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Chapter 10

General discussion

HPV-based cervical screening: rationale, expectations and future perspectives of the new Dutch screening programme

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Abstract

Based on scientific data showing that HPV testing provides better protection against cervical precancer and cancer than cytology, in 2011 the Dutch Health Council advised the Minister of Welfare, Health and Sports to replace cytology by HPV testing in the Dutch population-based screening programme. After a successful evaluation of the feasibility of HPV-based screening in 2014, primary HPV testing for cervical screening was implemented in 2017. The Netherlands has been one of the first countries worldwide to implement nationwide HPV-based screening and its experience with the new programme is therefore followed with great interest. In this manuscript, we present an overview of the studies that were instrumental in the choice of HPV assay and triage strategy, the adjustment of screening starting and exit ages and intervals, and the implementation of HPV self-sampling. Finally, we review the cost-effectiveness of the proposed new screening algorithm and we explore future perspectives. The rationale behind the new Dutch HPV-based screening programme, which is based on risk management, could serve as a guidance to other countries that are planning to implement HPV-based screening in the near future.

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1. Introduction

Since the lead time between cervical intraepithelial neoplasia (CIN) to cervical cancer is relatively long, and since CIN lesions can be detected and treated effectively, cervical cancer is a preventable disease.¹ Cervical screening programmes aim to detect and treat cervical precancer in order to prevent the development of cervical cancer. Several countries, including Australia and New Zealand, the Nordic countries, the United Kingdom, Italy, and the Netherlands, have nationwide or regionally organized cervical screening programmes.² In the Netherlands, regional screening was established in the early seventies and nationwide organized screening was implemented in 1994.³

Since the introduction of cervical screening in the seventies, screening programmes have been based on cytomorphological evaluation of cells exfoliated from the cervical surface (i.e. cervical cytology).⁴ However, cervical cytology has two main limitations as a primary screening test: its moderate sensitivity (50–70%) for detection of high-grade CIN and its limited reproducibility due to its subjective character.^{5,6} Even in countries with adequate cytology quality assurance systems these limitations remain of great influence on the performance of screening programmes.^{7,9} Nevertheless, cytology-based screening programmes have been effective in decreasing cervical cancer mortality and incidence by 50–80% as compared to the pre-screening era.^{5,10-14}

In recent years, the decrease in cervical cancer incidence seems to have levelled off.¹⁵⁻¹⁸ This indicates that the maximum impact of cytology-based screening programmes has been reached. Consequently, a change regarding the primary screening test was needed to facilitate further reduction in cervical cancer incidence. Persistent infection with high-risk human papillomavirus (HPV) is the main cause for cervical cancer development, and this knowledge has given rise to the development of HPV assays for use in cervical screening.¹⁹⁻²² Clinical studies have evaluated the use of HPV testing for cervical screening. Four European randomised trials (Swedescreen, POBASCAM, ARTISTIC and NTCC) showed that HPV testing significantly reduced the detection of cervical precancer and cancer (CIN3+) at the second screen with 47–66% as compared to conventional cytology.²³⁻²⁷ Based on these data and data from North-American countries^{28,29}, in 2011 the Dutch Health Council advised the Ministry of Health to replace cytology by HPV testing for cervical screening.³⁰

Most HPV infections clear spontaneously. Only a small proportion of HPV infections persist and, eventually, may develop into CIN3+.^{20,31} Adjunct triage testing of HPV-positive women is required to identify women with clinically relevant cervical

disease. Various strategies have been proposed for triage of HPV-positive women. The clinical performance of these strategies varies between studies and currently there is no consensus on the optimal management of HPV-positive women.³²⁻³⁷ In addition to establishing the most suitable triage strategy, decisions about the HPV assay, adjustment of screening starting and exit ages and intervals, and the implementation of HPV self-sampling have to be made prior to the implementation of HPV-based screening, and finally, a cost-effectiveness evaluation of the proposed new screening algorithms should be conducted.

