3 and cancer).

Harms versus benefits

Table 2 shows the number of positive screen test and number of referrals (i.e. 'harms') per CIN2+ and CIN3+ lesion detected (i.e. 'benefits') in one screening round, for both the hrHPV-based and cytology-based screening programme. We found that in the new programme, the harms per benefit increased by approximately 45% in one screening round for CIN 2+ lesions and by 51% for CIN3+ lesions. For example, to detect one CIN3+

Table 1: *Findings after referrals for colposcopy by screening programme, referral type and age, per 1,000 women screened.*

Rate per 1,000 screened women	HPV								Cytology							
	Direct**				Indirect**				Direct**				Indirect**			
	Overall	29-39	40-54	55-61	Overall	29-39	40-54	55-61	Overall	29-39	40-54	55-61	Overall	29-39	40-54	55-61
No follow-up with cytology or histology test*	6.0	12.5	5.2	2.3	3.4	6.0	3.1	1.9	0.5	0.8	0.4	0.4	2.3	4.0	2.3	0.9
Cytology only	0.7	1.1	0.6	0.4	0.1	0.3	0.1	0.1	0.2	0.2	0.2	0.1	0.2	0.3	0.2	0.1
No dysplasia	3.9	6.5	3.9	2.0	1.6	2.6	1.5	1.0	0.6	0.8	0.5	0.5	1.8	2.8	1.8	0.9
CIN1	6.3	12.8	5.6	2.4	2.1	3.8	2.1	1.0	0.9	1.7	0.8	0.4	3.0	5.8	3.0	0.9
CIN2	4.7	10.6	4.0	1.3	1.2	2.2	1.1	0.5	2.0	4.7	1.5	0.6	2.3	4.8	2.1	0.7
CIN3	6.9	17.2	5.3	1.7	1.1	2.4	0.8	0.5	4.9	12.5	3.5	1.0	1.4	3.5	1.2	0.3
Cancer	0.4	0.9	0.4	0.1	0.0	0.0	0.0	0.0	0.3	0.6	0.3	0.1	0.0	0.1	0.0	0.0

N.B. Cases with a histological record that is coded as 'no diagnosis' (average of 1.2% of total cases) are included in the denominator but not presented in the table. Please refer to Additional file 1for a comprehensive explanation of age group criteria.

* These women are referred for colposcopy but no follow up examination has been registered in PALGA. These women are either lost to follow up or only colposcopy is performed.

** Pearson's chi-square test significantly different for the distribution of outcomes between test types ($p < 0.001$).

Table 2: *Number of positive screen tests and number of referrals per detected CIN2+ or CIN3+ lesion.*

		Cytology	*HPV*	*Difference per round (%)*
POSITIVE SCREENS				
		Total*		
Number of positives needed to detect one:	**CIN2+**	4.4	6.3	44
	CIN3+	7.2	10.8	50
REFERRALS				
		Total*		
Number of referrals needed to detect one:	**CIN2+**	1.9	2.7	47
	CIN3+	3.0	4.6	53
		HSIL		
Number of referrals needed to detect one:	**CIN2+**	1.3	1.3	-2
	CIN3+	1.8	1.8	-2
		ASC-US/LSIL		
Number of referrals needed to detect one:	**CIN2+**	3.0	4.7	57
	CIN3+	7.5	12.0	60

NB. Triage algorithms for ASC-US/LSIL screens differ between the cytology-based and hrHPV-based programmes; in the hrHPV-based programme, all hrHPV-positive, ASC-US/LSIL screens are directly referred whereas, in the cytology-based programme, ASC-US/LSIL screens were triaged for repeat cytology after six months.

* Total include all positive hrHPV tests irrespective of the reflex cytology result (includes hrHPV-positive screens with reflex cytology of NILM, inadequate or missing).

lesion in the cytology-based programme, 3.0 women where referred, compared to 4.6 in the hrHPV-based programme. This difference was mostly due to the increase in referrals of hrHPV-positive screens with ASC-US/LSIL cytology in the hrHPV-based programme, which stemmed from a national policy change to refer, rather than observe, hrHPV-positive screens with ASC-US/LSIL results.

DISCUSSION

Main findings

The nationwide implementation of primary high-risk HPV DNA screening in the Netherlands has been successful, with the programme now fully implemented and results generally as expected, apart from a lower than anticipated participation rate. In the first year, we observed a participation rate of 61%, which was lower than observed in the previous cytology-based programme (64%). Screen positivity was higher in the hrHPV-based programme. The cytology programme recommended observation of ASC-US/LSIL results, while the hrHPV-based programme recommended colposcopic referral for

hrHPV-positive, ASC-US/LSIL results. As expected, this increased both the number of colposcopic referrals and CIN2+ lesions detected.

Factors influencing participation rates

The introduction of self-sampling had been expected to increase participation, as a previous Dutch study (PROHTECT) found that screening non-attenders who were offered self-sampling were more likely to be screened than non-attenders.[22] While 8% of screened women used self-sampling, this did not increase overall participation, suggesting that switching is occurring. Information about switching was not publicly reported in 2017 official monitoring report,[23] and further research is needed into the characteristics of women who choose for self-sampling to provide reliable estimates of this indicator. One important difference between PROHTECT and the real-world implementation was that women needed to opt-in to self-sampling in the screening programme. Secondly, the four-month waiting period for the self-sampling kit may have delayed uptake of screening amongst women who opted-in. The self-sampling kit may be used by women who find it more convenient than attending the GP; one of the main reasons identified in a Dutch study for using a self-sampling kit.[24] Finally, although self-sampling is generally acceptable to women,[12] 23% of self-sampling kits requested by the 2017 cohort have not yet been returned (as of December 2018; personal communication, RIVM, 21 December 2018). Although the return of these kits would not have a large effect on overall participation, the reasons for not returning them should be further investigated.

Organisational factors, such as the phased roll-out of the new programme and changes in the invitation process may also have resulted in lower participation. Due to the phased roll-out of the new programme over the first quarter of 2017, women had less time to take up their screening invitations compared with the cytology-based programme, although we still observed a lower participation rate when calculating it based on 18 months of data. If the phased implementation is the cause of lower participation, we would expect participation to increase in coming months. In the cytology-based programme, GP practices could invite patients for screening, rather than women receiving an invitation from the regional screening organisation. Women who received invitations sent from GP practices were more likely to participate in the cytology-based programme than women who received invitations from screening organisations.[25] Discontinuing the involvement of GP practices in the invitation and reminder process may have led to a decline in participation, as invitations are now sent from organisations that may be unfamiliar to women; this needs further investigation.

Comparison with other studies

The hrHPV positivity rate was higher than anticipated at 9.1%, as a previous population-based Dutch study (DuSC) found a hrHPV positivity rate of 8% amongst women of

screening age.[26] This difference may be explained by differences in sociodemographic characteristics of women participating in the programme overall and the women included in DuSC. It could also be that there has been an increase in the incidence of hrHPV infections over time. The higher than expected hrHPV positivity rate may explain differences between the estimated referral rate of 3.4% (based on modelling)[6] and the observed referral rate of 3.9%. We found 48.2% CIN2+ detection in all women with histologically confirmed diagnosis, which was higher than the rate predicted by modelling (45%), which may be due to differences in the assumed test characteristics and the real-world performance of the hrHPV test.[6]

One surprising finding was that hrHPV positivity was lower in self-samples than in the clinician-collected samples, contrary to previous Dutch studies. One population-based study found higher hrHPV positivity in self-samples than in clinician-collected samples[12] and one randomised non-inferiority trial (IMPROVE) found equivalent hrHPV positivity between the two test types, although IMPROVE used a different clinician-collected test than is used in the screening programme.[27] Despite this, we found higher CIN2+ detection in self-sampling than in clinician-collected sampling. This may indicate that the self-sampling test has a higher CIN2+ specificity than the clinician-collected test, in contrast to results from IMPROVE, which reported CIN2+ specificity of the self-test was non-inferior (relative accuracy of 1.00).[27] Further analysis of the self-sampling kit within the screening programme is needed, controlling for background risk and population factors.

Triage of hrHPV-positive women

A higher CIN2+ detection rate was found in the hrHPV programme than in the cytology-based programme. This was expected based on the results of four large randomised trials of HPV screening.[1] However, in the new hrHPV screening programme, more referrals per screening round were needed to detect one CIN2+ lesion compared with cytology-based screening, mainly due to an increase in the number of referrals amongst women with ASC-US/LSIL cytology. This increase potentially leads to more harms for women, including anxiety for women unnecessarily referred[19] or potential overtreatment of low-grade lesions. Therefore, optimising triage to reduce unnecessary referrals should be a priority. Different triage strategies for hrHPV-positive screens have been proposed, including (but not limited to) p16/Ki67 dual staining, hrHPV genotyping, methylation, HPV E6 protein assays or combinations of these strategies.[28] Risk-based management could also be explored, in which risk factors (such as a woman's screening history) are taken into account when triaging hrHPV-positive, ASC-US primary screens.[29] The performance of additional triage tests in the Dutch setting, as well as the feasibility of implementation and any impacts on programme cost-effectiveness and the balance of harms versus benefits of the screening programme need to be considered prior

to changing the triage algorithm. The harms benefits ratio of the old cytology-based programme was considered acceptable in the Netherlands, and while in one round of screening the hrHPV-based screening programme had a more unfavourable balance, reducing the number of total screening rounds in the hrHPV-based programme (from seven to five for many woman) will result in similar overall life-time harms-benefits ratio to that of the cytology-based programme.

International comparisons

In several countries, hrHPV-based screening has been implemented, but published results are only available from Italy and Turkey. In Italy, HPV-based screening was implemented in 2012 in 19 screening programmes across ten regions. The direct referral rate from the Italian programme was comparable with the Dutch programme at 2.9%.[10] In 2014, primary HPV screening was implemented in Turkey; however, direct comparison of results is difficult due to a low participation rate (36.5%) and incomplete histological follow-up data.[9] Neither study compared hrHPV-based screening with cytology-based screening. In general, the quality of a cytology-based programme influences such a comparison. In the Netherlands, the quality of the cytology-based programme was consistently high, with low rates of unsatisfactory smears and a high positive predictive value for CIN2+ lesions compared with other European countries.[30] In a country with a less highly-performing cytology programme, the incremental effects of HPV-based screening versus cytology-based screening would be different.

Future implications for hrHPV in partly vaccinated cohorts

Given the increased sensitivity of hrHPV testing for CIN2+ lesions, detection rates are expected to be higher in the first round, as both prevalent and incident lesions are detected. As the programme reaches a steady state, and fewer prevalent lesions are detected, we expect that detection of CIN3+ lesions will decrease, as seen in the POBASCAM trial.[31] Therefore, it will be necessary to compare results from the first and subsequent screening rounds. In the Netherlands, hrHPV vaccination was offered in a catch-up programme to girls aged 13 to 16 years in 2009, meaning the first cohort of partly vaccinated women will be eligible for screening in 2023. This may necessitate changes to the programme, due to an anticipated reduction in HPV16/18 infections. Modelling has shown that with herd immunity levels greater than 50%, a reduction in the number of screening rounds may need to be considered to maintain programme cost-effectiveness in the Netherlands.[32] Finally, for full evaluation of the new screening programme, calculation of interval cancer incidence is essential to approximate the sensitivity of one screening round. Women are at highest risk of an interval cancer diagnosis four to six years after a negative screen,[33] as the screening interval is five years. As

such, the first opportunity for comparison of this indicator will come five years after the implementation of hrHPV-based screening.

Strengths and limitations of this study

This is the first study to report the results of the nationwide implementation of a hrHPV-based screening using prospectively-collected cyto- and histopathological data. We have been able to compare this reliably with the previous cytology-based programme due to the nationwide coverage of PALGA. The large number of screens included in our study has allowed us to make statistically robust comparisons between indicators of the two programmes. Our study has some limitations. The follow-up time included in our study was shorter for the hrHPV-based programme than the cytology-based programme, as the hrHPV-based programme was implemented more recently. We are unable to analyse characteristics of non-attenders to the programme, as characteristics of these women are not captured by PALGA. We are also unable to differentiate loss to follow-up after referral for colposcopy from cases where women attended colposcopy, but no cytology or histological diagnostic test was performed. This information is unavailable for both the hrHPV-based programme and the cytology-based programme. As such, we cannot investigate whether adherence to referral advice has changed over time. Furthermore, compliance to referral, used to differentiate cytology only and no follow-up with cytology or histology in Table 1, may have been underestimated for hrHPV screening due to the shorter follow-up time for the hrHPV-based programme; however, without data on colposcopies, the extent of this underestimation is unknown. The identifier used in PALGA to link records is non-unique (based on the first eight letters of a woman's surname and her date of birth). This means that records from multiple women could be linked to one identifier (called an administrative fusion). It is unlikely that there is a difference in the number of administrative fusions between the two programmes and therefore, we expect that this has not influenced our results. Finally, because the cytology-based programme recommended observation of ASC-US/LSIL results, while the hrHPV-based programme recommended colposcopic referral for hrHPV-positive, ASC-US/LSIL results, distinguishing the relative impact of the hrHPV test itself versus the lower threshold for referral on both unnecessary testing and CIN2+ detection is difficult.

CONCLUSIONS

This is the first time that results of nationwide implementation of hrHPV-based screening have been reported using high-quality data with extended follow-up. Our results show implementation of the hrHPV-based programme has been successful. However, the lower participation rate in the hrHPV-based programme needs to be investigated further to ensure that the screening programme remains effective and efficient. Detection of CIN2+ lesions was higher in the hrHPV-based programme at the cost of more unnecessary referrals. Careful consideration needs to be given to potentially changing triage of HPV-positive screens to reduce unnecessary referrals. Ongoing monitoring of the hrHPV-based programme is essential to ensure that a reasonable balance of benefits and harms continues to be achieved.

LIST OF ABBREVIATIONS

ASC-US – atypical squamous cells of undetermined significance
CIN – Cervical intraepithelial neoplasia
GP – general practitioner
hrHPV – high-risk human papillomavirus
HSIL – high-grade squamous intraepithelial lesion
LSIL – low-grade squamous intraepithelial lesion
PALGA – Nationwide network of cyto- and histopathology in the Netherlands
NILM – Negative for intraepithelial lesion or malignancy
RIVM – Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)

DECLARATIONS

Ethics approval and consent to participate

This study is exempt from ethical approval by a medical ethical committee under Dutch law. Non-identifiable data was used for this study and data was used after approval by PALGA.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands, but restrictions apply to the availability of these data.

Competing interests

CA, HvA and IdK report receiving funding from the Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu) for the conduct of this study. AM reports receiving funding from the Facilitaire Samenwerking Bevolkingsonderzoeken for work related to this study and funding from DDL Laboratories outside of the study. All other authors have no conflicts of interest to declare.

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involvement in the study design, data collection, data analysis, interpretation of the data, writing of the report, or the decision to submit the paper for publication.

Authors' contributions

CA wrote the manuscript, with assistance from HvA and IdK. CA, HvA and IdK selected indicators and defined the cohorts. HvA conducted the data analysis, CA checked the data analysis and finalised tables and figures with assistance from IdK. AS created the datasets and reviewed drafts of the manuscript. WM, BvH, HN, AvB, HvL, JH, AM, KH and JV were involved in the collection and processing samples for the population-based cervical cancer screening programme and reviewed drafts of the manuscript. FvK and RS contributed to programme planning, programme governance and reviewed drafts of the manuscript.

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ADDITIONAL FILE 1: DETAILED DESCRIPTION OF METHODS FOR CALCULATING RESULTS

Supplement to: Aitken CA, van Agt HME, Siebers AG et al. Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study

To calculate results for our study, we used extracts of all cervical cytology and histology records from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). Primary screening tests were selected from 1 January 2015 to 31 March 2016 for the cytology cohort and from 1 January 2017 to 30 June 2018 for the hrHPV cohort. We chose not to select 1 January 2016 to 31 March 2017 as the comparison period for cytology, due to an overlap with the new programme. The maximum follow-up time for the cytology cohort was 40 months and four days for screens taken on 1 January 2015 (end date of dataset: 4 May 2018) and the maximum follow-up time for the hrHPV cohort was 20 months and 28 days for screens taken on 1 January 2017 (end date of dataset: 28 September 2018).

Ages included in analysis

Due to changes in the organisation of invitations, grouping of age is slightly different between the old cytology-based programme and the new hrHPV-based programme. In the cytology-based programme, women could be invited at different dates in the year that they were eligible for screening; this could be at the start of the year they were eligible for screening, on their birth date or other time during the year that they were eligible for screening. Invitations could also be sent by different organisations (the regional screening organisation, the woman's GP or a combined approach). In the hrHPV-based programme, women are sent an invitation letter on their birth date from their regional screening organisation. Due to these differences, many women aged 29, 34, 39, 44, 49, 54 and 59 had primary screening in the cytology cohort between 1 January 2015 and 31 March 2016. The age categories outlined in Table A1 for the cytology cohort have been used for many years to categorise age in the annual screening programme Monitor published by the Dutch National Institute for Public Health and the Environment. For this reason, we have used these age groupings for the cytology cohort in our study.

Table A1 shows how age group was defined in our analysis. A very small number of 29-year olds (36 in total) had a primary screening test recorded in the hrHPV-based programme between 1 January 2017 and 30 June 2018; these women were included in the 30 years age group.

Participation

In the cytology-based programme, participants were defined by the number of screening test results from clinician-based sampling, performed between 1 January 2015 and 31 March 2016. The eligible population was based on the number of women who would reach screening age in 2015 in the Dutch population on 1 January 2015 (i.e. aged 29, 34, etc.), adjusted for the risk of having their cervix removed by hysterectomy.

In the hrHPV-based programme, participants were defined by the number of screening test results from clinician-based sampling or self-sampling, performed between 1 January 2017 and 30 June 2018. The eligible population was based on the number of women who would reach screening age in 2017 in the Dutch population on 1 January 2017 (i.e. aged 29, 34, etc.), adjusted for the risk of having their cervix removed by hysterectomy.

Referral

Table A2 and Table A3 shows the definitions used to calculate the direct and indirect referral rates in the cytology-based programme and hrHPV-based programme.

In the cytology-based programme, there were two triages for repeat cytology (first indirect at 6 months and second indirect at 12 months; see Figure 1a). Therefore, the indirect referral rate combines first and second indirect referrals. This rate was calculated amongst women who complied to the advice for repeat cytology within 365 days from the primary screening test for 6 months repeat cytology, and within 630 days from the 6 months cytology test for 12 months repeat cytology.

In the hrHPV-based programme, indirect referral rates were calculated in women who complied to the advice for repeat cytology within 365 days from of the date of primary screening.

Detection

Table A2 and Table A3 shows the definitions used to calculate the detection rates in the cytology-based programme and hrHPV-based programme.

Detection rates were calculated in women who were referred to the gynaecologist (due to their result on the screening test or their result from repeat cytology) and complied to the referral advice. In Figure 2, all detection rates are calculated amongst women who complied with referral advice within 150 days of a primary screening or follow-up test. In Tables 1 and 2, compliance within 150 days was only used to define the 'no follow-up with cytology or histology test' and 'cytology only' groups.

Women who complied to referral (i.e. they had an examination after 150 days from the referral advice, either from screening test of repeat cytology) but did not have a histology result were assumed to have had a cytology test only. The most severe histological

diagnosis that was recorded within the episode of screening was used to categorise histology results.

Colposcopies without a histology or cytology test were not registered in the PALGA database. Referred women who did not comply, according to the definition, may therefore consist of women who are lost to follow-up or women who had colposcopy without histology or cytology.

Harms vs. benefits

To estimate the harms-benefits ratio of screening, we calculated the number of screen positives per detected CIN2+ and CIN3+ case and number of referrals per detected CIN2+ and CIN3+ case.

Table A1: *Age groupings used in analysis by programme type.*

	Age groupings used in monitoring reporting	
Label used in this study	**Cytology-based programme**	**hrHPV-based programme**
30 years	29-33 years	29*-34 years
35 years	34-38 years	35-39 years
40 years	39-43 years	40-44 years
45 years	44-48 years	45-49 years
50 years	49-53 years	50-54 years
55 years	54-58 years	55-59 years
60 years	59-63 years**	60-64 years**

* 36 women aged 29 years had screening registered as part of the hrHPV-based screening programme in 2017.

** The maximum age of women included in this study was 61 years, however, five-year age categories are used in the Monitoring reports for the cervical cancer screening programme.

Table A2: *Calculation of the indicators shown in Figure 2 for participation, referral and detection within the new hrHPV-based screening programme, 2017 cohort.*

Indicator	Numerator	Denominator
Participation		
Participation rate	*Participants*, i.e. number of screening tests from clinician-based sampling or self-sampling, performed between 1 January 2017 and 30 June 2018.	*Eligible population*, i.e. number of women at screening ages in the Dutch population on 1 January 2017, adjusted for the risk of having their cervix removed by hysterectomy.
Referral		
hrHPV positivity	*Screen positives*, i.e. number of hrHPV positive screening tests	Participants
Cytology assessments amongst screen positives	Number of hrHPV positives with a cytology result	Screen positives
Referral rate from primary screening (direct referral)	*Direct referrals*, i.e. number of hrHPV positive screening tests with ASC-US+ cytology result	Number of screen positives with cytology assessment
Advice for follow-up smear after 6 months	*Triage cytology advice,* i.e. number of screen positives with NILM cytology	Number of screen positives with cytology assessment
Referral rate from follow-up smear (indirect referral)	*Indirect referrals*, i.e. number of follow-up smears with an ASC-US+ cytology result	Number of triage cytology performed within 365 days from the screening test.
Detection		
Histology or cytology test performed amongst direct referrals	*Histology or cytology test in direct referrals*, i.e. number of screen positives with ASC-US+ cytology where an examination was performed within 150 days from the screening test	Direct referrals
CIN2+ detection from direct referrals	Number of histological confirmed CIN2+ lesions	Histology or cytology test in direct referrals
Histology or cytology test performed in indirect referrals	*Histology or cytology test in indirect referrals*, i.e. number of follow-up smears with an ASC-US+ cytology result where an examination was performed within 150 days from follow-up smear.	Indirect referrals
CIN2+ rate from indirect referrals	Number of histological confirmed CIN2+ lesions	Histology or cytology test in indirect referrals

Table A3: *Calculation of the indicators for participation, referral and detection in the old cytology-based screening programme, cohort 2015, and within the new hrHPV-based screening programme, 2017 cohort.*

Indicator	Cohort	Numerator	Denominator
Participation			
Participation rate *Figure 2*	Cytology cohort	*Participants*, i.e. number of screening test results from clinician-based sampling, performed between 1 January 2015 and 31 March 2016.	*Eligible population*, i.e. number of women at screening ages in the Dutch population on 1 January 2015 and adjusted for the risk of having their cervix removed by hysterectomy.
	hrHPV cohort	*Participants*, i.e. number of screening test results from clinician-based sampling or self-sampling, performed between 1 January 2017 and 30 June 2018.	*Eligible population*, i.e. number of women at screening ages in the Dutch population on 1 January 2017 and adjusted for the risk of having their cervix removed by hysterectomy.
Referral			
Screen positivity *Figure 3*	Cytology cohort	*Screen-positives*, i.e. number of screening tests with ASC-US+ cytology	Participants
	hrHPV cohort	*Screen positives*, i.e. number of hrHPV positive screening tests	Participants
Referral rate from primary screening (direct referral) *Figure 3, Figure 5, Table 1, Table 2*	Cytology cohort	*Direct referrals*, i.e. number of screen positive women with HSIL cytology result	Participants
	hrHPV cohort	*Direct referrals,* i.e. number of hrHPV positive screening tests with ASC-US+ cytology result	Participants
Referral rate from follow-up smear (indirect referral) *Figure 5, Table 1, Table 2*	Cytology cohort	*Indirect referrals*, Number of follow-up smears at first or second repeat cytology, with HSIL cytology result	Participants
	hrHPV cohort	*Indirect referrals*, Number of follow-up smears with ASC-US+ cytology result	Participants
Detection			

Table A3: *Calculation of the indicators for participation, referral and detection in the old cytology-based screening programme, cohort 2015, and within the new hrHPV-based screening programme, 2017 cohort. (continued)*

Indicator	Cohort	Numerator	Denominator
CIN2+ *Figure 5, Table 1, Table 2*	Cytology cohort	Number of CIN2+ lesions found in referred women (direct and indirect).	Participants
	hrHPV cohort	Number of CIN2+ lesions found in referred women (direct and indirect).	Participants
All findings *Table 1, Table 2*	Cytology cohort	Number of findings in referred women (direct and indirect). For cytology only group, women must have had an examination within 150 days of primary screening (direct referrals) or within 150 days of repeat cytology test (indirect referrals).	Participants
	hrHPV cohort	Number of findings in referred women (direct and indirect). For cytology only group, women must have had an examination within 150 days of primary screening (direct referrals) or within 150 days of repeat cytology test (indirect referrals).	Participants

Chapter 2.2

Cost-effectiveness of HPV-based cervical screening based on first year results in the Netherlands: a modelling study

Erik E.L. Jansen[1], Steffie K. Naber[1], Clare A. Aitken[1], Harry J. de Koning[1], Marjolein van Ballegooijen[1], Inge M.C.M. de Kok[1].

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam

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ABSTRACT

Objective

We aim to compare the cost-effectiveness of the old cytology programme with the new high-risk human papillomavirus (hrHPV) screening programme, using performance indicators from the new Dutch hrHPV screening programme.

Design

Model-based cost-effectiveness analysis.

Setting

The Netherlands.

Population

Dutch 30-year-old unvaccinated females followed up lifelong.

Methods

We updated the microsimulation screening analysis (MISCAN) model using the most recent epidemiological and screening data from the Netherlands. We simulated both screening programmes, using the screening behaviour and costs observed in each programme. Sensitivity analyses were performed on screening behaviour, utility losses and discount rates.

Main Outcome Measures

Cervical cancer incidence and mortality rates, number of screening tests and repeat tests, colposcopy referrals by lesion grade, costs from a societal perspective, quality-adjusted life-years (QALYs) gained and cost-effectiveness.

Results

The new Dutch cervical cancer screening programme decreased the cervical cancer mortality by 4% and the incidence by 1% compared to the old programme. Colposcopy referrals of women without cervical intra-epithelial neoplasia grade 2 or worse increased by 172%, but 13% more QALY's were still achieved. Total costs were reduced by 21%, mainly due to fewer screening tests. Per QALY gained, the hrHPV programme cost 46% less (€12,225) than the cytology programme (€22,678) and hrHPV-based screening remained more cost-effective in all sensitivity analyses.

Conclusions

The hrHPV-based screening programme was found to be more effective and costeffective than the cytology programme. Alternatives for the current triage strategy should be considered to lower the number of unnecessary referrals.

Tweetable abstract

First results after implementation confirm that HPV screening is more cost-effective than cytology screening.

INTRODUCTION

In January 2017, the Dutch population-based cervical cancer screening programme switched the primary screening test from cytology to the high-risk human papillomavirus (hrHPV) test. Women can now choose either to have a cervical smear taken by their general practitioner (GP) or to use a self-sampling kit. The latter option was added as an alternative screening method to increase attendance rates in women who feel uncomfortable with taking a test at their GP. The implementation of this new programme was based on, amongst other considerations, cost-effectiveness analyses showing that primary hrHPV screening is more cost effective than primary cytology screening.[1,2] However, as no other country had implemented primary hrHPV screening up to that time, many model inputs had to be based on assumptions, potentially biasing the results.[1,2]

The Dutch cervical cancer screening programme has been monitored for decades, using high-quality data.[3] However, information on important performance indicators (such as the participation rate, use of self-sampling, positivity rates, referral rates, precancerous cervical intraepithelial neoplasia (CIN) detection rates and costs) of the primary hrHPV-based screening programme has only recently been published.[4] Some key indicators were found to be unfavourable for the effectiveness of the new programme, such as a drop of three percentage points in screening participation as well as a lower adherence to triage testing.[4,5] This unique information from the implementation of hrHPV-based screening can now be used as reliable model input for a cost-effectiveness analysis to compare the new programme with the old cytology-based screening programme.

Using this newly available monitoring data, we aimed to answer the following research question: What are the costs, effects and cost-effectiveness of the newly implemented cervical cancer screening programme using primary hrHPV-testing compared to the old cytology-based screening programme? We will simulate scenarios where a 30-year-old cohort of unvaccinated women are offered either the full cytology-based programme or the full hrHPV-based programme and follow these women up until death. For these women, we will present costs per life-years gained and costs per quality-adjusted life-

years (QALYs) gained as the main outcome. The number of referrals to a gynaecologist and detected CIN, most of which will not progress to cancer, will be presented, as these are considered to be important harmful effects of screening.[6,7] These results are useful for policymakers of similar countries to decide whether a switch to primary hrHPV screening is beneficiary for their country.

METHODS

To estimate the effects of both the cytology screening programme and the hrHPV-based screening programme in The Netherlands, the MISCAN-Cervix (Microsimulation Screening Analyses-Cervix) model was used.[1, 8-10] An extensive model description can be found in Appendix S1. In short, MISCAN-Cervix is a microsimulation model, coded in Borland Delphi 7, that simulates the natural history of cervical cancer in a hypothetical population. Women have an age-specific risk to acquire one or multiple hrHPV infections which may or may not progress sequentially to CIN1, CIN2 and CIN3 or regress at any time. A CIN3 may progress to a micro-invasive cancer and later into more invasive cancer stages before it is clinically detected. Different screening strategies can be simulated in this population to quantify and compare the harms and benefits of each strategy (Appendix S1: Figures S1-S4, Table S1). As described in Appendix S1, many model assumptions are based on high quality data from the Netherlands Cancer Registry (NCR) and the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), both having a national coverage.[11, 12] To reduce the impact of random variability on the predicted outcomes, the model simulates a large population of 10 million women and applies the same sequence of random numbers in each simulation.

Model updates

For this analysis, we extended and recalibrated (Appendix S1: Figure S6-S9) the existing model using the most recent cancer and screening data from the NCR and PALGA[11, 12] in order to incorporate three new features compared to the previously published model. First, hrHPV infections in the model are now type-specific, allowing for different progression probabilities per hrHPV type. Four groups of hrHPV types were defined based on their oncogenicity and their presence in different HPV vaccines.[13, 14] HPV16, HPV18, other hrHPV types covered by the nonavalent vaccine (HPV-31/33/45/52/58), and the remaining seven hrHPV types (HPV-35/39/51/56/59/66/68). Second, FIGO2+ cancers were split up into FIGO2, FIGO3 and FIGO4, as survival probabilities differ between those stages. Third, the test characteristics of both cytology and the hrHPV test were updated based on evidence from published literature and to be able to fit well to observed data on interval cancers and false positive rates by hrHPV status.[15-18] In this updated version, 12% of exist-

ing precancerous lesions are consistently missed by cytology, and the probability of an abnormal cytological result is higher in hrHPV-positive women (calibrated parameters, see Table S3 in Appendix S1). Multiple studies found the concordance between hrHPV tests from different manufacturers to be lower in lower grade lesions (≤ CIN1), suggesting that more hrHPV infections are missed.[15, 19] Therefore, we now assume that for hrHPV-positive women the sensitivity of the hrHPV test increases with the severity of their lesion.

Screening programmes

In the Dutch cytology programme, women aged 30–60 years were invited for screening every five years. Women with a high-grade squamous intraepithelial lesion (HSIL) or worse were directly referred to colposcopy, while women with a low-grade cytological abnormality (i.e. atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion) were invited for a repeat test after six months. The vast majority of the executive laboratories analysed those cervical smears using both cytology and hrHPV testing, although some still used cytology only.[20] When an HSIL or worse was found at this co-test, the woman was referred to colposcopy. Women testing hrHPV-positive were also referred to colposcopy if they had low-grade cytological abnormalities result. Women testing negative on both tests were discharged from follow-up while the remaining women were invited for a repeat cytology test after 12 months (Appendix S1: Figure S5).

In the hrHPV-based screening programme, women are still invited every five years at the ages 30–60; however the screening interval has been extended to ten years for women testing hrHPV-negative at age 40 or 50 and there is an extra invitation at age 65 for women testing hrHPV-positive at age 60. After a positive hrHPV test, the sample is analysed with cytology, after which women with abnormal cytology results are referred to a gynaecologist, while women with normal cytology are invited for a repeat cytology test after six months (Appendix S1: Figure S5). Women who are uncomfortable with taking a test at their GP can request a self-sampling kit, although if their test result is hrHPV-positive, they still need a smear taken by their GP to test for cytological abnormalities.

In the Netherlands, primary screening and follow-up tests are fully paid for by the government. If a woman is referred for colposcopy, health insurance covers the diagnosis and treatment costs. Health insurance is obligatory in the Netherlands and each insured person is also liable for an excess.

Model assumptions – Demographic characteristics, epidemiology and natural history

A cohort of ten million women was simulated and followed until death. This cohort represents 30-year old Dutch women in 2019 with regard to their remaining life expectancy (54.3 years), hysterectomy probabilities, hrHPV epidemiology and progression probabilities to CIN and cancer as described in Appendix S1.

Model assumptions –screening behaviour

The screening behaviour of all women in The Netherlands is registered on an individual level in PALGA. Based on these observations, we were able to accurately model the screening behaviour in both programmes. As described in more detail in Appendix S1, the screening behaviour during the cytology programme was based on all women invited in 2015 and the screening behaviour during the hrHPV programme was based on all women invited in 2017.

Participation by age

The age-specific attendance at the primary test differs between the programmes. Table 1 shows the percentage of the female population without a hysterectomy that participates in screening; in the hrHPV-based programme this can either be the regular GP test or a self-sampling kit.

For most ages, the attendance rates could be directly observed in the first screening round after implementation of hrHPV screening. However, in this first screening round, all women aged 45 and 55 were invited for screening, whereas in future rounds only those that tested hrHPV-positive in the preceding round or did not participate the preceding round will be invited. Therefore, fewer women will participate at those ages than currently observed in the first screening round (calculations presented above Appendix S1: Table S2). Also, in this first screening round no women aged 65 were invited yet as they first had to test hrHPV-positive at age 60 first. Therefore, we assumed the participation rate for women at age 65, who tested hrHPV-positive at age 60, to be the same as age 60.

Distribution of screenings across the population

The chance that an individual woman participates in a screening round is not entirely random; the total attendance is assumed to be distributed among 90% of the female population that potentially participates in screening, while the remaining 10% never attends a GP test ('never attenders') and have a 2.6 times higher background risk for acquiring an hrHPV infection (calibrated parameter, see Appendix S1). Also, if a woman attends one screening round, she is more likely to attend the next round and vice versa.

Of all self-sampling users in the new screening programme, 10.6% were assumed to have been never attenders in the old screening programme, based on screening histories in the previous two screening rounds (calculations described in Appendix S1). Since women aged 30 or 35 were not invited at least twice before, the proportion of young women taking a self-sample that would otherwise be never attenders was assumed to be equal to the weighted average proportion of 40-60 year old women. For all ages, the total screening attendance was higher in the cytology-based programme than in the hrHPV-based programme (Table 1).

Table 1. *Modelled screening behaviour by type of screening programme: base case assumptions*

Screening behaviour	Cytology-based screening programme	hrHPV-based screening programme
*GP test participation by age in all women of the population**		
- 30 years	52.3%	43.4%
- 35 years	57.9%	49.3%
- 40 years	64.3%	56.4%
- 45 years	67.6%	15.6%**
- 50 years	70.4%	61.5%
- 55 years	69.6%	12.7%**
- 60 years	66.8%	60.3%
- 65 years	NA	3.1%***
*Self-sampling participation by age**		
- 30 years	NA	5.5%
- 35 years	NA	4.8%
- 40 years	NA	4.5%
- 45 years	NA	0.9%**
- 50 years	NA	4.6%
- 55 years	NA	1.0%**
- 60 years	NA	5.7%
- 65 years	NA	0.2%***
Adherence to cytology after a positive self-sample	NA	90.1%
Adherence to triage testing		
- 6 months after primary test	92.2%	77.1%
- 6 months after primary self-sample	NA	41.6%
- 18 months after primary test	67.3%	NA
Adherence to a referral for colposcopy after a…		
- Direct referral (ASC-US/LSIL)	NA	88.4%
- Direct referral (HSIL)	97.0%	96.9%
- Referral at 6 months after primary test (ASCUS/LSIL)	97.5%	88.4%
- Referral at 6 months after primary test (HSIL)	97.5%	96.9%
- Referral at 18 months after primary test	52.4%	NA

ASC-US, atypical squamous cells of undetermined significance; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NA, not applicable.

* Simulated participation rate in all women excluding those who have had a hysterectomy and those with a prevalent diagnosed cancer.

** Participation in the general population is much lower at ages 45 and 55 because significantly fewer women are invited for screening at these ages (i.e. only those who do not participate or test hrHPV-positive in the preceding screening round).

*** Participation in the general population is much lower at age 65 because significantly fewer women are invited for screening at this age (i.e. only those who test hrHPV-positive at age 65).

Participation in triage testing and colposcopy

Adherence to triage testing and colposcopy was monitored in both programmes. In the hrHPV-based programme, the adherence to triage testing was lower in self-sampling users (41.6%) than in women who attended the primary test at their GP (77.1%). Also, adherence to colposcopy was higher in women with HSIL (96.1%) than in women with lower grade cytology results (88.4%). In the cytology-based programme, the adherence to triage testing at 18 months after the primary test (67.3%) was lower than at 6 months after the primary test (92.2%). The adherence to colposcopy at 18 months (52.4%) was considerably lower than after a direct referral or a referral 6 months after the primary test (97% and 97.5% respectively).

Model assumptions – test characteristics, costs and utilities

The sensitivity and specificity of both cytology and the hrHPV-test are presented in Table S3 of Appendix S1. The test characteristics of cytology were calibrated to observed data, whereas the test characteristics of the hrHPV-test were derived from literature[15, 21] as described in Appendix S1.

All costs and utilities applied are presented in Table 2. The cost-effectiveness analysis was performed using a societal perspective. All costs presented are in euros (€) and are indexed to the year 2019.[22, 23] The utilities for screening and disease are obtained from an empirical Dutch study by de Kok et al. using the SF-6D questionnaire.[24] Costs and effects were discounted annually by 3% as suggested by Sanders and colleagues in their recommendations for cost-effectiveness analyses.[25]

Sensitivity analyses

Multiple univariate sensitivity analyses have been performed. First, we assumed the screening attendance and/or triage adherence as observed in the cytology-based programme (Table 1) to also hold for the hrHPV-based programme. Second, we used an alternative published disutility set.[1] Last, we performed the analyses using discount rates of 4% for costs and 1.5% for effects as is the guideline of the National Health Care Institute in The Netherlands.[26]

Core outcomes

Outcomes of interest were total number of screening tests, referrals to colposcopy, cancer incidence, cancer mortality, costs, life-years gained and QALYs gained compared to a situation without screening. All outcomes will be presented per 100 000 30-year-old women followed for their remaining life.

Table 2. *Base-case assumptions on costs and disutilities applied for screening, diagnosis and treatment*

	Disutility (%)[24]	Duration of disutilty (months)[24]	Costs	
			€ (2019)	Source
SCREENING				Dutch public health subsidy scheme[22]
Primary cytology programme				
Primary cytology test	0	0	70	
Repeat cytology test	0.03	15	51	
Reflex hrHPV test after cytology repeat test	0	0	139	
Primary hrHPV-test programme				Dutch public health subsidy scheme[22]
Primary hrHPV-test	0	0	58	
Primary hrHPV self-sampling kit	0	0	43	
Reflex cytology after hrHPV-test	0	0	26	
Repeat cytology after hrHPV self-sampling	0.03	1	52	
Repeat cytology after 6 months	0.03	6	53	
DIAGNOSIS AND TREATMENT				Report on the effects and costs of cervical cancer screening in the Netherlands in 2006[23]
No CIN detected	0.03	1	316	
CIN1	0.03	1	986	
CIN2	0.03	1	1,461	
CIN3	0.03	1	1,710	
FIGO1A	0.08	12	5,601	
FIGO1B	0.08	12	13,283	
FIGO2+ clinically detected	0.14	12	12,226	
FIGO2+ screen detected	0.14	12	13,092	
Cancer survivor	0.03	120	0*	
Palliative care	0.5	12	29,745	

CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynaecology and Obstetrics; HPV, human papillomavirus.
*Costs included in treatment costs.

Ethics approval and patient involvement

Ethical approval by a medical ethical committee was not required under Dutch law as no patients were involved in the development of the research and only non-identifiable data was used for this study.

RESULTS

Model calibration

After calibration, the model outcomes fitted the observed age-specific cervical cancer incidence rates, cervical cancer stage distribution, detection rates of CIN and cervical

cancer, hrHPV positivity rates and the hrHPV-type distribution by age and by lesion grade (Appendix S1, Figures S10-S15). The model also validated well with age-specific cervical cancer mortality rates observed in the Netherlands in 2004-2013 (Appendix S1: Figure S16).

Table 3. *Base case results per 100 000 women simulated lifelong*

	Screen strategy			Difference between hrHPV and Cytology (%)
	No screening	Cytology	hrHPV	
Effects (numbers, undiscounted)				
Total screening tests		444,356	364,306	-18
- Primary screening tests (GP)	-	422,959	281,710	-33
- Primary self-samples	-	-	25,797	NA
- Reflex cytology after positive GP test	-	-	33,906	NA
- Cytology smear after positive self-sample	-	-	3,384	NA
- Tests 6 or 18 months after primary test	-	21,397	19,509	-9
Referrals to colposcopy	-	7,746	12,841	+66
- No lesion present	-	1,458	5,242	+260
- CIN 1	-	1,514	2,851	+88
- CIN 2	-	1,523	2,039	+34
- CIN 3 / AIS	-	3,070	2,509	-18
- Screen detected cervical cancer	-	181	200	+10
Clinically detected cervical cancers	1,157	522	496	-5
Total cervical cancers	1,157	704	697	-1
Cervical cancer mortality	440	215	206	-4
Life-years gained compared to no screening	-	5,163	5,250	+2
QALY's gained compared to no screening	-	4,580	5,161	+13
Costs (€ millions, undiscounted)				
Screening tests	-	33	19	-41
Diagnosis and treatment of precancerous lesions and false-positive referrals	-	9	12	+24
Diagnosis and treatment of cervical cancer	14.7	8	8	-2
Palliative care	13.1	6	6	-4
Total costs	27.7	57	45	-21
Cost-effectiveness (in €, discounted yearly by 3% for both costs and effects)				
Costs per life-year gained compared to no screening	-	15,247	10,890	-29
Costs per QALY gained compared to no screening	-	22,678	12,225	-46

AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; GP, general practitioner; hrHPV, high-risk human papillomavirus; NA, not available because this was not present in the cytology programme; QALY, quality adjusted life-year.

Effects, costs and cost-effectiveness

Table 3 presents the base-case results per 100 000 30-year-old women followed for their remaining life. The table includes the predicted effects, costs and cost-effectiveness of offering either no cervical cancer screening at all, the cytology screening programme or the hrHPV-based screening programme. Compared to the cytology programme, the hrHPV-based programme used fewer screening tests (-18%), referred more women to colposcopy (+66%), decreased the cancer incidence (-1%) and mortality (-4%) and reduced the total costs (-21%). The extra referrals to colposcopy were predominantly among women with ≤ CIN1 and the decrease in total costs was mainly due to the lower number of screening tests.

The cost-effectiveness of the hrHPV-based programme was more favourable than that of the cytology-based programme. When compared to no screening, the cytology programme cost €22,678 per QALY gained, while this was €12,225 (-46%) for the hrHPV-based programme. Per life-year gained, the cytology programme cost €15,247, while this was €10,890 (-29%) for the hrHPV-based programme.

Sensitivity analyses

Figure 1 shows that when the attendance rates at primary screening in the hrHPV-programme were assumed to be equal to those of the cytology programme, the cost-effectiveness of the hrHPV-based programme slightly deteriorated from €12,225 to €12,951 per QALY gained. Assuming the same adherence in the triage across both programmes also slightly deteriorated the cost-effectiveness of the hrHPV-based programme (€13,108 per QALY gained). When both equal screening attendance and equal triage adherence were assumed, the cost-effectiveness would deteriorate to €13,757. Nevertheless, under these assumptions, the hrHPV-based programme would still remain more cost effective than the cytology-based programme (€22,678 per QALY gained).

Using the alternative set of disutilities or discount rates improved the cost-effectiveness of both programmes substantially, however the hrHPV-based programme remained the most cost-effective option of the two in both cases.

DISCUSSION

Main findings

According to our modelling analyses, the recent switch from cytology to hrHPV testing in the Dutch cervical cancer screening programme will improve its cost-effectiveness. Compared to the lifetime cytology-based screening programme, the lifetime hrHPV-based programme is expected to incur considerably fewer costs (-21%) for a modestly higher number of life-years (+2%) gained and 13% more QALYs gained.

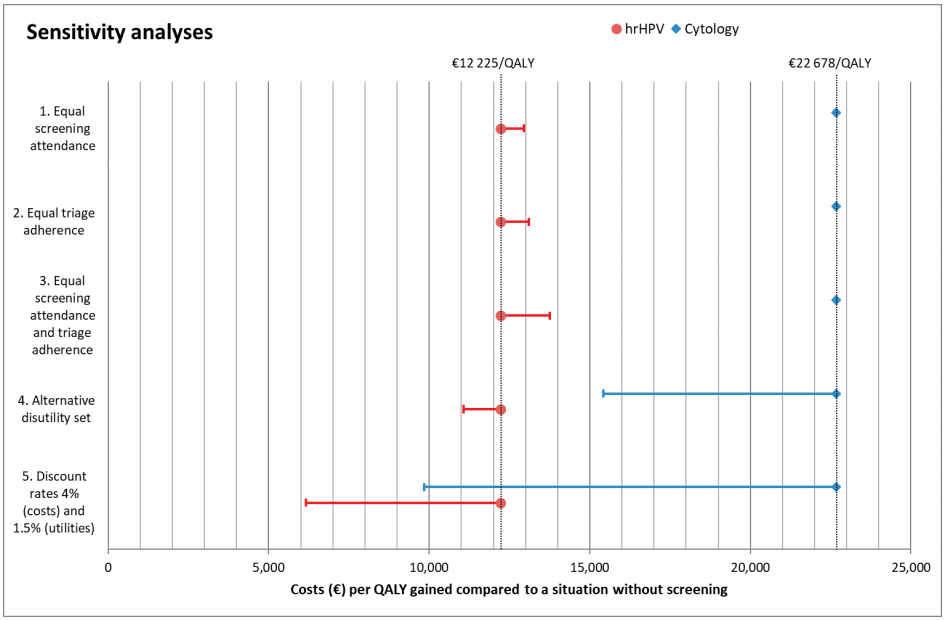

Figure 1. *Results of the sensitivity analyses.* The red dots and blue diamonds indicate the base-case cost-effectiveness of the hrHPV-based programme and the cytology-based programme respectively. The horizontal lines indicate how the cost-effectiveness of each programme would change when: (1) the attendance to primary screening in the hrHPV-based programme would be equal to that of the cytology programme; (2) the adherence to triage testing would be equal to that of the cytology programme; (3) both the attendance to primary screening and the adherence to triage testing would be equal to that of the cytology programme; (4) an alternative published utility set was applied to the results of both programmes[1]; (5) costs would be discounted with 4% annually and utilities with 1.5% annually, as is recommended in The Netherlands.[26]

hrHPV, high-risk human papillomavirus; QALY, Quality adjusted life year.