The Netherlands is one of the first countries worldwide to implement nationwide HPV-based screening, and its experience with the new programme is therefore followed with great interest. In this manuscript we shortly discuss the organisational structure of the new Dutch cervical screening programme and the scientific evidence that contributed to the design of the programme.

2. Organisation of screening in the Netherlands

The Ministry of Health (MOH) provides the budget for screening and delegates the implementation of a screening programme to the National Institute of Public Health and Environment (RIVM). The RIVM directs and monitors the implementation of screening, while the regional screening organisations are responsible for the practical execution of the screening programme.

The Dutch Health Council advises the MOH about major changes regarding screening. The Dutch Health Council is an independent organization in which experts of the field are appointed. If the Health Council issues a positive advice regarding a new development, the MOH takes the final decision whether to implement the new development or not. If it is decided that the development should be implemented, the RIVM is responsible for implementation and monitoring. To obtain support from health care professionals, the RIVM appoints a programme committee with representatives of the associations of professionals (e.g. general practitioners, pathologists, gynecologists, technicians, etc.) that advises the RIVM and the regional screening organisations on the practical organisation and implementation of the new screening programme.

3. HPV assays suitable for use in HPV-based cervical screening

HPV assays should have an optimal balance between clinical sensitivity and specificity for detection of CIN3+.^{31,38} An HPV assay with limited sensitivity may fail to detect clinically relevant HPV infections, while the use of a very sensitive HPV assay will have limited clinical specificity, causing unnecessary referrals and excessive follow-up of test-positive women. In the four European randomised clinical trials (Swedescreen, POBASCAM, ARTISTIC and NTCC) that demonstrated efficacy of HPV-testing, the GP5+/6+ PCR enzyme immunoassay (EIA) and the Hybrid Capture-2 (HC2) assays were used.²³⁻²⁷ Consequently, an international team of experts formulated equivalence criteria in which data from these trials were used to set a standard for test performance and characteristics (Table 1).³⁹ Only assays that have been proven to fulfil these criteria can be considered as clinically validated and can be used for cervical screening purposes.

Table 1. Requirements for HPV assays in primary cervical screening (adapted from Meijer et al. *Int J Cancer* 2009).

1	Clinical sensitivity for CIN2+ of $\geq 90\%$ as compared to the comparator assay*
2	Clinical specificity for CIN2+ of $\geq 98\%$ as compared to the comparator assay*
3	Intra- and inter-laboratory reproducibility with a lower confidence bound $\geq 87\%$

* Comparator assay = HC2 or GP5+/6+ PCR EIA.

CIN2+ = cervical intraepithelial neoplasia grade 2 or worse.

In 2015, a systematic review was conducted in which seven HPV assays were identified to fully match the equivalence criteria: HC2 (Qiagen, Gaithersburg, MD, USA), GP5+/6+ PCR-EIA (Labo Biomedical Products B.V., Rijswijk, The Netherlands), Abbott RT hrHPV test (Abbott, Wiesbaden, Germany), cobas 4800 HPV test (Roche Molecular System, Pleasanton, CA, USA), PapilloCheck HPV-Screening test (Greiner Bio-One, Frickenhausen, Germany), BD Onclarity HPV assay (BD Diagnostics, Sparks, MD, USA) and HPV-Risk assay (Self-Screen B.V., Amsterdam, The Netherlands).^{40,41} Accordingly, these assays are considered to be acceptable for use in HPV-based cervical screening. After a tendering procedure in which several assays were compared with respect to performance, quality and price criteria, a five year contract was awarded to Roche for the use of the cobas 4800 HPV test as the primary test in the Dutch cervical screening programme (Table 2).

Table 2. Overview of the changes regarding the previous, cytology-based and the new, HPV-based screening programme in the Netherlands.

	Previous cervical screening programme (until December 2016)	New cervical screening programme (started January 2017)
Primary screening test	Cytology on cervical scrape	HPV test on cervical scrape
Triage test	In case of BMD cytology: repeat cytology (and optional HPV test) after 6 and 18 months	In case of HPV-positive test result: cytology and repeat cytology after 6 months
First screen	At age 30	At age 30
Last screen	At age 60	- At age 60; - If HPV-positive at age 60: repeat at age 65
Screening intervals	5 years	- 5 years - If HPV-negative at age 40 or 50: interval 10 years
Self-sampling	n/a	Self-sampling for non-responders on request
Estimated cervical cancer incidence and mortality	Incidence: ~700 Mortality: ~210	Incidence: ~600 Mortality: ~175
Estimated costs	~€45 million per year	- ~€50 million per year in the first five years after implementation; - ~€40 million per year after the first five years

BMD = borderline or mild dyskaryosis; n/a = not applicable.

4. Strategies for triage of HPV-positive women

4.1. Triage strategy requirements

Various strategies have been proposed for triage of HPV-positive women, but currently there is no consensus on the optimal management of HPV-positive women. A triage strategy should balance safety, in terms of CIN3+ detection, and screening-related burden, in terms of colposcopy referrals. The most optimal balance may differ from country to country, depending on locally accepted risks and available resources.⁴²

In studies evaluating the clinical performance of triage strategies, safety and screening-related burden are represented by the negative predictive value (NPV) and the positive predictive value (PPV), respectively. NPV and PPV thresholds are used to evaluate the acceptability of triage strategies. As referral of women for colposcopy is done on the basis of short-term CIN3+ risks, thresholds are based on results from cross-sectional studies with two to three year follow-up results.

An accepted safety threshold is a minimal CIN3+ NPV of 98%, which translates into a maximum CIN3+ risk of 2% within the subsequent two to three years.^{32,33,43} This NPV threshold is based on the CIN3+ risk among women with borderline or mild dyskaryosis (BMD) cytology (comparable to atypical squamous cells of undetermined significance (ASC-US) or low grade squamous intraepithelial lesion (LSIL) in the Bethesda classification) at baseline and normal cytology at 6 and 18 months follow-up. In the previous Dutch cytology-based screening programme, these women had a CIN3+ risk of 1.2% and were referred back to routine screening.^{44,45} Consequently, a short-term CIN3+ risk threshold of 2% was used, indicating that regular five-yearly screening intervals could be maintained for women with a CIN3+ risk of 2% or lower (Figure 1).

The PPV of a triage strategy greatly impacts colposcopy referral rates and the associated costs. Within the USA, women with a short-term CIN3+ risk, or equivalently, a PPV of 10% or higher are directly referred for colposcopy. Within the Netherlands, a minimal CIN3+ PPV of 20% has been used based on the PPV of ~20% in the previous cytology based screening programme. This means that only women with a short-term CIN3+ risk of 20% or higher are directly referred for colposcopy (Figure 1).^{32,33}

Cross-sectional studies with short-term (2-3 year) CIN3+ risks:

- Required to evaluate the acceptability of triage strategies
- Accepted short-term CIN3+ risks thresholds in the Netherlands:
 - <2% maintain regular screening intervals
 - 2-20% follow-up within 6-18 months required
 - >20% direct referral for colposcopy

Follow-up studies with long-term (>3 years) CIN3+ risks:

- Required to evaluate the extension of screening intervals

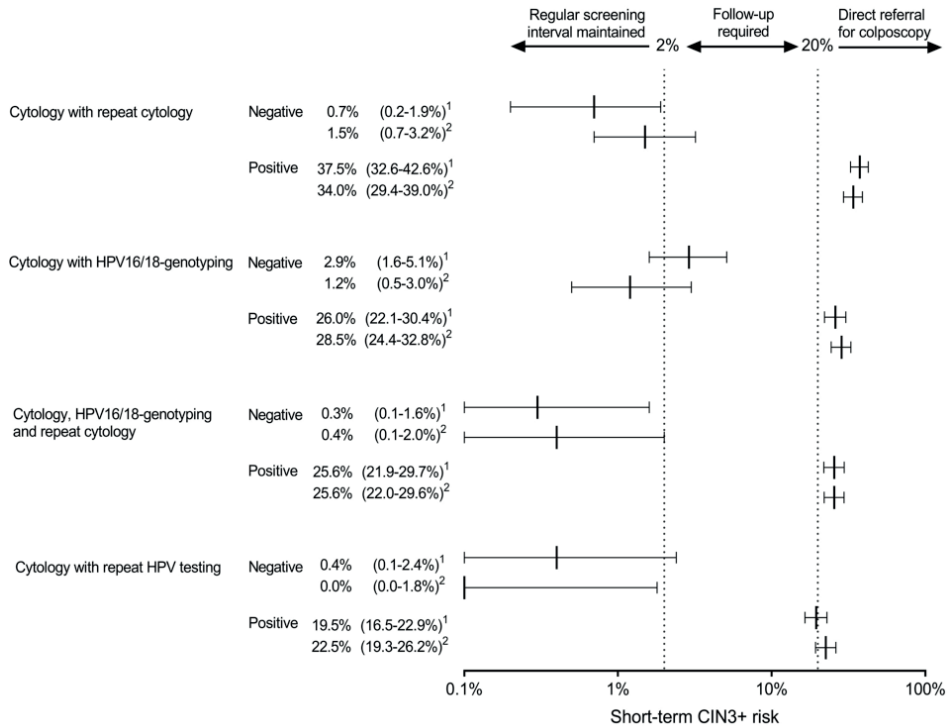


Figure 1. Overview of the short-term CIN3+ risk estimates of various triage strategies within the post-hoc analyses performed in the VUSA-Screen and POBASCAM cohorts (adapted from ¹VUSA-Screen cohort [Rijkaart et al. Int J Cancer 2012] and ²POBASCAM cohort [Dijkstra et al. Cancer Epidemiol Biomark Prev 2014])

CIN3+ = cervical intraepithelial neoplasia grade 3 or worse.

4.2. Currently accepted triage strategies

4.2.1. Cytology with repeat cytology

Rijkaart et al. evaluated short-term CIN3+ risks within the Dutch VUSA-Screen cohort study (25,871 women screened with cytology and HPV co-testing).^{25,44,46} Results showed that HPV-positive women had a short-term CIN3+ risk of 13%. Highest short-term CIN3+ risks among HPV-positive women were observed for women with abnormal cytology (\geq BMD): 42%. Consequently, HPV-positive women with abnormal cytology should be directly referred for colposcopy. Short-term CIN3+ risk of HPV-positive women with normal cytology was 5.2% and was between the 2% and 20% risk thresholds, indicating that follow-up testing of HPV-positive women with normal cytology is required. The short-term CIN3+ risk decreased to 1.6% when repeat cytology at 6 to 12 months follow-up was also normal, sufficiently low to maintain regular screening intervals. HPV-positive women with abnormal cytology at one year follow-up had a short-term CIN3+ risk of 25% and for these

women, similar as for HPV-positive women with abnormal cytology at baseline, direct referral for colposcopy is required.

Additional evidence supporting triage of HPV-positive women with baseline and repeat cytology came from post-hoc analyses within the two Dutch cohorts of women screened with HPV and cytology contesting (VUSA-Screen and POBASCAM), consisting of 1303 and 1100 HPV-positive women respectively.^{32,33} In these post-hoc analyses, different triage strategies consisting of combinations of cytology, HPV testing and/or HPV-genotyping were evaluated. Triage strategies with baseline and repeat cytology performed well relative to other triage strategies with respect to NPV and PPV (resp. ~99% and ~36%)(Figure 1) and colposcopy referral rates (~39%).