The reduction in total costs by switching to the hrHPV-based screening programme is almost completely due to the reduction in screening costs. The predicted increase in life-years gained is explained by the lower cancer incidence and cancer mortality in the hrHPV-based programme, in which more precancerous lesions are detected and treated despite lower attendance rates. We found that the increase in detection of low grade precancerous lesions is substantial. As most low grade lesions will not progress to cancer, the number of women who are referred to a gynaecologist unnecessarily increases as well, causing anxiety for these women and potentially leading to overtreatment. However, the reduction in QALYs resulting from unnecessary referrals does not outweigh the QALYs gained because of the lower cancer incidence and cancer mortality.

The number of detected CIN3 lesions does not increase with the switch to hrHPV screening. Although the HPV test is more sensitive for CIN3 lesions than cytology, fewer CIN3 lesions are prevalent at screening because more low-grade lesions are picked up

before progression towards CIN3. The number of cancers detected by screening does increase, which is caused by the introduction of the extended screening intervals, allowing more lesions to progress to cancer before the next screening round.

Sensitivity analyses on screening behaviour and utilities consistently showed a more favourable cost-effectiveness of the hrHPV-based programme.

Limitations and strengths

In the Netherlands, the first cohort of women vaccinated against HPV-16 and HPV-18 will enter the screening programme in 2023. We compared the effects of hrHPV-based screening with those of cytology-based screening for unvaccinated women only. The results of both programmes are likely to be different for vaccinated and unvaccinated women in vaccinated cohorts.[10, 27] Therefore, the cost-effectiveness of screening in vaccinated populations needs further investigation.

Also, the attendance for primary screening for women aged 45, 55 or 65 could not yet be observed in the first round of the hrHPV-based programme, as the eligibility for screening at those ages normally depends on the results of the preceding round.

Furthermore, we compared the cost-effectiveness between both programmes by dividing the total costs by the total QALYs gained. Although this method does capture the overall cost-effectiveness of each programme, different cost types might be allocated to different parties depending on how the programme is funded. Because of that, costs may rise for some parties, especially those paying for diagnosis and treatment of low grade lesions. If more costs would be allocated to participating women, this may lead to different screening behaviour.

To the authors' knowledge, this is the first modelling study to use observed data from an implemented hrHPV-based organised screening programme as model inputs. The national pathology database, PALGA, which was the main source for calibrating the model and obtaining model inputs for this analysis, contains high-quality data on an individual level about results of both hrHPV-testing and cytology. Because this detailed, robust data could be used, the screening behaviour in both programmes could be modelled very accurately, thereby reducing uncertainty of the outcomes.

Furthermore, univariate sensitivity analyses were performed varying several important assumptions. The hrHPV-based screening programme remained more cost effective in all sensitivity analyses.

Interpretation

The main reason the hrHPV-based screening programme was found to be more cost effective than the cytology-based programme is because the hrHPV-based screening programme has lower screening costs while retaining the protection for cervical cancer. These screening costs are lower due to the reduced number of screening rounds

combined with lower unit costs for primary hrHPV testing versus cytology. The retained protection at longer intervals has also been demonstrated by follow-up studies of the POBASCAM trial and the ARTISTIC trial.[28, 29] Therefore, reducing the number of screening rounds can be concluded to be a safe way to improve the cost-effectiveness of hrHPV-based screening programmes.

The finding that the hrHPV-based screening programme is more cost effective than the cytology-based screening programme is in line with previous modelling studies assessing the cost-effectiveness of comparable cytology-based and hrHPV-based screening programmes.[1, 2, 27, 30] Although the methods and assumptions used in previous studies vary widely, none of them used inputs that were observed after implementation of an hrHPV-based programme. Because of that, the same screening attendance was assumed for both programmes. When comparing the difference in effects between both programmes in this study with that of previous studies, one should be aware of this difference in assumptions on screening behaviour.

The lower observed attendance rate in the hrHPV-based screening programme might be directly related to specific organisational changes that were implemented next to the switch in screening protocol.[4] For example, GPs are no longer able to personally invite women for screening. Therefore, the lower attendance rates in hrHPV-based screening might not be applicable to other countries implementing hrHPV-based screening.

Previous studies showed that offering hrHPV self-sampling could increase the participation in women who would otherwise not attend screening.[31] Now that the hrHPV self-sampling kit has been found to be non-inferior to a GP-test,[19] offering hrHPV self-sampling could improve the effectiveness of screening programmes.[19, 32] This is dependent on the proportion of regular attendees that would switch to self-sampling and the proportion of never attenders, with a higher background risk, that will now participate in self-sampling.[32]

We showed that the switch to the hrHPV-based screening programme leads to an increase in the detection rates of low-grade CIN lesions. Most of the detected low-grade lesions will not progress.[7] Previous studies on triage strategies have shown that the number of unnecessary referrals to colposcopy could be reduced by the use of genotyping.[33] Genotyping is not used in the current Dutch hrHPV-based screening programme, but should be considered to reduce the number of colposcopies.

CONCLUSION

Even though lower participation in primary screening and lower adherence to triage testing were observed after the introduction of the hrHPV-based screening programme in the Netherlands, the cost-effectiveness is still estimated to be more favourable in the

hrHPV-based programme than in the old cytology-based programme. However, there is a substantial increase in the number of women who are unnecessarily referred to a gynaecologist increases substantially, so alternatives for the currently used triage strategy should be investigated.

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Disclosure of interests

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Contribution to authorship

EJ, HdK, IdK, MvB and SN contributed to the study concept and design. Model design was by EJ, IdK, MvB and SN. CA and EJ interpreted the observational data used for model inputs. Model analyses were by EJ, IdK and SN. The manuscript was drafted by EJ and IdK and all authors contributed to revising the manuscript and approved the final version of the manuscript.

Details of ethics approval

Ethical approval by a medical ethical committee was not required under Dutch law as no patients were involved in the development of the research and only non-identifiable data was used for this study.

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APPENDIX S1: MISCAN-CERVIX MODEL DESCRIPTION

Appendix to: *Cost-effectiveness of HPV-based cervical screening based on first year results in the Netherlands: a modelling study*

Erik E.L. Jansen[1], Steffie K. Naber[1], Clare A. Aitken[1], Harry J. de Koning[1], Marjolein van Ballegooijen[1], Inge M.C.M. de Kok[1].

1. Department of Public Health, Erasmus MC University Medical Center Rotterdam

Appendix available by scanning the QR code or at this link: https://obgyn.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2F1471-0528.16400&file=bjo16400-sup-0001-AppendixS1.pdf

Part 3

Attendance

Chapter 3.1

Investigating the decrease in participation in the Dutch cervical cancer screening programme: the role of personal and organisational characteristics

Clare A. Aitken*,[1] Sylvia Kaljouw*,[1] Albert G. Siebers,[2,3] Matilde Bron,[4] Anne Morssink,[5] Folkert J. van Kemenade,[6] Inge M.C.M de Kok[1]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam
2. PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands
3. Department of Pathology, Radboud University Medical Center
4. Bevolkingsonderzoek Noord
5. Bevolkingsonderzoek Oost
6. Department of Pathology, Erasmus MC, University Medical Center Rotterdam
* These authors contributed equally to this study.

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ABSTRACT

Declining attendance in the Dutch cervical cancer screening programme was recently observed, coinciding with preparations for implementing primary hrHPV-based screening, which was implemented in January 2017. We aimed to investigate which factors were related to decreased attendance. We conducted a population-based cohort study including all women aged 30 to 60 years who were eligible for screening between 2014 and 2018. Attendance was defined as participation in the screening programme within 15 months of the start of the invitation-eligible year. We used data from the Dutch pathology archive (PALGA) linked with data from Statistics Netherlands to investigate population characteristics (position in the household, household income, socio-economic status, number of people in the household, migration background, age) and data from the five Dutch screening organisations (SO) to investigate the effect of cessing self-inviting GP's ('inviting organisation'). SO's were termed SO 1 to 5. Higher attendance rates were observed in women who were employed (60.8%), married (62.9%), Dutch (61.2%), in the highest income bracket (63.4%), living in households with four persons (65.3%) and women who were invited by their GP (69.8%). Differences in personal characteristics did not explain the decline in attendance rates. By adjusting for whether the GP or the SO sent the invitation, the differences in attendance rates between 2014-2015 and 2016 and between 2014-2015 and 2017-2018 were explained in some screening organisations. Removing the possibility for GPs to send invitations explains some of the decline in participation, although this did not account for the total change in attendance.

Keywords: Cervical cancer screening, screening attendance, organised screening

1. INTRODUCTION

Organised cancer screening programmes are only able to provide maximum benefit to the population if attendance is high. Women who do not participate in cervical cancer screening make up the majority of cervical cancer diagnoses.[1] Therefore, monitoring the attendance rate is an important part of quality assurance in organised screening programmes.

In the Netherlands, participation in the cervical cancer screening programme had been relatively stable. Over the period 2012 to 2015, attendance rates ranged between 64.4% and 66.2%.[2] In January 2017, a new high-risk human papillomavirus (hrHPV) based screening programme was introduced nationwide. The implementation took place over the first quarter of 2017, however, some changes were already made in 2016 (e.g. accelerated invitations, reminders were stopped earlier, women could only participate until 1 December 2016, GP invitations were stopped). Given the changes in 2016, a lower participation rate was not surprising (60.3%),[2] however following the first year of the new programme, attendance declined further (2017: 57.4%).[3] Screening organisations anticipated some catch up attendance because of the transition. However, in 2018, the attendance rate remained below 60%.[4] Lower participation in the new programme was unexpected, as hrHPV self-sampling is now offered as an alternative screening method for women who did not feel comfortable with being screened by their general practitioner (GP). Self-sampling has been shown to be a promising strategy to encourage participation amongst non-responders to regular screening programme invitations.[5, 6]

When the new screening programme was introduced, day-to-day management was streamlined. All five screening organisations in the Netherlands (SO; responsible for the implementation of the programme across five geographical regions) implemented standardised invitation and reminder policies, after which all invitations were sent by the SO's following the birthdate of each eligible woman. Previously, some general practices sent invitations to their patients on behalf of the SO's and the time of the year when women were invited varied.

Changes to both the primary test and policies seem to have affected attendance, however it is unclear what is driving the change. We aimed to investigate this by analysing attendance rates and attenders in the Dutch cervical screening programme leading up to, during, and after the implementation of the new hrHPV-based screening programme. Specifically, we aimed to investigate what factors influence attendance, and what factors have influenced the decrease in attendance between 2014 and 2018.

2. MATERIALS AND METHODS

2.1 Setting

Organised cervical cancer screening has been offered in the Netherlands for more than thirty years. Since 1996, women aged 30 to 60 years have been invited to participate every five years. Before 2017, women were screened using cervical cytology. Starting in 2017, hrHPV-based primary screening was implemented, including the option of self-sampling.

2.2 Participants

All women aged 30 to 60 years who are living in the Netherlands are invited for screening every five years. Women who were eligible to receive an invitation for screening in years 2014 to 2018 based on their year of birth were included in our study (Table A1).

2.3 Data sources

We used two datasets that each combined two data sources; one dataset containing information about population characteristics and one dataset containing information about organisational factors. Detailed information about the contents of each dataset is outlined below. For legal and practical reasons, linkage between population characteristics data and organisational factors data was not possible. Therefore, we conducted separate, parallel analyses with the two datasets.

2.3.1 Population characteristics

To investigate population characteristics, we linked data from the nationwide network of cyto- and histopathology (PALGA) with socio-economic information from Statistics Netherlands (*Centraal Bureau voor de Statistiek*, acronym CBS). This dataset is further referred to as **PALGA/CBS** (Figure 1). PALGA has complete coverage of all pathology labs in the Netherlands.[7] We selected primary screening tests of women who participated in 2014 – 2018. Screening tests that were recorded within 15 months of the start of year of invitation eligibility were included (e.g. for women eligible for invitation in 2014, smears recorded between 1 January 2014 and 31 March 2015 were included). We requested that CBS select data for women in the target population for screening (Table A1). Deterministic linkage was used. 99.3% of PALGA records could be matched with a CBS identifier. The linkage rate between the two datasets was 57.4%, because non-attenders had no information in PALGA.

Information about personal characteristics (migration background, income, socioeconomic status and household composition) was provided for each year (2014 to 2018) that a woman had data recorded in CBS; therefore, each woman in the dataset had a maximum of five values for each variable. We assigned each record to a screening invita-

tion year (2014 – 2018) based on their age on 1 January (i.e. a woman was allocated to 2014 if her age was 29, 34, 39, 44, 49, 54 or 59 years on 1 January 2014). Based on the invitation year, we selected values for each CBS variable for each woman.

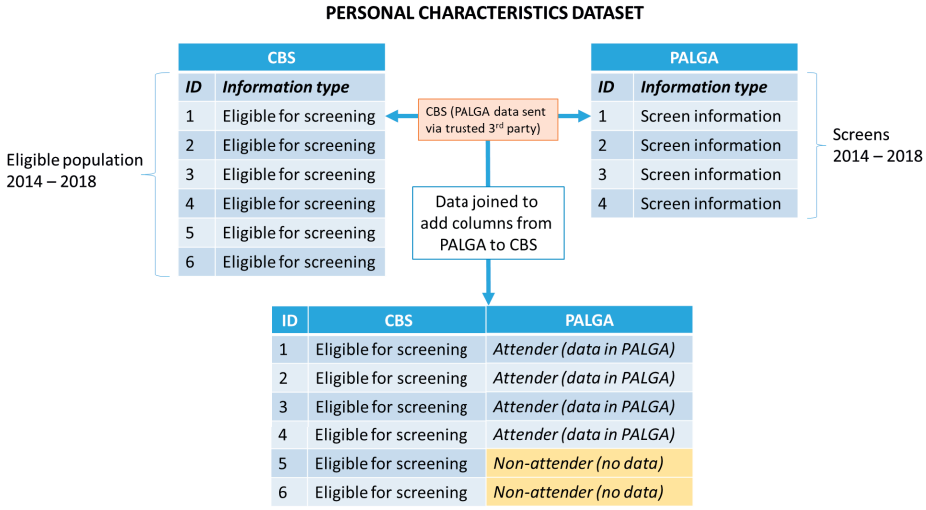

Figure 1: *Process to create PALGA/CBS dataset.*
NB. Each cell represents information from one unique woman invited for screening. Orange box contains the party that was responsible for data linkage. Yellow rows represent cases that are defined as 'non-attenders'.

2.3.2 Organisational factors

In order to classify organisational factors, we obtained data from the five SO's about all invitations sent during the period 2014 – 2018. This dataset was the result of merging two registries; one used in the new hrHPV-based programme ('ScreenIT') and one used in the old cytology-based programme ('CIS'). This dataset is further referred to as **ScreenIT/CIS** (Figure 2). This dataset included information about date of invitation, participation and inviting organisation (SO or GP)

2.4 Data definitions

We defined attenders as women who had a screening test within 15 months of the beginning of the year of invitation (e.g. for women eligible for invitation in 2018, attenders had screens recorded between 1 January 2018 and 31 March 2019). Non-attenders were women without a screening test recorded. In practice, this was done slightly differently in each dataset. In PALGA/CBS data, non-attenders were defined as women who are in the target population (i.e. in CBS) but did not have a matched link between PALGA and CBS (i.e. not in PALGA; Figure 1). In ScreenIT/CIS, non-attenders were all women who

were invited but did not have a screen recorded within 15 months of the start of the invitation year. There were a higher number of attenders in ScreenIT, but fewer non-attenders compared to PALGA/CBS (Figure A1).

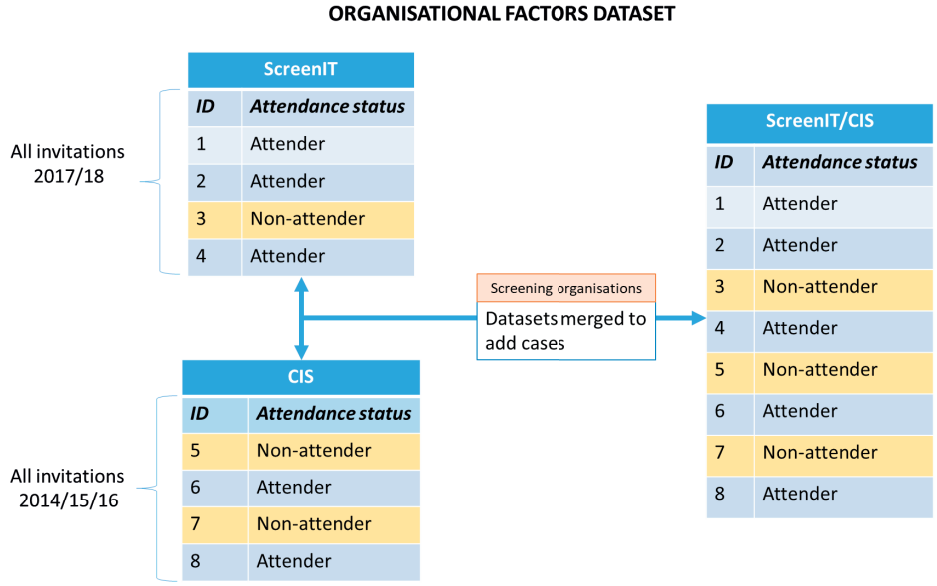

Figure 2: *Process to create ScreenIT/CIS dataset.*
NB. Each cell represents information from one unique woman invited for screening. Orange box contains the party that was responsible for data linkage. Yellow rows represent cases that are defined as 'non-attenders'.

In both datasets, we combined invitation year into three categories; the old cytology-based programme (2014-2015), the transition year (2016) and the new hrHPV-based programme (2017-2018).

We named the five SO's SO 1 to 5 in order to pseudonymise them. The SO that a woman is allocated to is based on the council area in which the woman lives. SO is automatically recorded in PALGA and ScreenIT/CIS. For non-attenders in PALGA/CBS, there was no SO region information. We had information about city council area for each woman from CBS and a concordance between SO regions and city council areas from PALGA. Using this information, we were able to allocate non-attenders to a SO.

2.4.1 Population characteristics

Socio-economic status was determined by CBS based on income source. If a person has multiple sources of income in a particular year, the income source that contributes the largest amount is used to classify this variable into one of 14 categories. We grouped this variable into broader categories: employed; not employed, social welfare; not employed, in education; no income.

Position in the household was determined by CBS by comparing each household member to the main breadwinner and was classified as: breadwinner without partner; breadwinner with partner; married partner; unmarried partner; adult child; other household member.

We classified the number of people living in a household into six categories: one; two; three; four; five; six or more.

Standardised household income percentile was calculated by CBS for private households, excluding student houses. We grouped this variable into four categories: 1–24%; 25–49%; 50– 74%; 75–100%.

For migration background, we combined CBS variables 'migration generation' and 'country of origin'. Migration generation was determined by country of birth of women themselves and their parents; a person was classified as Dutch if both parents were born in the Netherlands, a first generation migrant was a person who was born abroad and has at least one parent who was also born abroad and a second generation migrant was a person who was born in the Netherlands with a least one parent born abroad. Country of origin was determined by the country of birth of either the woman's parents or themselves. Country of origin was classified by CBS into 'Western' (Europe excluding Turkey, North America, Oceania, Indonesia and Japan) and 'non-Western' (Africa, Latin America and Asia [excluding Indonesia and Japan] and Turkey).[8] Based on these two variables, we categorised women into the following groups: Dutch; non-Western, first generation; non-Western, second generation; Western, first generation; Western, second generation.

2.4.2 Organisational factors

Inviting organisation was automatically recorded in ScreenIT/CIS. This could be either the SO or the woman's registered general practice. GPs could only send screening invitations in the old cytology-based programme. This practice stopped in 2016. Table A2 contains information on the proportion of invitations sent by self-inviting GP practices.

2.5 Statistical analysis

Data management and analysis was conducted using IBM SPSS Statistics for Windows v25 (Armonk, NY, IBM Corporation) and RStudio (using R v.3.6.2; Boston, MA). Because our endpoint, attendance, has high prevalence in our population (~60%), odds ratios would have been overinflated.[9] Due to this, we performed multivariate Poisson regression analysis. To control for the fact that invitation and reminder policies were directly related to SO between 2014 and 2016 (see Table 2A), we calculated one model per SO.

2.5.1 Population characteristics

We used R package 'mice' to impute missing values in 'standardised income percentile' using five iterations.[10] We performed pooled multivariate Poisson regression analysis per

SO to investigate which personal characteristics impacted the decrease in attendance between 2014 and 2018.

2.5.2 Organisational factors

We used IBM SPSS Statistics for Windows v25 to calculate multivariate Poisson regression per SO to investigate whether the inviting organisation impacted the decrease in attendance between 2014 and 2018.

2.6 Data availability

Results of this study are based on our own calculations on publically available data from CBS (dataset name: "Erasmus_MC_BVO_2014_2018_V1_DEF.sav"). This is available upon request to CBS (microdata@cbs.nl). Data from PALGA is available upon request after approval by the Scientific Committee of PALGA. Data from ScreenIT/CIS is available upon request from the Dutch SO's.

2.7 Ethical approval

The Medical Ethics Committee of Erasmus MC University Medical Center reviewed the protocol for the linkage of PALGA with CBS and confirmed that it was not subject to the *Medical Research Involving Human Subjects Act* in the Netherlands and, therefore, exempt from ethics approval (MEC-2019-0672). All data owners gave approval for the use of their data for the purposes of this study in compliance with GDPR.

3. RESULTS

3.1 Attendance trends and descriptives

Table 1 shows descriptives by SO for personal characteristics by attendance status. Compared to non-attenders, the cohort of attenders had a higher proportion of women who were Dutch (from 73% in SO 4 to 90% in SO 2), were employed (from 76% in SO 4 to 79% in SO 1) and were in the highest income bracket (from 29% in SO 2 to 41% in SO 1).

Figure 3 shows attendance rates by SO, year of eligibility for invitation and data source. For all SO's, there has been a decline in participation in the screening programme from 2014-2015 to 2017-2018. In each SO, the attendance rates are lower calculated in the PALGA/CBS dataset than in the ScreenIT/CIS data. The largest drop in attendance rate was seen in SO 3, dropping from 67.0% in 2014-2015 to 58.6% in 2017-2018 (using PALGA/CBS data). Calculating attendance rates in ScreenIT/CIS resulted in higher attendance in all SO's across all years, mainly due to a lower number of non-attenders in ScreenIT/CIS (Figure A1).

Table 1: *Distribution of co-variates by attendance status and screening organisations, the Netherlands, 2014 – 2018*

	SO 1			SO 2			SO 3			SO 4			SO 5		
	Attenders	**Non -attenders**	***p***	**Attenders**	**Non - attenders**	***p***	**Attenders**	**Non -attenders**	***p***	**Attenders**	**Non -attenders**	***p***	**Attenders**	**Non -attenders**	***p***
Data source															
N in PALGA/CBS	576,273	471,169		220,782	160,713		450,647	270,793		490,133	423,928		489,713	338,025	
N in ScreenIT/CIS	596,872	458,395		226,592	141,533		453,994	248,417		511,482	399,388		502,588	297,002	
*Inviting organisation**															
Screening organisation	85.4%	90.4%	<0.01	97.7%	98.7%	<0.01	71.3%	81.9%	<0.01	80.6%	87.7%	<0.01	83.9%	88.3%	<0.01
Self-inviting GP practice	14.6%	9.6%		2.3%	1.3%		28.7%	18.1%		19.4%	12.3%		16.1%	11.7%	
Invitation age															
30 years	11.9%	17.5%	<0.01	10.1%	14.7%	<0.01	10.5%	15.0%	<0.01	11.2%	17.0%	<0.01	10.1%	15.0%	<0.01
35 years	12.3%	15.4%		11.3%	12.5%		11.8%	12.8%		12.4%	14.7%		11.4%	12.6%	
40 years	13.8%	12.8%		12.9%	11.6%		13.2%	11.8%		13.6%	12.7%		12.8%	11.2%	
45 years	16.8%	13.9%		16.6%	14.6%		16.8%	14.2%		16.6%	14.0%		16.3%	13.9%	
50 years	16.8%	13.8%		17.4%	15.2%		17.5%	14.8%		17.0%	13.7%		17.7%	15.2%	
55 years	15.6%	13.5%		16.9%	15.4%		16.4%	15.5%		16.0%	14.0%		17.3%	15.8%	
60 years	12.8%	13.1%		14.8%	16.0%		13.8%	15.9%		13.3%	13.8%		14.3%	16.3%	
Migration background															
Dutch	75.3%	60.7%	<0.01	90.1%	85.7%	<0.01	86.6%	79.6%	<0.01	73.4%	58.7%	<0.01	84.3%	74.0%	<0.01
Non-western, first generation	11.0%	18.6%		3.3%	5.3%		5.2%	8.2%		13.1%	20.0%		5.5%	9.0%	
Non-western, second generation	2.8%	5.3%		0.6%	1.0%		1.0%	2.1%		2.8%	5.6%		1.0%	2.2%	
Western, first generation	5.4%	9.9%		2.8%	4.3%		3.0%	5.2%		5.6%	10.6%		4.4%	9.1%	
Western, second generation	5.5%	5.5%		3.2%	3.7%		4.2%	4.9%		5.0%	5.1%		4.9%	5.8%	
Socio-economic status (based on income source)															
Employed	78.5%	68.1%	<0.01	76.6%	66.3%	<0.01	77.8%	67.3%	<0.01	76.3%	65.2%	<0.01	77.7%	66.8%	<0.01
Not employed, social welfare	13.7%	20.4%		14.0%	22.2%		13.2%	21.2%		13.8%	21.2%		13.6%	21.8%	
Not employed, in education	0.4%	0.7%		0.4%	0.8%		0.3%	0.5%		0.4%	0.8%		0.2%	0.4%	
No income	7.4%	10.8%		9.0%	10.8%		8.8%	11.0%		9.5%	12.7%		8.5%	11.0%	

* Data from ScreenIT/CIS

Continued Table 1: *Distribution of co-variates by attendance status and screening organisations, the Netherlands, 2014 – 2018*

	SO 1			SO 2			SO 3			SO 4			SO 5		
	Attenders	Non-attenders	*p*	Attenders	Non-attenders	*p*	Attenders	Non-attenders	*p*	Attenders	Non-attenders	*p*	Attenders	Non-attenders	*p*
Number of people in the household															
One person	14.0%	20.1%	<0.01	10.7%	17.4%	<0.01	9.4%	16.9%	<0.01	12.2%	19.1%	<0.01	9.6%	16.3%	<0.01
Two people	28.7%	29.9%		30.6%	31.9%		28.1%	30.8%		29.2%	30.6%		30.2%	33.3%	
Three people	20.8%	20.4%		20.3%	20.1%		20.7%	20.3%		22.0%	21.0%		21.8%	21.5%	
Four people	26.4%	19.2%		27.4%	20.3%		29.0%	20.5%		26.0%	18.7%		28.5%	19.9%	
Five people	7.9%	7.0%		8.7%	7.3%		9.8%	7.8%		8.0%	7.0%		8.0%	6.4%	
Six or more people	2.1%	3.5%		2.2%	3.0%		3.0%	3.7%		2.5%	3.7%		1.9%	2.6%	
Standardised income percentile															
1 – 24%	14.2%	23.5%	<0.01	16.9%	25.3%	<0.01	14.5%	22.8%	<0.01	15.7%	25.8%	<0.01	13.6%	22.6%	<0.01
25 – 49%	17.6%	19.0%		23.4%	23.7%		21.6%	22.0%		18.3%	19.7%		19.4%	20.8%	
50 – 74%	26.8%	23.0%		30.0%	25.4%		30.1%	25.8%		27.0%	23.0%		29.9%	25.7%	
75 – 100%	40.9%	31.5%		29.1%	22.9%		33.2%	26.5%		38.4%	28.4%		36.6%	28.2%	
Missing	0.6%	2.9%		0.6%	2.7%		0.5%	2.9%		0.6%	3.2%		0.5%	2.8%	
Position in the household															
Breadwinner without partner	24.5%	32.0%	<0.01	19.2%	27.4%	<0.01	17.1%	25.9%	<0.01	22.9%	31.9%	<0.01	17.8%	26.2%	<0.01
Breadwinner with partner	15.4%	14.6%		14.9%	14.0%		13.2%	12.8%		13.3%	13.0%		13.0%	12.9%	
Married partner	44.7%	35.9%		51.3%	41.9%		55.5%	44.7%		50.1%	38.9%		53.9%	43.2%	
Unmarried partner	13.7%	13.4%		13.3%	13.7%		12.5%	12.7%		12.0%	12.0%		13.5%	13.8%	
Adult child	0.9%	2.2%		0.7%	1.8%		0.9%	2.4%		0.9%	2.2%		1.0%	2.3%	
Other household member	0.9%	2.1%		0.6%	1.3%		0.8%	1.6%		0.8%	1.9%		0.8%	1.6%	

NB: Proportions are rounded to one decimal place and, therefore, may not sum to 100%.

Supplementary figures A2 to A8 show attendance rates by personal characteristics and inviting organisation. The highest attendance rates were amongst women who were employed (Figure A4; 60.8%), married (Figure A6; 62.9%), Dutch (Figure A7; 61.2%), in the highest income bracket (Figure A5; 63.4%) or living in households with four persons (Figure A3; 65.3%). Attendance rates were significantly higher amongst women who were invited by their GP than women invited by their SO (Figure A8; 69.8%).

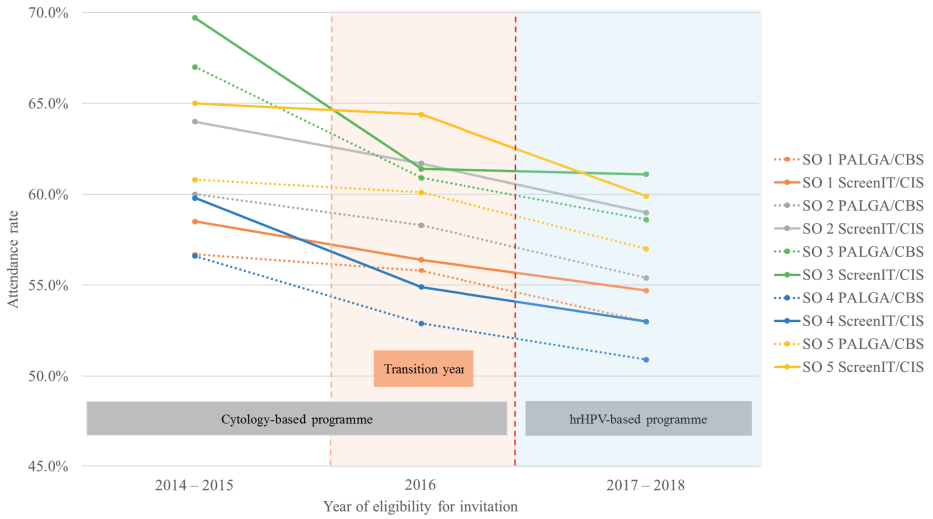

Figure 3: *Attendance rates by screening organisation, year of eligibility for invitation and data source, 2014 to 2018.*

3.2 Factors affecting attendance

3.2.1 Population characteristics (PALGA/CBS data)

Table 2 shows the results of Poisson regression analysis for attendance using PALGA/CBS data, by year of eligibility for invitation, unadjusted and adjusted for population characteristics. In the unadjusted models, the relative risk (RR) of participation in the screening programme was significantly lower in all five SO's in 2016 and 2017-2018 compared with 2014-2015. Following adjustment, there was almost no change in the RR of participation for any of the five SO's; that is, all RRs were still significantly lower in 2016 and 2017-2018 compared with 2014-2015. RRs of attendance compared to 2014-2015 were lowest in SO 3 (2016: RR 0.909 (95% CI: 0.901 – 0.917); 2017-2018: RR 0.876 (95% CI: 0.870 – 0.883)).

Supplementary tables A3 to A7 show the RR of attendance for each of the population characteristic included in our analysis. Factors affecting attendance followed similar patterns across all SO's. Women aged 35 years and older had a significantly higher RR of attendance than women aged 30 years. Compared to women who were Dutch, all other migration background groups had a lower RR of attendance. Following adjustment, only

married women had a significantly higher RR of attendance compared to women who were the main breadwinner without a partner, with the exception of SO's 1 and 5, in which the increased risk was non-significant.

Table 2: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by year of eligibility for invitation, unadjusted and adjusted for population characteristics, the Netherlands, 2014 – 2018*

	Unadjusted model	**Adjusted models**		
	Model 1[1]	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**
	RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
SO 1				
2014–2015	1.000 (ref)	1.000 (ref)	1.000 (ref)	1.000 (ref)
2016	0.985 (0.978 – 0.992)	0.988 (0.981 – 0.995)	0.987 (0.980 – 0.994)	0.988 (0.981 – 0.995)
2017–2018	0.931 (0.926 – 0.937)	0.940 (0.934 – 0.945)	0.944 (0.938 – 0.950)	0.944 (0.938 – 0.950)
SO 2				
2014–2015	1.000 (ref)	1.000 (ref)	1.000 (ref)	1.000 (ref)
2016	0.971 (0.960 – 0.982)	0.971 (0.960 – 0.983)	0.971 (0.959 – 0.982)	0.971 (0.960 – 0.982)
2017–2018	0.922 (0.912 – 0.931)	0.924 (0.914 – 0.933)	0.926 (0.916 – 0.935)	0.926 (0.916 – 0.935)
SO 3				
2014–2015	1.000 (ref)	1.000 (ref)	1.000 (ref)	1.000 (ref)
2016	0.908 (0.901 – 0.916)	0.909 (0.901 – 0.917)	0.908 (0.900 – 0.916)	0.909 (0.901 – 0.917)
2017–2018	0.873 (0.866 – 0.879)	0.875 (0.868 – 0.881)	0.876 (0.869 – 0.882)	0.876 (0.870 – 0.883)
SO 4				
2014–2015	1.000 (ref)	1.000 (ref)	1.000 (ref)	1.000 (ref)
2016	0.935 (0.927 – 0.943)	0.939 (0.931 – 0.947)	0.938 (0.930 – 0.946)	0.939 (0.931 – 0.946)
2017–2018	0.897 (0.891 – 0.903)	0.906 (0.900 – 0.913)	0.908 (0.902 – 0.915)	0.908 (0.902 – 0.915)
SO 5				
2014–2015	1.000 (ref)	1.000 (ref)	1.000 (ref)	1.000 (ref)
2016	0.988 (0.981 – 0.996)	0.990 (0.983 – 0.998)	0.989 (0.981 – 0.996)	0.989 (0.982 – 0.997)
2017–2018	0.934 (0.928 – 0.941)	0.939 (0.933 – 0.946)	0.941 (0.935 – 0.947)	0.941 (0.935 – 0.948)

RR: relative risk; CI: confidence interval.

NB: Estimates are rounded to three decimal places.

[1] Unadjusted model. Year of eligibility for invitation only.

[2] Adjusted model. Year of eligibility for invitation and migration background.

[3] Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household and standardised household income percentile.

[4] Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household, standardised household income percentile and age.

Table 3: *Results of Poisson regression analysis for attendance using ScreenIT/CIS data, by year of eligibility for invitation, unadjusted and adjusted for inviting organisation the Netherlands, 2014 – 2018*

	Unadjusted model	**Adjusted model**
	Model 1[1]	**Model 2[2]**
	RR (95% CI)	**RR (95% CI)**
SO 1		
2014–2015	1.000 (ref)	1.000 (ref)
2016	0.964 (0.958 – 0.971)*	1.028 (1.020 – 1.035)*
2017–2018	0.935 (0.930 – 0.941)*	0.997 (0.990 – 1.003)
SO 2		
2014–2015	1.000 (ref)	1.000 (ref)
2016	0.963 (0.953 – 0.974)*	0.971 (0.960 – 0.982)*
2017–2018	0.921 (0.913 – 0.930)*	0.928 (0.920 – 0.937)*
SO 3		
2014–2015	1.000 (ref)	1.000 (ref)
2016	0.881 (0.874 – 0.888)*	0.990 (0.980 – 1.000)*
2017–2018	0.876 (0.870 – 0.882)*	0.984 (0.975 – 0.993)*
SO 4		
2014–2015	1.000 (ref)	1.000 (ref)
2016	0.919 (0.912 – 0.925)*	0.998 (0.990 – 1.007)
2017–2018	0.887 (0.881 – 0.892)*	0.964 (0.957 – 0.971)*
SO 5		
2014–2015	1.000 (ref)	1.000 (ref)
2016	0.991 (0.984 – 0.998)*	1.034 (1.026 – 1.043)*
2017–2018	0.921 (0.915 – 0.927)*	0.961 (0.954 – 0.968)*

* $p < 0.05$

NB: Estimates are rounded to three decimal places

[1] Unadjusted model. Year of eligibility for invitation only.

[2] Adjusted model. Year of eligibility for invitation and inviting organisation.

3.2.2 Organisational factors (ScreenIT/CIS)

Table 3 shows the results of Poisson regression analysis for attendance using ScreenIT/CIS data, by year of eligibility for invitation, unadjusted and adjusted for inviting organisation. In the unadjusted models, the RR of participation in the screening programme was significantly lower in all five SO's in 2016 and 2017–2018 compared with 2014 –2015. Following adjustment for inviting organisation (either SO or GP), there was no significant difference between the RR of participation in SO 1 for participation in 2017-2018 (RR 0.997 (95% CI: 0.990 – 1.003)) and in SO 4 for participation in 2016 (RR 0.998 (95% CI: 0.990 – 1.007)). Following adjustment, the RR of participation was higher in 2016 compared to 2014-2015 in both SO 1 (RR 1.028 (95% CI: 1.020 – 1.035)) and SO 5 (RR 1.034 (95% CI: 1.026 – 1.043)).

4. DISCUSSION

Our aim was to investigate which factors influence attendance, and which factors have influenced the decrease in attendance between 2014 and 2018. Cessing the use of self-inviting general practices appears to have had an impact on attendance. Following adjustment for inviting organisation, RRs moved closer to 1 in all SO's. The importance of GP invitations in the Dutch screening programme has been previously observed; Tacken and colleagues found that the odds of attendance in a Dutch population increased when invitations and reminders were sent by a woman's GP (OR compared to SO invitation: 1.73 (95% CI: 1.15–2.60)).[11] Greater involvement by GPs in the cervical screening programme was previously shown to increase attendance rates[12] and compliance with follow-up advice.[13] The effect of having an invitation sent by the GP has been shown to have a greater impact in groups that have lower attendance rates, such as young women, women with a migration background and women with a lower SES.[14] The Health Council of the Netherlands advised in 2011, based on findings from an expert committee that included GPs, that more GPs should be involved in the invitation process as this is the most effective method for promoting attendance, especially in particular population subgroups.[15] The more personal approach of being contacted by a trusted healthcare provider, rather than a government organisation, may have encouraged some women to participate. Re-instating GP invitations may have a positive impact on future attendance.

Results of our study show that, although there are differences between the personal characteristics of attenders and non-attenders, these differences do not explain the decline in attendance. Like in other organised European screening programmes, attendance in the Dutch programme was lower amongst women with a migration background,[16-19] women in lower income brackets[17, 20] and women who live alone or are not married.[18, 20, 21] Addressing disparities in participation across population subgroups is necessary to ensure that screening benefits all eligible women.

Self-sampling has been shown to reduce non-attendance, however, lower participation in the Dutch programme comes in spite of the introduction of self-sampling. This may, in part, be due to the fact that women in the Dutch programme need to order their self-sampling kit via a web portal. Studies have found that sending self-sampling kits directly to non-responders increased participation[5, 22, 23] and that sending self-sampling kits directly to women has been shown to be more effective at increasing participation than 'opt-in' strategies.[24-26] Having to actively obtain a kit has shown mixed results; some studies show that offering the opportunity to order or collect a self-sampling kit results in higher participation[6, 22] and some studies show no increase compared to standard procedures.[23, 27] Making it easier to order the kit or sending the kit directly to non-responders may improve uptake in the Dutch programme. However, a Danish study found

that not all non-attenders respond equally to the offer of self-sampling; non-attending women from lower socio-economic status, with a migration background and who found cervical cancer screening irrelevant to them were all less likely to use self-sampling.[28]

Despite the difference made to RRs by adjusting for inviting organisation, estimates in all but one SO remained significantly lower in 2017-2018. There are some additional organisational factors that we were unable to control for that may also have impacted attendance. In the old cytology-based programme, smears could be taken by GPs without the invitation letter, meaning that women could be screened by their GP even if they had come to the clinic for another reason; a screen within the programme was registered if it was specified as such on the laboratory form. In the new hrHPV-based programme, screening within the programme is only possible if a women brings her invitation letter to the GP, as it contains personalised stickers that need to be stuck to the sample vial for lab processing. It could be that more women were screened in the old programme because it was simply easier to have a screen registered as being taken in the programme. The hrHPV test itself may also be a barrier for some women to participate. However, several studies on regional implementation of primary HPV screening have not shown lower attendance in comparison to cytology-based screening,[29-32] suggesting that the test itself may not be the reason for decreased attendance.

Our study has several strengths. We have a unique dataset with information about the personal characteristics of both attenders and non-attenders to the screening programme. Our datasets were large and had population-wide coverage. Because of this, we can be certain that our statistical estimates are robust. Our study is also the first to show attendance behaviours in a nationally implemented hrHPV-based cervical screening programme.

Our study also has some limitations. Some non-attenders would be ineligible for screening due to hysterectomy. While hysterectomy information is available in ScreenIT/CIS, we did not use this for adjustment as it is incomplete (only available if a woman reports this to the SO). We were unable to use hysterectomy data to adjust the eligible population in PALGA/CBS due to left-censoring in our PALGA extract and the linkage protocol used (i.e. we only linked primary screening programme screens, not histological examinations). If adjustment was possible, attendance would be slightly higher in all years (due to a smaller denominator). However, it is unlikely that ineligibility due to hysterectomy has changed over our study period, so we expect this has not impacted our results. The difference between attendance rates between ScreenIT/CIS and PALGA/CBS were due to lower numbers of non-attenders and overall records in ScreenIT/CIS (Figure A1). The exact reasons for this difference are unclear, but may be due to a lower number of invitations sent than women in the population, due to opt-outs and some women not being at risk, i.e. having no cervix. Socioeconomic status is a combination of factors related to income, education and occupation,[33] however, we did not include

education level as a co-variate. Educational status data was only complete from registry data for a selection of women in our cohort. As such, we chose not to include this information in our study.

5. CONCLUSION

Removing the possibility for GPs to send invitations explains a large part of the decline in participation in the Dutch cervical cancer screening programme, although this did not account for the total change in attendance. While certain population groups had lower attendance rates, personal characteristics of attenders and non-attenders do not explain the decline in participation. Other factors, such as necessitating the invitation letter be taken to the screening appointment or attitudes to hrHPV screening, should be investigated as additional causes for reduced attendance. GP invitations should be reintroduced to increase attendance.

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CONTRIBUTIONS TO AUTHORSHIP

CAA and SK contributed equally to this study. IdK was responsible for study design and acquisition of data from CBS with contribution from CAA. AM obtained and compiled contextual and policy information from the five SO's and was responsible for writing the study protocol for the analysis of the SO data. CAA made requests for PALGA data, with contribution from IdK and FvK. AGS created the PALGA dataset and collaborated with ZorgTTP and CBS to facilitate data linkage. MB was responsible for obtaining, linking and collating ScreenIT/CIS data. MB also provided expert advice on ScreenIT/CIS data definitions. CAA and SK both analysed data; SK performed statistical modelling on PALGA/CBS data and CAA ran statistical models on ScreenIT/CIS data. CAA drafted the original manuscript with significant contribution from SK. All authors critically evaluated the manuscript and provided feedback that was used to write the final version. All authors have read and agreed to the final version of the manuscript.

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DECLARATION OF INTERESTS

CAA, SK and IdK report receiving funding from the RIVM to conduct this study.

A. SUPPLEMENTARY MATERIALS

Table A.1: *Eligibility for invitation by year and age*

	Invitation year				
Age	**2014**	**2015**	**2016**	**2017**	**2018**
30 years	1984	1985	1986	1987	1988
35 years	1979	1980	1981	1982	1983
40 years	1974	1975	1976	1977	1978
45 years	1969	1970	1971	1972	1973
50 years	1964	1965	1966	1967	1968
55 years	1959	1960	1961	1962	1963
60 years	1954	1955	1956	1957	1958

Table A.2: *Summary of invitation and reminder policies with the Dutch cervical cancer screening programme*

	2014	**2015**	**2016**	**2017**	**2018**
			% invited by GP*		
SO 1	33% (32.2%)	0% (30.2%)	0% (0%)	0% (0%)	0% (0%)
SO 2	4.8% (4.8%)	4.8% (4.6%)	0% (0%)	0% (0%)	0% (0%)
SO 3	80% (66.2%)	80% (57.9%)	0% (0%)	0% (0%)	0% (0%)
SO 4	40% (41.0%)	40% (39.8%)	0% (0%)	0% (0%)	0% (0%)
SO 5	41% (36.0%)	40% (35.5%)	0% (0%)	0% (0%)	0% (0%)
			'Weeks to first reminder' policy		
SO 1	12 weeks	12 weeks	12 weeks	16 weeks	16 weeks
SO 2	16 weeks	16 weeks	16 weeks	16 weeks	16 weeks
SO 3	6 weeks	6 weeks	6 weeks	16 weeks	16 weeks
SO 4	12 weeks	12 weeks	Variable**	16 weeks	16 weeks
SO 5	14 weeks	14 weeks	16 weeks	16 weeks	16 weeks

* Proportions as reported by SO's. Actual proportions found in data are reported in brackets.

** Reminders were sent at 12, 16, or 9 weeks due to the transition to the new hrHPV-based programme.

Table A.3: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 1, the Netherlands, 2014 – 2018, rounded estimates*

	Univariate models	**Multivariate model***
	RR (95% CI)	**RR (95% CI)**
Year of invitation		
2014 – 2015	1.000 (ref)	1.000 (ref)
2016	0.985 (0.978 – 0.992)	0.988 (0.981 – 0.995)
2017 – 2018	0.931 (0.926 – 0.937)	0.944 (0.938 – 0.950)
Invitation age		
30 years	1.000 (ref)	1.000 (ref)
35 years	1.089 (1.079 – 1.100)	1.027 (1.016 – 1.038)
40 years	1.254 (1.244 – 1.265)	1.143 (1.132 – 1.153)
45 years	1.312 (1.303 – 1.322)	1.166 (1.155 – 1.176)
50 years	1.319 (1.309 – 1.328)	1.169 (1.159 – 1.179)
55 years	1.291 (1.281 – 1.301)	1.171 (1.161 – 1.182)
60 years	1.203 (1.193 – 1.214)	1.136 (1.125 – 1.147)
Migration background		
Dutch	1.000 (ref)	1.000 (ref)
Non-western, first generation	0.697 (0.689 – 0.706)	0.777 (0.768 – 0.786)
Non-western, second generation	0.644 (0.629 – 0.660)	0.744 (0.727 – 0.760)
Western, first generation	0.665 (0.654 – 0.677)	0.722 (0.710 – 0.734)
Western, second generation	0.915 (0.903 – 0.926)	0.932 (0.920 – 0.943)
Socio-economic status		
Employed	1.000 (ref)	1.000 (ref)
Not employed, social welfare	0.771 (0.763 – 0.778)	0.884 (0.875 – 0.892)
Not employed, in education	0.649 (0.605 – 0.693)	0.868 (0.824 – 0.913)
No income	0.781 (0.771 – 0.790)	0.861 (0.851 – 0.872)
Number of people in the household		
One person	1.000 (ref)	1.000 (ref)
Two people	1.172 (1.164 – 1.180)	1.123 (1.112 – 1.134)
Three people	1.204 (1.195 – 1.213)	1.166 (1.154 – 1.177)
Four people	1.360 (1.352 – 1.369)	1.267 (1.254 – 1.279)
Five people	1.259 (1.248 – 1.270)	1.217 (1.202 – 1.232)
Six or more people	0.929 (0.910 – 0.948)	1.064 (1.042 – 1.086)
Standardised income percentile		
1 – 24%	1.000 (ref)	1.000 (ref)
25 – 49%	1.273 (1.263 – 1.284)	1.137 (1.126 – 1.148)
50 – 74%	1.414 (1.405 – 1.423)	1.196 (1.185 – 1.206)
75 – 100%	1.480 (1.471 – 1.488)	1.226 (1.215 – 1.237)
Position in the household		
Breadwinner without partner	1.000 (ref)	1.000 (ref)

Table A.3: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 1, the Netherlands, 2014 – 2018, rounded estimates (continued)*

	Univariate models	**Multivariate model***
	RR (95% CI)	**RR (95% CI)**
Breadwinner with partner	1.166 (1.158 – 1.175)	0.948 (0.937 – 0.960)
Married partner	1.249 (1.242 – 1.255)	1.007 (0.997 – 1.017)
Unmarried partner	1.150 (1.142 – 1.159)	0.948 (0.937 – 0.960)
Adult child	0.698 (0.671 – 0.726)	0.649 (0.620 – 0.678)
Other household member	0.696 (0.668 – 0.724)	0.697 (0.666 – 0.727)

NB. Estimates rounded to three decimal places.

* Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household, standardised household income percentile and age.

Table A.4: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 2, the Netherlands, 2014 – 2018, rounded estimates*

	Univariate models	**Multivariate model***
	RR (95% CI)	**RR (95% CI)**
Year of invitation		
2014 – 2015	1.000 (ref)	1.000 (ref)
2016	0.971 (0.960 – 0.982)	0.971 (0.960 – 0.982)
2017 – 2018	0.922 (0.912 – 0.931)	0.926 (0.916 – 0.935)
Invitation age		
30 years	1.000 (ref)	1.000 (ref)
35 years	1.139 (1.121 – 1.157)	1.073 (1.055 – 1.091)
40 years	1.248 (1.230 – 1.265)	1.152 (1.134 – 1.170)
45 years	1.254 (1.237 – 1.271)	1.143 (1.125 – 1.160)
50 years	1.260 (1.244 – 1.277)	1.158 (1.141 – 1.175)
55 years	1.239 (1.223 – 1.256)	1.173 (1.156 – 1.191)
60 years	1.155 (1.137 – 1.172)	1.141 (1.123 – 1.159)
Migration background		
Dutch	1.000 (ref)	1.000 (ref)
Non-western, first generation	0.788 (0.765 – 0.811)	0.895 (0.871 – 0.918)
Non-western, second generation	0.768 (0.713 – 0.823)	0.882 (0.827 – 0.938)
Western, first generation	0.792 (0.767 – 0.818)	0.851 (0.826 – 0.877)
Western, second generation	0.921 (0.897 – 0.944)	0.947 (0.924 – 0.971)
Socio-economic status		
Employed	1.000 (ref)	1.000 (ref)
Not employed, social welfare	0.757 (0.745 – 0.769)	0.858 (0.844 – 0.872)
Not employed, in education	0.712 (0.649 – 0.776)	0.862 (0.798 – 0.926)
No income	0.873 (0.858 – 0.887)	0.898 (0.882 – 0.914)
Number of people in the household		
One person	1.000 (ref)	1.000 (ref)
Two people	1.239 (1.224 – 1.254)	1.146 (1.127 – 1.166)
Three people	1.267 (1.251 – 1.283)	1.184 (1.163 – 1.205)
Four people	1.414 (1.399 – 1.429)	1.287 (1.264 – 1.309)
Five people	1.353 (1.334 – 1.372)	1.237 (1.212 – 1.263)
Six or more people	1.110 (1.080 – 1.141)	1.085 (1.050 – 1.121)
Standardised income percentile		
1 – 24%	1.000 (ref)	1.000 (ref)
25 – 49%	1.233 (1.219 – 1.247)	1.109 (1.094 – 1.123)
50 – 74%	1.325 (1.312 – 1.337)	1.159 (1.145 – 1.174)
75 – 100%	1.365 (1.352 – 1.378)	1.186 (1.171 – 1.202)
Position in the household		
Breadwinner without partner	1.000 (ref)	1.000 (ref)

Table A.4: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 2, the Netherlands, 2014 – 2018, rounded estimates (continued)*

	Univariate models	**Multivariate model***
	RR (95% CI)	**RR (95% CI)**
Breadwinner with partner	1.212 (1.197 – 1.226)	0.972 (0.953 – 0.991)
Married partner	1.280 (1.269 – 1.291)	1.022 (1.005 – 1.040)
Unmarried partner	1.164 (1.149 – 1.179)	0.960 (0.940 – 0.979)
Adult child	0.715 (0.665 – 0.765)	0.629 (0.577 – 0.681)
Other household member	0.849 (0.797 – 0.902)	0.762 (0.707 – 0.817)

NB. Estimates are rounded to three decimal places.

* Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household, standardised household income percentile and age.

Table A.5: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 3, the Netherlands, 2014 – 2018, rounded estimates*

	Univariate models	**Multivariate model***
	RR (95% CI)	**N (95% CI)**
Year of invitation		
2014 – 2015	1.000 (ref)	1.000 (ref)
2016	0.908 (0.901 – 0.916)	0.909 (0.901 – 0.917)
2017 – 2018	0.873 (0.866 – 0.879)	0.876 (0.870 – 0.883)
Invitation age		
30 years	1.000 (ref)	1.000 (ref)
35 years	1.126 (1.114 – 1.139)	1.059 (1.046 – 1.071)
40 years	1.214 (1.202 – 1.227)	1.115 (1.103 – 1.128)
45 years	1.235 (1.224 – 1.247)	1.119 (1.107 – 1.131)
50 years	1.234 (1.223 – 1.246)	1.125 (1.113 – 1.137)
55 years	1.188 (1.177 – 1.200)	1.117 (1.105 – 1.129)
60 years	1.099 (1.087 – 1.111)	1.082 (1.070 – 1.095)
Migration background		
Dutch	1.000 (ref)	1.000 (ref)
Non-western, first generation	0.802 (0.789 – 0.815)	0.888 (0.874 – 0.902)
Non-western, second generation	0.700 (0.671 – 0.729)	0.784 (0.755 – 0.813)
Western, first generation	0.765 (0.747 – 0.782)	0.820 (0.802 – 0.837)
Western, second generation	0.911 (0.896 – 0.925)	0.936 (0.921 – 0.951)
Socio-economic status		
Employed	1.000 (ref)	1.000 (ref)
Not employed, social welfare	0.774 (0.766 – 0.783)	0.880 (0.870 – 0.890)
Not employed, in education	0.717 (0.663 – 0.771)	0.877 (0.823 – 0.932)
No income	0.869 (0.859 – 0.879)	0.897 (0.885 – 0.908)
Number of people in the household		
One person	1.000 (ref)	1.000 (ref)
Two people	1.251 (1.240 – 1.262)	1.182 (1.167 – 1.197)
Three people	1.307 (1.296 – 1.319)	1.240 (1.225 – 1.255)
Four people	1.457 (1.446 – 1.468)	1.336 (1.320 – 1.352)
Five people	1.401 (1.387 – 1.414)	1.295 (1.277 – 1.313)
Six or more people	1.188 (1.169 – 1.208)	1.157 (1.134 – 1.180)
Standardised income percentile		
1 – 24%	1.000 (ref)	1.000 (ref)
25 – 49%	1.238 (1.227 – 1.249)	1.112 (1.101 – 1.124)
50 – 74%	1.321 (1.312 – 1.331)	1.150 (1.138 – 1.161)
75 – 100%	1.352 (1.343 – 1.362)	1.174 (1.161 – 1.186)
Position in the household		
Breadwinner without partner	1.000 (ref)	1.000 (ref)

Table A.5: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 3, the Netherlands, 2014 – 2018, rounded estimates (continued)*

	Univariate models	**Multivariate model***
	RR (95% CI)	**N (95% CI)**
Breadwinner with partner	1.206 (1.196 – 1.217)	0.960 (0.946 – 0.974)
Married partner	1.288 (1.280 – 1.296)	1.015 (1.002 – 1.027)
Unmarried partner	1.186 (1.175 – 1.197)	0.960 (0.946 – 0.974)
Adult child	0.747 (0.716 – 0.779)	0.642 (0.609 – 0.675)
Other household member	0.877 (0.844 – 0.911)	0.767 (0.732 – 0.803)

NB. Estimates are rounded to three decimal places.

* Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household, standardised household income percentile and age.

Table A.6: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 4, the Netherlands, 2014 – 2018, rounded estimates*

	Univariate models	**Multivariate model***
	RR (95% CI)	**N (95% CI)**
Year of invitation		
2014 – 2015	1.000 (ref)	1.000 (ref)
2016	0.935 (0.927 – 0.943)	0.939 (0.931 – 0.946)
2017 – 2018	0.897 (0.891 – 0.903)	0.908 (0.902 – 0.915)
Invitation age		
30 years	1.000 (ref)	1.000 (ref)
35 years	1.142 (1.130 – 1.153)	1.069 (1.057 – 1.081)
40 years	1.276 (1.265 – 1.287)	1.152 (1.140 – 1.164)
45 years	1.334 (1.323 – 1.345)	1.174 (1.163 – 1.186)
50 years	1.360 (1.349 – 1.370)	1.189 (1.178 – 1.201)
55 years	1.315 (1.304 – 1.325)	1.179 (1.167 – 1.190)
60 years	1.220 (1.209 – 1.232)	1.143 (1.131 – 1.155)
Migration background		
Dutch	1.000 (ref)	1.000 (ref)
Non-western, first generation	0.730 (0.721 – 0.738)	0.821 (0.812 – 0.830)
Non-western, second generation	0.624 (0.607 – 0.641)	0.731 (0.714 – 0.749)
Western, first generation	0.641 (0.628 – 0.653)	0.703 (0.691 – 0.716)
Western, second generation	0.904 (0.891 – 0.916)	0.921 (0.908 – 0.934)
Socio-economic status		
Employed	1.000 (ref)	1.000 (ref)
Not employed, social welfare	0.747 (0.739 – 0.755)	0.880 (0.871 – 0.890)
Not employed, in education	0.617 (0.573 – 0.662)	0.870 (0.824 – 0.914)
No income	0.807 (0.798 – 0.817)	0.871 (0.860 – 0.881)
Number of people in the household		
One person	1.000 (ref)	1.000 (ref)
Two people	1.233 (1.223 – 1.242)	1.153 (1.141 – 1.165)
Three people	1.289 (1.279 – 1.299)	1.218 (1.205 – 1.231)
Four people	1.448 (1.438 – 1.457)	1.314 (1.300 – 1.328)
Five people	1.341 (1.328 – 1.353)	1.258 (1.242 – 1.274)
Six or more people	1.038 (1.018 – 1.057)	1.101 (1.079 – 1.124)
Standardised income percentile		
1 – 24%	1.000 (ref)	1.000 (ref)
25 – 49%	1.283 (1.273 – 1.293)	1.131 (1.120 – 1.142)
50 – 74%	1.434 (1.425 – 1.443)	1.189 (1.178 – 1.200)
75 – 100%	1.518 (1.509 – 1.528)	1.227 (1.216 – 1.238)
Position in the household		
Breadwinner without partner	1.000 (ref)	1.000 (ref)

Table A.6: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 4, the Netherlands, 2014 – 2018, rounded estimates (continued)*

	Univariate models	**Multivariate model***
	RR (95% CI)	**N (95% CI)**
Breadwinner with partner	1.196 (1.187 – 1.206)	0.954 (0.942 – 0.966)
Married partner	1.321 (1.314 – 1.328)	1.029 (1.018 – 1.040)
Unmarried partner	1.180 (1.170 – 1.190)	0.958 (0.945 – 0.971)
Adult child	0.712 (0.682 – 0.742)	0.639 (0.608 – 0.671)
Other household member	0.713 (0.681 – 0.745)	0.688 (0.655 – 0.722)

NB. Estimates are rounded to three decimal places.

* Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household, standardised household income percentile and age.

Table A.7: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 5, the Netherlands, 2014 – 2018, rounded estimates*

	Univariate models	**Multivariate model***
	RR (95% CI)	**N (95% CI)**
Year of invitation		
2014 – 2015	1.000 (ref)	1.000 (ref)
2016	0.988 (0.981 – 0.996)	0.989 (0.982 – 0.997)
2017 – 2018	0.934 (0.928 – 0.941)	0.941 (0.935 – 0.948)
Invitation age		
30 years	1.000 (ref)	1.000 (ref)
35 years	1.150 (1.138 – 1.162)	1.075 (1.062 – 1.087)
40 years	1.264 (1.252 – 1.275)	1.147 (1.135 – 1.159)
45 years	1.274 (1.262 – 1.285)	1.136 (1.125 – 1.148)
50 years	1.272 (1.261 – 1.284)	1.135 (1.123 – 1.146)
55 years	1.240 (1.228 – 1.251)	1.138 (1.127 – 1.150)
60 years	1.131 (1.119 – 1.142)	1.094 (1.082 – 1.106)
Migration background		
Dutch	1.000 (ref)	1.000 (ref)
Non-western, first generation	0.758 (0.745 – 0.770)	0.845 (0.832 – 0.858)
Non-western, second generation	0.646 (0.617 – 0.674)	0.731 (0.703 – 0.760)
Western, first generation	0.660 (0.647 – 0.674)	0.715 (0.701 – 0.729)
Western, second generation	0.879 (0.866 – 0.892)	0.910 (0.897 – 0.923)
Socio-economic status		
Employed	1.000 (ref)	1.000 (ref)
Not employed, social welfare	0.757 (0.749 – 0.766)	0.865 (0.856 – 0.875)
Not employed, in education	0.693 (0.629 – 0.757)	0.887 (0.822 – 0.951)
No income	0.844 (0.834 – 0.854)	0.900 (0.889 – 0.911)
Number of people in the household		
One person	1.000 (ref)	1.000 (ref)
Two people	1.228 (1.218 – 1.239)	1.146 (1.132 – 1.159)
Three people	1.288 (1.277 – 1.298)	1.199 (1.184 – 1.213)
Four people	1.459 (1.449 – 1.470)	1.306 (1.291 – 1.321)
Five people	1.396 (1.383 – 1.410)	1.272 (1.254 – 1.289)
Six or more people	1.102 (1.080 – 1.124)	1.139 (1.113 – 1.165)
Standardised income percentile		
1 – 24%	1.000 (ref)	1.000 (ref)
25 – 49%	1.265 (1.252 – 1.277)	1.129 (1.117 – 1.140)
50 – 74%	1.387 (1.376 – 1.398)	1.185 (1.173 – 1.196)
75 – 100%	1.445 (1.434 – 1.456)	1.224 (1.212 – 1.235)
Position in the household		
Breadwinner without partner	1.000 (ref)	1.000 (ref)

Table A.7: *Results of Poisson regression analysis for attendance using PALGA/CBS data, by model covariates, univariate and multivariate models, SO 5, the Netherlands, 2014 – 2018, rounded estimates (continued)*

	Univariate models	**Multivariate model***
	RR (95% CI)	**N (95% CI)**
Breadwinner with partner	1.193 (1.183 – 1.203)	0.948 (0.934 – 0.961)
Married partner	1.296 (1.289 – 1.304)	1.011 (0.999 – 1.023)
Unmarried partner	1.180 (1.170 – 1.190)	0.949 (0.936 – 0.963)
Adult child	0.794 (0.766 – 0.823)	0.682 (0.652 – 0.712)
Other household member	0.829 (0.797 – 0.861)	0.745 (0.710 – 0.780)

NB. Estimates are rounded to three decimal places.

* Adjusted model. Year of eligibility for invitation, migration background, socio-economic status (based on income source), number of persons in household, position in household, standardised household income percentile and age.

Attendance

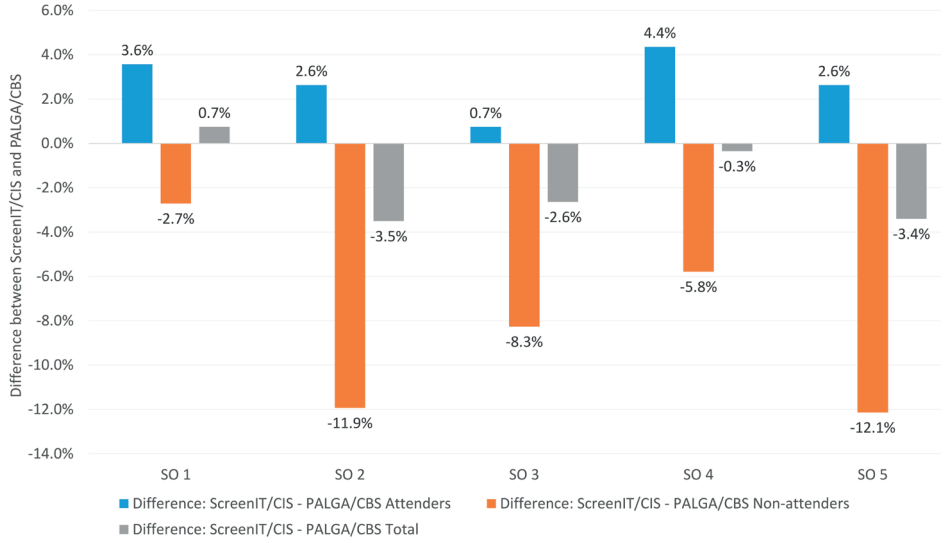

Figure A.1: *Difference* between number of records in ScreenIT/CIS and PALGA/CBS by SO, the Netherlands, 2014 – 2018*

* Difference between number of records was calculated as the difference between records in ScreenIT/CIS and PALGA/CBS divided by the number of records in ScreenIT/CIS (((ScreenIT/CIS – PALGA/CBS)/PALGA/CBS)*100).

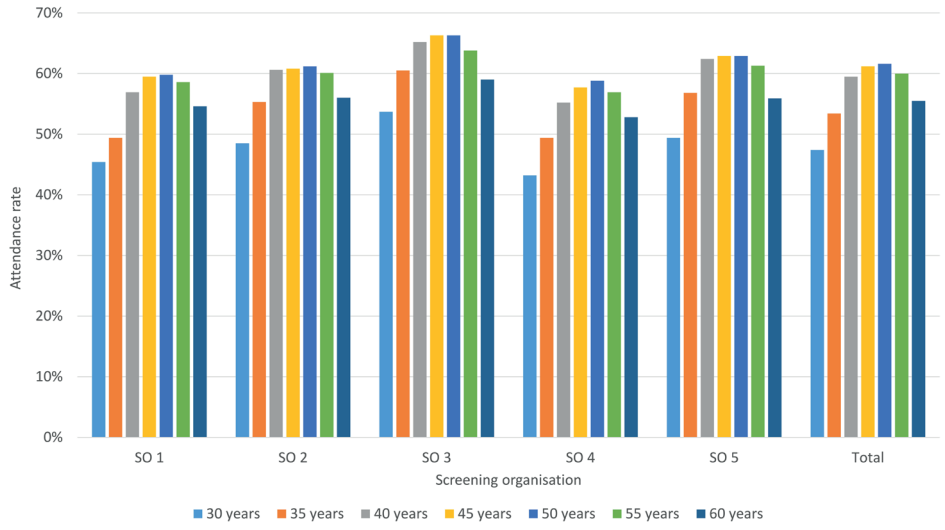

Figure A.2: *Attendance rates by age and SO, PALGA/CBS data*

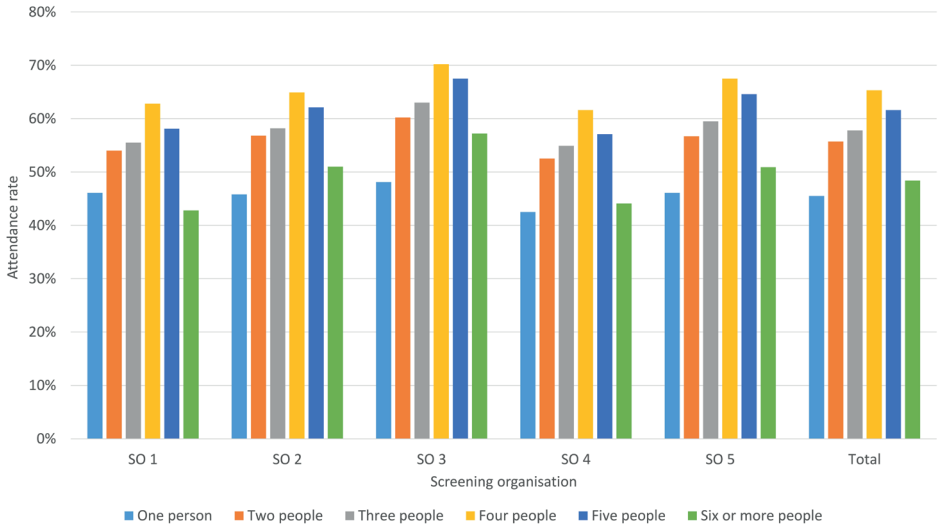

Figure A.3: *Attendance rates by number of persons in the household and SO, PALGA/CBS data*

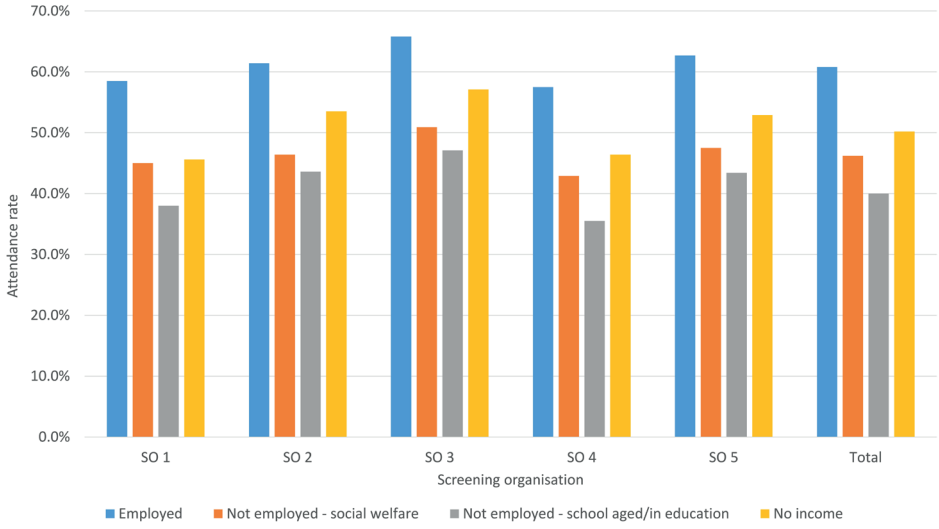

Figure A.4: *Attendance rates by SES (based on income source) and SO, PALGA/CBS data*

Attendance

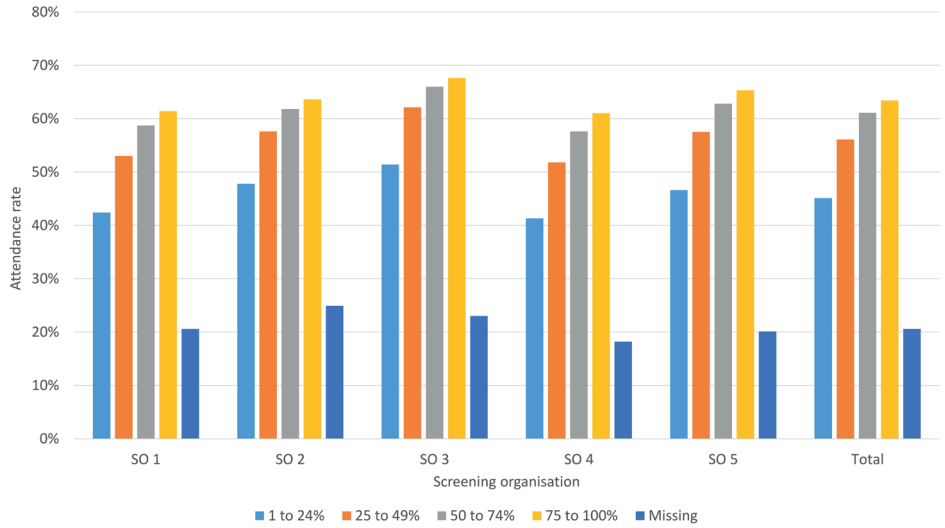

Figure A.5: *Attendance rates by standardised income percentile and SO, PALGA/CBS data, the Netherlands, 2014 – 2018*

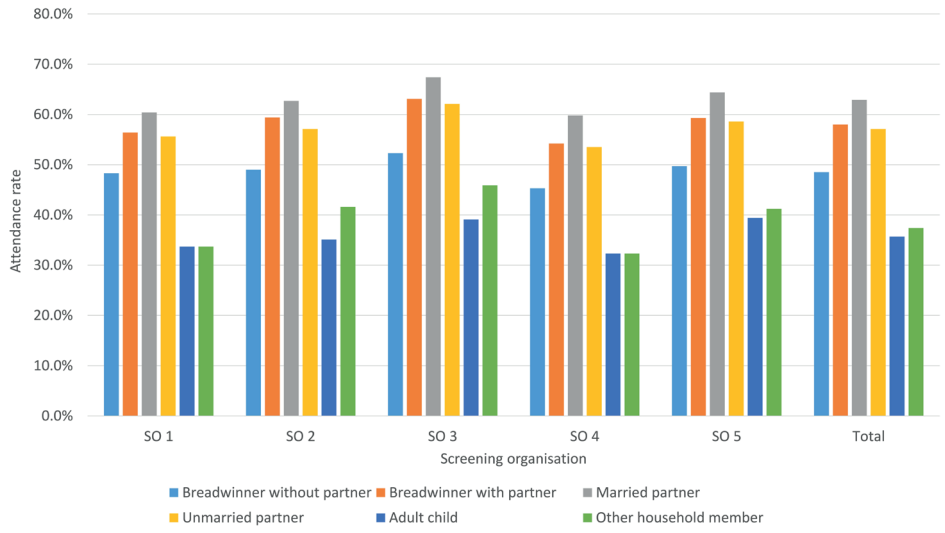

Figure A.6: *Attendance rates by position in the household and SO, PALGA/CBS data, the Netherlands, 2014 – 2018*

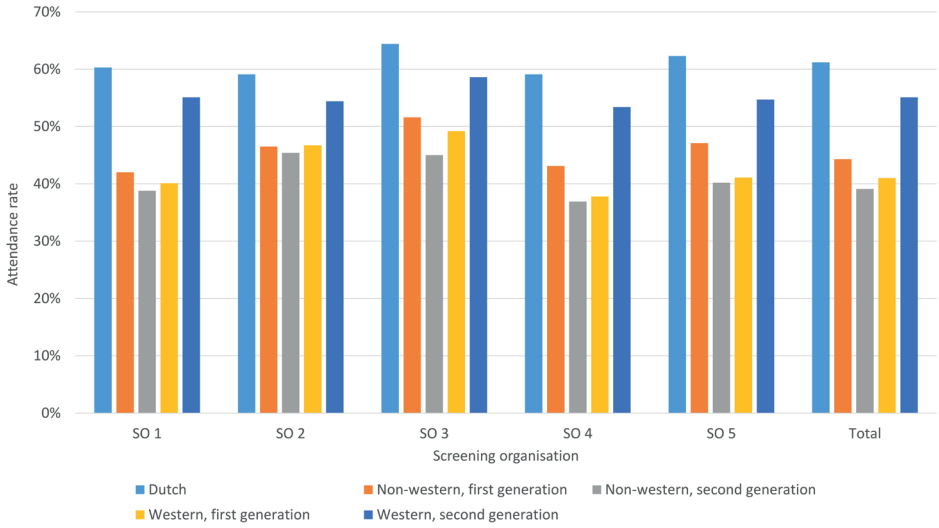

Figure A.7: *Attendance rates by migration background and SO, PALGA/CBS data, the Netherlands, 2014 – 2018*

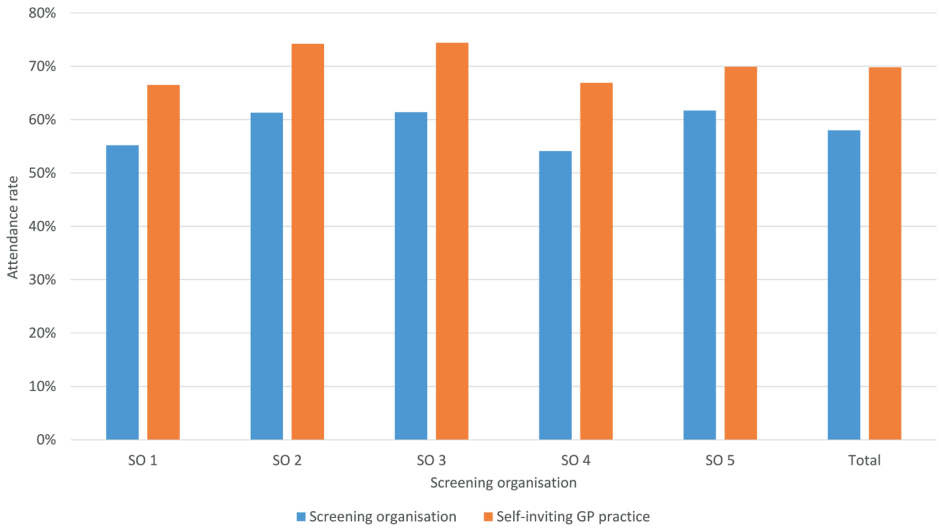

Figure A.8: *Attendance rates by inviting organisation and SO, ScreenIT/CIS data, the Netherlands, 2014 – 2018*

Part 4

Test and referral

Chapter 4.1

An indication of the impact of knowledge of HPV positivity on cytology triage in primary high-risk HPV screening

Clare A. Aitken[1], Kim M. Holtzer-Goor[2], Anne Uyterlinde[3], Adriaan J.C. van den Brule[4], Hans C. van der Linden[4], Cornelis J. Huijsmans[4], Inge M.C.M. de Kok[1], Folkert J. van Kemenade[5]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam
2. Centre for Population Screening, National Institute for Public Health and the Environment
3. Facilitaire Samenwerking Bevolkingsonderzoeken
4. Pathologie-DNA, Jeroen Bosch Hospital
5. Department of Pathology, Erasmus MC, University Medical Center Rotterdam

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ABSTRACT

Objective

Several studies have shown that there is an upward shift in the classification of cervical cytology when high-risk HPV (hrHPV) status is known to be positive. The Netherlands implemented primary hrHPV screening with reflex cytology as the primary screening test in 2017. Prior to implementation of the new programme, we aimed to investigate whether knowledge of hrHPV status influences cytology rating.

Methods

Using a set of 200 cytology slides that had been previously tested, two pairs of cytotechnicians rated 100 slides per pair twice; first without knowledge of hrHPV status and then, after a wash-out period of two months, with knowledge of hrHPV status.

Results

We found that hrHPV positive slides were more likely to be rated up over the referral threshold (i.e. from negative for intraepithelial lesion or malignancy to atypical squamous cells of undetermined significance+) than hrHPV negative slides at the second review when hrHPV status was known (relative risk = 3.2; 95% CI: 1.3 – 7.9).

Conclusions

If the same upward shift in ratings were to be observed in the national programme, it may have implications for referrals of women with low-grade lesions.

INTRODUCTION

In 2017, the Netherlands implemented primary high-risk HPV (hrHPV) screening in the national cervical cancer screening programme, replacing primary cytology. All eligible women (aged 30 to 60 years) are offered hrHPV screening every five years, with reflex cytology when hrHPV is found.

Several studies have found that knowledge of positive HPV status can result in upward rating of cervical cytology.[1-6] In the renewed Dutch programme, all cytology slides reviewed will be hrHPV positive. An upward shift in cytology rating may result in more referrals. We aimed to investigate whether cytotechnicians would classify cytology slides higher when positive hrHPV status is known.

METHODS

A set of 200 unmarked glass slides (~50% hrHPV positive), taken between August 2013 and July 2014 and adjusted for age and expected proportion of cytological abnormalities, was selected from the Dutch screening comparison study (DuSC).[7] This set was divided into two sets of 100, each allocated to a pair of cytotechnicians for review.

Four experienced cytotechnicians volunteered for this study and were grouped into two pairs. Prior to the implementation of the hrHPV screening programme, each pair reviewed 100 slides twice: once without hrHPV status, and after a two-month wash-out, with hrHPV status and reordered slides. Analysts were asked to rate slides in one of the following categories (equivalent Bethesda classification shown in brackets):

- Pap 0 (Inadequate quality)
- Pap 1 (Negative for intraepithelial lesion or malignancy (NILM))
- Pap 2 (Atypical squamous cells of undetermined significance (ASC-US))
- Pap 3a1 (Low-grade squamous intraepithelial lesion (LSIL))
- Pap 3a2 (High-grade squamous intraepithelial lesion (HSIL))
- Pap 3b (HSIL)
- Pap 4 (Carcinoma in situ or worse)

There were 800 individual observations from the entire dataset; 400 observations from each review (100 paired observations per cytotechnician). Twenty slides (10% of sample; 9 hrHPV positive, 11 hrHPV negative) were excluded due to the incorrect hrHPV status being accidentally provided at the second review, resulting in 360 paired observations from 180 slides. Switches in rating between review 1 and 2 were classified as upgrades (e.g. NILM to ASC-US), downgrades (e.g. LSIL to NILM), no change (e.g. NILM at both ratings) or to/from inadequate. Ratings from NILM to ASC-US+ or vice versa were classified

as switches over or below the referral threshold. The net increase/decrease in referrals was calculated by subtracting the number of upgrades over the referral threshold at the second review from the number of downgrades below the referral threshold at the second review.

Data analysis was performed using SAS Base 9.4 and IBM SPSS Statistics v25. The highest classification was selected for three records categorised in multiple categories (e.g. 'Pap 0/1'). Risk estimates were calculated. Proportional risk difference was calculated using Wald asymptotic test of equality. Wald asymptotic confidence limits were calculated for proportions.

RESULTS

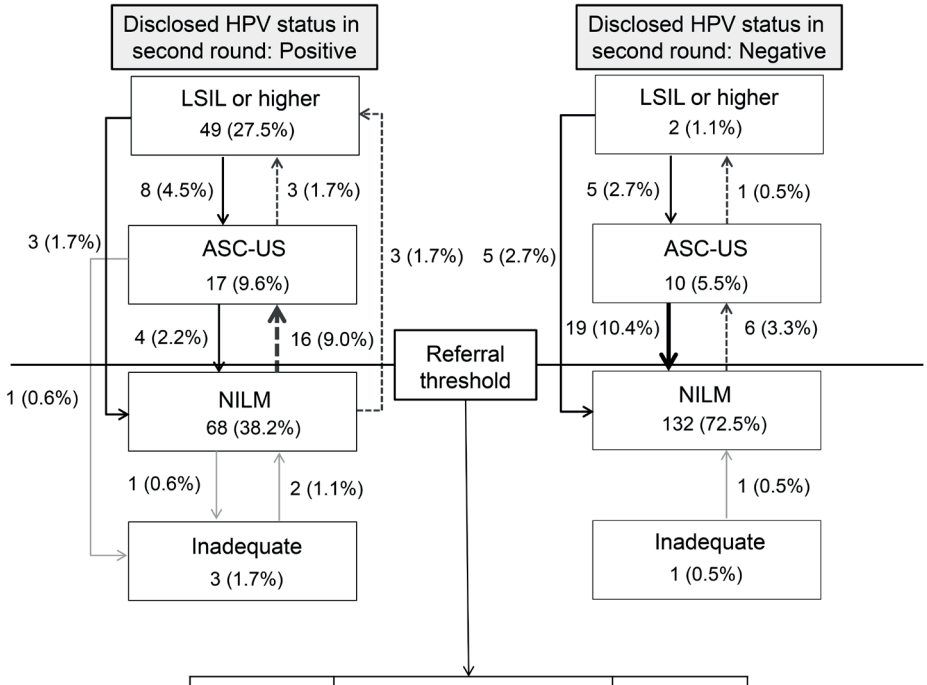
HrHPV positive slides were more likely to be upgraded over the referral threshold at the second review than hrHPV negative slides (relative risk (RR) = 3.2; 95% CI: 1.3 – 7.9). There was a net increase in ratings that would result in referral between the first and second review of 12 for hrHPV positive slides and a net decrease of 18 for hrHPV negative slides.

Overall, hrHPV negative slides were downgraded 29 times (15.9%; 95% CI: 10.6% - 21.3%), compared with 15 times (8.4%; 95% CI: 4.3% – 12.5%) for hrHPV positive slides (p = 0.03). Conversely, hrHPV positive slides were upgraded 22 times (12.4%; 95% CI: 7.8% - 17.2%), compared with seven times (3.8%; 95% CI: 1.0% - 6.7%) for hrHPV negative slides ($p = 0.003$). Results by Bethesda classification are shown in Figure 1.

DISCUSSION

This study suggests there may be an upward shift in the rating of cervical cytology slides when positive hrHPV status is known. Our results show that hrHPV positive slides were rated upwards more often than hrHPV negative slides, and more often over the referral threshold. This is consistent with previous literature.[3,4] Upgrading cytology when hrHPV status is positive was previously observed in Dutch observational data. Between 2007 and 2016, hrHPV testing was used in some laboratories as an additional test at six months for women with ASC-US/LSIL at primary screening. Under this policy, significantly fewer slides were rated NILM, and significantly more slides were rated ASC-US/LSIL at six-month follow-up when hrHPV status was known.[8] Similar results were also seen in the regular monitoring of the Dutch national screening programme, with more slides rated at ASC-US or higher when hrHPV testing was performed at six-month follow-up.[9]

Two studies[1,2] found that prior knowledge of hrHPV status resulted in an increased sensitivity for CIN 2+ lesions, which points to an increase in true positive referrals. How-



hrHPV positive	Changes over referral threshold	hrHPV negative
19	Upgrades	6
7	Downgrades	24
12	*Net increase in referrals*	*-18*

Figure 1: *Flowchart of switches in cytology ratings between slide review 1 and slide review 2 by hrHPV status, rounded percentages*

NILM: Negative for intraepithelial lesion or malignancy

ASC-US: Atypical squamous cells of undetermined significance

LSIL: Low-grade squamous intraepithelial lesion

Numbers in the figure represent pairs of observations for one analyst, not the total count of slides; 360 pairs of observations are included in this figure.

Percentages are rounded to one decimal place. As such, totals may not sum to 100%.

Dashed black arrows represent upgrades and solid black arrows represent downgrades. Solid grey arrows represent changes to or from 'inadequate'.

ever, first results of the new hrHPV screening programme show both increased CIN 2+ detection and more unnecessary referrals (<CIN 2) compared with the cytology-based programme,[10] suggesting that there may be an influence of upward cytology ratings on the number of referrals of women with low-grade lesions. As all women with hrHPV positive, ASC-US+ primary screens are directly referred in the new hrHPV-based programme,

an increase in slides rated as ASC-US may lead to more women with low-grade lesions being referred unnecessarily. This is concerning, as overtreatment of low-grade lesions also presents risks of harm. To mitigate the impact of potential cytology upgrading within the Dutch programme, training was provided at all five screening programme laboratories on morphological differences between Pap classifications (personal communication, 28 February 2018) and professional education continues to be provided.

This study has several strengths. Because this study was conducted prior to implementation of the new hrHPV screening programme, cytotechnicians were still reviewing both hrHPV positive and negative slides. The cytotechnicians in this study were experienced in evaluating cervical cytology. The distribution of age and abnormalities reflects the screened population, as slides were drawn from the screening programme. The study also has some limitations. The small sample size has an impact on statistical power. Additionally, 10% of slides were excluded, due to incorrect HPV status provided at the second review.

CONCLUSION

Our study suggests that knowledge of hrHPV status may result in an upward shift in cytology ratings. While appropriate training is being provided to cytotechnicians, continued monitoring of unnecessary referrals will be essential, to mitigate risks of overtreatment following referrals of women with low-grade lesions.

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DECLARATION OF CONFLICTING INTERESTS

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Chapter 4.2

Reducing unnecessary referrals for colposcopy in hrHPV-positive women within the Dutch cervical cancer screening programme: a modelling study

Sylvia Kaljouw[1], Erik E.L. Jansen[1], Clare A. Aitken[1], Lotte M. Harrijvan[1], Steffie K. Naber[1], Inge M.C.M. de Kok[1]

1. Department of Public Health, Erasmus MC University Medical Center Rotterdam

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ABSTRACT

Background

With the implementation of primary high-risk human papillomavirus (hrHPV) screening in the Netherlands, an increase was observed in the number of unnecessary referrals (<=Cervical Intraepithelial Neoplasia (CIN) 1) to colposcopy. We aimed to investigate which alternative triage strategies safely reduce unnecessary referrals in HPV-based cervical cancer screening programmes.

Methods

Microsimulation model MISCAN was used to simulate an unvaccinated cohort of ten million 30-year old Dutch women. We calculated unnecessary referrals, cervical cancer incidence, mortality, costs and QALYs for 24 triage strategies. Condition for direct referral (atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), conditional on HPV-genotype 16/18/other high risk (OHR)), type of triage test (cytology alone or combined with hrHPV) and time to triage test (6 or 12 months) was varied.

Results

The 24 triage strategies had varying effects on the number of unnecessary referrals ranging from -72% to +35%. Adjusting conditions for referral to 'HPV16/18+ and ASC-US+' and 'HPVOHR+ and HSIL+' and extending the interval between tests to 12 months resulted in a reduction in unnecessary referrals of 40% (incidence +0%, mortality -1%). Reduction in unnecessary referrals without genotyping was achieved by adjusting conditions for direct referral to LSIL (12 months to repeat test) (unnecessary referrals -37%, incidence +2%, mortality +0%).

Conclusions

To reduce the number of unnecessary referrals without increasing incidence and mortality by more than 2% in the Dutch cervical cancer screening programme, genotyping for HPV16 or HPV16/18 should be implemented with 12 months to repeat testing.

BACKGROUND

Many high-income countries have recently made the transition from primary cytology screening to primary high-risk human papillomavirus (hrHPV) DNA screening in their cervical cancer screening programmes.[1-3] In 2017, the Netherlands became the first country to implement a national cervical cancer screening programme based on primary hrHPV screening for all women, either by clinician-collected testing or self-sampling, and reflex cytology triage. Women aged 30 to 60 years are eligible for invitation. Women who test hrHPV-positive with cytological abnormalities (atypical squamous cells of undetermined significance (ASC-US) or higher) are referred to the gynaecologist, and hrHPV-positive women without cytological abnormalities are invited for a repeat cytology test after six months.

Not all women who are referred from cervical cancer screening programmes require treatment because low-grade lesions (< CIN 2) can regress without intervention. These women are unnecessarily referred. The first results of the hrHPV screening programme showed that the number of unnecessary referrals to the gynaecologist increased after implementation,[4] which confirmed model estimates from prior to the programme's implementation.[5] Increases in unnecessary referrals can lead to increased costs and colposcopy capacity problems.[6] It can also be distressing and cause anxiety for women.[7] Additionally, unnecessary treatment of detected regressive or non-progressive pre-invasive lesions can cause physical distress, such as pain, bleeding, and discharge, and has been associated with preterm births.[8] Therefore, limiting unnecessary referrals and treatment can reduce harms related to treatment. Following the successful implementation of the programme in the real-life setting, reducing the number of unnecessary referrals was identified as the first opportunity to optimise the new screening programme.

Currently available technologies that can be used to optimise the triage algorithm as a fast and easy way to achieve a reduction in unnecessary referrals are 1) adding genotyping to the triage algorithm, 2) changing the cytology cut-off for direct referral (LSIL instead of ASC-US), and 3) lengthening the time to repeat cytology testing. The latter is based on the fact that most hrHPV infections regress within one to two years,[9] which means that most infections are probably not yet regressed within 6 months (i.e. the current repeat interval). However, the impact of these potential changes on unnecessary referrals and cervical cancer epidemiology has not yet been quantified.

We aimed, using microsimulation modelling, to identify a triage strategy which results in a quickly achievable reduction of the number of unnecessary referrals, without increasing cervical cancer incidence and mortality beyond what is considered acceptable. We calculated the effects of implementing the following possible options (or combinations thereof): adding genotyping on HPV16 or HPV16/18; adding a repeat hrHPV test; increasing time to repeat test, and; changes to the referral threshold after the baseline cytology test.

METHODS

In order to estimate the costs and health effects of different triage strategies, we conducted analysis using the MISCAN-Cervix microsimulation model. MISCAN-Cervix is a well-documented semi-Markov microsimulation software program. We used the recently calibrated version of MISCAN-Cervix described previously by Jansen and colleagues.[6]

MISCAN-Cervix model

MISCAN-Cervix generates a large hypothetical population with individual life histories. For this study, we simulated a cohort of ten million unvaccinated 30-year-old women based on Dutch demographic[10] and hysterectomy data.[11] Women in the simulated population can acquire one or more hrHPV infections during their life. These infections are categorised in four groups, based on their oncogenicity and their presence in different vaccine types (i.e. the bi-, quadri-, and nonavalent vaccine). These groups are (1) HPV-16, (2) HPV-18, (3) Other high risk HPV types (HPV-OHR; HPV-31/33/45/52/58/35/39/51/56/59/66/68). In MISCAN-Cervix, a distinction is made between HPV-31/33/45/52/58 and HPV-35/39/51/56/59/66/68, but results for these two groups are presented together in this study. The infection either clears or leads to the development of pre-invasive cervical lesions. These lesions can either regress or develop into invasive cervical cancer, classified in FIGO (International Federation of Gynecology and Obstetrics) stages 1A, 1B, 2, 3, and 4. In the model, death can occur from cervical cancer or from other causes. Multiple infections can occur at the same time, which are independent of each other. Interventions such as hysterectomy, treatment, and screening can affect these life histories. Pre-invasive stages and FIGO 1A cases can only be detected by screening, as these are assumed to be asymptomatic, whereas FIGO 1B or worse can also be clinically diagnosed.

Disease development

The model divides cervical disease into nine sequential stages: hrHPV infection, three pre-invasive stages (CIN grade 1, 2, and 3), and five invasive stages (FIGO stages 1A, 1B, 2, 3, and 4). The risk of acquiring an hrHPV infection is age- and type-specific. In the model, most HPV infections are transient. Lesions in pre-invasive stages can also regress. While pre-invasive lesions can develop without an HPV infection (in which case they will always regress in our model), cervical cancer can only develop in the presence of a hrHPV infection. The durations of HPV infections as well as most pre-invasive and invasive cancer stages are modelled as exponential distributions with different average durations, as shown in Table 1.

Table 1: *Average sojourn time until progression or regression and cytology/HPV test characteristics per stage.*

HPV infection present	Disease status	Mean duration (Weibull distribution)	Probability of a positive test result		
			*Cytology ≥ASC-US***	*Cytology ≥HSIL***	*Positive hrHPV-test****
≥1 HPV infection	no CIN present	1 year[29,30]	17.1%	0.0%	55.0%
≥1 HPV infection	CIN1	1.5 years[31]	36.2%	2.6%	72.0%
≥1 HPV infection	CIN2	2 years[31]	37.1%	10.7%	94.0%
≥1 HPV infection	CIN3ºaoº	14.3/5.7 years*[a]	75.4%	51.6%	94.0%
≥1 HPV infection	FIGO 1A	4 years[a]	85.1%	64.7%	94.0%
≥1 HPV infection	FIGO 1B	2.2 years[a]	85.1%	64.7%	94.0%
≥1 HPV infection	FIGO 2	1.7 years[a]	85.1%	64.7%	94.0%
≥1 HPV infection	FIGO 3	1.7 years[a]	85.1%	64.7%	94.0%
≥1 HPV infection	FIGO 4	0.7 years[a]	85.1%	64.7%	94.0%
No HPV	no CIN present	-	0.6%	0.04%	0.0%
No HPV	CIN1	1.5 years[31]	36.2%	2.6%	0.0%
No HPV	CIN2	2 years[31]	37.1%	10.7%	0.0%
No HPV	CIN3	14.3/5.7 years*[a]	75.4%	51.6%	0.0%
No HPV	FIGO 1A	4 years[a]	85.1%	64.7%	0.0%
No HPV	FIGO 1B	2.2 years[a]	85.1%	64.7%	0.0%
No HPV	FIGO 2	1.7 years[a]	85.1%	64.7%	0.0%
No HPV	FIGO 3	1.7 years[a]	85.1%	64.7%	0.0%
No HPV	FIGO 4	0.7 years[a]	85.1%	64.7%	0.0%

[a] Calibrated in MISCAN-cervix

* Progressive CIN 3/Regressive CIN 3

** Probability to test positive the first time a women with this lesion present attends screening. 12% of the CIN lesions will be missed systematically over time.

*** The same test characteristics are assumed for GP smears as for self-sampling kits

hrHPV = high-risk human papillomavirus; CIN = cervical intraepithelial neoplasia; ASC-US = Atypical squamous cells of undetermined significance; LSIL = Low-grade squamous intraepithelial lesion; HSIL = High-grade squamous intraepithelial lesion, FIGO = International Federation of Gynecology and Obstetrics

To account for different cancer risk levels for different HPV genotypes, the progression probabilities for the different health stages are dependent on the genotype of the HPV infection [see Appendix A]. The progression probabilities per group of HPV genotypes were found through calibration. Progression probabilities for an HPV-16 infection are higher than average for all lesion grades, whereas those for an HPV-35/39/51/56/59/66/68 infection are lower for all lesion grades. For HPV-18 infections, the progression probabilities are generally higher than those of HPV-31/33/45/52/58 infections, although this does depend on the lesion grade.[6]

Test characteristics

The test characteristics for cytology were calibrated based on CIN detection rates and interval cancers between 2004-2013 (Table 1). The test characteristics for the HPV test were based on literature.[12, 13] The test characteristics for the HPV self-test were assumed to be equal to those of the regular HPV test. Furthermore, the sensitivity of colposcopy is assumed to be 100%.

Triage strategies

We estimated the costs and health effects of 24 different triaging strategies (including the current triage strategy; Figure 1)). These were subdivided into six categories. Table 2 contains information about all 24 strategies. Visual representations of the six categories of strategies can be found in Appendix B. For each category of strategies, we estimated effects based on both a six-month period and a 12-month period to repeat testing.

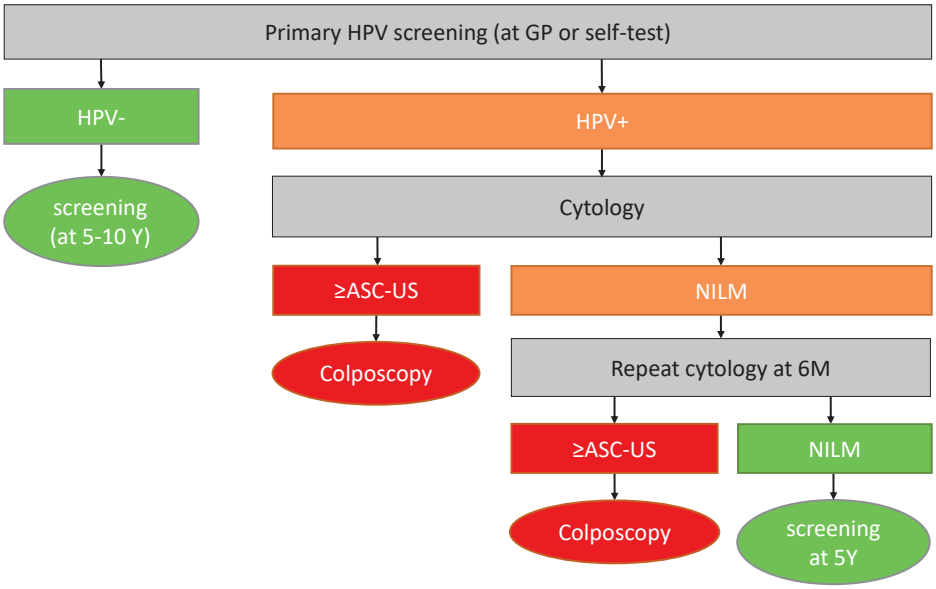

Figure 1: *Current HPV-based screening and triage algorithm.*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: Primary screening could be conducted by a general practitioner or by using a self-sampling kit. Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

Table 2: *Strategies based on months to repeat test, repeat test type and direct referral conditions. Strategy 1.1 is the current strategy.*

Category	Strategy	Triage interval (months)	Triage tests	Direct referral conditions
1	*1.1; 1.2*	6; 12	Cytology	HPV positive, ASC-US+
2	*2.1; 2.2*	6; 12	hrHPV, Cytology	HPV positive, ASC-US+
3	*3.1; 3.2*	6; 12	Cytology	HPV positive, HSIL+
3	*3.3; 3.4*	6; 12	Cytology	HPV positive, LSIL+
4	*4.1; 4.2*	6; 12	hrHPV, Cytology	HPV positive, HSIL+
4	*4.3; 4.4*	6; 12	hrHPV, Cytology	HPV positive, LSIL+
5	*5.1; 5.2*	6; 12	Cytology	HPV16/18 positive, ASC-US+ or other hrHPV positive, HSIL+
5	*5.3; 5.4*	6; 12	Cytology	HPV16/18 positive, ASC-US+ or other hrHPV positive, LSIL+
5	*5.5; 5.6*	6; 12	Cytology	HPV16 positive , ASC-US+ or other hrHPV positive, HSIL+
5	*5.7; 5.8*	6; 12	Cytology	HPV16 positive , ASC-US+ or other hrHPV positive, LSIL+
6	*6.1; 6.2*	6; 12	Cytology	HPV16/18 positive or other hrHPV positive, HSIL+
6	*6.3; 6.4*	6; 12	Cytology	HPV16 positive or other hrHPV positive, HSIL+

The first alternative strategy is to extend the time to repeat cytology (TTR) from 6 months to 12 months (Strategy name: '12mthTTR'). In the second category, we added an HPV test to the repeat test after six months. In this strategy, the repeat test for HPV positive, cytology negative women consists of an HPV test first and a cytology reflex test if the HPV test is positive. If both are positive, women are referred for colposcopy (Strategy names: 'ExtraHPV', 'ExtraHPV-12mthTTR').

For the third category of triage strategies, we increased the referral threshold after the reflex cytology to either low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL) (Strategy names: 'CytLSIL', 'CytHSIL', 'CytLSIL-12mthTTR', 'CytHSIL-12mthTTR').

The fourth category is a combination of the second and third category: an HPV test was added to the repeat test after six months and the referral threshold after the initial reflex cytology was increased to LSIL or HSIL, respectively (Strategy names: 'ExtraHPV-CytLSIL', 'ExtraHPV-CytHSIL', 'ExtraHPV-CytLSIL-12mthTTR', 'ExtraHPV-CytHSIL-12mthTTR'.)

In the fifth category, the initial triage of hrHPV-positive women was based on both the cytology result and the hrHPV genotype. We simulated two scenarios in which women who were positive for HPV16 or HPV18 were referred as usual, but women who were HPV-OHR positive were only directly referred if they had at least an LSIL or HSIL cytology result. In two additional similar scenarios, only women with HPV16 were referred as usual (Strategy names: '16/18+ASC-US+/OHR+LSIL,' '16/18+ASC-US+/OHR+HSIL', '16/18+ASC-

US+/OHR+LSIL-12mthTTR', '16/18+ASC-US+/OHR+HSIL-12mthTTR', '16+ASC-US+/OHR+LSIL', '16+ASC-US+/OHR+HSIL', '16+ASC-US+/OHR+LSIL-12mthTTR', '16+ASC-US+/OHR+HSIL-12mthTTR').

Finally, in the sixth category we simulated one scenario in which women who were positive for HPV16 were referred to the gynaecologist directly, without cytological testing. The remaining hrHPV-positive women were only referred if they had at least an HSIL cytology result. In another scenario, women with HPV18 were referred directly as well, irrespective of the cytology result (Strategy names: '16/18+/OHR+LSIL', '16/18+/OHR+HSIL', '16/18+/OHR+LSIL-12mthTTR', '16/18+/OHR+HSIL-12mthTTR').

Key outcomes

Outcomes of interest are the number of unnecessary referrals, cervical cancer mortality, cervical cancer incidence, total costs and number of lost quality-adjusted-life-years (QALYs). We defined clinically relevant lesions as being CIN 2 or higher, meaning all referrals resulting in a diagnosis of lower than CIN 2 were considered unnecessary. We calculated a woman's QALYs by subtracting disutilities caused by either screening-related events or due to disease from the total number of life-years lived. The values of the disutilities are determined by the duration of the event and a weight reflecting the severity of the event. We used a similar approach to determine the total costs of screening; for each screening- or disease-related event, there are associated costs which are summed over the lifetime of all simulated women. The assumptions for QALYs and costs can be found in Appendix C. All outcomes are presented per 100,000 30-year-old women followed lifelong. Suitable strategies are defined as those which result in a decrease in unnecessary referrals and less than 2% increase in cervical cancer incidence or mortality. We allowed for an increase up to 2% to account for random variation in model outcomes.

Base case analysis

In the base case analysis, we assumed attendance rates of primary screening and adherence to repeat testing and colposcopy referral to be 100%. In this way, we tailor the triage strategy to women who attend the screening programme and we avoid unnecessary screening of these women. In addition, we applied disutilities from screening and colposcopy referrals as reported in the Dutch utility study by de Kok and colleagues.[14]

Sensitivity analyses

In univariate sensitivity analyses, we varied several uncertain parameters to investigate their influence on the model outcomes. For screening behaviour, we performed three different sensitivity analyses (details can be found in Appendix D). First, we assumed attendance and adherence as observed in 2017 in the Netherlands in order to get an estimate of how each strategy would perform in the context of current screening at-

tendance rates.[6] Secondly, we used the attendance and adherence as observed in 2017, but we decreased the adherence for the repeat test to 69% if the time to repeat test was increased to 12 months, based on the participation for triage cytology after 12 months in the old Dutch cytology-based programme.[15] As a third scenario, we applied the attendance rates as observed in 2014-2016 in the Netherlands, when a cytology-based screening algorithm was used. In this period the attendance and adherence were somewhat higher than in 2017 (assuming that in the future the attendance will return to the previous rates again).[4] In the second sensitivity analysis we used alternative disutility assumptions.[16, 17] In the third sensitivity analysis, we increased sensitivity of the cytology test after a positive HPV test by 50% for CIN 1 and CIN 2 as compared to the test characteristics in the base case analysis. Higher sensitivity has been measured when the cytology test is used as a reflex or repeat test as compared to use as a primary test.[18] Lastly, we considered the effect of a change in the outcome measure by increasing the threshold for clinically relevant lesions from CIN 2 to CIN 3.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design, interpret the results or contribute to writing or editing of this document. We do not intend to disseminate our results to patients or women eligible for screening.

RESULTS

Base case analysis

The current screening programme resulted in 361 cancer diagnoses, 74 cervical cancer deaths and 19,838 unnecessary referrals per 100,000 women (Table 3). The strategies with direct referral for HPV16 or HPV16/18 positive women (category 6) cause an increase in unnecessary referrals (Figure 2). Therefore, this category of strategies does not meet the defined criteria of a preferred strategy. Furthermore, all the strategies where the cytology referral threshold is increased ('(ExtraHPV-)CytLSIL/HSIL', category 3 and 4) cause a relatively large increase in mortality and incidence. Therefore, these strategies are also not preferred. One exception is the strategy where the referral threshold is increased to LSIL and the time to repeat testing is extended to 12 months ('CytLSIL-12mthTTR', Table 2 (3.4)). Lastly, the strategy where the referral threshold is increased to HSIL for all HPV-positive women who do not have HPV-16 with six months to repeat test ('16+ASC-US+/OHR+HSIL', Table 2 (5.5)), causes an increase in both incidence and mortality of slightly more than 2% and is therefore excluded from the preferred strategies.

Table 3: *Percentage change in unnecessary referrals, mortality, incidence, costs and QALYs lost for selected strategies.*

Nr.	Strategy name*		Unnecessary Referrals	Mortality	Incidence	Costs (€)	QALYs lost
1.1	**Current**		**19,838**	**74**	**361**	**61,458,537**	**2,591**
1.2	12mthTTR	%	-7%	-2%	-1%	-1%	28%
2.1	ExtraHPV	%	-12%	1%	1%	-1%	1%
2.2	ExtraHPV-12mthTTR	%	-17%	-1%	-1%	-2%	29%
3.4	CytLSIL-12mthTTR	%	-37%	0%	2%	-5%	40%
5.1	16/18+ASC-US+/OHR+HSIL	%	-32%	1%	2%	-4%	6%
5.2	16/18+ASC-US+/OHR+HSIL-12mthTTR	%	-40%	-1%	0%	-6%	39%
5.3	16/18+ASC-US+/OHR+LSIL	%	-19%	1%	1%	-2%	3%
5.4	16/18+ASC-US+/OHR+LSIL-12mthTTR	%	-26%	-2%	-1%	-3%	34%
5.6	16+ASC-US+/OHR+HSIL-12mthTTR	%	-45%	0%	2%	-7%	42%
5.7	16+ASC-US+/OHR+LSIL	%	-21%	1%	1%	-3%	4%
5.8	16+ASC-US+/OHR+LSIL-12mthTTR	%	-29%	-1%	0%	-4%	35%

* Strategies are only included if they increase cervical cancer incidence and mortality with at most 2%. The values of the current strategy are highlighted in bold.

Figure 2 also shows that only extending the time to repeat test to 12 months ('12mthTTR', Table 2 (1.2)) does not increase the incidence of or mortality from cervical cancer. On the contrary, it decreases incidence and mortality (-1.2% and -1.7%, respectively, Table 3) while also reducing the number of unnecessary referrals. In general, strategies with 12 months to repeat test result in a larger reduction of unnecessary referrals than strategies with 6 months to repeat test without deteriorating mortality or incidence.

The largest reductions in unnecessary referrals without substantial increase in mortality or incidence are achieved by genotyping for HPV16 (-45%, '16+ASC-US+/OHR+HSIL-12mthTTR' (5.6)) or HPV16/18 (-40%, '16/18+ASC-US+/OHR+HSIL-12mthTTR' (5.2)) while allowing direct referral for HPV-OHR with HSIL+ cytology, with time to repeat test set to 12 months. Without genotyping, the largest reduction (-37%) in unnecessary referrals is achieved by increasing the threshold for direct referral from ASC-US to LSIL while setting time to repeat test to 12 months ('CytLSIL-12mthTTR' (3.4)).

As expected, we found that the total cost of the screening programme decreases linearly with the decrease in unnecessary referrals (Figure 3). Finally, the QALYs lost increase linearly with the decrease in unnecessary referrals, as the number of repeat tests increases (Figure 3).

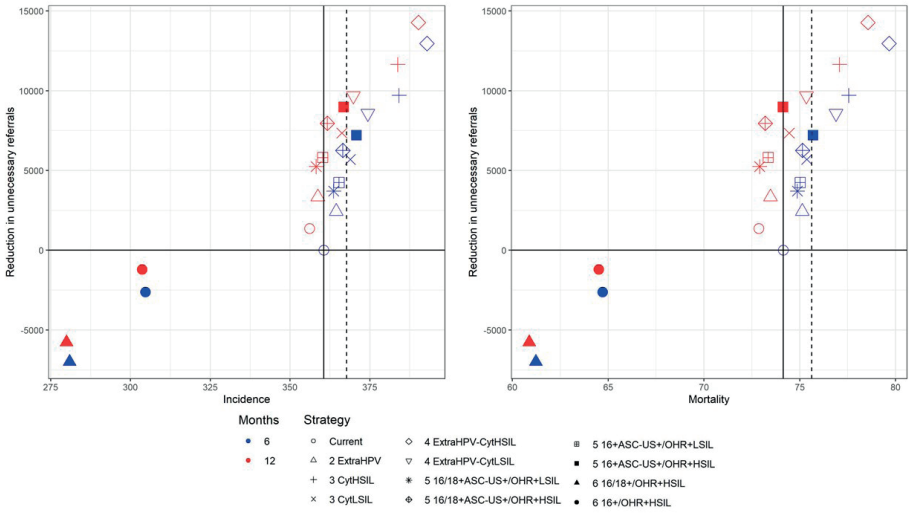

Figure 2: *Reduction in unnecessary referrals plotted against incidence and mortality for all 24 strategies (per 100,000 women).*

The vertical and horizontal solid lines represent the current triage strategy. The dotted vertical line represents the 2% cut-off for mortality and incidence. Strategies on the left of this line and above the horizontal line are considered preferred.

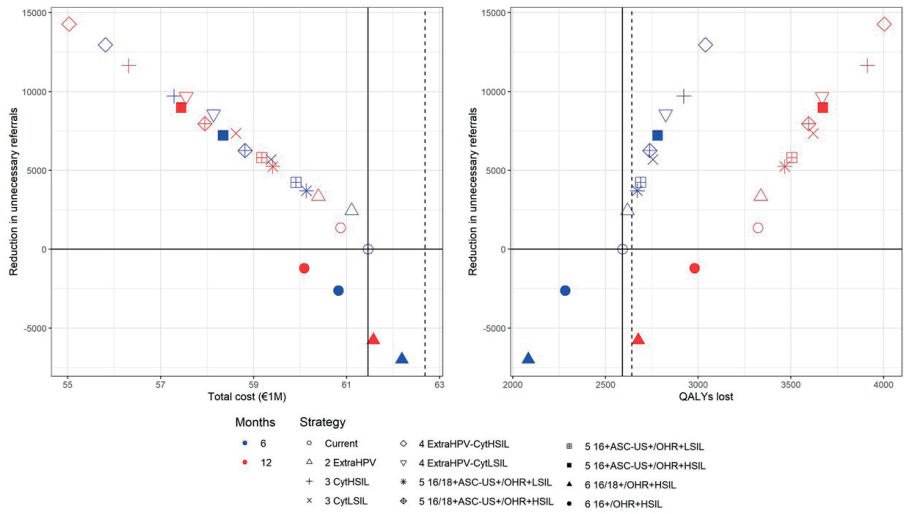

Figure 3: *Reduction in unnecessary referrals plotted against total costs and QALYs lost for all 24 strategies (per 100,000 women).*

The vertical and horizontal solid lines represent the current triage strategy. The dotted vertical line represents a 2% increase in total cost or QALYs lost.

Sensitivity analysis

A detailed overview of the results of the sensitivity analyses can be found in Appendix E. We found that the results of the study are relatively robust for changes in attendance and adherence. None of the sensitivity analyses we have done for attendance and adherence have caused a shift in the preferred strategies.

The number of QALYs lost decreased significantly when applying the alternative set of assumptions for disutilities due to screening and treatment.[16, 17] This effect is especially large for strategies with twelve months to repeat testing.

We found that the results of this study are robust to the described increases in sensitivity of the cytology test. The changes made have no substantial effect on the number of unnecessary referrals, mortality from or incidence of cervical cancer. Lastly, we found that the strategies based on genotyping result in a slightly larger reduction in unnecessary referrals, compared to the other strategies, when increasing clinical relevance from CIN2+ to CIN3+ due to the higher prevalence of HPV16 in this group. However, we did not find a change in preferred strategies.

DISCUSSION

The aim of this study was to identify a triage strategy that results in a quickly achievable, safe reduction of the number of unnecessary referrals for colposcopy in the Dutch hrHPV-based cervical screening programme. We found that changing the conditions for referral based on HPV 16/18 genotyping resulted in a substantial reduction in unnecessary referrals without increasing mortality or incidence. Similar results were also found by increasing the threshold for direct referral to LSIL for all HPV genotypes. For all strategies, 12 months to repeat test, compared to six months, resulted in the largest reduction in unnecessary referrals. Univariate sensitivity analyses showed that the results are robust to changes in attendance, test characteristics, and clinical relevance threshold.

In the base case analysis, we found that the number of QALYs lost increases substantially when the number of unnecessary referrals decreases. The reasons for this are twofold. Firstly, decreasing the number of referrals results in more women being advised to have repeat testing. In our base-case disutility set, repeat testing has a higher disutility weight than referral. Secondly, increasing the time to repeat testing from 6 months to 12 months amplifies this effect while decreasing the number of referrals, since the disutility is applied for a longer period.[14] When using a different set of disutility assumptions, the number of QALY's lost were lower, because a longer period of uncertainty distressed women who were surveyed less.[16, 17] Given the large variation in women's preference,

we decided not to focus on QALYs lost as a main outcome measure, instead focusing on outcomes that could be measured more objectively.

The HPV16/18 genotyping strategies resulted in a large reduction in unnecessary referrals without increasing mortality or incidence. This is explained by the fact that 70 to 76% of cervical cancers worldwide are caused by these two types of hrHPV infections.[19] By only raising the referral threshold for the remaining hrHPV types, the number of unnecessary referrals decreases without a large increase in the risk of leaving progressive lesions undetected. An increase in the time to repeat test also has a positive impact on the unnecessary referrals. An explanation for this is that a longer time to repeat test allows the HPV infection to clear, since cervical cancer is a relatively slow growing cancer.

Our study has several strengths. All simulations were done with a validated model, which used data directly observed from the new hrHPV-based screening programme as input. MISCAN-Cervix is a well-used, published microsimulation model, which is used in comparative modelling studies and uses input values taken from observed data and from the peer-reviewed literature. Moreover, we evaluated many strategies that are easy to implement. This makes the results of the study directly applicable and relevant for practice in many countries that consider implementing primary HPV screening. In addition, in sensitivity analyses we considered a wide range of different values for adherence, two sets of disutility assumptions and two sets of test characteristics for cytology. As the conclusions of the study did not change with these sensitivity analyses, we can conclude that the results of this study are robust to changes in assumptions.

Our study also has some limitations. There are a few alternative triaging methods that we did not consider, such as personalised (based on previous screen test results) screening strategies, co-testing, and new technologies. A Dutch study found women are at higher risk of a CIN 3+ lesions in the years following a hrHPV-positive screen, even if they have a hrHPV-negative screen in the subsequent screening round,[20] suggesting that personalised screening strategies based on factors like screening history may be beneficial. This was not considered as a viable option for triage optimisation at this time due to logistical reasons. Although co-testing is common practice in several Western countries, it has been found to be inefficient in modelling studies[21] and, thus, was not considered. New technologies such as methylation, dual staining for p16/Ki67 or HPV E6/7 mRNA testing have been shown to be promising triage options, with better sensitivity and specificity than cytology only.[22-25] However, these technologies are still under investigation and not ready to implement in a running programme. Furthermore, implementing these technologies would require infrastructural changes to be made, such as extra training for cytotechnicians and pathologists, as well as changing screening laboratory workflow. Given our aim was to find an alternative triage strategy that could be rapidly implemented, these technologies were not considered. Finally, the quality of a model is always dependent on the data used and the assumptions made.

However, in the Netherlands, we have a population-based registry that contains data on all screening-indicators that we use for development of the model. Still, the assumptions for participation, test characteristics and disutilities are less certain when making changes to the screening programme that are not implemented yet (i.e. no observed data yet). We performed sensitivity analysis on the parameters that are most uncertain, to show the robustness of the results and found that they did not change our conclusions.

This is the first study to compare so many strategies for triaging hrHPV-positive women in order to investigate unnecessary referrals versus cancer incidence and mortality. A smaller study has previously been published, which focused on determining the optimal triage strategy for a smaller subgroup of HPV-OHR positive women.[26] They found that, for HPV-OHR positive women who had low-grade cytology, 12 month follow-up was the most cost-effective triage option, as it balanced the benefits of surveillance with harms of unnecessary referrals. For the group with high-grade baseline cytology, on the other hand, it was found to be cost effective to advise direct referral to colposcopy. While direct comparison with these results is difficult, our study also found that risk stratification by HPV type and cytology grade are important for finding the optimal triage strategy for different groups of women.

We found that genotyping based on HPV-16/18 can improve the efficiency of triaging HPV-positive women. The same conclusion was reached by a recent data study on the implementation phase of the hrHPV-based screening programme in Norway, where CIN3+ risk was estimated for cytology results and HPV genotypes. By inviting women with HPV-OHR and low-grade cytology for a repeat test instead of referring these women for colposcopy, the harms and benefits of the screening programme were found to be more balanced.[27]

Internationally, the reduction in unnecessary referrals that can be achieved by implementing HPV 16/18 genotyping should encourage policymakers to consider hrHPV testing systems that allow for this feature; at a minimum, screening programme managers should consider the availability of systems that can distinguish HPV16 and HPV18 from HPV-OHR. Of course, policymakers need to evaluate the needs and requirements of their own settings prior to implementing a test system, but in the decision-making process, hrHPV genotyping should be considered as a possible addition to new HPV-based cervical cancer screening programme algorithms.

From 2023, the first cohort of women that were eligible for HPV vaccination will enter the screening programme in the Netherlands. Although our study did not include vaccinated women within the simulated cohort, this important change to the eligible population will necessitate reassessment of the triage algorithm in the coming decade. Women vaccinated with a bivalent vaccine are protected against HPV16 and HPV18 infections, which has been shown in other countries to reduce risk of CIN lesions amongst

both vaccinated and unvaccinated women (protected by herd immunity effects).[28] Without a more efficient triage strategy, such as genotyping, vaccinated women may be more likely to be unnecessarily referred to the gynaecologist. The balance between harms and benefits of screening for vaccinated women could be improved by including genotyping on HPV16/18 in the triage strategy.

CONCLUSION

This study aimed to identify a triage strategy that results in a quickly achievable reduction of the number of unnecessary referrals with the Dutch cervical cancer screening programme, without deteriorating mortality from and incidence of cervical cancer. It is the first study where such a wide range of strategies is modelled to find the best strategy for all HPV positive women. We found that adding genotyping for HPV16 and/or HPV18 to the referral algorithm while increasing the referral threshold for HPV-OHR to HSIL substantially decreases the number of unnecessary referrals without increasing cervical cancer incidence or mortality. Extending the time to repeat testing from six to 12 months also reduced unnecessary referrals. Based on our findings, we recommend implementing genotyping as a triage strategy for HPV-positive women in the Dutch cervical cancer screening programme, with possible extension of the time to repeat testing.

DECLARATIONS

Conflicts of interests

All authors have completed the ICMJE uniform disclosure form and declare: All authors report receiving funding from the Dutch National Institute for Public Health and the Environment for the conduct of this study.

Authors' contributions

Contributors: SK wrote the first draft of the manuscript with contributions from EELJ and IMCMdK. SK and EELJ did the analyses. CAA coordinated the analysis of data for input into the model. All authors edited and approved the final version of the article. SK, EELJ, CAA, LMH, SKN and IMCMdK contributed to the development and conduct of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SK and IMCMdK are the guarantors.

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Ethics approval

Ethical approval by a medical ethical committee was not required under Dutch law as no patients were involved in the development of the research and only non-identifiable data was used for this study.

Transparency statement

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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APPENDICES

Supplement to: S Kaljouw, EEL Jansen, CA Aitken et al. Reducing unnecessary referrals for colposcopy in hrHPV-positive women within the Dutch cervical cancer screening programme: a modelling study

Appendix A: Transition probabilities per HPV genotype and age group as defined in MISCAN-Cervix.

Table S1 *Transition probabilities (regression and progression) per HPV type, age group and current state, as defined in MISCAN-Cervix.*

HPV type	Age	Regression		Probability	Progression		Probability
		From	To		From	To	
HPV 16	15	HPV 16	No HPV	0.968	HPV 16	CIN 1	0.032
HPV 16	25	HPV 16	No HPV	0.978	HPV 16	CIN 1	0.022
HPV 16	35	HPV 16	No HPV	0.886	HPV 16	CIN 1	0.114
HPV 16	50	HPV 16	No HPV	0.762	HPV 16	CIN 1	0.238
HPV 16	75	HPV 16	No HPV	0.993	HPV 16	CIN 1	0.007
HPV 18	15	HPV 18	No HPV	0.943	HPV 18	CIN 1	0.057
HPV 18	25	HPV 18	No HPV	0.962	HPV 18	CIN 1	0.038
HPV 18	35	HPV 18	No HPV	0.801	HPV 18	CIN 1	0.199
HPV 18	50	HPV 18	No HPV	0.582	HPV 18	CIN 1	0.418
HPV 18	75	HPV 18	No HPV	0.988	HPV 18	CIN 1	0.012
HPV 9V	15	HPV 9V	No HPV	0.975	HPV 9V	CIN 1	0.025
HPV 9V	25	HPV 9V	No HPV	0.983	HPV 9V	CIN 1	0.017
HPV 9V	35	HPV 9V	No HPV	0.913	HPV 9V	CIN 1	0.087
HPV 9V	50	HPV 9V	No HPV	0.817	HPV 9V	CIN 1	0.183
HPV 9V	75	HPV 9V	No HPV	0.995	HPV 9V	CIN 1	0.005
HPVOHR	15	HPVOHR	No HPV	0.975	HPVOHR	CIN 1	0.025
HPVOHR	25	HPVOHR	No HPV	0.983	HPVOHR	CIN 1	0.017
HPVOHR	35	HPVOHR	No HPV	0.913	HPVOHR	CIN 1	0.087
HPVOHR	50	HPVOHR	No HPV	0.818	HPVOHR	CIN 1	0.182
HPVOHR	75	HPVOHR	No HPV	0.995	HPVOHR	CIN 1	0.005
HPV 16	20	CIN 1	HPV 16	0.556	CIN 1	CIN 2	0.444
HPV 16	35	CIN 1	HPV 16	0.038	CIN 1	CIN 2	0.962
HPV 16	50	CIN 1	HPV 16	0.519	CIN 1	CIN 2	0.481
HPV 16	65	CIN 1	HPV 16	0.869	CIN 1	CIN 2	0.131
HPV 18	20	CIN 1	HPV 18	0.880	CIN 1	CIN 2	0.120
HPV 18	35	CIN 1	HPV 18	0.741	CIN 1	CIN 2	0.259
HPV 18	50	CIN 1	HPV 18	0.870	CIN 1	CIN 2	0.130

Table S1 *Transition probabilities (regression and progression) per HPV type, age group and current state, as defined in MISCAN-Cervix. (continued)*

HPV type	Age	Regression		Probability	Progression		Probability
		From	To		From	To	
HPV 18	65	CIN 1	HPV 18	0.965	CIN 1	CIN 2	0.035
HPV 9V	20	CIN 1	HPV 9V	0.736	CIN 1	CIN 2	0.264
HPV 9V	35	CIN 1	HPV 9V	0.427	CIN 1	CIN 2	0.573
HPV 9V	50	CIN 1	HPV 9V	0.714	CIN 1	CIN 2	0.286
HPV 9V	65	CIN 1	HPV 9V	0.922	CIN 1	CIN 2	0.078
HPVOHR	20	CIN 1	HPVOHR	0.877	CIN 1	CIN 2	0.123
HPVOHR	35	CIN 1	HPVOHR	0.732	CIN 1	CIN 2	0.268
HPVOHR	50	CIN 1	HPVOHR	0.866	CIN 1	CIN 2	0.134
HPVOHR	65	CIN 1	HPVOHR	0.964	CIN 1	CIN 2	0.036
NoHPV	20	CIN 1	No HPV	0.762	CIN 1	CIN 2	0.238
NoHPV	35	CIN 1	No HPV	0.485	CIN 1	CIN 2	0.515
NoHPV	50	CIN 1	No HPV	0.743	CIN 1	CIN 2	0.257
NoHPV	65	CIN 1	No HPV	0.930	CIN 1	CIN 2	0.070
HPV 16	20	CIN 2	CIN 1	0.518	CIN 2	CIN 3	0.482
HPV 16	35	CIN 2	CIN 1	0.459	CIN 2	CIN 3	0.541
HPV 16	50	CIN 2	CIN 1	0.766	CIN 2	CIN 3	0.234
HPV 16	65	CIN 2	CIN 1	0.704	CIN 2	CIN 3	0.296
HPV 18	20	CIN 2	CIN 1	0.815	CIN 2	CIN 3	0.185
HPV 18	35	CIN 2	CIN 1	0.792	CIN 2	CIN 3	0.208
HPV 18	50	CIN 2	CIN 1	0.910	CIN 2	CIN 3	0.090
HPV 18	65	CIN 2	CIN 1	0.886	CIN 2	CIN 3	0.114
HPV 9V	20	CIN 2	CIN 1	0.657	CIN 2	CIN 3	0.343
HPV 9V	35	CIN 2	CIN 1	0.615	CIN 2	CIN 3	0.385
HPV 9V	50	CIN 2	CIN 1	0.833	CIN 2	CIN 3	0.167
HPV 9V	65	CIN 2	CIN 1	0.789	CIN 2	CIN 3	0.211
HPVOHR	20	CIN 2	CIN 1	0.729	CIN 2	CIN 3	0.271
HPVOHR	35	CIN 2	CIN 1	0.696	CIN 2	CIN 3	0.304
HPVOHR	50	CIN 2	CIN 1	0.868	CIN 2	CIN 3	0.132
HPVOHR	65	CIN 2	CIN 1	0.833	CIN 2	CIN 3	0.167
NoHPV	20	CIN 2	CIN 1	0.609	CIN 2	CIN 3	0.391
NoHPV	35	CIN 2	CIN 1	0.561	CIN 2	CIN 3	0.439
NoHPV	50	CIN 2	CIN 1	0.810	CIN 2	CIN 3	0.190
NoHPV	65	CIN 2	CIN 1	0.760	CIN 2	CIN 3	0.240
HPV 16	20	CIN 3	CIN 2	0.930	CIN 3	CC	0.070
HPV 16	35	CIN 3	CIN 2	0.882	CIN 3	CC	0.118
HPV 16	50	CIN 3	CIN 2	0.865	CIN 3	CC	0.135
HPV 16	65	CIN 3	CIN 2	0.090	CIN 3	CC	0.910

Table S1 *Transition probabilities (regression and progression) per HPV type, age group and current state, as defined in MISCAN-Cervix. (continued)*

HPV type	Age	Regression		Probability	Progression		Probability
		From	To		From	To	
HPV 18	20	CIN 3	CIN 2	0.561	CIN 3	CC	0.439
HPV 18	35	CIN 3	CIN 2	0.254	CIN 3	CC	0.746
HPV 18	50	CIN 3	CIN 2	0.147	CIN 3	CC	0.853
HPV 18	65	CIN 3	CIN 2	0.090	CIN 3	CC	0.910
HPV 9V	20	CIN 3	CIN 2	0.970	CIN 3	CC	0.030
HPV 9V	35	CIN 3	CIN 2	0.949	CIN 3	CC	0.051
HPV 9V	50	CIN 3	CIN 2	0.942	CIN 3	CC	0.058
HPV 9V	65	CIN 3	CIN 2	0.090	CIN 3	CC	0.910
HPVOHR	20	CIN 3	CIN 2	0.981	CIN 3	CC	0.019
HPVOHR	35	CIN 3	CIN 2	0.968	CIN 3	CC	0.032
HPVOHR	50	CIN 3	CIN 2	0.963	CIN 3	CC	0.037
HPVOHR	65	CIN 3	CIN 2	0.090	CIN 3	CC	0.910
No HPV	20	CIN 3	CIN 2	1.000	CIN 3	CC	0.000*
No HPV	35	CIN 3	CIN 2	1.000	CIN 3	CC	0.000*
No HPV	50	CIN 3	CIN 2	1.000	CIN 3	CC	0.000*
No HPV	65	CIN 3	CIN 2	1.000	CIN 3	CC	0.000*

hrHPV = high-risk human papillomavirus; CIN = cervical intraepithelial neoplasia; CC = cervical cancer

* CIN 3 lesions can never transition to cervical cancer without an HPV infection

Appendix B Visual representation of triage strategies

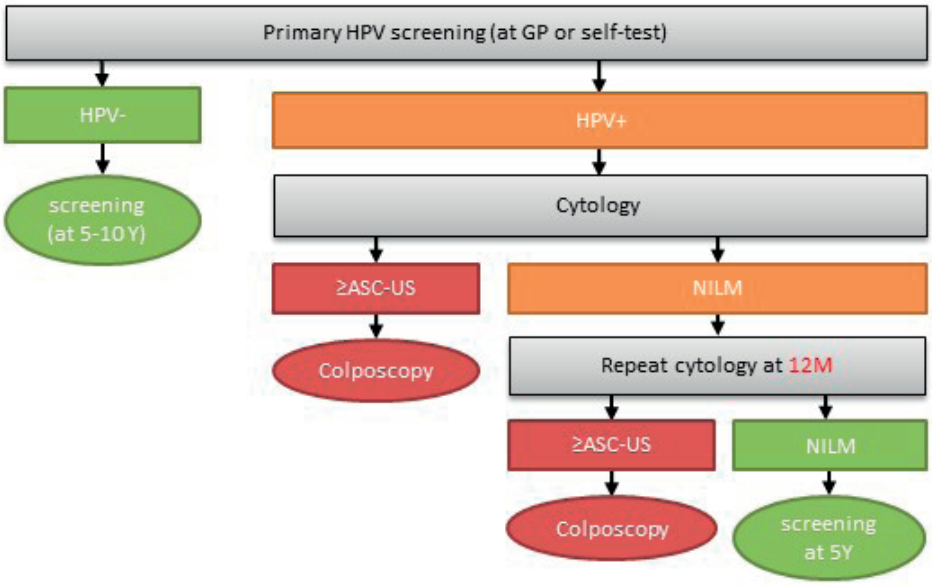

Figure S1: *Category 1 - Extend time to repeat test to 12 months*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted in red text. Primary screening can be conducted by a general practitioner or via self-sampling, Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

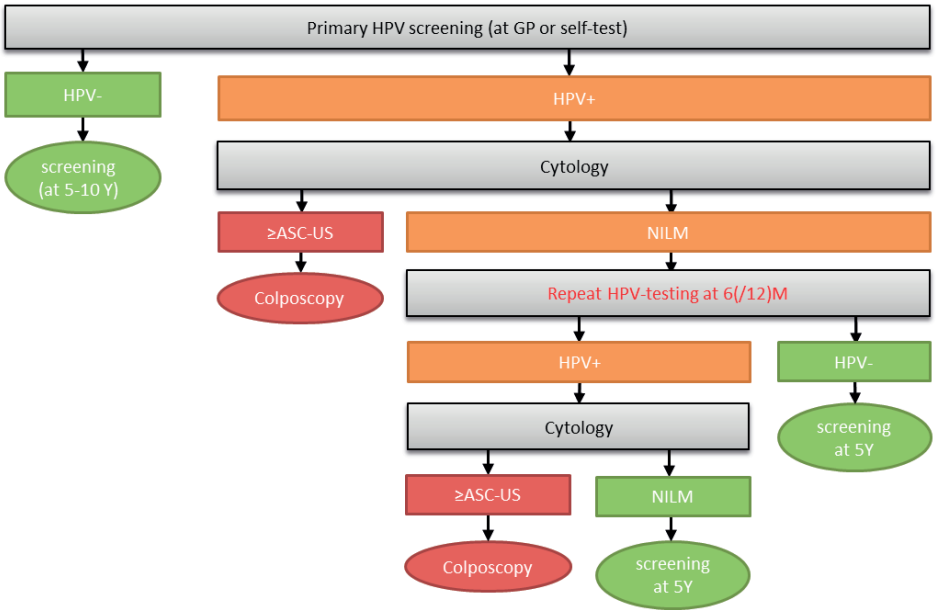

Figure S2: *Category 2 - Add HPV test to repeat test*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted in red text. Primary screening can be conducted by a general practitioner or via self-sampling. Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

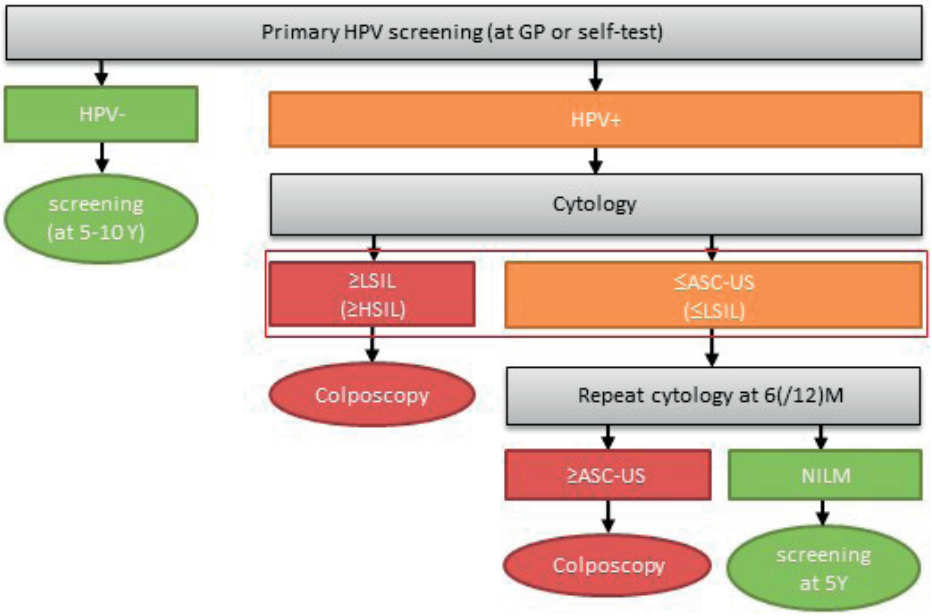

Figure S3: *Category 3 - Increase referral threshold to LSIL/HSIL (two strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted in a red box. Primary screening can be conducted by a general practitioner or via self-sampling. Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

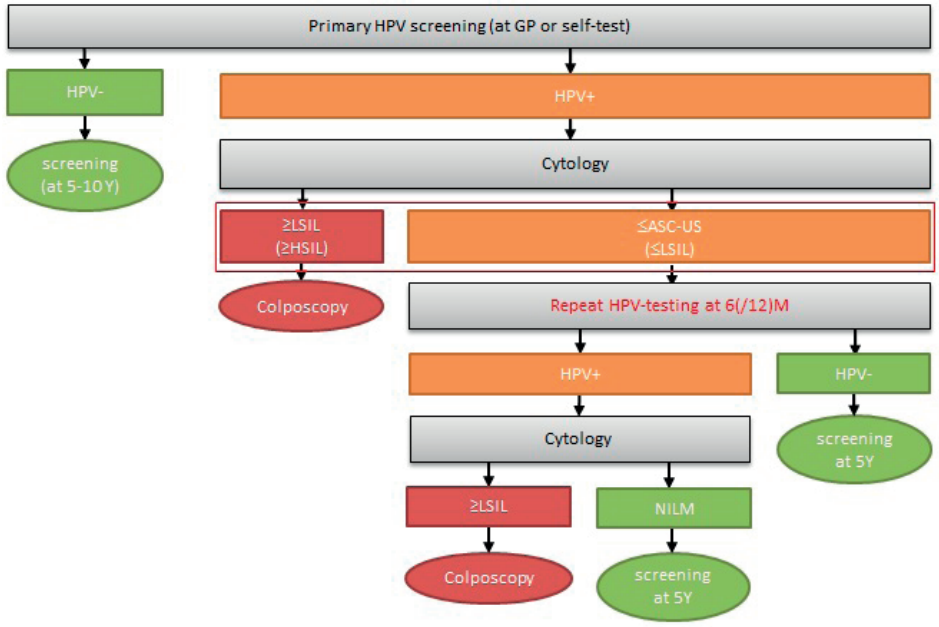

Figure S4: *Category 4 - Combination of categories 2 and 3 (two strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted in red text and a red box. Primary screening can be conducted by a general practitioner or via self-sampling. Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

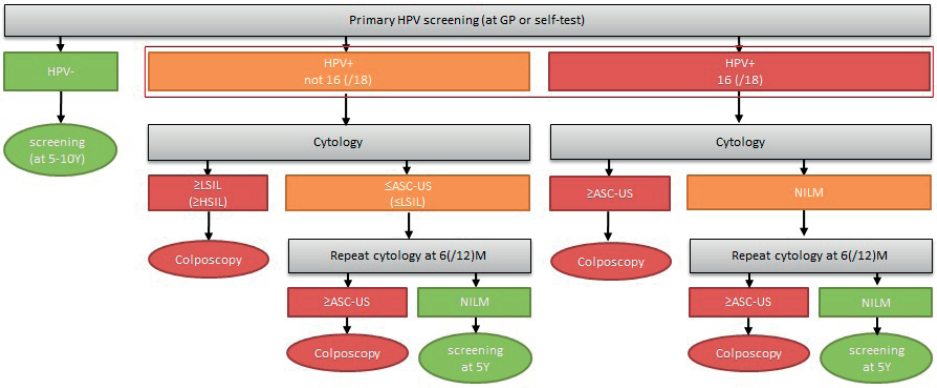

Figure S5: *Category 5 - HPV genotyping and increase referral threshold to LSIL/HSIL (four strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted in a red box. Primary screening can be conducted by a general practitioner or via self-sampling. Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

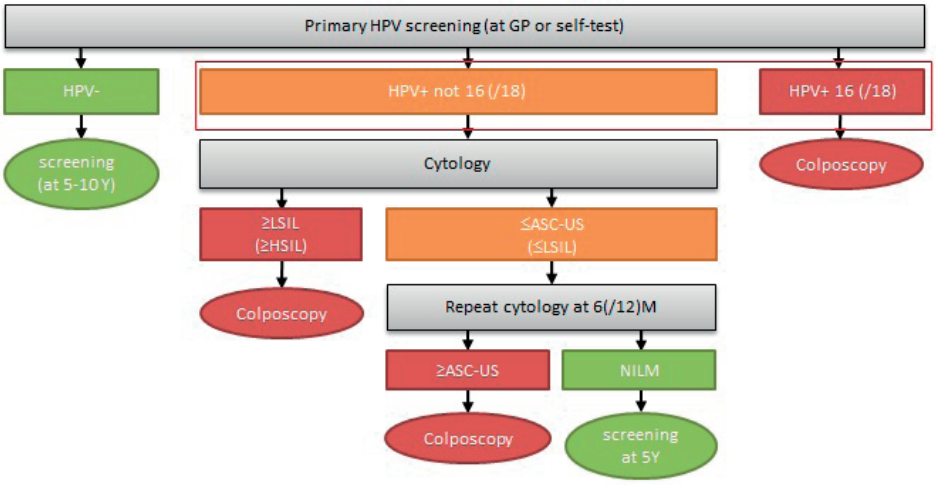

Figure S6: *Category 6 - HPV genotyping and direct referral (two strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted in a red box. Primary screening can be conducted by a general practitioner or via self-sampling. Women who are hrHPV-negative at age 60 exit the programme and do not receive another screening invitation.

Appendix C: Assumptions for costs and quality-adjusted life years

Table S2: *Assumptions for costs and quality-adjusted life years (QALYs) lost in the base case analysis*

	Unit costs (€)	QALYs lost per month	Duration in months
SCREENING			
Primary hrHPV-test	58	0	0
Primary hrHPV selftest	43	0	0
Reflex cytology after hrHPV-test	26	0	0
Repeat cytology after hrHPV selftest	52	0.03	1
Repeat cytology after 6 months	53	0.03	6
DIAGNOSIS AND TREATMENT			
No CIN	316	0.03	1
CIN1	986	0.03	1
CIN2	1 461	0.03	1
CIN3	1 710	0.03	1
FIGO1A	5 601	0.08	12
FIGO1B	13 283	0.08	12
FIGO2+ clinically detected	12 226	0.14	12
FIGO2+ screen-detected	13 092	0.14	12
Cancer survivor	0*	0.03	120
Palliative care	29 745	0.5	12

* Costs are included in treatment

Appendix D: Assumptions for attendance and adherence in sensitivity analyses

Table S3: *Assumptions for attendance and adherence in sensitivity analyses.*

Screening behaviour	Current programme	Current programme, 12m lower	Cytology programme
GP-test participation by age in all women of the population*			
30	43.4%	43.4%	52.3%
35	49.3%	49.3%	57.9%
40	56.4%	56.4%	64.3%
45	58.6%/15.6%**	58.6%/15.6%**	67.6%
50	61.5%	61.5%	70.4%
55	62.7%/12.7%**	62.7%/12.7%**	69.6%
60	60.3%	60.3%	66.8%
65	NA/3.1%***	NA/3.1%***	NA
Self-sampling participation by age*			
30	5.5%	5.5%	NA
35	4.8%	4.8%	NA
40	4.5%	4.5%	NA
45	4.4%/0.9%**	4.4%/0.9%**	NA
50	4.6%	4.6%	NA
55	4.8%/1.0%**	4.8%/1.0%**	NA
60	5.7%	5.7%	NA
65	NA/0.2%***	NA/0.2%***	NA
Adherence to cytology after a positive self-sample	90.1%	90.1%	NA
Adherence to triage testing (6/12m)			
- after primary office-based test	77.1%	69.0%	92.2%
- after primary self-sampling test	41.6%	69.0%	NA
Adherence to a referral for colposcopy after a			
- direct referral (ASC-US/LSIL)	88.4%	88.4%	NA
- direct referral (HSIL)	96.9%	96.9%	97.0%
- referral at 6 months after primary test (ASCUS/LSIL)	88.4%	88.4%	97.5%
- referral at 6 months after primary test (HSIL)	96.9%	96.9%	97.5%

* Simulated participation rate in all women excluding those who have had a hysterectomy and those with a prevalent diagnosed cancer.

** Participation in the general population is much lower at ages 45 and 55 from the second screening round, because significantly fewer women are invited for screening at these ages (i.e. only those who do not participate or test hrHPV-positive in the preceding screening round).

*** Participation in the general population is much lower at age 65 because significantly fewer women are invited for screening at this age (i.e. only those who test hrHPV-positive at age 65).

HPV = human papillomavirus; NA = not applicable; ASC-US = Atypical squamous cells of undetermined significance; LSIL = Low-grade squamous intraepithelial lesion; HSIL = High-grade squamous intraepithelial lesion.

Appendix E: Results from sensitivity analyses

Table S4: *Results of sensitivity analysis on attendance and compliance rates (per 100,000 women).*

ATTENDANCE	Strategy	1.2	2.1	2.2	3.4	5.1	5.2	5.3	5.4	5.6	5.7	5.8
	Months to repeat testing	12	6	12	12	6	12	6	12	12	6	12
	Value (base case)	%	%	%	%	%	%	%	%	%	%	%
Base case analysis												
Unnecessary referrals	19,838	-7%	-12%	-17%	-37%	-32%	-40%	-19%	-26%	-45%	-21%	-29%
Mortality	74	-2%	1%	-1%	0%	1%	-1%	1%	-2%	0%	1%	-1%
Incidence	361	-1%	1%	-1%	2%	2%	0%	1%	-1%	2%	1%	0%
Costs (€)	61,458,537	-1%	-1%	-2%	-5%	-4%	-6%	-2%	-3%	-7%	-3%	-4%
QALYs lost	2,591	28%	1%	29%	40%	6%	39%	3%	34%	42%	4%	35%
Current screening programme												
Unnecessary referrals	8,077	-6%	-10%	-14%	-37%	-35%	-43%	-17%	-24%	-49%	-20%	-27%
Mortality	192	-1%	1%	0%	1%	0%	0%	0%	-1%	1%	0%	0%
Incidence	652	0%	0%	0%	1%	0%	0%	-1%	-1%	1%	0%	-1%
Costs (€)	43,963,363	-1%	0%	-1%	-3%	-3%	-4%	-1%	-2%	-4%	-1%	-2%
QALYs lost	5,073	5%	0%	6%	8%	1%	8%	0%	6%	9%	1%	7%
Current screening programme, low attendance for 12 months to repeat test												
Unnecessary referrals	8,077	-8%	-	-15%	-39%	-	-45%	-	-25%	-51%	-	-29%
Mortality	192	0%	-	0%	1%	-	0%	-	0%	2%	-	0%
Incidence	652	-1%	-	0%	1%	-	0%	-	-1%	1%	-	0%
Costs (€)	43,963,363	5%	-	-1%	-3%	-	-4%	-	-2%	-5%	-	-2%
QALYs lost	5,073	-8%	-	5%	8%	-	7%	-	6%	9%	-	7%
Cytology screening programme												
Unnecessary referrals	10,096	-7%	-12%	-17%	-39%	-34%	-43%	-20%	-28%	-48%	-23%	-31%
Mortality	187	-1%	0%	0%	0%	0%	-1%	0%	-1%	0%	0%	0%
Incidence	627	0%	0%	0%	1%	1%	0%	0%	0%	1%	1%	0%
Costs (€)	46,575,467	-1%	0%	-1%	-3%	-3%	-4%	-2%	-3%	-5%	-2%	-3%
QALYs lost	4,987	7%	0%	7%	11%	2%	10%	1%	9%	11%	1%	9%

Table S5: *Results of sensitivity analysis on disutility assumptions (per 100,000 women).*

DISUTILITIES	Strategy	1.2	2.1	2.2	3.4	5.1	5.2	5.3	5.4	5.6	5.7	5.8
	Months to repeat testing	12	6	12	12	6	12	6	12	12	6	12
	Value (base case)	%	%	%	%	%	%	%	%	%	%	%
Normal[1]												
Unnecessary referrals	19,838	-7%	-12%	-17%	-37%	-32%	-40%	-19%	-26%	-45%	-21%	-29%
Mortality	74	-2%	1%	-1%	0%	1%	-1%	1%	-2%	0%	1%	-1%
Incidence	361	-1%	1%	-1%	2%	2%	0%	1%	-1%	2%	1%	0%
Costs (€)	61,458,537	-1%	-1%	-2%	-5%	-4%	-6%	-2%	-3%	-7%	-3%	-4%
QALYs lost	2,591	28%	1%	29%	40%	6%	39%	3%	34%	42%	4%	35%
Alternative[2,3]												
Unnecessary referrals	19,838	-7%	-12%	-17%	-37%	-32%	-40%	-19%	-26%	-45%	-21%	-29%
Mortality	74	-2%	1%	-1%	0%	1%	-1%	1%	-2%	0%	1%	-1%
Incidence	361	-1%	1%	-1%	2%	2%	0%	1%	-1%	2%	1%	0%
Costs (€)	61,458,537	-1%	-1%	-2%	-5%	-4%	-6%	-2%	-3%	-7%	-3%	-4%
QALYs lost	2,843	3%	1%	3%	5%	0%	3%	0%	3%	4%	0%	4%

Table S6: *Results of sensitivity analysis on assumptions for test characteristics of cytology test (per 100,000 women).*

TEST CHARACTERISTICS	Strategy	1.2	2.1	2.2	3.4	5.1	5.2	5.3	5.4	5.6	5.7	5.8
	Months to repeat testing	12	6	12	12	6	12	6	12	12	6	12
	Value (base case)	%	%	%	%	%	%	%	%	%	%	%
Normal												
Unnecessary referrals	19,838	-7%	-12%	-17%	-37%	-32%	-40%	-19%	-26%	-45%	-21%	-29%
Mortality	74	-2%	1%	-1%	0%	1%	-1%	1%	-2%	0%	1%	-1%
Incidence	361	-1%	1%	-1%	2%	2%	0%	1%	-1%	2%	1%	0%
Costs (€)	61,458,537	-1%	-1%	-2%	-5%	-4%	-6%	-2%	-3%	-7%	-3%	-4%
QALYs lost	2,591	28%	1%	29%	40%	6%	39%	3%	34%	42%	4%	35%
Higher sensitivity (+50% for CIN 1 and CIN 2)												
Unnecessary referrals	21,957	-5%	-11%	-14%	-34%	-29%	-37%	-17%	-24%	-42%	-20%	-26%
Mortality	72	-1%	1%	-1%	0%	1%	-2%	0%	-2%	-1%	1%	-1%
Incidence	342	-1%	1%	0%	1%	1%	0%	0%	-1%	1%	1%	0%
Costs (€)	63,781,599	-1%	-1%	-2%	-4%	-4%	-5%	-2%	-3%	-6%	-2%	-3%
QALYs lost	2,472	28%	1%	29%	40%	6%	40%	3%	34%	43%	4%	36%

Table S7: *Results of sensitivity analysis on assumptions for clinical relevance threshold (per 100,000 women).*

CLINICAL RELEVANCE	Base case	1.2	2.1	2.2	3.4	5.1	5.2	5.3	5.4	5.6	5.7	5.8
	Months to repeat testing	12	6	12	12	6	12	6	12	12	6	12
	Value	%	%	%	%	%	%	%	%	%	%	%
>=*CIN2*												
Unnecessary referrals	19,838	-7%	-12%	-17%	-37%	-32%	-40%	-19%	-26%	-45%	-21%	-29%
Mortality	74	-2%	1%	-1%	0%	1%	-1%	1%	-2%	0%	1%	-1%
Incidence	361	-1%	1%	-1%	2%	2%	0%	1%	-1%	2%	1%	0%
Costs (€)	61,458,537	-1%	-1%	-2%	-5%	-4%	-6%	-2%	-3%	-7%	-3%	-4%
QALYs lost	2591	28%	1%	29%	40%	6%	39%	3%	34%	42%	4%	35%
>=*CIN3*												
Unnecessary referrals	24,206	-6%	-10%	-14%	-32%	-28%	-35%	-16%	-23%	-40%	-18%	-25%
Mortality	74	-2%	1%	-1%	0%	1%	-1%	1%	-2%	0%	1%	-1%
Incidence	361	-1%	1%	-1%	2%	2%	0%	1%	-1%	2%	1%	0%
Costs (€)	61,458,537	-1%	-1%	-2%	-5%	-4%	-6%	-2%	-3%	-7%	-3%	-4%
QALYs lost	2,591	28%	1%	29%	40%	6%	39%	3%	34%	42%	4%	35%

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Chapter 4.3

Risk of gynaecological cancer after atypical glandular cells found on cervical cytology: a population-based cohort study

Clare A. Aitken[1], Erik E.L. Jansen[1], Albert G. Siebers[2,3], Anne-Marie L.D. van Haaften-de Jong[4], Folkert J. van Kemenade[5], Inge M.C.M. de Kok[1]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam
2. PALGA, The nationwide network and registry of histo-and cytopathology in the Netherlands
3. Department of Pathology, Radboud University Medical Center
4. Department of Obstetrics and Gynaecology, HagaZiekenhuis
5. Department of Pathology, Erasmus MC, University Medical Center Rotterdam

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ABSTRACT

Background

Atypical glandular cells (AGC) are rare abnormalities found on cervical cytology associated with a range of lesions of the female reproductive system. We compared the risk of cervical and other gynaecological cancers following AGC on cervical cytology with the risk following squamous cell abnormalities of comparable severity.

Methods

We used data from the Dutch Pathology Archive (PALGA) from 2000-2015 to categorise cervical cytology tests into groups based on most severe cytological abnormality and correlated follow-up advice (normal cytology and 'no follow-up' advice, squamous-cell based-, AGC-based, and combined AGC/squamous-cell based each with either repeat testing or referral advice). Cancer data were linked from the Netherlands Cancer Registry. Cox proportional hazard models were calculated stratified by age (younger (<50 years) and older (50+ years)), adjusted for number of previous primary cytology tests.

Results

8,537,385 cytology smears and 9,061 cancers were included. When repeat cytology testing was advised, hazard ratios (HR) of cervical cancer (younger women – HR: 6.91, 95% CI: 5.48 – 8.71; older– HR: 3.98, 95% CI: 2.38 - 6.66) or other gynaecological cancer diagnosis in younger women (HR: 2.82, 95% CI: 1.39 - 5.74) were significantly higher after an AGC-based abnormality compared with squamous-based abnormalities. Hazards were also significantly higher for 'referral' advice cytology, except for cervical cancer amongst older women (HR: 0.88, 95% CI: 0.63 – 1.21).

Conclusions

AGC indicates an increased risk of gynaecological cancer compared to squamous-based abnormalities of comparable severity.

Impact

Gynaecologists should be alert for cervical and endometrial cancers when examining women referred following AGC.

INTRODUCTION

Atypical glandular cells (AGC) are rare cytological abnormalities, detected in less than 1% of cervical smears.[1] Interpretation of AGC can be challenging for cytotechnicians and pathologists,[2] partly because associated conditions can range widely, from benign lesions to cancers.[3] Cancers include cervical adenocarcinoma, which organised cervical screening has had little impact on the incidence of,[4 5] as well as other gynaecological cancers such as endometrial and ovarian cancers.[6-9] The type of lesion that is indicated by AGC has been shown to differ by age, with squamous cell abnormalities (cervical intraepithelial neoplasia (CIN) grades 2 or 3) most commonly found in younger women and endometrial cancer most commonly found in women aged 50 years and older.[6]

Cervical cancer screening programmes are aimed at detecting pre-malignant and malignant cervical lesions, with the goal of preventing incidence of, and mortality from, cervical cancer. This has been largely achieved in the Netherlands, with incidence and mortality reduction in the period following the introduction of organised screening.[10] Although detection of other gynaecological cancers is beyond the scope of organised cervical cancer screening programmes, some women may have benefited from the incidental detection of non-cervical, AGC-related lesions following cervical cytology.

Large, population-based datasets are needed for investigating the risk of gynaecological cancer following AGC because AGC is a uncommon diagnosis. However, these type of studies are scarce, with most AGC research focusing on only limited numbers of clinical samples. One large population-based study[11] found that AGC was associated with a persistent, long-term risk of cervical cancer in particular AGC cervical adenocarcinoma. However, other AGC-related cancers were not considered as endpoints in this study. Robust, population-based estimates of the risk of non-cervical gynaecological cancers after AGC are needed to inform and refine management strategies for these women. This is particularly pertinent in the Netherlands because not all women with an AGC on cervical cytology were referred directly to the gynaecologist prior to 2017. To that end, we aimed to investigate what is the risk of particular gynaecological cancers for women after a smear where AGC are detected as compared to this risk after squamous abnormalities with comparable severity.

MATERIALS AND METHODS

Study design

We conducted a population-based retrospective cohort study including cervical cytology tests taken in the Netherlands from the Dutch cervical cancer screening programme between 1 January 2000 and 31 December 2015. Women aged 29 to 63 years were

included. In the case that a woman has participated more than once in the screening programme, each screen was included (when the screen met the criteria outlined in section *"Data analysis and variables"*). In our study, the risk of cancer is the immediate risk following a cytology smear, as we identified which screen was most proximal in time to the cancer diagnosis.

Setting

Between 1996 and 2016, primary cervical cytology screening was offered as part of the nationally-coordinated organised screening programme in the Netherlands. In 2017, the national screening programme transitioned to primary high-risk human papillomavirus (hrHPV) screening. Women between 30 to 60 years were invited for screening every five years. Quality of the programme is high, with low rates of cancers after normal cytology[12] and a participation rate of around 65%.[13]

During the period of this study, the primary screening test was either conventional cytology or liquid-based cytology, with an increase in the use of liquid-based cytology over the period 2000 to 2012.[14] Cervical cytology is graded using the CISOE-A system, the Dutch nationwide, pro-forma classification system for cervical cytology[15] which is easily convertible to other classification systems, such as Pap classification and The Bethesda System for Reporting Cervical Cytology (Table 1).[16] CISOE-A is tri-axial classification with specific information on squamous cells, glandular cells and 'other' cells. The CISOE-A classification is used to determine the follow-up advice that a woman receives following primary screening. The screening programme algorithm can be found in Figure S1.

Based on the results of primary cytology screening, women receive an advice to either return to regular screening (negative cytology; NILM), receive a repeat cytology test after 6 months (low-grade cytological abnormalities; ASC-US/LSIL) or were referred directly to a gynaecologist (high-grade cytology abnormalities; HSIL). Women with lower-grade AGC lesions (AGC of endocervical origin only) were advised to attend repeat cytology testing after 6 months. Women with AGC of endometrial or ovarian origin or women with cytology indicating adenocarcinoma in situ were referred directly to a gynaecologist.

During most of the period of this study, national guidelines were in place for the diagnosis and treatment of cervical abnormalities; one set of guidelines covered the period 2004 – 2014[17] and one set covering 2015 to present.[18] The CISOE-A score is used by gynaecologists to determine the correct diagnostic strategy. Women with squamous cervical abnormalities on their cytology receive colposcopy and dependant on the colposcopic image and the CISOE-A score and other factors (such as age, depth and visibility of lesion, transformation zone type), gynaecologists determine whether biopsies or a large excision of the cervix were required for diagnosis and/or treatment. Random biopsies of the cervix are not standard practice in the Netherlands. In the case of AGC abnormalities, the CISOE-A score is used to determine if ultrasound or colposcopy is

Table 1: *Concordance between CISOE-A, Pap and Bethesda grading systems. Adapted from Oncoline*[30]

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), of endocervical origin only
E4-5	Pap 3a1	AGC, endocervical origin only *(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 or ovarian (but not endocervical origin)
E6, O6	Pap 3b	AGC, E6 high grade neoplasia or AIS. *(If not endocervical, then O6 in case of endometrial-, ovarian- or other cells)*
S6	Pap 3b	HSIL (including atypical squamous cells, includes ASC-H in NL)
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	ASC-H

required for diagnosis. When endometrial cancer is suspected, the most recent national guidelines state that imaging can be conducted and pre-operative histological samples can be taken within an outpatient clinic to help gynaecologists reach a diagnosis.[19]

Data sources

We used data from the nationwide network of cyto- and histopathology in the Netherlands (PALGA) and from the Netherlands Cancer Registry (NCR). PALGA has complete coverage of all pathology labs within the Netherlands.[20] The NCR is the national oncological registry in the Netherlands with data on all cancer patients and has data from 1989 onwards.[21] For this study, we collaborated with PALGA to create a dataset comprising of an extract of cervical cytology, hrHPV test results and histology records for cervical, uterine and ovarian cancers. Data from PALGA contains an individual, pseudonimised identifier (PALGA ID) based on the first eight letter of the woman's surname (maiden surnames are used for married women) and date of birth which can be used to follow screening histories.

Data analysis and variables

We used CISOE-A to group cytology smears into seven categories based on the type of cytological abnormality [either normal, squamous cell abnormality, AGC abnormality, combined squamous/AGC abnormality] and the follow-up advice that is given on the basis of the severity of the abnormality [return to regular screening, repeat cytology testing, referral to gynaecologist]. The combination of these categories resulted in seven groups:

- Normal cytology [NILM equivalent];
- Repeat, Squamous [ASC-US/LSIL equivalent];
- Repeat, AGC [Endocervical origin only];
- Repeat, AGC/Squamous;
- Referral, Squamous [HSIL/Carcinoma-in-situ equivalent];
- Referral AGC [Endometrial/ovarian origin/adenocarcinoma-in-situ]; and,
- Referral AGC/Squamous.

AGC or squamous cell abnormalities were classified based on the highest CISOE-A score; that is, if both AGC and squamous abnormalities were reported, the most severe abnormality was used for grouping. Cytology results were only classified as combined AGC/squamous when the squamous and other cell abnormalities were of equal severity. Coding of these categories were reviewed by a pathologist and cytology data expert. Any cytology tests that could not be classified in one of the seven groups (e.g. due to invalid or incomplete CISOE-A coding) were excluded from the analysis.

We also received data from the NCR for gynaecological cancers (cervical, uterine [including endometrial], ovarian and other gynaecological cancers: ICD-10 codes C53, C54, C56, C57) including information about topography and morphology. Vulva (C51) and vaginal (C52) cancer were excluded as they are not associated with AGC. We included only invasive cancers in our analysis. We created six diagnosis groups: cervical cancer –squamous, cervical cancer – adenocarcinoma, cervical cancer – other, endometrial cancers, ovarian cancers and other cancers. Morphology groupings of different cervical types are based on the International Classification of Disease for Oncology, 3rd edition.[22] Detailed information about coding of these groups can be found in Table S1. For survival analysis, we collapsed these categories into cervical cancers and other cancers.

There is also information about cancer diagnoses available in PALGA. We used the PALGA diagnosis date to calculate follow-up time, as these records had a more exact date of diagnosis than available in our NCR extract. We included cancers where there was both a NCR record, a histological record of cancer, adenocarcinoma-in-situ or CIN 3 recorded in PALGA and the difference between the dates of these records was no more than 90 days (to compensate for potential differences in dates of registration in the two datasets). In cases where one woman had more than one cancer diagnosis, we only considered the first diagnosis.

Figure S2 shows the process of data management and linkage. Linkage keys were created deterministically, based on matching of variables including PALGA ID, postcode, date of birth, date of diagnosis and lab number. Depending of the number of variables that matched, a rating was given from 1 (most trustworthy link) to 12 (least trustworthy link). We included cases with linkage rating 1 to 9.

Statistical methods

Data analysis and management was conducted using SAS Base 9.4 and RStudio (R v3.6.1, packages epitools, survminer and survival). For the purposes of statistical analysis, we split the sample into women aged 49 years and younger and women aged 50 years and older, because differences in risk have been shown by age in previous research.[23] Life-years at risk will be counted until whichever of these events occurs first: a diagnosis of one of the cancers listed above; the next primary cytology screening (either within the screening programme or by indication/opportunistic screening); 31st December 2015; a hysterectomy recorded in PALGA; or 8.5 years of follow-up, as this contains one complete screening round and beyond, covering women overdue for screening. We excluded all cytology tests of a woman that occurred after either a cancer diagnosis or a hysterectomy.

We calculated relative risks within advice groups. We calculated cumulative incidence of cervical squamous cell cancers, cervical adenocarcinomas and endometrial cancers using Kaplan-Meier estimates. Cox proportional hazards models were calculated both unadjusted and adjusted for the number of previous primary cytology tests. We used the number of previous cytology tests as a proxy for screening history, in order to adjust for differences in risk of invasive cervical cancer in women who have never been screened. Any groups in which there are 5 or less cancer diagnoses are not presented. *P* values less than or equal to 0.05 were considered significant.

Patient involvement

No patients or patient groups were involved in the design or conduct of this study.

Ethical approval

This study used a retrospective, anonymised dataset from PALGA. The board of PALGA approved the use of data for this study. The request for NCR data was approved by the NCR.

Funding

This study was conducted as part of the Evaluation of the Dutch cervical cancer screening programme, which is funded by the Dutch National Institute from Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu).

RESULTS

Table 2 shows the number of cytology tests included in this study by smear-result group and number of cancers by type. A total of 8,537,385 primary screening programme cytology smears could be classified in one of the seven categories. The majority of cytology smears were classified as normal (96.5%), followed by low-grade ('Repeat, squamous': 2.6%) and high-grade ('Referral, squamous': 0.7%) squamous cell abnormalities. AGC was diagnosed rarely; 'Repeat, AGC' results accounted for 0.16% of all smear results and 'Referral, AGC' results accounted for 0.04% of all smear results. The mean age per smear-result group differed: 'Referral, squamous' women were the youngest (38.2 years) and 'Referral, AGC' women were the oldest (47.2 years).The mean and median time to diagnosis following screening was shortest for cancers diagnosed following 'Referral' screens and longest following normal cytology.

Figures 1a and 1b show the proportion of cancer diagnoses for each smear-result group by age for the three cancers with the most diagnoses in our dataset (cervical squamous-cell, cervical adenocarcinoma, endometrial). In both younger and older woman, a higher proportion of cancers were diagnosed following 'Referral, AGC' smears, however, the type of cancers diagnosed following 'Referral, AGC' smears differed by age. Amongst younger women the proportion of cervical adenocarcinoma is highest whereas in older women the highest proportion of cancers diagnosed were endometrial cancers.

Table 3 shows the crude relative risk of a cancer diagnosis compared with squamous smear-result groups for five cancer types (results for 'other gynaecological cancers' are not shown due to small numbers). The crude absolute risk of cancer was higher for the 'Referral, AGC' smear-result group compared to 'Referral, Squamous' as indicated by the higher relative risk for almost all cancer types. The relative risk of an adenocarcinoma diagnosis was higher than the relative risk of a squamous cervical cancer diagnosis for 'Repeat, AGC' (squamous – RR: 1.94; adenocarcinoma – RR: 46.97), 'Referral, AGC' (squamous – RR: 0.50; adenocarcinoma – RR: 26.43), and 'Referral, AGC/Squamous' (squamous – RR: 1.69; adenocarcinoma – RR: 13.38) smear-result groups compared to the respective squamous smear-result groups.

Figures S3 to S8 show cumulative event curves for the three cancers with the most diagnoses in our dataset (cervical squamous-cell, cervical adenocarcinoma, endometrial). Cumulative event curves were higher following 'AGC' cytology than 'squamous' cytology for cervical adenocarcinomas and for endometrial cancers following a 'referral'-advice cytology test. For endometrial cancers diagnosed following 'repeat'-advice cytology tests, the cumulative event curves were higher for following 'AGC' cytology than 'squamous' cytology, however, the confidence interval overlapped at some points on the curve.

Table 2: *Descriptive statistics by result of primary cytology screening and cancer type, 1 January 2000 to 31 December 2015*

CYTOLOGY SCREENS							
	Return to regular screening	***Repeat cytology within six months***			***Referral to gynaecologist***		
	Normal cytology	AGC	Squamous	AGC/ Squamous	AGC	Squamous	AGC/ Squamous
N (% of total)	8,241,096 (96.53%)	13,237 (0.16%)	218,458 (2.56%)	2,126 (0.02%)	3,164 (0.04%)	57,780 (0.68%)	1,524 (0.02%)
Mean age (SD)	44.3 (9.4)	42.5 (8.4)	41.4 (8.8)	42.5 (8.5)	47.2 (9.4)	38.2 (8.1)	39.2 (8.4)
CANCERS (N, % cases following all screens with smear-result group)							
Mean time to diagnosis in months (SD)	35.1 (25.6)	15.6 (19.2)	24.7 (21.2)	22.2 (25.9)	4.5 (8.0)	4.9 (9.7)	4.7 (11.5)
Median time to diagnosis in months	31	9	16	11	2	2	2
Cervical cancer –squamous	365 (0.00%)	30 (0.23%)	255 (0.12%)	6 (0.28%)	34 (1.07%)	1,235 (2.14%)	55 (3.61%)
Cervical cancer - adenocarcinoma	141 (0.00%)	74 (0.56%)	26 (0.01%)	6 (0.28%)	123 (3.89%)	85 (0.15%)	31 (2.03%)
Cervical cancer - other	113 (0.00%)	19 (0.14%)	18 (0.01%)	–	43 (1.36%)	77 (0.13%)	14 (0.92%)
Endometrial cancers	3,634 (0.04%)	19 (0.14%)	118 (0.05%)	–	276 (8.72%)	24 (0.04%)	
Ovarian cancers	1,897 (0.02%)	–	48 (0.02%)	–	18 (0.57%)	11 (0.02%)	–
Other gynaecological cancers	238 (0.00%)	–	8 (0.00%)	–	7 (0.00%)	–	–

AGC: Atypical glandular cells, SD: Standard deviation

– Cells suppressed as contains cells less than 5.

Table 3. *Relative risk of cancer compared to squamous cytology, by cancer type, cytology type and advice class*

	Cervical cancer – Squamous	Cervical cancer - Adenocarcinoma	Cervical cancer - other	Endometrial cancer	Ovarian cancer
	RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Repeat cytology within six months					
Squamous (ref)	1.0	1.0	1.0	1.0	1.0
AGC	1.94* (1.33 – 2.83)	46.97* (30.06 – 73.41)	17.42* (9.15 – 33.18)	2.66* (1.64 – 4.31)	–
AGC/Squamous	2.42* (1.08 – 5.43)	23.71* (9.78 – 57.55)	–	–	–
Referral to gynaecologist					
Squamous (ref)	1.0	1.0	1.0	1.0	1.0
AGC	0.50* (0.36 – 0.75)	26.43* (20.10 – 34.76)	10.20* (7.03 – 14.78)	210.01* (138.60 – 318.21)	29.88* (14.12 – 63.20)
AGC/Squamous	1.69* (1.30 – 2.20)	13.83* (9.19 – 20.80)	6.89* (3.91 – 12.15)	–	–

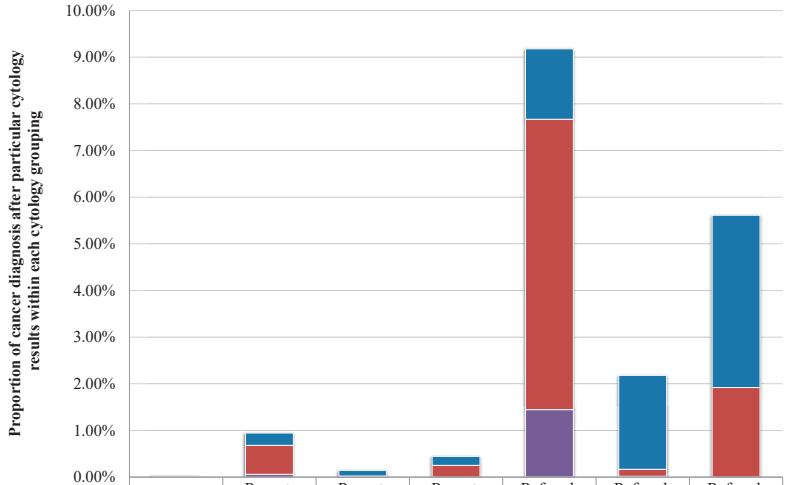
* *P* value < 0.05.
– Estimates not presented as less than 5 cancers were in these cells.
AGC: Atypical glandular cells, RR: Relative risk, CI: Confidence interval

Table 4 shows unadjusted and adjusted hazards of a cancer diagnosis after AGC and AGC/squamous cytology result compared with squamous cytology results by age and referral type. Amongst younger women, the hazards of both a cervical cancer diagnosis or other gynaecological cancer diagnosis was significantly higher for 'Repeat, AGC' and 'Referral, AGC' smear-result groups. The same was found for women aged 50 years and older, except for 'Repeat, AGC' smear-result group for other cancers diagnoses and 'Referral, AGC' smear-result group for cervical cancer diagnoses, both of which had no significant difference in hazards compared to squamous smear-result groups.

DISCUSSION

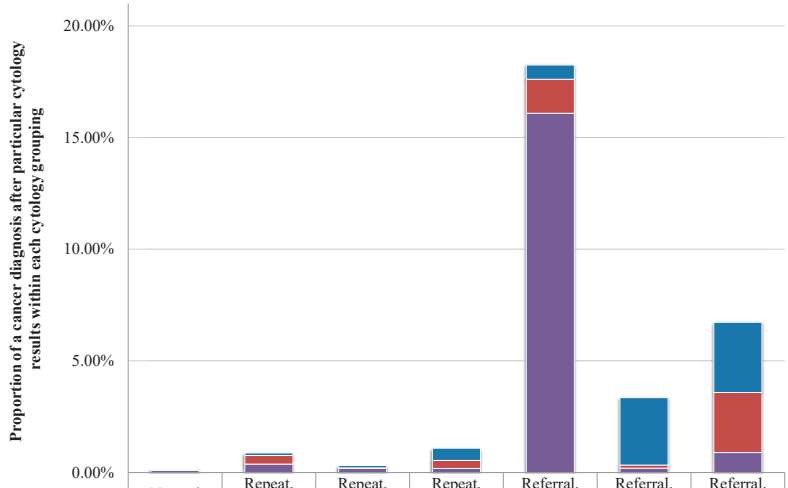
Results of our study confirm that AGC found on cervical cytology indicates an increased risk of a cancer diagnosis compared with normal cytology and squamous cell abnormalities of equal severity. The risk of a cancer diagnosis after a normal cytology test is very low in comparison to the other cytology groups, which is expected given the low rate of cervical cancer after normal cytology in the Netherlands.[12 14] Therefore, the comparisons between AGC and Squamous cytology results are of more interest for the management of patients, as cytology smears of comparable severity were given similar advice for follow-up. For all but two smear-result groups , AGC smears had a higher risk of cancer than squamous cell abnormalities of equal severity. The increased risk of a

FIGURE 1a: YOUNGER WOMEN



	Normal	Repeat, AGC	Repeat, Squamous	Repeat, AGC/Sq	Referral, AGC	Referral, Sq	Referral, AGC/Sq
Cervical - squamous	0.00%	0.26%	0.12%	0.19%	1.51%	2.01%	3.69%
Cervical - adeno	0.00%	0.62%	0.01%	0.25%	6.22%	0.15%	1.92%
Endometrial	0.01%	0.06%	0.01%	0.00%	1.45%	0.02%	0.00%

FIGURE 1b: OLDER WOMEN



	Normal	Repeat, AGC	Repeat, Squamous	Repeat, AGC/Sq	Referral, AGC	Referral, Sq	Referral, AGC/Sq
Cervical - squamous	0.00%	0.12%	0.11%	0.54%	0.64%	3.01%	3.14%
Cervical - adeno	0.00%	0.38%	0.00%	0.36%	1.53%	0.14%	2.69%
Endometrial	0.11%	0.38%	0.21%	0.18%	16.08%	0.20%	0.90%

Figure 1: *Proportion of cervical squamous-cell cancers, cervical adenocarcinomas and endometrial cancers diagnosed after various cytology results (numerator: total cancers detected after specific cytology result; denominator: all smears within each cytology result group), by cancer diagnosis*

a. Women aged 49 years and younger

b. Women aged 50 years and older

Table 4: *Results of Cox Proportional Hazards models comparing AGC and AGC/Squamous cytology results with Squamous cytology results within repeat/referral groups, by age and cancer type*

	Cervical cancers		Other cancers	
	Unadjusted HR (95% CI)	**Adjusted HR* (95% CI)**	**Unadjusted HR (95% CI)**	**Adjusted HR* (95% CI)**
Women aged 29 to 49 years				
Repeat cytology within six months				
Squamous (ref)	1.0	1.0	1.0	1.0
AGC	7.05 (5.59 – 8.87)**	6.91 (5.48 – 8.71)**	2.79 (1.37 – 5.66)**	2.82 (1.39 – 5.74)**
AGC/Squamous	3.39 (1.68 – 6.86)**	3.32 (1.64 – 6.71)**	–	–
Referral to gynaecologist				
Squamous (ref)	1.0	1.0	1.0	1.0
AGC	4.56 (3.86 – 5.39)**	4.57 (3.86 – 5.40)**	47.37 (27.01 – 83.06)**	44.43 (25.28 – 78.10)**
AGC/Squamous	2.98 (2.39 - 3.71)**	2.98 (2.39 - 3.71)**	–	–
Women aged 50 years and older				
Repeat cytology at six months				
Squamous (ref)	1.0	1.0	1.0	1.0
AGC	4.38 (2.64 – 7.29)**	3.98 (2.38 – 6.66)**	1.48 (0.86 – 2.52)	1.41 (0.82 – 2.42)
AGC/Squamous	6.68 (2.68 – 16.65)**	6.06 (2.42 – 15.16)**		
Referral to gynaecologist				
Squamous (ref)	1.0	1.0	1.0	1.0
AGC	0.89 (0.65 – 1.23)	0.88 (0.63 – 1.21)	79.31 (48.58 – 129.50)**	79.75 (48.85 – 130.20)**
AGC/Squamous	1.92 (1.12 - 3.30)**	1.86 (1.09 – 3.19)**	–	–

* Adjusted for number of previous primary cytology tests
** *P* value < 0.05
– Estimates not presented as less than 5 cancers were in these cells.
AGC: Atypical glandular cells, HR: hazard ratio

cervical cancer diagnosis is related to the significantly higher risk of adenocarcinoma after AGC. These results are similar to those reported by Wang and colleagues.[11]

Age is also a key factor associated with the risk of cancer after AGC. Cheng and colleagues found that women aged 60 years and older were more likely to have a diagnosis of cervical, uterine or ovarian cancer following AGC than women aged 35 years and younger.[24] Our study supports this finding, with a higher proportion of cancer diagnosis following screening amongst women aged 50 years and older. However, only comparing between age groups misses an important finding – that in both younger and older women, AGC cytology has a higher risk of a cancer diagnosis compared with squamous cell abnormalities. We also found that the type of cancer AGC indicates varied by age; in younger women, the largest proportion of the risk was due to cervical adenocarcinoma and, in older women, endometrial cancers. Other studies have also shown the association between age and type of cancer diagnosed after AGC.[23] Age is associated with the

likelihood of an hrHPV infection, which is highest in younger women and declines with age,[25] which is, in turn, related to whether the cancer diagnosis after AGC is hrHPV related (i.e. cervical cancers) or not.

The impact of hrHPV screening on AGC cytology and cancer detection

The impact of the introduction of primary hrHPV screening on the detection of malignancies following AGC is of interest, as many countries are transitioning from cytology-based to hrHPV-based screening. In 2017, primary hrHPV screening replaced cytology-based screening in the organised screening programme in the Netherlands. We did not include information about hrHPV status in our analysis, as the use of hrHPV testing was limited during the study period and only used for triage of low-grade repeat cytology (see Figure A1). In the new hrHPV-based Dutch screening programme, all women who are hrHPV positive and have a cytological abnormality of any kind are now directly referred. Several studies have reported on the impact of hrHPV positivity on AGC cytology[8 26 27] and results indicate that primary hrHPV screening is capable of detecting relevant cervical lesions, regardless of whether the origin is cervical squamous or cervical glandular epithelium.

However, a previous review found that women aged over 50 years with hrHPV-negative AGC cytology had an increased risk of a non-cervical cancer diagnosis.[23] We found that in both younger and older women, there was increased risk of a non-cervical cancer diagnosis after AGC cytology. Looking from the perspective of those women already diagnosed with cancer, one study of women with endometrial cancer found the majority of women with a high-grade cancer diagnosis had abnormal cervical cytology.[28] These two findings indicate that cervical cytology may have been of some use in the detection of other gynaecological cancers. As primary hrHPV screening is implemented, we expect to see a reduction in the number of cytology tests with AGC results in women over 50 years, as AGC in this age group is more likely to indicate a non-hrHPV related cancer. While the detection of these cancers is not the goal of cervical screening, some women may have benefited from incidental detection. Within the new hrHPV screening programme, women who test hrHPV negative at 40 or 50 years are given a longer screening interval of 10 years. It should be communicated explicitly to these women that if they experience clinical symptoms, they should see their GP for assessment, irrespective of their prior hrHPV test results.

Management strategies for women with AGC cytology

Our results show that the risk of a cancer diagnosis is high immediately following an AGC cytology result and suggest that management strategies for women with AGC must ensure that women receive adequate diagnostics and surveillance immediately following a AGC cytology result. As referral and treatment advice within cervical cancer

screening programmes is based on the risk of pre-cancerous lesions, our results support referring all women with AGC, given the increased risk of cancer. Given the small number of AGC abnormalities found, referring all women with AGC would be unlikely to impact on colposcopy capacity and may mean clinically significant lesions are detected sooner.

Glandular cell abnormalities may be more difficult to detect at colposcopy, as most lesions are located higher in the cervical canal. Because of this, Dutch guidelines recommend conisation, which allows for better assessment of the endocervical canal.[18] Furthermore, these guidelines suggest discussing hysterectomy with women when adenocarcinoma in situ is suspected, in cases where the possibility of invasive cancer has been excluded as far as possible. Hysterectomy may be appropriate for women over 50 years given the high risk of endometrial cancer found in our study, and the fact these women may have reached menopause. However, for women who are younger than 50 or women who do not want a hysterectomy, offering both cervical and endometrial biopsy in order to determine the origin of the AGC and inform further treatment strategies may be a practical alternative to more invasive treatment.

Strengths and limitations

Our study has several strengths. To our knowledge, this is the largest study of cancer risk following AGC cytology, with over 8 million screening tests included. We used a large and comprehensive national dataset to select cytological smears taken within our study period. We then supplemented this data with detailed information from the NCR to provide accurate diagnostic data. As AGC is an uncommon cytological abnormality, the size of our dataset has allowed us to explore trends in the incidence of multiple types of gynaecological cancers after AGC with robust estimates.

Our study also has some limitations. We did not have access to data on deaths and emigration to censor life-years at risk. In the Netherlands, linkage of demographic and medical record data on the individual level is difficult for practical and privacy reasons. However, emigration rates amongst women aged 40 years and older are low.[29] Therefore, we do not believe this impacted significantly on our results. We used data from PALGA on hysterectomy to censor screens from women following a hysterectomy. There is a small proportion of women (estimated between 1.5% – 2%, based on a small check by PALGA) who had a partial excision of the uterus who are classified as having a hysterectomy. Therefore, some women who were still at risk of a cancer may have been censored too early. Finally, there may be some degree of verification bias in types of cancers diagnosed after an abnormal cytology, as the CISOE-A score is used by gynaecologists to inform diagnostic strategies.

CONCLUSION

The presence of AGC on cervical cytology indicates an increased risk of cervical adenocarcinoma and other gynaecological cancers compared to both normal cytology and squamous cell abnormalities of comparable severity. Our results indicate that women who present with AGC on cervical cytology warrant direct referral and should be provided with diagnostic assessment of both endocervical and endometrial tissue given the risk of both cervical and other cancers in this group. Managing these women effectively and ensuring a complete diagnostic workup is important to ensure that cancers are detected and treated as early as possible.

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We wish to thank Dr Nicolien van Ravesteyn for her helpful comments on our manuscript.

Conflict of interest disclosure

The funder had no involvement in the design, conduct or reporting of the study; the writing of the manuscript; or the decision to publish the manuscript. All authors declare that they have no financial disclosures or conflicts of interest.

Contributions to authorship

I.M.C.M.de Kok, F.J. van Kemenade and A.G. Siebers were responsible for the developing the concept for the study. I.M.C.M.de Kok, F.J. van Kemenade, A.G. Siebers, C.A. Aitken and E.E.L. Jansen were involved in designing the project and outlining the outcomes to be measured. A.G. Siebers created the PALGA dataset with linkage to the national cancer registry data, with input from C.A. Aitken and E.E.L. Jansen. C.A. Aitken performed the data analysis, with assistance from E.E.L. Jansen and I.M.C.M. de Kok in checking the methods and from A.G. Siebers and F.J. van Kemenade in validating the groupings of cytology results and cancer diagnoses. A.L.D. van Haaften-de Jong provided clinical knowledge and advice. C.A. Aitken wrote the manuscript with contribution from all other authors.

Ethical approval

This study used a retrospective, anonymised dataset from PALGA. The board of PALGA approved the use of data for this study. The request for NCR data was approved by the NCR.

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SUPPLEMENTARY MATERIALS

APPENDIX A: Methodological information

List of tables and figures

Test and referral

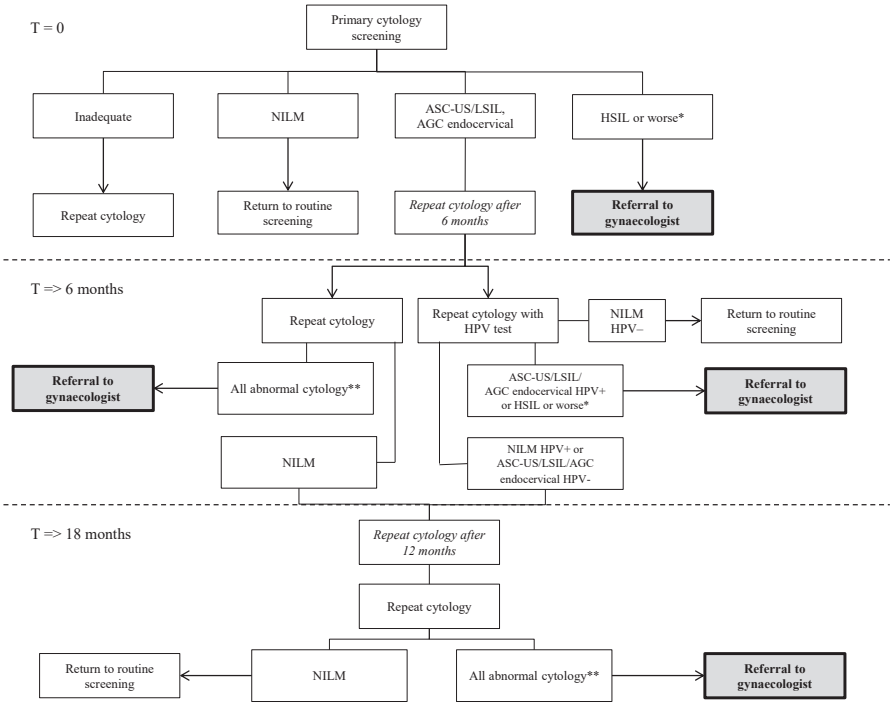

Figure S1: *Flowchart of referral pathways within Dutch cervical cancer screening programme (adapted from Bekkers et al.[1] and Aitken et al.[2])*

NB. At T => 6 months, either cytology only or HPV co-testing was performed, depending on the laboratory that processed the test.

* Includes HSIL, AGC endometrial, AGC favouring neoplasia, adenocarcinoma in situ, ASC-H and cancer irrespective of hrHPV status.

** Includes ASC-US, LSIL, AGC endometrial and HSIL or worse* cytology results.

T: time, NILM: Negative for intraepithelial lesion or malignancy, ASC-US: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, AGC: atypical glandular cells, HPV: human papillomavirus

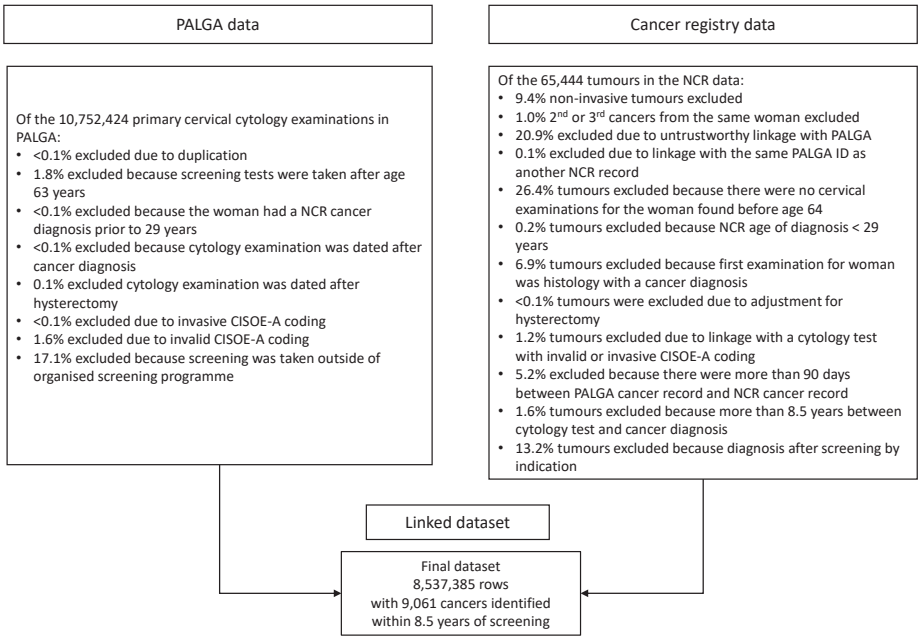

Figure S2: *Data linkage and management flowchart*

Table S1: *Cancer groups by topography and morphology codes*

Cancer type	Cancer group	Topography	Morphology*
Cervical	Cervical - squamous	C53.0, C53.1, C53.8, C53.9	M-805 – M-808, M-812, M-813
	Cervical - adenocarcinoma	C53.0, C53.1, C53.8, C53.9	M-814, M-816, M-819 – M-822, M-826 – M-833, M-835 – M-855, M-857, M-894
	Cervical - other	C53.0, C53.1, C53.8, C53.9	All other morphology codes not specified in other cervical groups
Other	Endometrial	C54.1	
	Ovarian	C56.9	
	Other	C54.0, C54.2, C54.3, C54.8, C54.9, C55.9, C57.0, C57.1	

* Grouping of morphology codes for differentiating different cervical types is based on Table 25 from the International Classification of Disease for Oncology, 3rd edition.[3]

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APPENDIX B: Further analysis and results

List of tables and figures

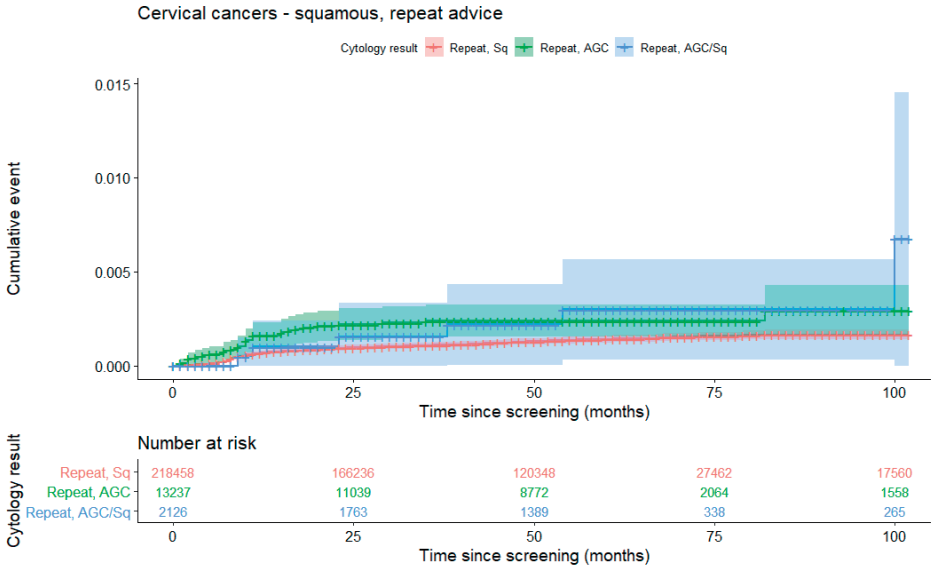

Figure S3: *Cumulative event curves for squamous cervical cancers by cytology type, repeat advice*

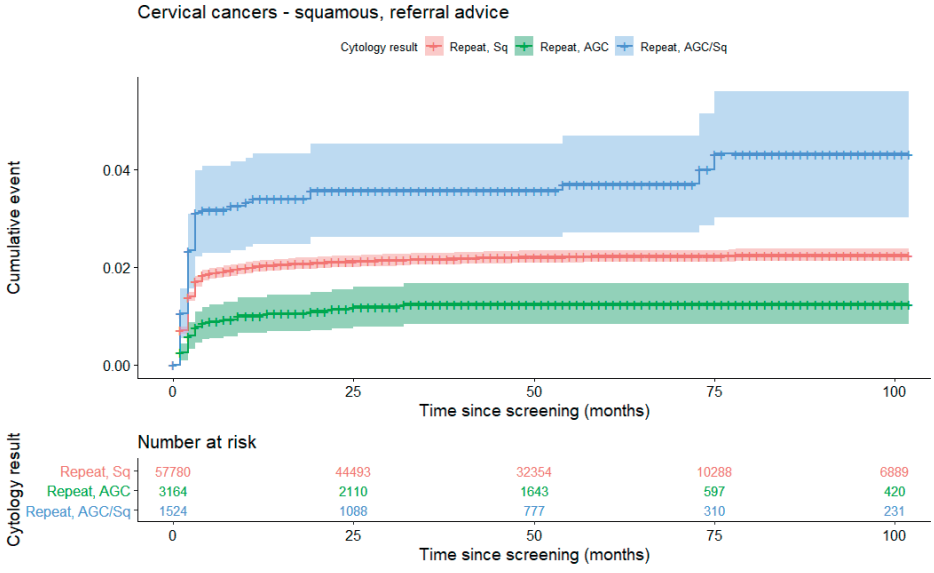

Figure S4: *Cumulative event curves for squamous cervical cancers by cytology type, referral advice*

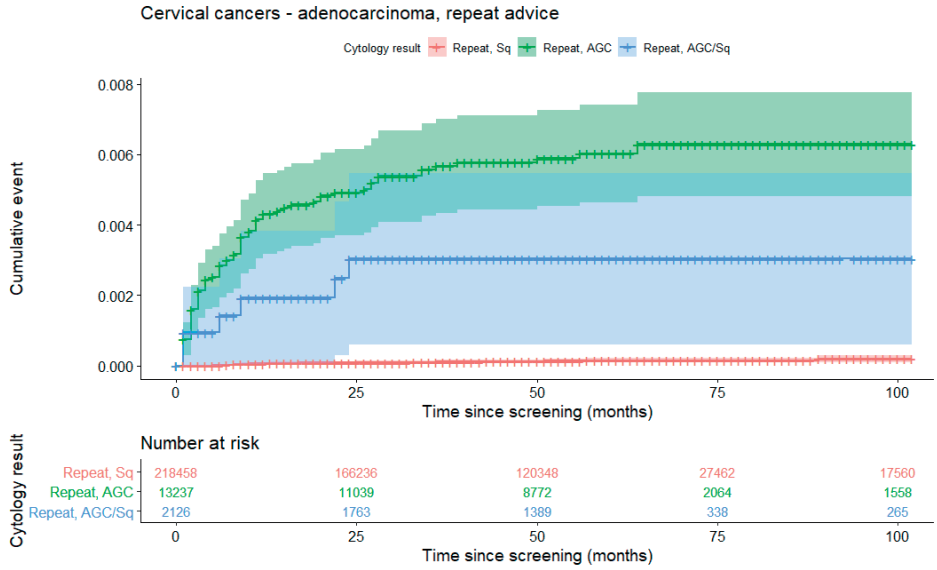

Figure S5. *Cumulative event curves for cervical adenocarcinomas by cytology type, repeat advice*

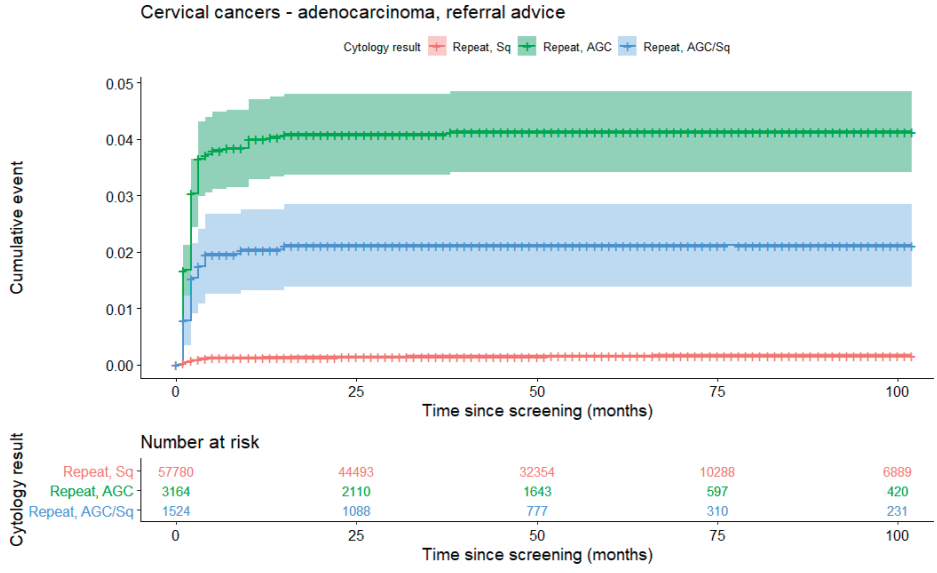

Figure S6. *Cumulative event curves for cervical adenocarcinomas by cytology type, referral advice*

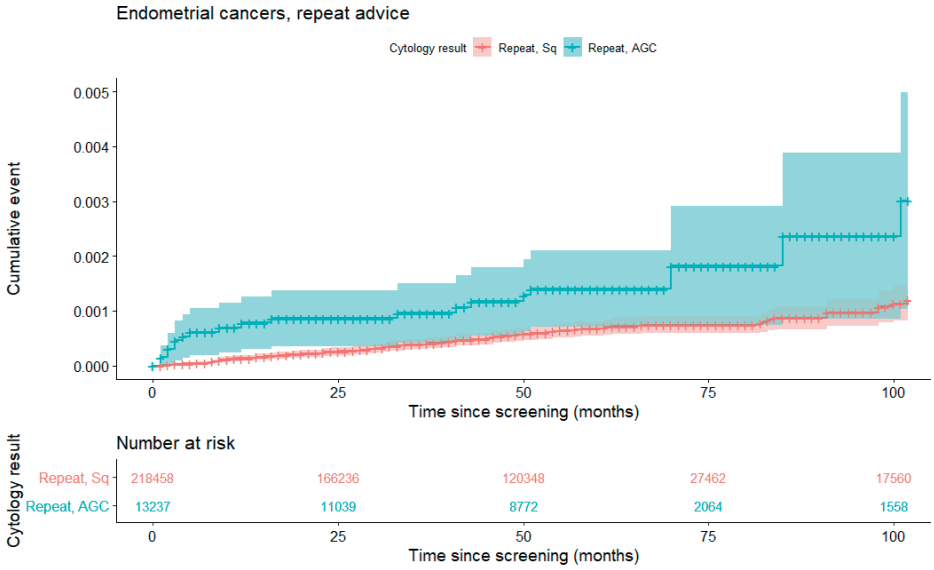

Figure S7: *Cumulative event curves for endometrial cancers by cytology type, repeat advice*

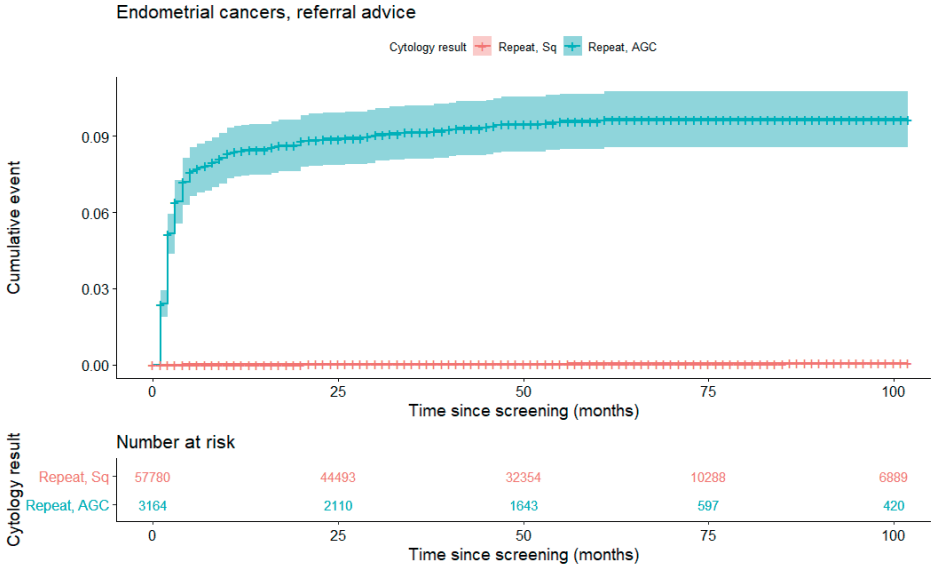

Figure S8: *Cumulative event curves for endometrial cancers by cytology type, referral advice*

Part 5

Diagnosis and treatment

Chapter 5.1

Management and treatment of cervical intraepithelial neoplasia in the Netherlands after referral for colposcopy

Clare A. Aitken[1], Albert G. Siebers[2,3], Suzette M. Matthijsse[1,4], Erik E.L. Jansen[1], Ruud L.M. Bekkers[5,6], Jeroen H. Becker[7], Bram ter Harmsel[8], Jan-Paul W.R. Roovers[9,10], Folkert J. van Kemenade[11], Inge M.C.M. de Kok[1]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam
2. PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands
3. Department of Pathology, Radboud University Medical Center
4. BresMed Health Solutions
5. Department of Gynecology, Catharina Hospital Eindhoven
6. Department of Gynecology, Radboud University Medical Center
7. Department of Obstetrics and Gynecology, St. Antonius Hospital Nieuwegein
8. Department of Gynecology, Roosevelt Kliniek
9. Bergman Clinics (Gynecology), Amsterdam
10. Department of Obstetrics and Gynecology, Amsterdam University Medical Centre
11. Department of Pathology, Erasmus MC, University Medical Center Rotterdam

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ABSTRACT

Introduction

The aim of this study was to describe trends in diagnosis and treatment of women referred from screening with cervical intraepithelial neoplasia (CIN) in the Netherlands, compare this to national guidelines and identify potential areas for improvement for the new primary high-risk HPV screening programme.

Material and methods

We conducted a population-based cohort study using data from Dutch pathology archive. Women aged 29-63 years who took part in the Dutch cervical screening programme between 1 January 2005 to 31 December 2014 were selected. Three referral groups were identified: direct referrals and those referred after either one (first indirect referrals) or two (second indirect referrals) repeat cytology tests, totaling 85,239 referrals for colposcopy. The most invasive management technique and most severe diagnosis of each screening episode were identified. Rates of management techniques were calculated separately by referral type, highest CIN diagnosis and age group.

Results

In all, 85.1% of CIN 3 lesions were treated with excision (either large excision or hysterectomy) and 26.4% of CIN 1 lesions were treated with large excision. Rates of overtreatment (CIN 1 or less) in see-and-treat management were higher for indirect referrals than for direct referrals and increased with age. Large excision rates increased with CIN diagnosis severity.

Conclusions

Despite guideline recommendation not to treat, CIN 1 lesions were treated in just over 25% of cases and approximately 15% of CIN 3 lesions were possibly undertreated. Given the expected increase in CIN detection in the new primary high-risk HPV screening programme, reduction in CIN 1 treatment and CIN 2 treatment in younger women is needed to avoid an increase in potential harm.

KEY MESSAGE

Both over- and undertreatment of cervical intraepithelial neoplasia occurs after referral from organized cervical screening, despite treatment guidelines being available.

INTRODUCTION

In the Netherlands, cervical intraepithelial neoplasia (CIN) detection rates have increased over the last decade, largely independent of socio-economic and demographic factors.[1] The replacement of conventional cytology by high-risk human papillomavirus (hrHPV) DNA testing as primary screening test in the Dutch Cervical Cancer Screening Program in 2017 will likely further increase CIN detection, given the higher sensitivity of hrHPV testing for CIN 2+ lesions.[2] Recent Dutch modeling estimated that the number of detected CIN lesions would increase by 196% for CIN 1 and 54% for CIN 2 over the lifetime of women entering the program in 2017 due to primary hrHPV screening.[3]

As more CIN lesions are detected, there is concern about overtreatment, which could result in increased harm associated with screening.[4] Evidence suggests that there is an association between excisional treatments for CIN and adverse obstetric outcomes including preterm birth and low birthweight.[5,6] Increasing excision volume has been associated with increased risk.[6,7] Additionally, a robust randomized controlled trial concluded that immediate side-effects of excisional treatments such as discharge and pain occur more frequently, more severely and for longer in women treated with large loop excision of the transformation zone (LLETZ) compared with both colposcopy-only and biopsy-diagnosed women.[8]

The Dutch Association of Obstetrics and Gynecology has published consensus-based guidelines for CIN treatment and management which detail the recommended treatment practices, including recommending no treatment of CIN 1 and excisional treatment of CIN 2+.[9] However, compliance with these guidelines has never been evaluated. The lack of evaluation of CIN management in the Dutch setting has been recognized by others[4] as a knowledge gap in an otherwise closely monitored program. Our study intends to objectify current clinical management of CIN to understand discrepancies between guideline recommendations and observed interventions. By doing so, we aim to identify potential areas for improvement for the new primary hrHPV screening program.

MATERIAL AND METHODS

National organized cervical screening has taken place in the Netherlands since the 1980s. Women are invited for cytology screening every five years from ages 30 to 60. Screening takes place within primary care. Women are referred to a gynecologist when colposcopy is required. Details of clinical guidelines for management of CIN are given in Table 1. Since 1998, the recommendations for management of abnormal cytology have been fairly stable, allowing for more reliable measurement of procedural parameters after colpos-

Table 1: *Summary of Dutch CIN treatment guidelines*

	2004 Guidelines[9]	**2015 Guidelines[21]**
Histological diagnosis at colposcopy	Targeted biopsies are required only with an atypical transformation zone.	Biopsy can be omitted if there is slight cytological dysplasia and no visible colposcopic abnormalities, in situations when the whole transformation zone can be seen. At least two random biopsies should be taken where there are severe cytological abnormalities with no colposcopic abnormalities. In the case of severe cytological and colposcopic abnormalities, either two targeted biopsies can be taken or 'see-and-treat' management can be used.
CIN 1	Generally not treated.	In principle, should not be treated. In the case of persistent low-grade cytology outside of reproductive age, treatment options may be discussed with the patient.
CIN 2	Should be treated, preferably by LLETZ*	Individual assessment is required, particularly in younger women, weighting up the risks and benefit of treatment. If treatment is decided on, LLETZ* is recommended.
CIN 3	Should be treated, preferably by LLETZ*	Should always be treated. Women with high-grade cytology (moderate dyskaryosis/dysplasia or worse) and colposcopy are eligible for see-and-treat management. LLETZ* recommended.
Glandular disease	Conization is preferred if there is suspicion of AIS	It should be discussed with the patient whether she wants an excisional treatment or hysterectomy, provided that invasive carcinoma is excluded as far as possible. Conization is preferred for AIS as it allows for better assessibility of the endocervical area and margins. If LLETZ is chosen, the pathologist must be notified for a better assessment of the margins.

* Large loop excision of the transformation zone
CIN: Cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ.

copy. In 2017, hrHPV testing replaced cytology as the primary screening test within the program.[10]

Our study is a population-based cohort study. Women aged 29 to 63 years who participated in the national screening program and received referral advice between 1 January 2005 and 31 December 2014 were included. Possible referral pathways within the Dutch screening program can be found in Figure 1. Three groups of referrals were identified:

- Direct referrals: Women who received referral advice after primary cytology of high-grade squamous intraepithelial lesion (HSIL)/adenocarcinoma in situ (AIS)/atypical endometrial glandular cells (AGC)/AGC favoring neoplasia/cancer. The classification ASC-H (atypical squamous cells cannot exclude HSIL) is not utilized in the Netherlands.
- First indirect referrals: Women who received referral advice for repeat testing six months after primary cytology of atypical squamous cells of undetermined significance (ASC-US)/low-grade squamous intraepithelial lesion (LSIL) or endocervical AGC.

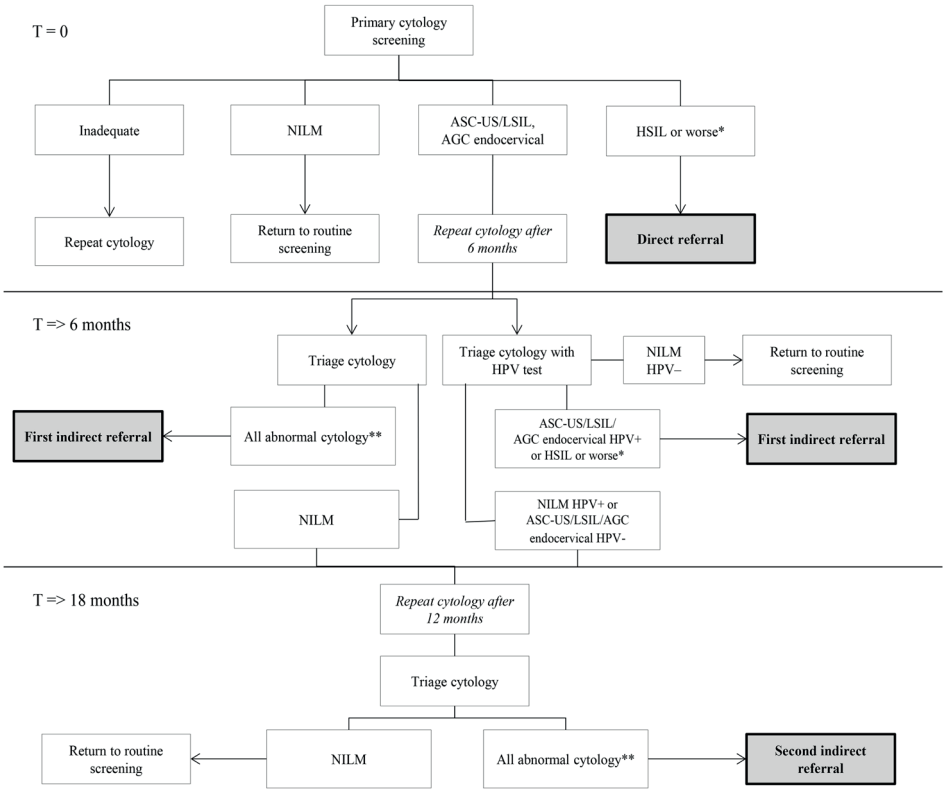


Figure 1: *Pathways to referral within the Dutch Cervical Cancer Screening Program, adapted from Bekkers et al.*[31] *and Rozemeijer*[32]

* Includes HSIL, AGC endometrial, AGC favor neoplasia, adenocarcinoma in situ and cancer irrespective of hrHPV status.

** Includes ASC-US, LSIL, AGC endometrial and HSIL or worse* cytology results.

ASC-US/LSIL: Atypical squamous cells of undetermined significance/ low-grade squamous intraepithelial lesion

AGC: Atypical glandular cells

HSIL: High-grade squamous intraepithelial lesion

- Second indirect referrals: Women who received referral advice after two triage cytology tests (at six and 18 months), with the first repeat cytology being negative, hrHPV-negative with endocervical ASC-US/LSIL/AGC or hrHPV positive with negative cytology, and second triage cytology being ASC-US or higher.

We excluded women with primary smears taken by a gynecologist, as women under the care of a gynecologist in the Netherlands are usually already receiving specialist care. Indirect referrals must have been referred within four years of primary screening to be included, in line with the definitions used in the monitoring of the national screening program. Repeat cytology testing at six months could be performed either with or with-

out hrHPV triage. As hrHPV triage was not standard practice in all pathology labs during the study period, we did not include hrHPV status information in our study.

There is no national registry of gynecological treatments in the Netherlands. Therefore, we used an extract of all cervical cytology and histology records from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). PALGA has a nationwide coverage of all pathology labs.[11] Women are identified by the first eight letters of their surname (maiden name is used for married women) and date of birth. Information about primary screening as well as up to five follow-up cytology and/or histology samples were selected. Follow-up of primary smears was included until the end of the database – 31st March 2016. We defined 'episode of screening' as the period starting with the primary screening test, possibly followed by follow-up tests and/or treatment and ending with the next primary cytology in the database. We only analyzed information recorded during this window (see Appendix S1). As PALGA is not a registry of treatments, we validated our results with two expert groups and with clinical data from one gynecology clinic (see Appendix S2).

Our primary outcome measure was the proportion of the most invasive diagnostic tests and therapeutic treatments by the most severe CIN diagnosis within a screening episode. Our secondary outcome measure was the proportion of overtreatment in see-and-treat management. The most severe diagnosis within the screening episode was identified from all diagnostic codes recorded after referral advice as follows: most to least severe – cancer, CIN 3, CIN 2, CIN 1, benign/reactive, cytology only, no diagnosis recorded.

Diagnostic tests and therapeutic treatments are pre-coded by PALGA. The most aggressive test/treatment of the episode after referral was ranked as follows: most to least aggressive - hysterectomy, large excision [including cone biopsy, LLETZ, other excisional treatments], polypectomy, endometrial curettage, endocervical curettage, punch biopsy [excluding cone biopsy], cytology only, other techniques. This ranking was verified by gynecologists and pathologists.

See-and-treat management involves combining colposcopy and treatment in the same outpatient visit.[12] A large excision in the next record after referral was considered indicative of see-and-treat management. We estimated possible overtreatment in see-and-treat management as the proportion of women with CIN 1 or lower histological diagnosis as the highest diagnosis of the episode who were treated with large excision at the first contact with a gynecologist divided by all women who were treated with large excision at the first contact with a gynecologist (definition from Ebisch et al[12]). Age at primary screening was grouped into 5-year age groups.

Statistical analysis

Chi-squared tests were performed to compare differences between proportions. Analysis of variance was used to compare mean ages across referral types. For one-way tables, a chi-square goodness of fit test was applied. Confidence intervals for proportions were calculated using a binomial distribution. All analyses were performed using SAS Base v9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

We used a retrospective, anonymized dataset from PALGA, which is exempt from ethical approval by a Medical Ethical Testing Committee. We obtained anonymized clinical data (only women referred from screening) for validation as part of the evaluation of the national cervical screening program (evaluation of national screening programs is legislated in the Population Screening Act in the Netherlands). We received written approval from the Medical Director of the specialist outpatient clinic to use their clinical data for research purposes.

RESULTS

From the 5,450,148 primary cytology smears taken within the screening program from women aged 29–63 years between 2005–2014, 98.9% were taken by a non-gynecologist and eligible for inclusion (n = 5,389,342). Of these smears, 44,209 (0.8%) resulted in a direct referral to a gynecologist, 34,282 (0.6%) resulted in a first indirect referral and 6,748 (0.1%) resulted in a second indirect referral (Table 2). The majority of referrals were within reproductive age range (29-43 years: 65.5%). The number of referrals was higher in the period 2010 - 2014 than in the period 2005 - 2009 for all referral types (Table 2).

Of all women directly referred, 81.1% were diagnosed with a CIN lesion (that is CIN 1, 2 or 3) within the episode of screening (Table 2). The proportion of indirectly referred women diagnosed with a CIN lesion was lower, 64.9% for first indirect referrals and 39.9% for second indirect referrals (Table 2). When restricted to only referrals that resulted in a histological diagnosis (i.e. excluding episodes with no recorded diagnosis or no histology taken), there were still differences in the proportion of episodes diagnosed with a CIN lesion between the referral groups (direct: 88.7%; first indirect: 78.1%; second indirect: 67.0%) and the differences were statistically significant (X^2 (2, N = 72,902) = 2,161.98, $p < 0.001$) (figures not presented). Among direct referrals, there was a higher proportion of women with a CIN 3 diagnosis (53.5%) than among indirect referrals (first indirect: 17.5%; second indirect: 8.8%) (Table 2).

The highest proportion of CIN lesions were diagnosed in women aged 29-33 years; 79.8% of all referrals in this age group were diagnosed with a CIN lesion (Figure 2). The

***Table 2**: Demographic characteristics of women referred for colposcopy following participation in the Dutch cervical screening program, all referral types, 2005–2014, rounded percentages*

Variable	Direct referrals *N (%)*	First indirect referrals *N (%)*	Second indirect referrals *N (%)*	*P*
Total referrals	44 209	34 282	6 748	
Total unique woman ID*	43 827	34 081	6 725	
Age				
Mean age	39.16 (*SD*: 8.58)	39.54 (*SD*: 8.49)	41.35 (*SD*: 8.74)	< 0.001
29–33	12 452 (28.2%)	9 086 (26.5%)	1 352 (20.0%)	< 0.001
34–38	9 373 (21.2%)	6 661 (19.4%)	1 117 (16.6%)	
39–43	8 151 (18.4%)	6 351 (18.5%)	1 250 (18.5%)	
44–48	6 027 (13.6%)	5 448 (15.9%)	1 196 (17.7%)	
49–53	3 944 (8.9%)	3 567 (10.4%)	1 005 (14.9%)	
54–58	2 527 (5.7%)	2 022 (5.9%)	513 (7.6%)	
59–63	1 735 (3.9%)	1 147 (3.4%)	315 (4.7%)	
Period				
2005–2009	20 630 (46.7%)	14 400 (42.0%)	2 803 (41.5%)	< 0.001
2010–2014	23 579 (53.3%)	19 882 (58.0%)	3 945 (58.5%)	
Highest diagnosis of the episode after referral				
No recorded diagnosis	1 770 (4.0%)	1 275 (3.7%)	835 (12.4%)	< 0.001
Cytology only	2 023 (4.6%)	4 540 (13.2%)	1 894 (28.1%)	
Benign/Other†	3 019 (6.8%)	6 072 (17.7%)	1 306 (19.4%)	
CIN 1	4 039 (9.1%)	9 024 (26.3%)	1 411 (20.9%)	
CIN 2	8 152 (18.4%)	7 219 (21.1%)	688 (10.2%)	
CIN 3	23 649 (53.5%)	5 996 (17.5%)	594 (8.8%)	
Cancer‡	1 557 (3.5%)	156 (0.5%)	20 (0.3%)	

* Some IDs have more than one referral within the same referral type. The number of unique IDs represents the number of individual women referred within the referral type.
†Benign/Other includes histological results that are lower grade than CIN 1.
‡ Includes micro-invasive and invasive disease
SD: Standard deviation; CIN: Cervical intraepithelial neoplasia
See Figure 1 for description of referral types.

proportion of episodes with no recorded diagnosis or no histology increased with age (Figure 2). In women aged 44 years and older, 61.3% of the no recorded diagnosis and 55.3% of the no histology group had no further primary screening episodes after referral, and the remainder had further cytology and/or histology tests taken in the next primary episode, which were excluded from analysis (figures not presented).

The more severe the CIN diagnosis, the higher the proportion of women treated with large excision (Table 3). Women who were directly referred and diagnosed with CIN 1

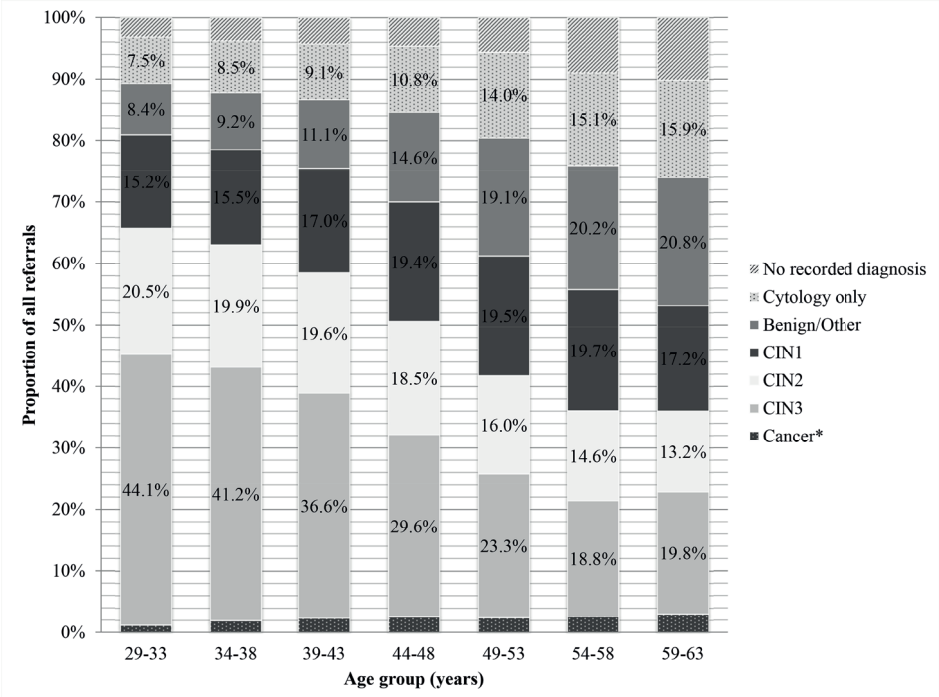


Figure 2: *Highest diagnosis of the screening episode within age groups, all women referred, rounded percentages*

* Includes micro-invasive and invasive disease

CIN: Cervical intraepithelial neoplasia

had higher rates of large excision treatment compared with women who were indirectly referred: 34.4% compared with 23.9% [first indirect] and 19.7% [second indirect]; X^2 (2, N = 14,474) = 193.1, $p < 0.001$). No age-dependency was seen in the percentage with large excision treatment of CIN 3 (figures not shown). For CIN 1 lesions, the proportion of treatment with large excision increased with age. Rates of treatment with large excision differed significantly between referral types across all age groups for CIN 1 lesions (from 13.1% to 50.4%) and for the four youngest age groups for CIN 2+ lesions (Figure 3).

See-and-treat management was observed more often in direct referrals than indirect referrals and was performed mostly in women with severe CIN lesions (Figure 4). Treatment of CIN 1 or lower in see-and-treat management increased with age across all referral types and were higher for indirect referrals in all age groups (Figure 5).

Table 3: *Most invasive management technique of the screening episode by most severe CIN diagnosis of the screening episode, rounded percentages*

	CIN I (%)	CIN 2 (%)	CIN3 (%)	*p*
	Direct referrals			
Hysterectomy	1.2	1.8	3.4	< 0.001
Large excision*	34.4	69.4	82.0	
Biopsy†	62.5	28.2	14.3	
Other techniques‡	1.9	0.6	0.3	
	First indirect referrals			
Hysterectomy	0.9	1.7	2.9	< 0.001
Large excision*	23.9	66.9	81.3	
Biopsy†	73.2	30.8	15.4	
Other techniques‡	1.9	0.6	0.4	
	Second indirect referral			
Hysterectomy	0.6	2.2	1.9	< 0.001
Large excision*	19.7	61.8	80.3	
Biopsy†	77.5	35.3	17.3	
Other techniques‡	2.2	0.7	0.5	
	All referrals			
Hysterectomy	1.0	1.8	3.3	< 0.001
Large excision*	26.4	68.0	81.8	
Biopsy†	70.7	29.7	14.6	
Other techniques‡	1.9	0.6	0.3	

* Large excision includes cone biopsy, LLETZ and other excisional therapies
† Includes all types of biopsies (exc. cone biopsy).
‡ Includes polypectomy, endometrial and endocervical curettage and histology not otherwise specified.
See Figure 1 for description of referral types

DISCUSSION

Despite recommendations not to treat CIN 1 lesions, we found that 26.4% of the diagnosed CIN 1 lesions underwent an excisional procedure, ranging from 13.2% to 50.4% depending on age and referral type. Compared to the European guidelines for clinical management of abnormal cervical cytology,[13] the Dutch CIN 1 advice in the 2004 Guidelines were quite conservative. Despite this, the proportion of CIN 1 treated with large excision is slightly higher than previously reported figures from Italian colposcopy audits[14,15] with the latest reporting 16% of CIN 1 lesions were treated and that increase in the proportion of CIN 1 that was not treated was observed between audit periods. However, compared with the European Federation for Colposcopy guidelines[16] that state 85% of excisional treatments should have a definitive histology of CIN 2+, our data shows the Dutch program exceeds this benchmark at 87%. To our knowledge, no other

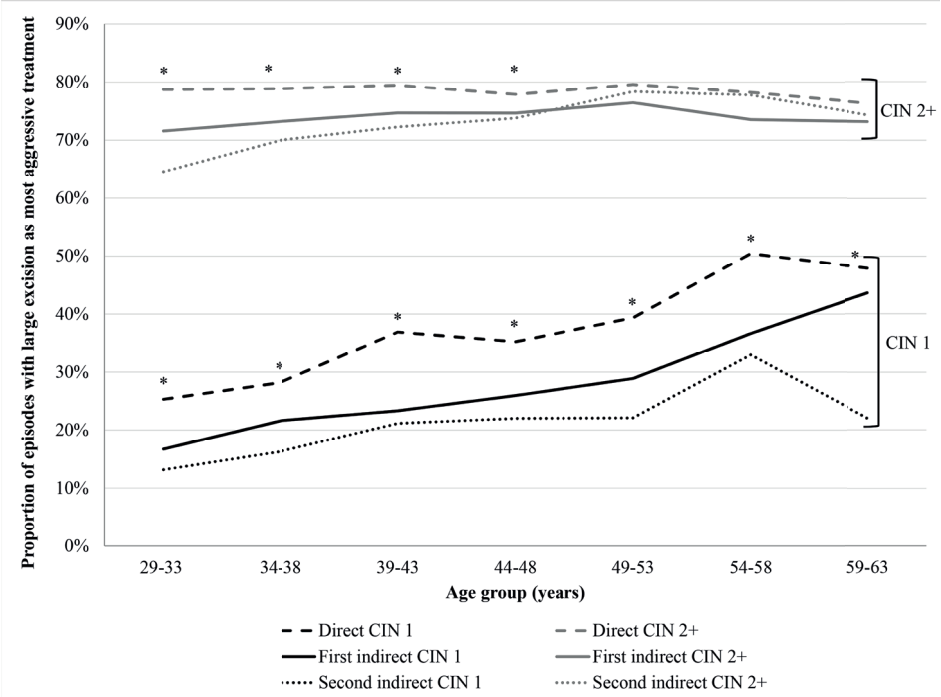
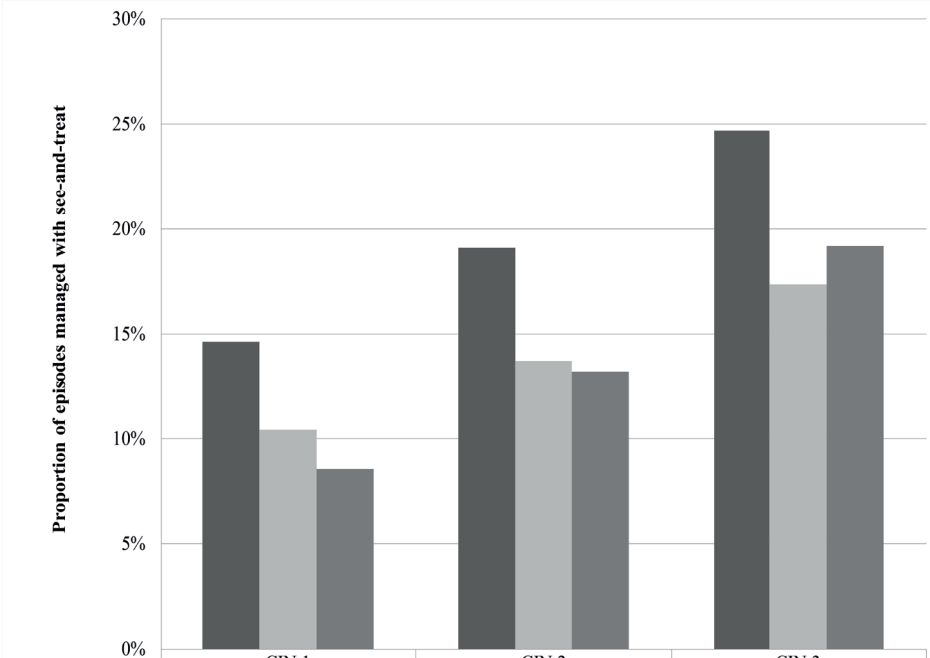


Figure 3: *Proportion of episodes with large excision as most aggressive treatment for CIN 1 and CIN 2+ (denominator: total episodes within each age group with the same highest diagnosis), by age group and referral type*
* Pearson's chi-squared test significantly different between referral types.
See Figure 1 for description of referral types
CIN: Cervical intraepithelial neoplasia

European countries have published CIN treatment rates by diagnosis in peer-reviewed journals, though Danish researchers have recommended monitoring of CIN treatment trends in light of increasing CIN treatment rates in Denmark.[17]

Monitoring of treatment rates can have a positive effect on compliance with guidelines by making practitioners cognizant of recommendations. A study from one US hospital found that active monitoring of excisional treatments led to an increase in guideline compliance and an decrease in inappropriate excisional treatments.[18] Regular monitoring should be implemented given the expected rise in CIN 1 diagnoses, due to the new, more sensitive hrHPV primary test. Modeling estimated that CIN 1 diagnoses will approximately double in the new screening program.[3] In the old cytology screening program, if CIN 1 treatment rate were 5% during the period of our study, rather than 26.4%, this would have resulted in approximately 300 fewer CIN 1 lesions treated with large excision per year. Under the new hrHPV screening program, the impact of reduced CIN 1 treatment rates could be even larger.



	CIN 1	CIN 2	CIN 3
Direct	14.6%	19.1%	24.7%
First indirect	10.4%	13.7%	17.4%
Second indirect	8.6%	13.2%	19.2%

Figure 4: *Proportion of episodes managed with see-and-treat* within each CIN diagnosis group and referral type, 2005-2014*

* See-and-treat management is defined as episodes where the first treatment after referral advice is large excision.

See Figure 1 for description of referral types

It is unrealistic to expect no CIN 1 treatment, as there will always be women with persistent or recurring low-grade abnormalities for whom treatment may be favorable or reassuring.[19] Guidelines are only one factor in clinical decision making for CIN; gynecologists consider information about colposcopy, cytology, hrHPV status, family planning, age, women's preferences and other factors when advising about treatment. Communication between pathologists and gynecologists also influences treatment decisions.[18] There may be situations where CIN 1 was preceded by HSIL cytology, hrHPV positivity and CIN 2+ colposcopic impression or biopsies. Additionally, in women with transformation zone type 3, diagnostic LLETZ after high-grade cytology is indicated in IARC guidelines.[20] In such situations, performing LLETZ may be a justifiable, appropriate treatment. Clarification of a reasonable rate of treatment for CIN 1 should be given in future guideline revisions, preferably accompanied by intuitive nomograms to assist in

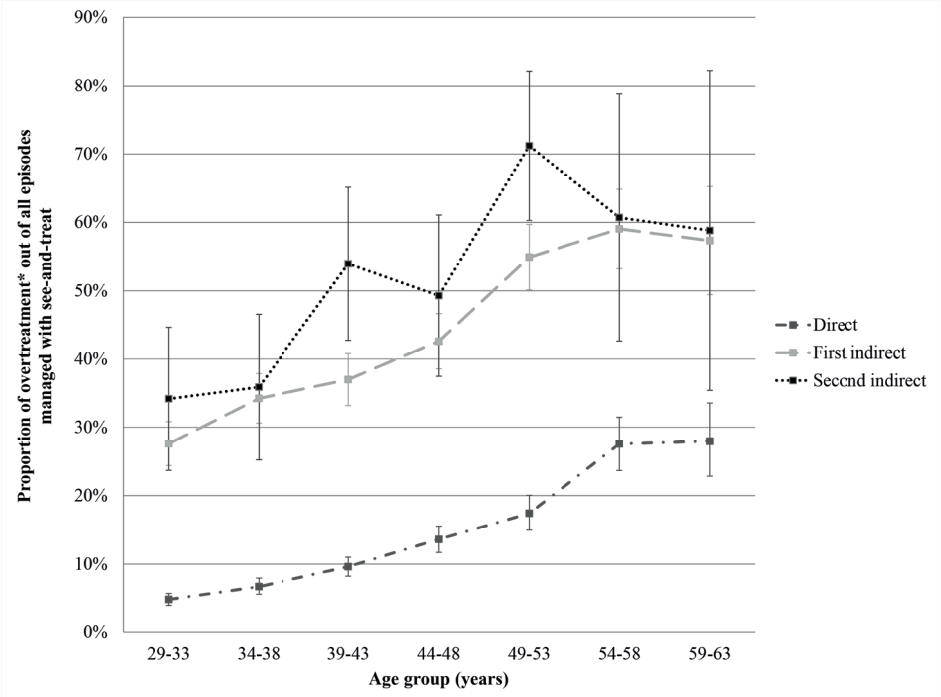


Figure 5: *Proportion of overtreatment* in see-and treat management by age group and referral type*
* Overtreatment in see-and-treat management is defined as the proportion of women with CIN 1 or lower histological diagnosis who were treated with large excision at the first contact with a gynecologist divided by all women who were treated with large excision at the first contact with a gynecologist.
See Figure 1 for description of referral types
CIN: Cervical intraepithelial neoplasia

decision making, for example, that hrHPV negative biopsies can be observed rather than treated.

The treatment guidelines were revised in 2015[21] and now advise see-and-treat for a subcategory of women. Although this approach has advantages (reduced loss to follow-up, convenience for women, lower costs),[22] overtreatment is a risk.[23] See-and-treat needs careful implementation to reduce overtreatment risks. We found that treatment of CIN 1 or lower was more frequent in indirect referrals than direct referrals, and increased with age. These findings are similar to those of other Dutch studies.[24] Given the higher number of CIN 1 and lower diagnoses in the two indirect referral groups, this finding is unsurprising. Our results are consistent with Ebisch and colleagues, who found women with low-grade cytology had higher overtreatment rates than women with high-grade cytology.[12] Restricting see-and-treat to women with concordant high-grade cytology and colposcopy could minimize overtreatment, as could the use of a grading system, such as the Swede score, which has shown to have high specificity for CIN 2+ lesions.[25]

It is not surprising that rates of treatment with large excision for CIN 2+ lesions vary little by age within referral types. Up until 2015, treatment guidelines for CIN 2 were not age-specific. However, the 2015 Guidelines[21] state that women with CIN 2 lesions should be individually assessed as to whether benefits of treatment outweigh the risks, largely related to future childbearing. Active surveillance of young women allows time for CIN 2 lesions to regress, which is likely to occur in most CIN 2 cases.[26] However, active surveillance also comes with the risk of loss to follow-up or progression to a higher-grade lesion. Going forward, we expect CIN 2 treatment will vary by age, as more young women are conservatively managed. As such, both the treatment and outcomes for women with CIN 2 lesions should be monitored to ensure that clinical practice reflects guidelines.

As expected, women diagnosed with CIN 3 had the highest rates of treatment with excisional techniques. This is consistent across referral types with no differences by age (figures not shown). On the other hand, between 14.6% and 17.8% of women diagnosed with CIN 3 were not managed with an excisional treatment (large excision or hysterectomy). This apparent undertreatment may be the result of several factors. Although uncommon in the Netherlands, these women may have been treated non-invasively using electrocoagulation, cryotherapy or imiquimod prescription and these procedures are not recorded in PALGA. Undertreatment may be overestimated due to data issues, such as records belonging to one woman not being properly linked. Finally, a clinician can decide to use an expectant management strategy if diagnostic biopsy removed most of the lesion. Regardless, guidelines state that CIN 3 should always be treated given the risks of progression; long-term follow-up of women in an unethical study in which treatment was delayed or withheld from women with high-grade lesions showed the cumulative incidence of cervical or vaginal vault cancer was 31.3% at 30 years, with a higher cumulative incidence (50.3%) amongst women with persistent high-grade lesions.[27] Timely and effective treatment of CIN 3 is therefore necessary to avoid the risk of disease progression. Communication of these results directly with gynecologists is essential, emphasizing that the benefits of treatment for these women greatly outweigh the risks.

Our study is the first to use a national database to investigate CIN treatment practices in the Netherlands. Analysis in this study was split by referral type, allowing us to investigate women with different risk profiles separately, as the severity of the initial cytology influences follow-up. Reflective of this, we found that women who are directly referred have a much higher proportion of CIN 3 diagnoses.

Our study has some limitations. We did not include information about hrHPV status in our analysis, as the practice of hrHPV testing was not universally conducted during the study period. However, knowledge of hrHPV status may have resulted in more aggressive treatment for women who were hrHPV positive. We were also unable to evaluate conization and large loop excisions separately, or analyze by depth of excision or lesion

size. This is not coded in PALGA. This information would be useful for stratification of results, as depth of excision can have implications for both the risk of adverse obstetric outcomes[5,6,28] and the risk of recurrent or progressive disease.[29] Furthermore, we do not have information about results of colposcopy. If a woman is referred to a gynecologist and examined with colposcopy, but has no accompanying test or treatment, no information is reported to PALGA.

Validation of our results with clinical data found that PALGA may slightly overestimate CIN 1 treatments (Appendix S2), although these clinical data came from a highly specialized clinic with physicians who almost exclusively treat cervical dysplasia. As such, treatment of CIN 1 with excision at this clinic is likely to occur less often than average. One Dutch study compared the impact of different CIN management strategies (more or less aggressive) in two hospital facilities in the same city and found that 68% less CIN 1 lesions were found with the less aggressive strategy.[30] As PALGA has national coverage, the treatment rates we observed were not influenced by policies or practices of any single clinic.

PALGA does not have a unique identification code to track women's screening history; women are identified by the first eight letters of their surname and date of birth. It is possible that tests of multiple women are attributed to a single identification code. In such cases, it is possible that follow-up was censored early for some women, leading to a misclassification of the highest diagnosis or most invasive treatment of the episode.

CONCLUSION

Our study shows that both under- and overtreatment takes place, despite guidelines being available. Regular monitoring of national trends and reviews of treatment rates should be implemented at each clinic that treats women for CIN, to make both gynecologists and pathologists aware of the guidelines and their own performance in relation to them. This may lead to greater compliance with the guidelines, reducing potential harms to women referred from screening.

ABBREVIATIONS

CIN – Cervical intraepithelial neoplasia
hrHPV – high-risk human papillomavirus
LLETZ – Large loop excision of the transformation zone
PALGA – Nationwide network of cyto- and histopathology in the Netherlands
ASC-US – atypical squamous cells of undetermined significance
LSIL – low-grade squamous intraepithelial lesion
HSIL – high-grade squamous intraepithelial lesion
AIS – adenocarcinoma in situ
AGC – atypical glandular cells

Conflict of interest statement

CA, EJ and IdK work on the Evaluation of Dutch National Cervical Cancer Screening Program project funded by the Dutch National Institute for Public Health and the Environment. RB has received speakers' fees from Roche Diagnostics and grants for contract research from SP-MSD.

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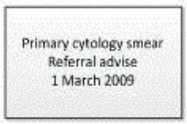
APPENDIX S1: DATA USED IN THIS STUDY

Data from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) was used to identify referrals from the Dutch National Cervical Cancer Screening Programme. This appendix explains which data was used in our results. Figure S1 outlines five fictitious example cases to demonstrate case- and data selection for this analysis. Explanation of these cases can be found in Supplementary Table 1.

Table S1: *Explanation of possible cases within PALGA*

Case	Referral type	Highest Diagnosis	Most invasive treatment	Notes
A	Direct	CIN 3	Large excision	The algorithm used in this analysis selects treatment and diagnosis variables from all secondary treatments regardless of chronological order, so the highest diagnosis and most invasive treatment in this screening episode are from different secondary tests.
B	Indirect	CIN 1	Biopsy	The secondary tests that are included in the analysis from this episode are two, three and four. The first secondary test results in referral advice, indicating the start of care by a gynaecologist.
C	Indirect	No histology	Cytology	This episode is counted in the total number of indirect referrals, but there is no CIN diagnosis, so this episode is not included in the main analysis in this study.
D	Direct	None	None	This woman may not have attended her referral appointment, or the colposcopy did not result in a histological or cytological examination. As such, there is no information for diagnosis or treatment for this screening episode.
E	None	None	None	This record is excluded as an indirect referral because the record that contains the referral advice after the primary cytology smear is in the next primary cytology episode. There are 421 records that are excluded from indirect referrals due to referral advice in the next primary screening round.

	Primary cytology smear indicating a direct referral or a revision within 6 months.
	Secondary test after a primary cytology that is not included in analysis of highest diagnosis or most invasive treatment. These tests are follow-up tests after a primary smear with advice of revision within 6 months.
	Secondary tests that are included on analysis are outlined as bold. The highest diagnosis and most invasive treatment of the episode are shown in bold and italic.
	Next primary cytology smear that is not counted in this analysis.

Legend for *Figure S1*

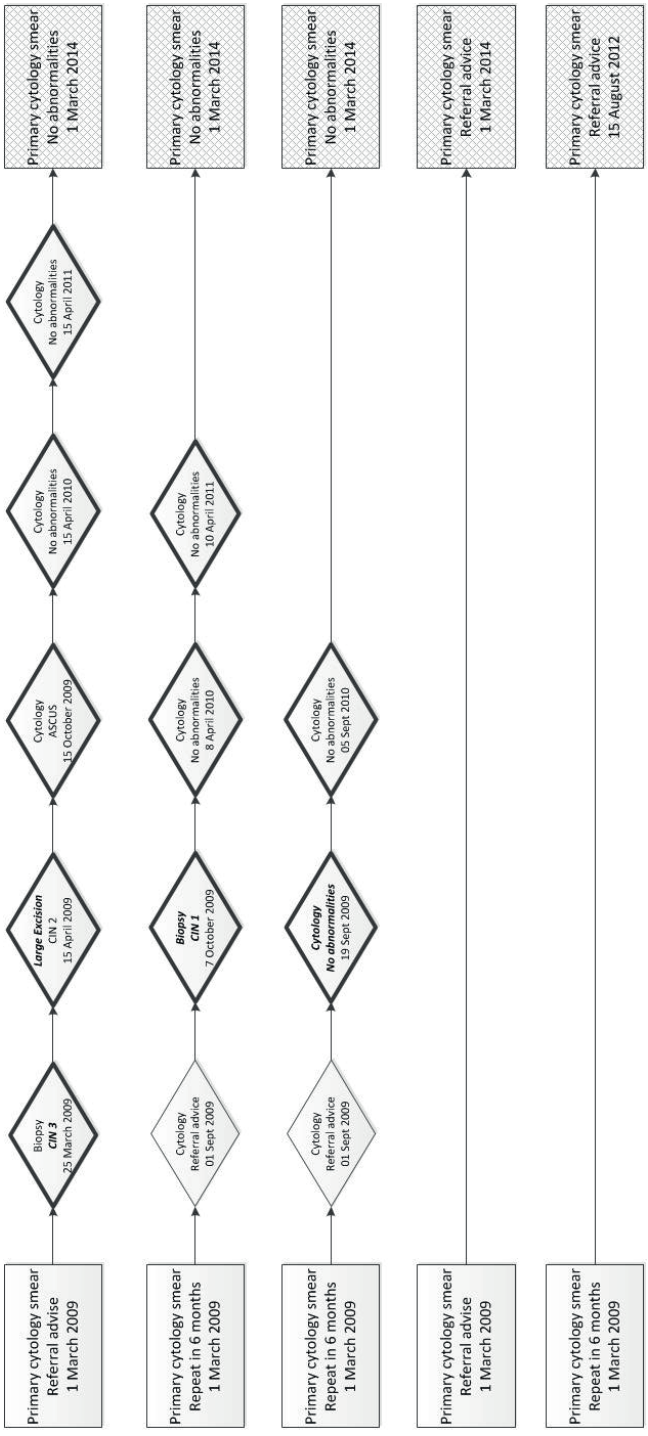


Figure S1: *Example cases - description of data used*

APPENDIX S2: VALIDATION OF RESULTS

Validation with experts

We consulted two expert groups and used clinical data from one specialist clinic to validate our results. Data experts at PALGA were consulted about quality of coding. The data in PALGA is based on information in pathologist reports. Reviews of histology records have previously been conducted by experts at PALGA to ensure that records are appropriately classified and have been found to be largely concordant with pathology reports.

Following this, three practicing Dutch gynaecologists (RB, BtH, JB) were asked whether the PALGA results were broadly reflective of the clinical practice in the Netherlands, in order to assess the face validity of our results. This assessment was based on their extensive knowledge of clinical practice in the Netherlands. They agreed that the results were broadly reflective of clinical practice.

Validation with clinical data

We compared a subset of our dataset with 2012 data from a specialist gynaecology outpatient clinic. This clinic has specialist physicians that primarily work with cervical dysplasia. To do this comparison, we created a subset of our PALGA data that matched the same year (2012) and same screening region that the clinic is located in.

The proportion of treatments (figure not shown) and diagnoses (Figure S2) were comparable in both datasets (with the exception of hysterectomies, which are not performed at the specialist outpatient clinic), as well as the rates of the use of large excision and biopsy in episodes with a CIN 2 or 3 diagnosis (figures not shown). Rates of treatment of CIN 1 lesions were lower at specialist clinic than in PALGA (Figure S3), however these differences may be explained by differences in policies and practices in various clinics in screening region covered by the PALGA dataset.

Conclusion of validation

Results of our validation found that PALGA reflects the distribution of diagnoses and treatments as found in a clinical dataset. Quality of coding was found to be good and face validity was checked by practicing gynaecologists. Based on the comparison with clinical data, the treatment rates for CIN 1 may be slightly overestimated, however the clinical data came from a highly specialised clinic. As such, CIN 1 treatment practices at this clinic are likely to be lower than average.

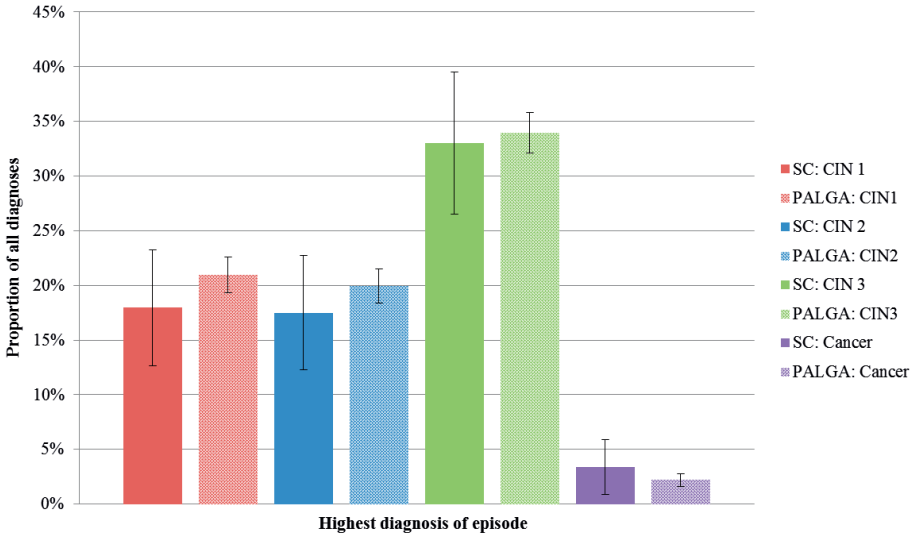


Figure S2: *Proportion of highest diagnosis of the episode by diagnosis and dataset, only CIN and cancer diagnoses shown, 95% confidence intervals*

SC: Specialist gynaecology outpatient clinic

CIN: Cervical intraepithelial neoplasia

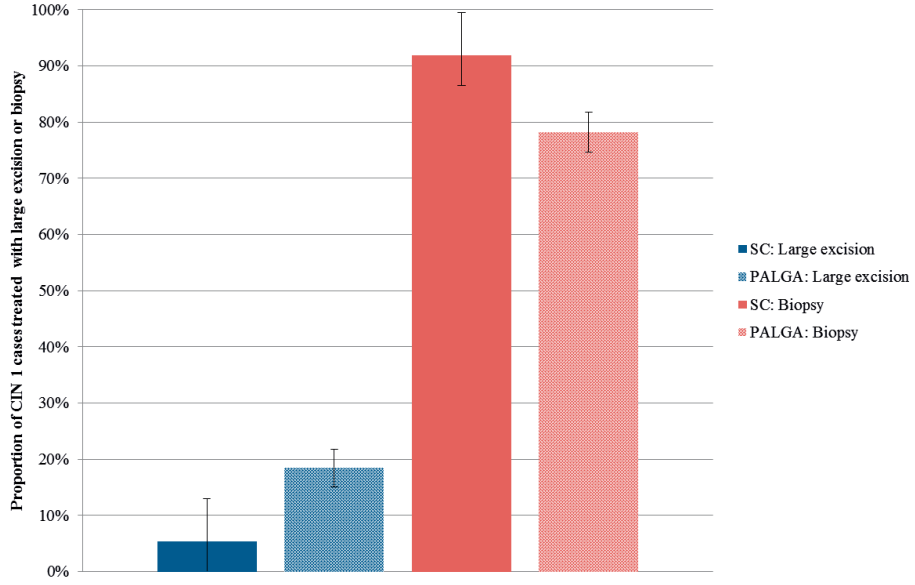


Figure S3: *Proportion of CIN 1 cases with large excision or biopsy as the most invasive technique used by data source, 95% confidence intervals*

SC: Specialist gynecology outpatient clinic

CIN: Cervical intraepithelial neoplasia

Part 6

Discussion

Chapter 6.1

Striking a balance: Complete evaluation of organised cervical cancer screening programmes is not possible until harms of screening are better quantified

Clare A. Aitken[1], Inge M.C.M de Kok[1]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam

Submitted

ABSTRACT

Organised cervical cancer screening programmes need to achieve a careful balance between benefits and harms to maximum effectiveness. Harms of screening can be psychological or physical and can occur at screening, during follow-up or during diagnosis and treatment. We aimed to outline potential harms in each phase of screening, synthesise a list of indicators for quantifying harms and explore why harms are not quantified more regularly. We reviewed three European indicator sets to identify indicators for harms and supplemented this list with additional indicators based on the literature. We identified 16 indicators that cover physical and psychological harms across the whole screening process. Despite multiple organisations identifying indicators measuring harms in their indicator sets, these indicators are not regularly reported. Challenges in quantifying indicators due to difficulties with data collection and lack of organisation should be addressed to facilitate more comprehensive reporting. Quantifying harms will become increasingly important as the underlying population risk for cervical lesions changes. The combination of hrHPV vaccination and hrHPV screening is driving this change in risk, and will necessitate a re-optimisation of organised screening programmes. Complete information about both benefits and harms is required for programme optimisation.

Chapter under embargo

Chapter 6.2

General discussion

This thesis aimed to evaluate each stage of the Dutch cervical cancer screening programme, from invitation to clinical care, as well as the overall screening programme with a focus on the transition from cytology-based screening to hrHPV-based screening.

Overall screening process

On the whole, the implementation of hrHPV-based screening in the Netherlands has been successful; our research presented in this thesis indicates that, following implementation, the programme performed as expected based on modelling. The implementation of the new hrHPV-based screening programme required substantial change to many processes and procedures in the programme and coordination of many different organisations. The switch to hrHPV-based screening across the first quarter of 2017 in all screening organisations should be seen as a success for all parties involved. Monitoring and evaluation of the transition from cytology-based screening to hrHPV-based screening has been able to provide insights to policymakers and health services managers about areas in which the programme could be further optimised.

What was the impact of implementation of the hrHPV-based screening programme on short-time programme indicators?

In **Chapter 2.1**, we investigated what the impact of implementation of the hrHPV-based screening programme was on short-time programme indicators. The implementation of hrHPV-based screening has led to an increase in CIN 2+ detection, with an corresponding increase in unnecessary referrals. The increased CIN 2+ detection rate was achieved by a higher positivity rate (increased from 5% in the cytology-based programme to 9% in the hrHPV-based programme; $p < 0.001$) and higher referral rate (from 1% in the cytology-based programme to 3% in the hrHPV-based programme; $p < 0.001$). However, more women who were referred did not have a clinically significant lesion. Our analysis found that the driver of unnecessary referrals was increased referrals amongst women with ASC-US/LSIL cytology, with an approximately 60% increase in the number of referrals needed to detect one CIN 2+/CIN 3+ lesion in this group. This indicates that too many women with low-grade lesions that are not clinically significant are being referred to the gynaecologist in the new hrHPV-based programme.

The increase in referral rates has also been seen in the Australian hrHPV-based screening programme. Australia also implemented nationwide hrHPV-based screening in 2017. Although there are differences between the Dutch and Australian programmes, both in programme dynamics (number of lifetime screens, included ages, triage algorithms) and background risk (as Australia implemented hrHPV vaccination in 2007), analysis of the first results of the Australian programme (though not based on nationwide data) also found that the direct referral rate (2.6%) was substantially higher than in the previous cytology-based programme (0.8%).[1] While, in both screening programmes, this was not

unexpected based on modelling, it is an area of possible optimisation for the Dutch programme now that implementation is complete. We explored this further in **Chapter 4.2**.

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?

In **Chapter 2.2,** we found that the cost-effectiveness of the hrHPV-based screening programme is still superior to cytology-based screening even when taking into account the lower-than-expected participation rates observed in **Chapter 2.1**. Our results show that hrHPV-based primary screening is estimated to decrease cervical cancer mortality (-4%) and incidence (-1%) compared to the old programme. Despite an increase in unnecessary referrals (+172%), hrHPV-based screening still results in more QALY's gained (+13%). The hrHPV-based programme was more cost-effective than cytology-based programme, costing 46% less per QALY gained; €12,225 per QALY gained for hrHPV-based screening versus €22,678 per QALY gained for cytology-based screening. Our results support modelling done prior to implementation of the programme.[2 3]

Chapter 2.2 showed that the total costs of the hrHPV-based programme were 21% lower than the old programme, which is mainly driven by lower costs of primary screening. This is due to a lower number of lifetime screening tests – from seven per woman in the cytology-based programme to as low as five per woman in the hrHPV-based programme. Extending the screening interval from five to ten years for hrHPV-based screening is considered to be safe for women aged 40 years and older who test hrHPV negative, based on analysis of the POBASCAM trial.[4] However, it is still unclear how women will respond to extended screening intervals once they are implemented. Various studies of acceptability of extending screening intervals have found that women are more likely to accept extended intervals if they are recommended by their healthcare provider[5 6] or if more information and education is provided about the rationale for extending intervals.[7 8] These studies investigated the willingness of women to have screening intervals extended up to five years. A screening interval of 10 years is considerably longer, and the feasibility of implementing extended screening intervals will partly depend on whether Dutch women will find this extension acceptable.

Also related to extended screening intervals, the differences seen between the clinician-collected test and self-sampling may impact on the implementation of the 10 year screening interval. Although the exact impact of the differences in hrHPV positivity on the test characteristics is still unclear, if self-sampling has a lower sensitivity for CIN 2+ than clinician-collected testing, extending the screening interval for women who used self-sampling and tested hrHPV-negative may not be advisable. This may impact the cost-effectiveness of the hrHPV-based programme, as more women would need to

be re-invited at ages 45 and 55. Further cost-effectiveness modelling should investigate this issue.

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?

We saw in **Chapter 2.1** that attendance in the new hrHPV-based screening programme was in 2017 lower than in the old cytology-based programme. In 2018,[9] attendance rates were still lower than in the old programme. We aimed in **Chapter 3.1** to investigate the decline in participation rates further, particularly focusing on whether the decline in participation could be explained by personal characteristics of women in the eligible cohort or by organisational factors.

Attendance rates did vary by personal characteristics of women; women who were employed (60.8%), married (62.9%), Dutch (61.2%), in the highest income bracket (63.4%), living in households with four persons (65.3%) and women who were invited by their GP (69.8%) had the highest attendance rates. Like in other organised European screening programmes, we found that attendance in the Dutch programme was lower amongst women with a migration background,[10-13] women in lower income brackets[11 14] and women who live alone or are not married.[12 14 15] However, our analysis found that personal characteristics were not associated with the decline in attendance in the programme. By adjusting for the organisation that sent the invitation (i.e. the GP or the screening organisation), the differences in attendance rates between 2014-2015 and 2016 and between 2014-2015 and 2017-2018 were explained in some screening organisations, indicating that removing self-inviting GPs from the programme has had some impact on attendance rates.

Targeted strategies for increasing attendance rates

Bongaerts and colleagues identified that targeted strategies for subpopulations had been shown to impact on participation in the cervical cancer screening programme in the Netherlands.[16] Women who do not attend screening are not a homogenous group, and therefore, multiple strategies may need to be adopted to reach all women. Marlow and colleagues used the Precaution Adoption Process Model to propose five categories of cervical cancer screening non-attenders: women unaware of screening, women unengaged by screening, women who were undecided, women who had decided not to be screened and women who intended to participate, but did not.[17]

Women who are unaware, unengaged or undecided about cervical cancer screening may not have received, or engaged with, the relevant information materials to make an informed choice about participation. Korfage and colleagues found that providing women with an information leaflet about cervical cancer screening increased knowl-

edge and informed decision making.[18] Women in the Netherlands already receive a leaflet about the cervical cancer screening programme with their invitation, but ensuring women engage with, and understand, the material is challenging.

Women who do not participate despite intending to may require different interventions to motivate attendance. Interviewing non-attenders in the English cervical cancer screening programme, Marlow and colleagues found that practical barriers, such as being busy with work, caring responsibilities or inconvenient clinic opening hours prevented women who intended to participate from acting on their intentions.[19] Forgetting to make an appointment was the primary reason given for non-attendance in a sample of Dutch non-participants.[20] Offering more convenience for these women could help reduce the so-called 'intention-behaviour gap'.[21] Barriers to making an appointment, such as finding it difficult to get through to one's general practice by phone, are possibly experienced by Dutch women who wish to be screened. Employing new technologies, such as online booking systems, could help facilitate participation. One study found that women who reported more barriers to participation were more likely to want to book their screening using an app or website.[22] Another possible way to reduce barriers would be for general practices to offer after-hours walk-in clinics for screening that could be accessed without an appointment. Although these would be difficult to implement in the Netherlands on a national level, general practices could be encouraged to offer such services.

The ideal participation rate for cervical cancer screening will never be 100%, because some women make an informed choice that screening is not beneficial for them. Women who actively choose not to participate in cervical cancer screening have been shown to decline screening for several reasons. Bennett and colleagues found that active decliners were more likely than intenders to: a) perceive that their risk of cervical cancer was low due to sexual behaviour, b) report that they had more important things to worry about than screening, and c) to have weighed up the risks and benefits and decided screening is not relevant for them.[23] Oscarsson and colleagues found that although many reasons were found for non-attendance, these could be grouped into three themes; 'I do not need to', 'I do not want to' and 'I do not give it priority'.[24] As with the intenders, some active decliners may respond to making screening more convenient. Self-sampling is one possible intervention to reduce barriers. Being sent a unsolicited self-sampling kit increased participation amongst Dutch non-attenders[25] and was identified as preferable to the current English screening programme in a study of non-attending young English women.[26]

However, as discussed in **Chapter 3.1**, the availability of self-sampling has not resulted in increased participation in the Dutch screening programme. This is likely a result of the need to order a kit, which adds additional steps (which could be barriers) from invitation to participation. Sending self-sampling kits directly to women who do not respond to

the initial screening invitation may increase attendance. However, the impact of this change would need to be carefully tested, perhaps in a small pilot, prior to implementation in order to evaluate if it would increase participation and what the impact on cost and waste would be.

Impact of definition of attendance

One limitation of our study in **Chapter 3.1** was that we used a standard definition of attendance (15-month attendance rates). This definition has been used in the annual short-term monitoring of the programme. However, it may be that this period was too short to capture participation in the new programme, given the phased implementation in 2017 and the delay period of four months between ordering the self-sampling kit and receiving it. We did an additional analysis aimed at investigating whether the decline in participation is due to delayed participation in the new hrHPV-based screening programme. We did this by exploring different definitions of attendance. We aimed to investigate if extending the number of months included in the calculation of the participation rate would result in comparable participation rates in 2014-2015 and 2017-2018.

We used the same ScreenIT/CIS dataset described in **Chapter 3.1** and defined attendance as participation in the screening programme at any date from the start of the year of invitation to a censor date, starting at 12 months (1 January up to, and including ,31 December), increasing the inclusion period in three-month increments to 36 months. Exact dates for each increment and invitation year can be found in Table 1.

Table 1: *End dates for investigating definition of participation rates*

	Invitation year				
Participation rate period	**2014**	**2015**	**2016**	**2017**	**2018**
12 months	31/12/2014	31/12/2015	31/12/2016	31/12/2017	31/12/2018
15 months	31/03/2015	31/03/2016	31/03/2017	31/03/2018	31/03/2019
18 months	30/06/2015	30/06/2016	30/06/2017	30/06/2018	30/06/2019
21 months	30/09/2015	30/09/2016	30/09/2017	30/09/2018	30/09/2019
24 months	31/12/2015	31/12/2016	31/12/2017	31/12/2018	31/12/2019*
27 months	31/03/2016	31/03/2017	31/03/2018	31/03/2019	*
30 months	30/06/2016	30/06/2017	30/06/2018	30/06/2019	*
33 months	30/09/2016	30/09/2017	30/09/2018	30/09/2019	*
36 months	31/12/2016	31/12/2017	31/12/2018	31/12/2019*	*

* Last screen recorded in the dataset was 20 November 2019, therefore these cells are censored.

Figure 1 shows attendance rates for periods 2014-2015, 2016 and 2017-2018 with extending inclusion periods for primary screens. Even after 36 months from the start of the invitation year, the attendance rate in 2017-2018 does not catch up with the attendance

rate in 2014-2015. This analysis suggests that using 15-month attendance rates did not affect the results in **Chapter 3.1** and shows that participation in the new hrHPV-based programme remains lower over time than in the last years of the old cytology-based programme.

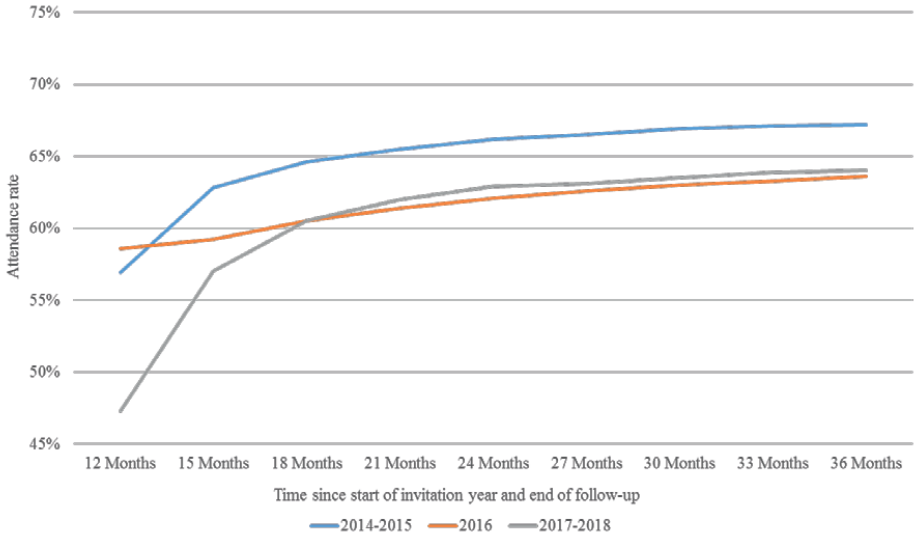


Figure 1: *Attendance rate by increasing inclusion period by year of invitation*
NB. Attendance rates in 2017-18 after 24 months are based only on data from 2017. Last date of screening in the dataset is in November 2019.

Other possible organisational factors

There were other changes to programme policies and procedures that we were unable to include in our study that could also have contributed to a declining participation rate. Another possible driver of the drop in attendance rates is the fact that gynaecologists are also no longer able to take screens within the screening programme, although the impact of making this change may be small. Having to take the invitation letter to the screening appointment, as discussed in **Chapter 3.1**, may also act as a barrier to screening. One reason that the letter is required is that it contains personalised stickers that need to be attached to the ThinPrep vial, making it easier to process the screening test in the laboratory. A possible solution would be to allow GPs to print these stickers themselves or obtain a unique identification number that could be written on the vial from a secure online portal. This would still allow the women to be screened within the programme without their letter and would not interrupt the processes in the screening labs.

Untangling the reasons for non-participation to increase uptake

The dynamics driving participation in organised cancer screening programmes are complex. While there have been some studies conducted in the Netherlands looking at the characteristics of non-attenders (including **Chapter 3.1**) and the reasons for not attending, there has been no research published on whether the reasons for non-attendance have changed since the implementation of hrHPV-based primary screening. Future research should be conducted to understand the reasons for non-attendance within the hrHPV-based programme. This type of information could help guide programme managers to select interventions that would have the greatest impact on the participation rate.

Test and referral

Are ratings of cytology slides by cytotechnicians influenced by the knowledge of hrHPV status?

Our small study, described in **Chapter 4.1**, into the potential impact of the knowledge of HPV status by cytotechnicians indicates that the knowledge of hrHPV status has some influence on the rating of cytology slides with low-grade abnormalities. If these slides are, in fact, normal, then 'upwards ratings' of slides may further contribute to the increased number of unnecessary referral in the new hrHPV-based programme. The reason this phenomenon was important to investigate is that all cytology slides that are now analysed in the new hrHPV-based programme are hrHPV-positive. As such, cytotechnicians are indirectly aware of the HPV status of every slide.

It seems that when slides are known to be hrHPV positive, cytotechnicians may err on the side of caution when reading slides. This results in them rating slides with features not related to cervical dysplasia as ASC-US, when without knowledge of hrHPV status, the slide may have been rated as normal. Such errors may be, in part, caused by cognitive biases. Confirmation bias, which is the tendency to seek out information that supports a belief or hypothesis that one already holds,[27] may be influencing decision-making in these cases. Making these judgements with the knowledge of hrHPV status is understandable, especially with knowledge of the natural history of cervical cancer and the causal role of hrHPV in cervical dysplasia. Interpreting cytology slides, by nature, is somewhat subjective, meaning good training and quality control are vital. Therefore, ongoing training and assessment of the accuracy of cytology ratings by both cytotechnicians and pathologists has been conducted since the implementation of the new programme, as well as monitoring the quality of cytology. These activities should continue in order to ensure quality remains high.

What are the options for optimising the triage algorithm of the hrHPV-based screening programme within the current parameters of the programme?

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. Any new triage algorithm would need to reduce unnecessary referrals with little to no impact on cervical cancer incidence and mortality and be easy to implement within the current laboratory procedures. In **Chapter 4.2**, we found that the most effective way to reduce unnecessary referrals with the technology and expertise available now is to implement HPV 16/18 genotyping and possibly to increase the interval to repeat testing from six to 12 months. Specifically, we found a reduction in unnecessary referrals of 45% by adjusting the conditions for referral to 'HPV16+ and ASC-US+' and 'HPV18+/HPV other high-risk types+ and HSIL+', while also extending the interval between the cytology negative primary test and the repeat test from six to 12 months. This was achievable with an estimated 2% increase in cervical cancer incidence and no increase in mortality.

Recent observational data further supports implementation of HPV 16 genotyping at a minimum, due to the increased risk of CIN 3+ following a HPV 16 infection.[28] As the HPV test system that is currently used in the Dutch programme is already capable of HPV 16/18 genotyping, there would be few costs and almost no infrastructure changes required for such a change. Given the number of key events on the horizon for the Dutch programme (including the second screening round, extended screening intervals, entry of partly vaccinated cohorts and re-tendering of tests), making large-scale changes to the triage algorithm involving new technologies is inadvisable at the moment. More needs to be known about test performance and the underlying disease risk in the population to make more complex changes to the triage algorithm. Because of this, implementation of HPV16/18 genotyping is the most logical step for optimising the triage algorithm on the short-term.

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?

Results from our study in **Chapter 4.3** suggest that women who have AGC on cervical cytology are at higher risk of both cervical and other gynaecological cancers compared to squamous cell abnormalities of comparable severity. This suggests that women who have an AGC on cervical cytology need to be referred directly. In the new hrHPV-based screening programme, this is already occurring for women who are hrHPV-positive with AGC on cervical cytology.

The detection of endometrial and ovarian cancers through cervical cancer screening in the Netherlands is not monitored. These incidental findings could be seen as a harm of screening (as we put forward in **Chapter 6.1**) for a number of reasons. Firstly, women

are not giving informed consent for being tested for these cancers when participating in cervical cancer screening. Secondly, incidentally-detected cancers may lead to overdiagnosis, especially in older women. However, incidental findings may also benefit women, allowing them to receive diagnosis and treatment for a cancer that may have otherwise been detected at a later stage. In women aged over 50 years with AGC, the risk of an endometrial cancer cancer after a severe AGC abnormality was particularly high. These cancers are not associated with hrHPV infections. One study found that HPV positivity of AGC cytology differed depending on the type of AGC abnormality detected; AGC cytology with a concurrent squamous abnormality had the highest HPV positivity rate (84%), with AGC cytology with atypical endometrial cells having a 0% HPV positivity rate.[29] Because of this, we anticipate that the implementation of hrHPV-based screening will lead to a reduction in the number of AGC cytology smears seen every year. This will be driven by a reduced number of AGC diagnoses related to non-HPV-related malignancies in older women.

Other issues with testing and referrals

Differences between self-sampling and clinician-collected sampling

The availability of self-sampling for all women who wish to request a kit is one of the most unique aspects of the hrHPV-based programme in the Netherlands. In most settings, self-sampling is used as a strategy for encouraging participation in non-responders only. In **Chapter 2.1**, we observed that the hrHPV positivity rate was different between the self-sampling test and the clinician-collected test, and amongst women directly referred and followed-up, there was a higher proportion of CIN 2+ detected amongst self-test users. These results were surprising given the previous studies conducted in the Netherlands found the hrHPV positivity rate to be either comparable[30] or higher[31] in self-samples compared with clinician-collected testing. Both of these studies were conducted within the screening programme, so were expected to provide a good indication of how the test would perform in the real-life setting. The results in **Chapter 2.1** may be due to differences in the types of women using the self-sampling test in the screening programme compared to previous studies or may be due to differences in the technical work-up of the tests within the programme completed to previous studies.

It is possible that differences exist between women using self-sampling and women who are screened by their GP. However, the fact that the overall participation rate is actually lower in the new screening programme[32] and the results of **Chapter 3.1** suggest the characteristics of women did not impact on the decline in participation rates, it can be speculated that self-sampling is largely reaching the population of potential attenders (i.e. women who would have attended the screening programme with or without the offer of self-sampling). Modelling suggests that a gain in health benefits by implementing self-sampling depends on increasing overall participation, particularly

amongst women who were high-risk never-attenders, and on limiting the number of 'switchers', i.e. women who have previously been screened by the GP.[33] To maximise the benefits of self-sampling in the programme, more active approaches may be needed to reach non- and never-attenders, as previously discussed in **Chapter 3.1** and section "*Targeted strategies for increasing attendance rates*". However, it is still unclear if women using self-sampling are potential attenders (i.e. women who would have otherwise attended by being screened by their GP) or non-attenders (i.e. women who would not have attended without the offer of self-sampling).

An alternative explanation for the difference between the two tests is that there is a difference in the way the tests are used within the screening programme versus previous studies of PCR self-sampling. The IMPROVE trial used a different clinician-collected test than is used in the screening programme,[30] which could explain why there is a difference between the results of the trial and the screening programme. The VERA study, which tested the concordance between self-sampling and the clinician-collected test in a sample of screening programme responders, used the same tests as used in the screening programme. This study showed that self-sampling resulted in a higher hrHPV positivity than in the clinician-collected samples.[31] The results in **Chapter 2.1** in a comparable population show the exact opposite result. It is possible that, although the test and the technology are the same, processes within the screening laboratories result in the difference between the two tests. In the VERA study, the self-sampling dry brushes were processed in 4.5mL of ThinPrep medium, whereas in the screening programme, self-samples are processed in 20mL of ThinPrep medium. Dilution with 20mL of medium may have resulted in a lower sensitivity for hrHPV in self-samples. Investigating possible differences should be a priority for further research.

Diagnosis and treatment

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?

In **Chapter 5.1**, we investigated CIN management and treatment following referral from the Dutch cervical cancer screening programme, and whether these were in line with the clinical guidelines. Our study showed that both over-and under-treatment was occurring following referral from the old cytology-based screening programme. Of particular concern was the overtreatment observed amongst certain groups who received see-and-treat management following referral. Our analysis suggests that there is room for improvement with compliance to the practice guidelines.

Our findings have been supported by an independent report on treatment and management of CIN in the 'Sensible care' (Zinnige Zorg) programme run by Zorginstituut

Nederland. Researchers at Zorginstituut Nederland also found overtreatment of CIN 1 lesions and substantial variation in the follow-up of women who were referred. They concluded that the clinical guidelines should be followed more closely. Estimates from their report suggest that there could be substantial savings for the Dutch healthcare system (€1.3 million in direct costs and €1 million in indirect costs) if the following issues were addressed: fewer women unnecessarily treated for CIN 1 and CIN 2; more women treated for CIN 3; clarity and uniformity of the follow-up pathways for women with CIN; variations in these pathways reduced, and; improvements in patient information to facilitate shared decision-making.[34] Ensuring that the CIN 1 and CIN 2 treatment guidelines are more closely followed is of more importance since the implementation of the new programme, as more women with low grade lesions are referred. Early indications reassuringly suggest that this increase in unnecessary referrals has led to an increase in overdiagnosis, but not overtreatment.[35] However, given that many of the potential harms of screening identified in **Chapter 6.1** can occur in the diagnosis and treatment stage of screening, regular monitoring of compliance with guidelines remains essential.

Improving programme monitoring with colposcopy data

In **Chapter 2.1**, we observed an increase in the rates of women who are referred, but do not comply with this referral advice, in the new hrHPV-based screening programme. In cases where women are referred from the screening programme with low-grade lesions and are found to have a normal colposcopic image, there is no indication to have any further tests at the initial colposcopy appointment. The increase we observed may not be a true increase in non-compliance, but caused by a lack of information in the current database used for monitoring and evaluation (PALGA). For these women, their colposcopy attendance is not recorded in PALGA because there was no cytological or histological test taken. Therefore, these women appear as lost-to-follow-up in the monitoring of the programme. Information about attendance at colposcopy, as well as detailed information about diagnostic or therapeutic procedures (including motivations for deviating from clinical guidelines), would add great value to both short-term monitoring of the programme and longer-term evaluation of changes in clinical practice. In the Dutch colorectal cancer screening programme, information about each colonoscopy performed in the programme is recorded in a gastroenterology clinical database and combined with data on invitations from the screening programme and pathology information from PALGA, amongst other data, to ensure that there is a comprehensive overview of all aspects of the programme.[36] A clinical database for colposcopy does not exist in the Netherlands. Building and implementing a national registry of colposcopy information that could be linked back to the ScreenIT system would provide more complete information about follow-up, diagnostics and treatment from women following referral from screening.

Future challenges and opportunities in the Dutch cervical cancer screening programme

Second screening round in 2022

In 2022, women who were invited for, and participated in, the first screening round in 2017 will be invited for their second round of hrHPV-based screening. We expect that in the second round of screening, there will be fewer CIN 2+ lesions detected (as seen in the POBASCAM trial[37]), as the first screening round detects prevalent disease and subsequent rounds detect incident disease. Monitoring of the results from the second round will be important for assessing if the sensitivity of clinician-collected sampling and self-sampling are equivalent to one another. CIN 2+ detection in the second round amongst women who participated in both screening rounds should be compared by the test type used in the first round. Additionally, the first opportunity to investigate interval cancers will occur following the second screening round. Interval cancers are a proxy for lack of sensitivity in the programme, as interval cancers indicate a missed premalignant lesion in the prior screening round. Most interval cancers in the Dutch programme are diagnosed at or shortly following the next screening round.[38] Comparing this indicator by test type will also be important for understanding the performance of each test within the programme.

Vaccinated populations entering the screening programme

In 2023, the first partly-vaccinated cohort of women will enter the Dutch cervical cancer screening programme. In the Dutch vaccination programme, two doses of the bivalent vaccination are offered to 12/13-year-old girls. Girls who are 15 years and wish to be vaccinated are offered three doses. In Scotland, the effect of HPV vaccination on CIN detection has already been observed, with an 88% reduction in CIN 2+ detected in partly vaccinated cohorts compared with unvaccinated cohorts.[39] There were also herd immunity effects observed, although the Scottish vaccination coverage rates were higher than observed in the Netherlands. In Sweden, the cumulative incidence of cervical cancer amongst young vaccinated women was found to be significantly lower than in young unvaccinated women (Adjusted IRR: 0.37 (95% CI: 0.21–0.57)).[40] With similar drastic reductions in disease prevalence expected in the Netherlands as well, the landscape for cervical cancer screening and prevention will shift, necessitating a rethink of the current screening paradigm. Modelling by Naber and colleagues found that the number of lifetime screens that are cost-effective depends on herd immunity rates. In a situation in which there is 50% herd immunity or higher, a less intense screening strategy (three instead of eight lifetime screens) was optimal.[41] Careful consideration needs to be given to what the most optimal screening strategy will be in the coming decades, and changes should be made to the programme to prevent over-screening where necessary.

Elimination of cervical cancer in the Netherlands

The WHO announced in 2018 that it would draft a global strategy for the elimination of cervical cancer in the Netherlands. Elimination of cervical cancer is defined as less than four cases per 100,000 women. The WHO strategy covers primary, secondary and tertiary prevention strategies (as discussed in **Chapter 1**), defining the following targets that every country must reach by 2030:

- 90% coverage of HPV vaccination of girls;
- 70% coverage of screening (70% of women are screened with high-performance tests by the ages of 35 and 45 years) and 90% treatment of precancerous lesions;
- Management of 90% of invasive cancer cases.[42]

In the Netherlands, there is still more work to do to meet these targets for both screening and vaccination coverage. HPV vaccination coverage in the 2004 cohort was 45.5%,[43] far below the target set of 90% by the WHO. In one large modelling study looking at the impact of these strategies in low- and middle-income countries, high HPV vaccination coverage was required for elimination over the long-term.[44] As such, increasing vaccination coverage is essential to elimination of cervical cancer in the Netherlands. Increasing participation in cervical cancer screening is also important to expediting elimination. The current attendance rate (57.6% in 2018[9]) is also lower than the WHO targets, but the difference between the target and the attendance rate is narrower than that for HPV vaccination coverage. An association between vaccination of daughters and the screening behaviour of mothers has been shown in a Dutch cohort, which found that girls' vaccination status was positively associated with the mothers' screening attendance.[45] This association can be seen in regional participation rates; the provinces of North Brabant, Gelderland and parts of Overijssel and North Limburg have high participation rates in both screening and HPV vaccination (Figures 2 and 3).

Many of the factors have been shown to influence participation in the HPV vaccination programme in the Netherlands are regionally specific, suggesting that a more tailored, regional approach to increasing participation in both programmes may be beneficial. One of the main predictors of vaccination uptake is religion and faith. Conservative Protestants often live in specific geographical regions in the Netherlands and tend to refuse vaccinations on religious grounds.[45] Identifying as religious was found to be a strong predictor of declining the HPV vaccination.[47] Areas with active anti-HPV vaccination groups also had lower rates of vaccine uptake.[48] Paradoxically, increased use of local media by the community health services (in Dutch: *gemeenschappelijke gezondheidsdienst* or GGD) was associated with lower participation rates compared with no media use.[48] Collaboration between GGD's and local schools and clinicians (GPs or gynaecologists) has shown to have a positive influence on participation.[48] Just as discussed in **Chapter 3.1**, GPs seem to play an important role in both screening and vaccination in the Nether-

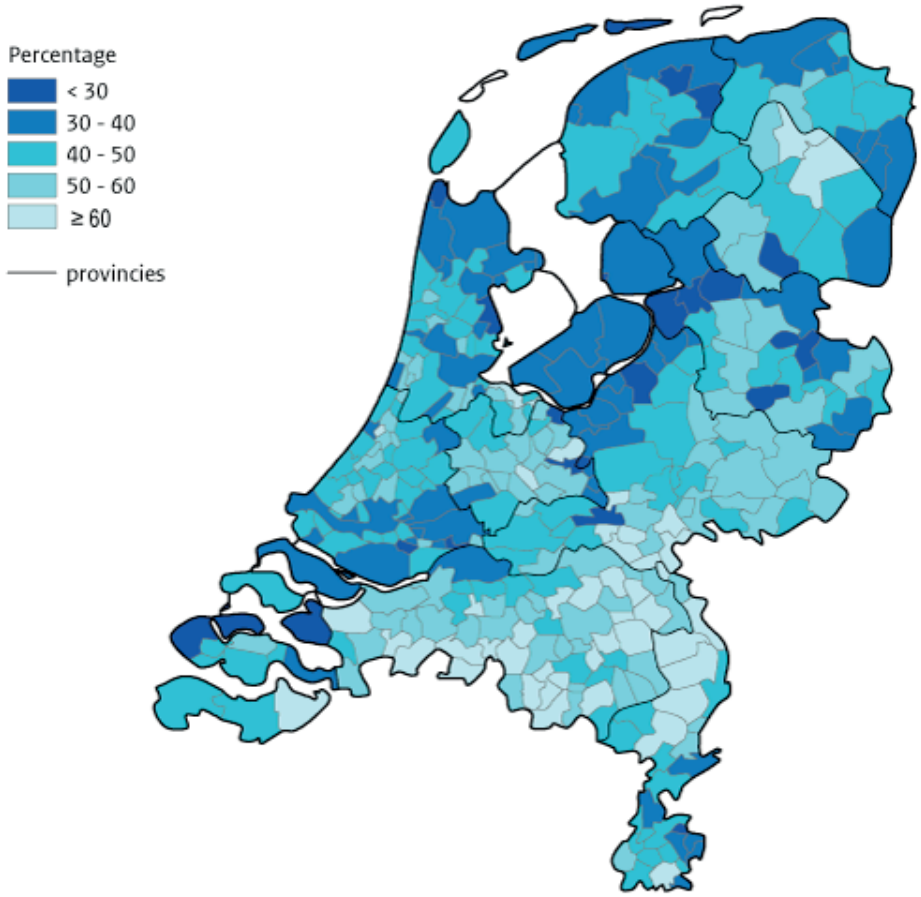


Figure 2: *HPV vaccination coverage, girls in birth cohort 2004, by city council region and province, 2019. Image source: Volksgezondsheidenzorg.info.*[46] *Data source: RIVM- Dienst Vaccinvoorziening en Preventieprogramma's. Grey lines denote city council regions, black boundaries denote borders of provinces.*

lands, and should continue to be involved in both programmes. Local collaborations to build trust and understanding between those eligible for screening and vaccination and the organisations offering these interventions may be useful in increasing participation rates going forward.

Conclusions

- The first results of the new hrHPV-based screening programme were consistent with expectations based on modelling.
- HrHPV-based primary screening results in higher CIN 2+ detection in round one of screening, at the expense of more unnecessary referrals.

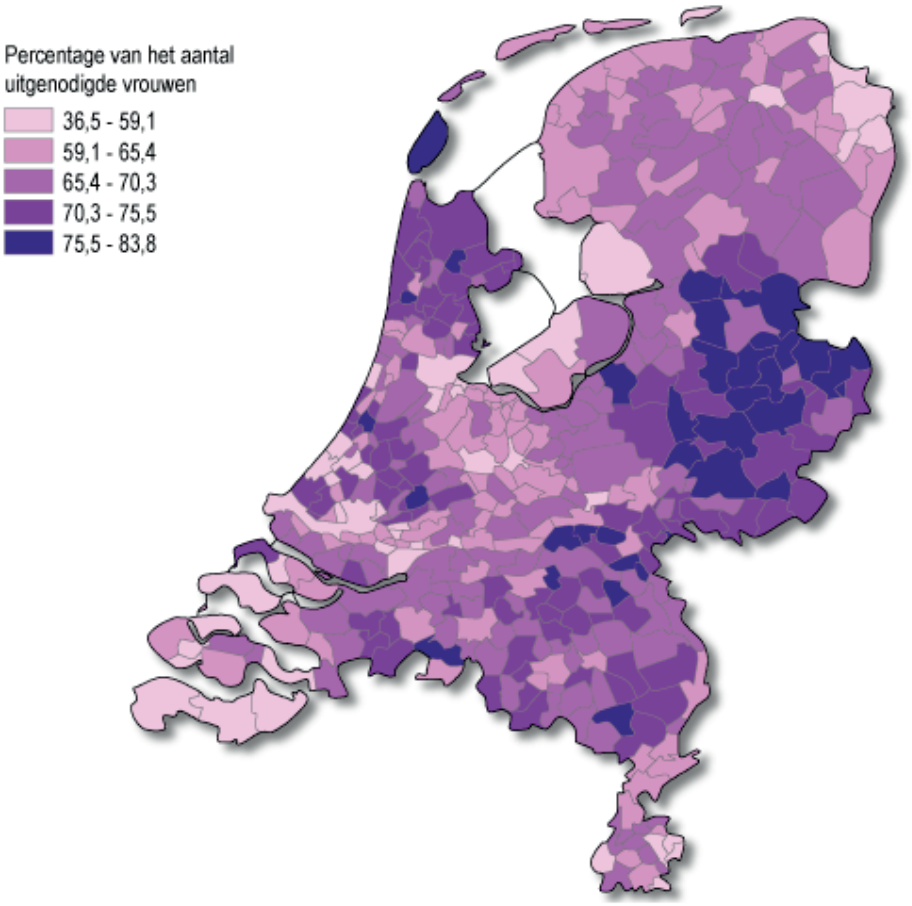


Figure 3: *Participation in the Dutch cervical cancer screening programme by city council region, 2012. Image source: Volksgezondsheidenzorg.info. Data source: Regional screening organisation. Colours denotes the attendance rates within city council regions. Lighter purple denote lower attendance and darker purple denotes higher attendance.*

- Despite higher than expected hrHPV positivity rates and lower participation rates, the new hrHPV-based screening programme is more cost-effective than the old cytology-based screening in the Netherlands.
- The fall in the participation rate in the new hrHPV-based programme is partly due to removing self-inviting GPs from the invitation policy.
- The number of unnecessary referrals could be reduced by implementing HPV16/18 genotyping to the triage algorithm and extending the interval to triage cytology from six to 12 months.

- Women with AGC on cervical cytology have a higher risk of both cervical and other gynaecological cancers than women with squamous-cell abnormalities of comparable severity.
- Knowledge of the hrHPV status of a cytology slide may lead to 'upwards rating' of slides, particularly from NILM to ASC-US.
- Following referral from the old cytology-based programme, both over- and undertreatment occurred.

Recommendations

- HPV genotyping should be implemented to reduce unnecessary referrals. This could be done without adding new technologies to the current programme infrastructure.
- The possibility of re-introducing the use of self-inviting general practices to the programme should be investigated.
- Further research should be conducted to understand why women do not participate in the new hrHPV-based screening programme. Findings from these studies should be used to inform strategies aimed at increasing participation.
- Implementing a colposcopy data collection system should be considered. This information should be linked to the national programme monitoring system to ensure complete monitoring of clinical care following referral from screening.
- Regular monitoring of harms of the screening process should be done by integrating datasets for clinically-reported issues (under- and overtreatment, incidental findings, obstetric complications) and implementing a 'patient experience' survey programme to measure the incidence of self-reported physical and psychological harms following screening.
- The differences in hrHPV positivity between hrHPV self-sampling and clinician-collected screening should be investigated, and this information should be used to inform any future changes to the implementation of self-sampling in the programme.
- Care should be taken to implement changes to the current programme one-by-one. Changing multiple aspects of the programme at once will make it challenging to monitor the programme, as the cause of any changes in outcomes will be more difficult to clarify.
- Short-term monitoring and in-depth evaluation should continue to be made a priority, given the number of key events (second screening round of the new programme, extended screening intervals, entry of partly vaccinated cohorts, re-tendering of tests) that will occur in the coming years.

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Summary

PART 1: GENERAL INTRODUCTION

Human papillomavirus (HPV) is a common sexually transmitted infection. The majority of sexually active individuals are likely to acquire an HPV infection at some time in their lives. There are more than 200 HPV types that infect humans; twelve types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are classified as carcinogenic to humans. These types are referred to as high-risk HPV (hrHPV). A persistent, transforming hrHPV infection can cause changes to the squamous and/or glandular cells of the uterine cervix. These changes can lead to cervical intraepithelial neoplasia (CIN), which are premalignant lesions of the cervix, or to invasive cervical cancer. HPV 16 and 18 are responsible for the majority of cervical cancers, in the range of 70%.

Prevention strategies for cervical cancer aim to reduce incidence of, and mortality from the disease. This thesis focuses on cervical cancer screening in the Netherlands. In the Netherlands, organised cervical cancer screening has been implemented for more than 30 years. Up until 2017, primary cytology-based screening was conducted. Primary hrHPV-based screening has been shown to provide better long-term protection against high-grade CIN lesions and be more cost-effective than cytology-based screening. Based on this evidence, primary hrHPV-based screening replaced cytology-based screening in the Dutch programme in January 2017. Transition to primary hrHPV-based cervical cancer screening involved the following changes:

- Use of hrHPV tests as the primary screening test;
- The introduction of hrHPV self-sampling as an available screening modality;
- Cytology triage after hrHPV positive screening;
- Changes to the triage and referral algorithm;
- Reduced number of screening rounds by offering an extended screening interval of 10 years to women aged 40 and 50 years who are hrHPV negative;
- Consolidation of the screening laboratories from approximately 40 labs to five labs;
- Standardisation of policies and procedures related to invitation.

The studies described in this thesis aimed 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 diagnosis and treatment (**Part 5**).

PART 2: OVERALL SCREENING PROCESS

Following the initial implementation of the primary hrHPV-based programme, 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. In **Chapter 2.1**, we found that the hrHPV-based screening programme resulted in higher screen positivity (9% vs. 5%) and higher direct referral rates (3% vs. 1%) compared to the old cytology-based programme. CIN2+ detection also increased in the hrHPV-based programme from 11 to 14 per 1,000 women screened. However, there was also an increase in unnecessary referrals; this difference was due to an increase in referrals of women with low-grade cytological abnormalities. In the hrHPV-based programme, the hrHPV positivity rate was higher in clinician-collected samples (9.2%) than in self-samples (7.6%). Participation in the hrHPV-based programme was significantly lower than in the cytology-based programme, despite the availability of self-sampling. In **Chapter 2.2,** we found that the cost-effectiveness of the hrHPV-based screening programme is still better than cytology-based screening programme, even when taking into account the lower-than expected participation rates observed in **Chapter 2.1**. Our results found that hrHPV-based primary screening is estimated to decrease cervical cancer mortality (-4%) and incidence (-1%) compared to the old programme. Despite an increase in unnecessary referrals (+172%), hrHPV-based screening still resulted in more QALY's gained (+13%) The hrHPV-based programme was more cost-effective than cytology-based programme, costing 46% less per QALY gained.

PART 3: ATTENDANCE

Cancer screening programmes can only be effective if a high proportion of people within the target population make an informed choice to participate. 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. In **Chapter 3.1**, we investigated the decline in participation further, particularly focusing on whether the decline in participation could be explained by personal characteristics of women or by changes to invitation policies. We found that attendance rates did vary by personal characteristics of women; women who were employed (60.8%), married (62.9%), Dutch (61.2%), in the highest income bracket (63.4%), living in households with four persons (65.3%) and women who were invited by their GP (69.8%) had the highest attendance rates. However, personal characteristics did not explain the decline in attendance rates. By adjusting for the organisation that sent the invitation (i.e. the GP or the screening organisation), the differences in attendance rates were explained in some screening organisations, indicating that removing self-inviting GPs from the programme has had some impact on attendance rates.

PART 4: TEST AND REFERRAL

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 the hrHPV positivity of a cytology smear, there is an upward bias in the rating of the slide. Whether this was likely to happen in the Dutch setting was unknown. Our study, described in **Chapter 4.1**, indicated that the knowledge of hrHPV status has some influence on the rating of cytology slides with low-grade abnormalities. HrHPV positive slides were more likely to be upgraded over the referral threshold at the second review than hrHPV negative slides. If these HPV positive slides, in fact, have no cell abnormalities, then 'upwards ratings' of slides may further contribute to the increased number of unnecessary referral in the new hrHPV-based programme.

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. We modelled potential options in **Chapter 4.2** to study whether HPV genotyping or extending the time to triage cytology would reduce unnecessary referrals without increasing cervical cancer incidence and mortality by more than 2%. We found that the most effective way to reduce unnecessary referrals with the currently available technologies is to implement HPV 16/18 genotyping and to increase the interval to repeat testing from six to 12 months. Specifically, we found a reduction in unnecessary referrals of 45% by adjusting the conditions for referral to 'HPV16+ and ASC-US+' and 'HPV18+/HPV other high-risk types+ and HSIL+', while also extending the interval between the cytology negative primary test and the repeat test from six to 12 months.

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. Results from our study in **Chapter 4.3** suggest that women who have AGC on cervical cytology are at higher risk of both cervical and other gynaecological cancers compared to squamous cell abnormalities of comparable severity. In the hrHPV-based screening programme, women with AGC on cervical cytology after a positive HPV test are directly referred to gynaecologists. As some cancers indicated by an AGC cytology are not related to HPV (e.g. endometrial cancer), the number of AGC screens is likely to reduce over time.

PART 5: DIAGNOSIS AND TREATMENT

Despite the risks associated with overtreatment following cervical screening, there was previously little evidence published about adherence to the published CIN treatment guidelines. If there were gaps between the guidelines and clinician practice in the old screening programme, these could be used to identify areas for potential improvement. In **Chapter 5.1**, we investigated CIN management and treatment following referral from the Dutch cervical cancer screening programme, and whether these trends were in line with the clinical guidelines. Despite guideline recommendations not to treat, we found CIN 1 lesions were treated in just over 25% of cases and approximately 15% of CIN 3 lesions were possibly undertreated. Our analysis suggests that there is room for improvement with compliance to the practice guidelines.

PART 6: GENERAL DISCUSSION

Organised cervical cancer screening programmes need to achieve a careful balance between benefits and harms to maximise effectiveness. In **Chapter 6.1**, we argued that harms of cervical cancer screening should be more regularly quantified as part of monitoring and evaluation of organised cervical cancer screening. Challenges in quantifying indicators due to difficulties with data collection should be addressed to facilitate more comprehensive reporting. In **Chapter 6.2**, the results of Chapters 2.1 to 5.1 were discussed in a broader context. Based on the findings of this thesis, we have drawn eight conclusions and put forward eight recommendations:

Conclusions

- The first results of the new hrHPV-based screening programme were consistent with expectations based on modelling.
- HrHPV-based primary screening results in higher CIN 2+ detection in one round of screening, at the expense of more unnecessary referrals.
- Despite higher than expected hrHPV positivity rates and lower participation, the new hrHPV-based screening programme is more cost-effective than the old cytology-based screening in the Netherlands.
- The fall in the participation rate in the new hrHPV-based programme is partly due to removing self-inviting GPs from the invitation policy.
- The number of unnecessary referrals could be reduced by implementing HPV16/18 genotyping to the triage algorithm and extending the interval to triage cytology from six to 12 months.

- Women with AGC on cervical cytology have a higher risk of both cervical and other gynaecological cancers than women with squamous-cell abnormalities of comparable severity.
- Knowledge of the hrHPV status of a cytology slide may lead to 'upwards rating' of slides, particularly from NILM to ASC-US.
- Following referral from the old cytology-based programme, both over- and undertreatment occurred.

Recommendations

- HPV genotyping should be implemented to reduce unnecessary referrals. This could be done without adding new technologies to the current programme infrastructure.
- The possibility of re-introducing the use of self-inviting general practices to the programme should be investigated.
- Further research should be conducted to understand why women do not participate in the new hrHPV-based screening programme. Findings from these studies should be used to inform strategies aimed at increasing participation.
- Implementing a colposcopy data collection system should be considered. This information should be linked to the national programme monitoring system to ensure complete monitoring of clinical care following referral from screening.
- Regular monitoring of harms of the screening process should be done by integrating datasets for clinically-reported issues (under- and overtreatment, incidental findings, obstetric complications) and implementing a 'patient experience' survey programme to measure the incidence of self-reported physical and psychological harms following screening.
- The differences in hrHPV positivity between hrHPV self-sampling and clinician-collected screening should be investigated, and this information should be used to inform any future changes to the implementation of self-sampling in the programme.
- Care should be taken to implement changes to the current programme one-by-one. Changing multiple aspects of the programme at once will make it challenging to monitor the programme, as the cause of any changes in outcomes will be more difficult to clarify.
- Short-term monitoring and in-depth evaluation should continue to be made a priority, given the number of key events (second screening round of the new programme, extended screening intervals, entry of partly vaccinated cohorts, re-tendering of tests) that will occur in the coming years.

Samenvatting

DEEL 1: ALGEMENE INLEIDING

Humaan papillomavirus (HPV) infectie is een veel voorkomende aandoening, die seksueel overdraagbaar is. De meeste seksueel actieve mensen lopen op enig moment in hun leven waarschijnlijk een HPV-infectie op. Er zijn meer dan 200 HPV-typen die mensen infecterenwaarvan twaalf typen (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) geclassificeerd zijn als kankerverwekkend voor de mens. Deze typen worden hoog-risico HPV (hrHPV) genoemd. Een aanhoudende hrHPV-infectie kan veranderingen in de plaveisel- en/of glandulaire cellen van de baarmoederhals veroorzaken. Deze veranderingen kunnen leiden tot cervicale intra-epitheliale neoplasie (CIN), dit zijn premaligne laesies van de baarmoederhals, of tot invasieve baarmoederhalskanker. HPV 16 en 18 zijn verantwoordelijk voor de meeste vormen van baarmoederhalskanker, ongeveer 70%.

Preventiestrategieën voor baarmoederhalskanker zijn gericht op het verminderen van de incidentie van en de mortaliteit door de ziekte. Dit proefschrift richt zich op screening op baarmoederhalskanker in Nederland. In Nederland wordt al meer dan 30 jaar georganiseerde baarmoederhalskankerscreening uitgevoerd. Tot 2017 werd screening op basis van cytologie uitgevoerd. Het is aangetoond dat primaire hrHPV-gebaseerde screening een betere langdurige bescherming biedt tegen hooggradige CIN-laesies en kosteneffectiever is dan screening op basis van cytologie. Daarom heeft primaire hrHPV-screening in januari 2017 de cytologie-gebaseerde screening vervangen in het Nederlandse bevolkingsonderzoek. De overgang naar primaire hrHPV-gebaseerde screening op baarmoederhalskanker bracht de volgende veranderingen met zich mee:

- Gebruik van hrHPV-testen als primaire screeningstest;
- De introductie van de zelfafnameset als mogelijke screeningsmodaliteit;
- Cytologietriage na hrHPV-positieve screening;
- Veranderingen in het triage- en verwijzingsalgoritme;
- Reductie van het aantal screeningsrondes door een verlengd screeningsinterval van 10 jaar aan te bieden aan vrouwen van 40 en 50 jaar die hrHPV-negatief zijn;
- Reductie in het aantal screeningslaboratoria van circa 40 labs tot vijf labs;
- Standaardisatie uitnodigingsbeleid en procedures.

De studies beschreven in dit proefschrift hadden tot doel het Nederlandse bevolkingsonderzoek naar baarmoederhalskanker als geheel te evalueren (**deel 2**), evenals elke fase van het screeningsproces: opkomst (**deel 3**), test en verwijzing (**deel 4**) en diagnose en behandeling (**deel 5**).

DEEL 2: ALGEHEEL SCREENINGPROCES

Na de implementatie van het primaire hrHPV-programma was het van cruciaal belang om te begrijpen of het programma presteerde zoals verwacht en hoe het nieuwe screeningsprogramma presteerde in vergelijking met het oude op cytologie gebaseerde screeningsprogramma. In **Hoofdstuk 2.1** ontdekten we dat het hrHPV-gebaseerde screeningsprogramma resulteerde in hogere screentest-positiviteit (9% vs. 5%) en hogere directe verwijzingspercentages (3% vs. 1%) in vergelijking met het oude op cytologie gebaseerde programma. De CIN2+ detectie nam ook toe in het op hrHPV gebaseerde programma, van 11 naar 14 per 1.000 gescreende vrouwen. Er was echter ook een toename van onnodige verwijzingen; dit verschil was vooral een toename van het aantal verwijzingen van vrouwen met laaggradige cytologische afwijkingen. In het hrHPV-programma was het hrHPV-positiviteitspercentage hoger voor uitstrijkjes (9,2%) dan voor de zelfafnameset (7,6%). De deelname aan het hrHPV-programma was significant lager dan aan het cytologie-programma, ondanks de beschikbaarheid van de zelfafnameset. In **Hoofdstuk 2.2** ontdekten we dat de kosteneffectiviteit van het hrHPV-gebaseerde screeningprogramma nog steeds beter is dan het op cytologie gebaseerde programma, zelfs als we rekening houden met de lager dan verwachte deelnamegraad die we in **Hoofdstuk 2.1** vonden. Onze resultaten toonden aan dat op hrHPV gebaseerde screening naar schatting de sterfte aan baarmoederhalskanker (-4%) en incidentie (-1%) verlaagt in vergelijking met het oude programma. Ondanks een toename van onnodige verwijzingen (+ 172%), leidde screening op basis van hrHPV nog steeds tot meer QALY's (+ 13%). Het op hrHPV gebaseerde programma was kosteneffectiever dan het op cytologie gebaseerde programma en kostte 46% minder per gewonnen QALY.

DEEL 3: OPKOMST

Kankerscreeningsprogramma's kunnen alleen effectief zijn als een groot deel van de mensen binnen de doelgroep een geïnformeerde keuze maakt om deel te nemen. Monitoring liet zien dat de deelname in het nieuwe hrHPV-programma lager was dan bij het oude op cytologie gebaseerde programma. Dit was onverwacht, zeker gezien de beschikbaarheid van zelfafnametests. In **Hoofdstuk 3.1** onderzochten we de afname van de deelname verder, in het bijzonder of de afname in deelname kan worden verklaard door persoonlijke kenmerken van vrouwen of door veranderingen in het uitnodigingsbeleid. We ontdekten dat de opkomstpercentages verschilden naargelang de persoonlijke kenmerken van vrouwen; vrouwen die werken (60,8% deelname), gehuwd zijn (62,9%), Nederlands zijn (61,2%), tot de hoogste inkomensgroep behoren (63,4%), woonachtig zijn in huishoudens met vier personen (65,3%) en vrouwen die waren uitgenodigd door

hun huisarts (69,8%) hadden de hoogste opkomstpercentages. Persoonlijke kenmerken verklaarden echter niet de daling van de opkomstcijfers. Door te corrigeren voor de organisatie die de uitnodiging heeft gestuurd (de huisarts of de screeningsorganisatie), werden de verschillen in opkomstpercentages bij sommige screeningsorganisaties verklaard, wat aangeeft dat het verwijderen van zelfuitnodigende huisartsen uit het programma enige impact heeft gehad op de opkomst.

DEEL 4: TEST EN VERWIJZING

In het nieuwe hrHPV-gebaseerde screeningsprogramma zijn alle cytologie testen die door cytologisch analist en pathologen worden onderzocht hrHPV-positief. Eerder onderzoek heeft aangetoond dat wanneer de professional die het cytologie preparaat beoordeelt zich bewust is van de hrHPV-positiviteit, deze het preparaat eerder als niet-normaal aanduidt. Het was niet bekend of dit in de Nederlandse setting ook zou gebeuren. Onze studie, beschreven in **Hoofdstuk 4.1**, toonde aan dat de kennis van de hrHPV-status enige invloed heeft op de beoordeling van cytologie preparaten met laaggradige afwijkingen. HrHPV-positieve cytologie preparaten werden bij de tweede beoordeling (waarbij de HPV status bekend was) vaker opgewaardeerd boven de verwijzingsdrempel dan hrHPV-negatieve cytologie preparaten. Als deze HPV-positieve vrouwen geen baarmoederhalsafwijkingen hebben, kunnen 'opgewaardeerde beoordelingen' van testen verder bijdragen aan het toegenomen aantal onnodige verwijzingen in het nieuwe op hrHPV gebaseerde programma.

Gezien het grote aantal onnodige verwijzingen van het nieuwe op hrHPV gebaseerde screeningsprogramma, is optimalisatie van het triage-algoritme nodig om mogelijke schade door onnodige verwijzingen te minimaliseren. In **Hoofdstuk 4.2** hebben we mogelijke opties gemodelleerd om te onderzoeken of HPV-genotypering of het verlengen van de tijd tot triage cytologie onnodige verwijzingen zou verminderen zonder de incidentie en mortaliteit van baarmoederhalskanker met meer dan 2% te verhogen. We ontdekten dat, met de momenteel beschikbare technologieen, is om HPV 16/18 genotypering te implementeren en het interval voor herhaalde tests te verlengen van zes naar twaalf maanden, de meest effectieve manier om onnodige verwijzingen te verminderen. Concreet vonden we een vermindering van onnodige verwijzingen met 45% door de voorwaarden voor verwijzing naar 'HPV16 + en ASC-US +' en 'HPV18 + / HPV andere hoogrisicotypes + en HSIL +' aan te passen, en tegelijkertijd ook het interval tussen de cytologie-negatieve primaire test en de herhalingstest van zes naar twaalf maanden te verlengen.

Atypische glandulaire cellen (AGC) zijn een zeldzame maar risicovolle cytologische afwijking. Er zijn aanwijzingen dat vrouwen met AGC een hoger risico lopen op

baarmoederhalskanker en andere gynaecologische kankers. In het oude op cytologie gebaseerde programma kregen sommige vrouwen met AGC-uitstrijkjes, afhankelijk van de ernst van de afwijking, het advies om de cytologie-test te herhalen in plaats van een directe verwijzing. Het risico op een kankerdiagnose bij deze groepen is niet eerder met Nederlandse gegevens onderzocht. Resultaten van onze studie in **Hoofdstuk 4.3** laat zien dat vrouwen met AGC op cervicale cytologie een hoger risico lopen op zowel baarmoederhalskanker als andere gynaecologische kankers in vergelijking met plaveiselcelafwijkingen van vergelijkbare ernst. In het op hrHPV gebaseerde screeningsprogramma worden vrouwen met AGC op cervicale cytologie na een positieve HPV-test direct doorverwezen naar gynaecologen. Echter, aangezien sommige kankers die door een AGC-cytologie worden aangetoond niet gerelateerd zijn aan HPV (bijv. endometrium carcinoom), zal het aantal vrouwen met een AGC uitslag dalen.

DEEL 5: DIAGNOSE EN BEHANDELING

Het is belangrijk dat de CIN-behandelrichtlijnen nageleefd worden, om de risico's van overbehandeling na cervicale screening te verminderen. In het verleden was er echter weinig bewijs voor het naleven van deze richtlijnen. Als er verschillen zijn tussen de richtlijnen en de huidige praktijk van de arts, zouden deze kunnen worden gebruikt om te identificeren waar verbeteringen mogelijk zijn. In **Hoofdstuk 5.1** onderzochten we CIN management en behandeling na verwijzing vanuit het Nederlandse bevolkingsonderzoek baarmoederhalskanker, en of deze trends overeenkwamen met de klinische richtlijnen. Ondanks aanbevelingen om niet te behandelen, vonden we dat CIN 1-laesies in iets meer dan 25% van de gevallen werden behandeld en dat ongeveer 15% van de CIN 3-laesies niet behandeld werd. Onze analyse suggereert dat er enige ruimte voor verbetering is bij het naleven van de praktijkrichtlijnen, wat belangrijk is om de nadelen van baarmoederhalskankerscreening te verlagen.

DEEL 6: ALGEMENE DISCUSSIE

Bij georganiseerde screeningprogramma's voor baarmoederhalskanker moet een zorgvuldige balans worden gevonden tussen voordelen en nadelen om de effectiviteit te maximaliseren. In **Hoofdstuk 6.1** hebben we beargumenteerd dat de schade van baarmoederhalskankerscreening regelmatiger moet worden gekwantificeerd als onderdeel van monitoring en evaluatie van georganiseerde baarmoederhalskankerscreening. Het gebrek aan gegevens moeten worden aangepakt om een beter inzicht in de nadelen van screening te verkrijgen. In **Hoofdstuk 6.2** worden de resultaten van de Hoofdstuk-

ken 2.1 t/m 5.1 in een bredere context besproken. Op basis van de bevindingen van dit proefschrift trekken we acht conclusies en doen we acht aanbevelingen:

Conclusies

- De eerste resultaten van het nieuwe op hrHPV gebaseerde screeningsprogramma waren in overeenstemming met de verwachtingen op basis van modellen.
- Op hrHPV gebaseerde primaire screening resulteert in hogere CIN 2+ detectie in de eerste ronde van screening, ten koste van meer onnodige verwijzingen.
- Ondanks hoger dan verwachte hrHPV-positiviteitspercentages en lagere deelname, is het nieuwe op hrHPV gebaseerde screeningsprogramma kosteneffectiever dan de oude op cytologie gebaseerde screening in Nederland.
- De daling van de deelname aan het nieuwe hrHPV-programma wordt mede veroorzaakt door het verwijderen van zelfuitnodigende huisartsen uit het uitnodigingsbeleid.
- Het aantal onnodige verwijzingen zou kunnen worden verminderd door HPV16 / 18-genotypering in het triage-algoritme te implementeren en het interval naar triagecytologie te verlengen van zes naar twaalf maanden.
- Vrouwen met AGC op cervicale cytologie hebben een hoger risico op zowel cervicale als andere gynaecologische kankers dan vrouwen met plaveiselcelafwijkingen van vergelijkbare ernst.
- Kennis van de hrHPV-status van een cytologie preparaat kan leiden tot het vaker beoordelen van een test als niet-normaal, met name van NILM tot ASC-US.
- Na verwijzing vanuit het oude screeningsprogramma trad zowel over- als onderbehandeling op.

Aanbevelingen

- HPV-genotypering moet worden geïmplementeerd om onnodige verwijzingen te verminderen. Dit zou kunnen worden gedaan zonder nieuwe technologieën toe te voegen aan de huidige programma-infrastructuur.
- De mogelijkheid om het gebruik van huisartsenpraktijken die zelf uitnodigen opnieuw in het programma op te nemen, moet worden onderzocht.
- Er moet verder onderzoek worden gedaan om te begrijpen waarom vrouwen niet deelnemen aan het nieuwe op hrHPV gebaseerde screeningsprogramma. De bevindingen van deze onderzoeken moeten worden gebruikt om strategieën te ontwikkelen die gericht zijn op het vergroten van de deelname.
- Het implementeren van een dataverzamelingssysteem voor colposcopiegegevens moet worden overwogen. Deze informatie moet worden gekoppeld aan het monitoringsysteem van het nationale programma om volledige monitoring van de klinische zorg na doorverwijzing door screening te garanderen.

- Regelmatige monitoring van de schade van het screeningproces moet worden gedaan door datasets voor klinische problemen (onder- en overbehandeling, incidentele bevindingen, obstetrische complicaties) te integreren en een patiëntervaring-onderzoeksprogramma te implementeren om de incidentie van zelfgerapporteerde lichamelijke en psychische schade na screening te meten.
- De verschillen in hrHPV-positiviteit tussen de zelfafnameset en het uitstrijkje moeten worden onderzocht, en deze informatie moet worden gebruikt als input voor toekomstige wijzigingen in de implementatie van zelfafname in het programma.
- Wijzigingen in het huidige programma moeten één voor één worden doorgevoerd. Als meerdere aspecten van het programma tegelijk wijzigen dan wordt het een uitdaging om het programma te monitoren, omdat de oorzaak van eventuele veranderingen in de uitkomsten moeilijker te achterhalen is.
- Monitoring op korte termijn en diepgaande evaluatie moeten een prioriteit blijven, gezien het aantal belangrijke gebeurtenissen (tweede screeningsronde van het nieuwe programma, verlengde screeningsintervallen, deelname van gedeeltelijk gevaccineerde cohorten, opnieuw aanbesteden van tests) dat in de komende jaren zal plaatsvinden.

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Chapter under embargo

About the Author

PhD Portfolio
Publication list
Curriculum vitae

PhD PORTFOLIO

Summary of PhD training and teaching

PhD Student: Clare Alexandra Aitken
PhD Period: 2016 – 2020
Erasmus MC department: Public Health
Promotors: Prof. dr. H.J. de Koning and Prof. dr. F.J. van Kemenade
Co-promotor: dr. I.M.C.M. de Kok

PhD Training	Year	Workload	
		ECTS	Hours
Training and education			
MSc in Health Sciences, specialisation Clinical Epidemiology (grade: 8.24)	2016 - 2019		
Principles of Research in Medicine and Epidemiology	2016	0.7	
Erasmus Summer Lectures: Advances in Epidemiological Analysis	2016	0.7	
Study Design (grade: 8.3)	2016	4.3	
Clinical Trials	2016	0.7	
Methodological Issues in Epidemiological Research (grade: 8.9)	2016	1.4	
Women's Health	2017	1.4	
Planning and Evaluation of Screening (grade: 7.5)	2017	1.4	
Quality of Life Measurement	2017	0.9	
Maternal and Child Health	2017	0.9	
Health Services: Research and Practice	2017	0.9	
Value-based Healthcare	2017	0.7	
Biostatistical Methods II: Classical Regression Models (grade: 9.1)	2017	4.3	
Fundamentals of Medical Decision Making	2018	0.7	
Advanced Topics in Decision-making in Medicine (grade: 8.0)	2018	2.4	
Health Economics	2018	0.7	
The Practice of Epidemiologic Analysis	2018	0.7	
Clinical Translation of Epidemiology (grade: 8.8)	2018	2.0	
Clinical Epidemiology (grade: 9.1)	2018	3.7	
Research Project (grade: 8.0)	2019	32.6	
Biostatistical Methods I: Basic Principles (exempt)		4.3	
English Language (exempt)		1.4	
Introduction to Medical Writing (exempt)		2.0	
Methods of Public Health Research (exempt)		0.7	
Language courses, Erasmus University Rotterdam	2017 – 2019		
Dutch A2.1 (grade: 8.8)	2017	2.5	
Dutch A2.2 (grade: 8.9)	2017	2.5	

PhD Training	Year	Workload	
		ECTS	Hours
Dutch B1.1 (grade: 8.5)	2017	2.5	
Dutch B1.2 (grade: 8.9)	2018	2.5	
Dutch B2.1 (grade: 7.8)	2018	2.5	
Dutch B2.2 (grade: pass)	2019	2.5	
Dutch language diplomas			
Inburgeringsdiploma *Dutch integration exams* *CEFR level: A2*	2018		40 hours
Staatsexamen Nederlands als tweede taal Programma I *State exams: Diploma Dutch as a second language, Programme I* *CEFR level: B1*	2018		20 hours
Other courses			
Scientific Integrity	2016	0.3	
Time Management	2016		4 hours
Biomedical English Writing and Communication	2018	3.0	
Didactische vaardigheden VO onderwijs	2018		4 hours
Presentations			
VO meetings, Department of Public Health	2016 – 2020		8 hours
Poster, Cancer Research UK Early Diagnosis Conference	2017	0.3	
Poster, IPVC 2017	2017	0.3	
Oral presentation, ICSN 2017	2017	0.6	
Poster, European Congress of Pathology 2017 (presented by co-author)	2017	0.3	
Oral presentation, Eurogin 2017	2017	0.6	
Invited speaker, NIHES PhD Open Evening	2018	0.6	
Oral presentation, IPVC 2018	2018	0.6	
Poster, IPVC 2018	2018	0.3	
Oral presentation, Eurogin 2018	2018	0.6	
Invited speaker, RIVM Bevolkingsonderzoek baarmoederhalskanker Expertmeeting	2019	0.6	
Poster, IPV 2020 (presented by co-author)	2020	0.3	
National and international conferences			
Cancer Research UK Early Diagnosis Conference *London: 23 – 24 February 2017*	2017		16 hours
IPV 2017 *Cape Town: 28 February – 4 March 2017*	2017		36 hours
ICSN 2017 *Bethesda: 19 – 21 June 2017*	2017		24 hours
Eurogin 2017 *Amsterdam: 8 – 11 October 2017*	2017		28 hours

PhD Portfolio

PhD Training	Year	Workload	
		ECTS	Hours
RIVM Early Diagnosis Conference *Utrecht: 9 November 2017*	2017		4 hours
IPV 2018 *Sydney: 2 – 6 October 2018*	2018		36 hours
Eurogin 2018 *Lisbon: 2 – 5 December 2018*	2018		28 hours
RIVM HPV Research Day *Bilthoven, 24 September 2019*	2019		8 hours
Teaching and supervising			
Lecturer, Monitoring and evaluation of screening, MSc Programme: Planning and Evaluation of Screening (NIHES)	2018, 2020		12 hours
Supervision, MSc intern, April –July 2018	2018		20 hours
Supervision, Bachelor Medicine Community Projects	2020		20 hours
Review activities			
Peer reviewer, BMJ Open, January 2020	2020		2 hours
Peer reviewer, PLoS One, February 2020	2020		2 hours
Peer reviewer, BMJ Open, March 2020	2020		3 hours
Peer reviewer, BMC Public Health, April 2020	2020		2 hours
Other activities			
Mentee – Mentoring programme MGZ	2017		5 hours
Member – NIHES Student Panel	2017-2018		20 hours
Member – Erasmus MC Research Masters Education Committee	2017-2018		20 hours
MGZ Activities Report Editorial committee	2018		20 hours
Organising committee – ICSN 2019	2018-2019		20 hours

PUBLICATION LIST

In this thesis

C.A. Aitken, I.M.C.M. de Kok. Striking a balance: Complete evaluation of organised cervical cancer screening programmes is not possible until harms of screening are better quantified. *Submitted*.

C.A. Aitken*, S. Kaljouw*, A.G. Siebers, M. Bron, A. Morssink, F.J. van Kemenade, I.M.C.M de Kok. Investigating the decrease in participation in the Dutch cervical cancer screening programme: the role of personal and organisational characteristics. *Accepted for publication by Preventive Medicine Reports*.

C.A. Aitken, E.E.L. Jansen, A.G. Siebers, A L.D. van Haaften-de Jong, F.J. van Kemenade, I.M.C.M. de Kok. Risk of gynaecological cancer after atypical glandular cells found on cervical cytology: a population-based cohort study. *Accepted for publication by Cancer Epidemiology, Biomarkers & Prevention*.

S. Kaljouw, E.E.L. Jansen, **C.A. Aitken**, L.M. Harrijvan, S.K. Naber, I.M.C.M. de Kok. Reducing unnecessary referrals for colposcopy in hrHPV-positive women within the Dutch cervical cancer screening programme: a modelling study. *Gynecologic Oncology, 2021, Online ahead of print*.

E.E.L. Jansen, S.K. Naber, **C.A. Aitken**, H.J. de Koning, M. van Ballegooijen, I.M.C.M. de Kok. Cost-effectiveness of HPV-based cervical screening based on first year results in the Netherlands : a modelling study. *BJOG, 2021;128(3):573-582. doi: 10.1111/1471-0528.16400*.

C.A. Aitken, H.M.E. van Agt, A.G. Siebers, F.J. van Kemenade, H.G.M. Niesters, W.J.G Melchers, J.E.M. Vedder, R. Schuurman, A.J.C. van den Brule, H.C. van der Linden, J.W.J. Hinrichs, A. Molijn, K.J. Hoogduin, B.M. van Hemel, I.M.C.M de Kok. Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. *BMC Medicine 2019;17(1):228*.

C.A. Aitken, K.M. Holtzer-Goor, A. Uyterlinde, A.J.C. van den Brule, H.C. van der Linden, C.J. Huijsmans, I.M.C.M. de Kok, F.J. van Kemenade. The impact of knowledge of HPV positivity on cytology triage in primary high-risk HPV screening. *J Med Screen 2019;26(4):221-24*.

C.A. Aitken, A.G. Siebers, S.M. Matthijsse, E.E.L. Jansen, R.L.M. Bekkers, J.H. Becker, B. Ter Harmsel, J.W.R Roovers, F.J. van Kemenade, I.M.C.M. de Kok. Management and treatment of cervical intraepithelial neoplasia in the Netherlands after referral for colposcopy. *Acta Obstet Gynecol Scand 2019;98(6):737-46*.

Other publications

R.L. Goetgebuer, J.E. Kreijne, **C.A. Aitken**, G. Dijkstra, F. Hoentjen, N.K. de Boer, B. Oldenburg, A.E. van der Meulen, C.I.J. Ponsioen, M.J. Pierik, F.J. van Kemenade, I.M.C.M. de Kok,

A.G. Siebers, J. Manniën, C.J. van der Woude, A.C. de Vries. Increased risk of high-grade cervical neoplasia in women with inflammatory bowel disease: a case-controlled cohort study. *Submitted.*

L.M. Kregting, N.T. van Ravesteyn, W. Spijker, T. Dierks, **C.A. Aitken**, H.A. Geuzinge, I.J. Korfage. Effects of a leaflet on breast cancer screening knowledge, explicit attitudes, and implicit associations. *Patient Educ Couns 2020;103(12):2499-2507.*

A.L Todd, **C.A. Aitken**, J. Boyd, M. Porter. Testing a health research instrument to develop a state-wide survey on maternity care. *Public Health Research & Practice 2016;26(1):e2611609.*

** These authors contributed equally to this study.*

Chapter under embargo