It should be noted that the performance of cytology and repeat cytology as a triage strategy largely depends on the quality of cytology, that varies widely among countries and is rather high in the Netherlands.^{5,47} Moreover, in the VUSA-Screen and POBASCAM studies cytology was read without knowledge of the HPV test result. In the new HPV-based screening programme, the HPV result is available, which is likely to lead to an increase in sensitivity at the cost of a decrease in specificity.⁴⁸⁻⁵⁰ This emphasizes the need for a more objective test for triage of HPV-positive women.

4.2.2. Cytology with HPV16/18-genotyping

A combination of cytology and HPV16/18-genotyping may achieve a clinical sensitivity that is high enough to obviate the need for repeat testing. This is an advantage as compliance with repeat testing is imperfect in real-life programmes. Multiple international studies evaluated the performance of combined cytology and HPV16/18-genotyping for triage of HPV-positive women. Despite the fact that several of these studies were not performed in population-based cohorts, overall results showed a high sensitivity for detection of CIN3+ and a limited PPV, resulting in high colposcopy referral rates.^{34,35} In the previously described post-hoc analyses within the VUSA-Screen and POBASCAM cohorts, NPV's for endpoint CIN3+ were 97.1% and 98.8%, respectively (Figure 1).^{32,33} With the addition of repeat cytology, NPV estimates increased to 99.7% and 99.6%, respectively. However, the advantage of a baseline only triage strategy would then no longer apply.

Multiple studies have confirmed the clinical value of HPV16/18-genotyping. For that reason, HPV16/18-genotyping has been implemented in several guidelines in the USA.⁸ Compared to cytology with repeat cytology, HPV16/18-genotyping has a relatively low PPV for detection of CIN3+, both for the strategy consisting of cytology and HPV16/18-genotyping without repeat cytology (~27%) as for the strategy with

repeat cytology (~26%). Because of this relatively high PPV, and because of the high quality of cytology in the Netherlands, cytology with repeat cytology is used for triage of HPV-positive women in the new Dutch screening programme. This choice has resulted in a relatively low colposcopy referral rate. However, a post-hoc analysis of the POBASCAM cohort evaluating several triage strategies using results from two consecutive HPV-based screening rounds, demonstrated that cytology with HPV16/18-genotyping would be a suitable strategy for triage of HPV-positive women in the second HPV-based screening round.

4.2.3. Repeat HPV testing

Testing for HPV clearance provides the highest protection against CIN3+ as women who have cleared the HPV infection are expected to have a very low CIN3+ risk. Several international studies showed that repeat HPV testing for triage of HPV-positive women has a high sensitivity for detection of CIN3+.^{36,37} In the aforementioned post-hoc analyses, strategies that included repeat HPV testing showed very high NPV estimates. For example, the strategy consisting of baseline cytology with repeat HPV testing showed NPV estimates well above the 98% threshold (~100%). However, PPV estimates varied around 20% (~21%), resulting in relatively high colposcopy referral rates (~69%)(Figure 1).^{32,33}

A recent post-hoc analysis performed within the POBASCAM cohort showed that HPV-positive women with a negative repeat HPV test after six to 18 months remain at increased HPV infection and high-grade CIN risk as compared to baseline HPV-negative women.⁵¹ It is hypothesized that a negative repeat HPV test does not always reflect actual HPV clearance, but can also be the result of a temporary decrease in viral load below the detection threshold of the HPV assay.⁵² These results indicate that screen HPV-positive women with a negative repeat HPV test and screen HPV-negative women require different long-term surveillance.

To conclude, strategies consisting of cytology with repeat cytology and/or HPV16/18 genotyping, and strategies including repeat HPV testing, seem acceptable for triage of HPV-positive women, as they have NPV estimates above 98% and PPV estimates above 20%. Within the Netherlands, it was decided to triage HPV-positive women with baseline cytology and repeat cytology after 6 months (Table 2). Cytology is repeated after 6 months to increase the sensitivity of the triage strategy.^{32,33} The follow-up moment was set at 6 months in order to limit the risk of losing women to follow-up. In addition to the high NPV and PPV estimates that are achieved with this strategy, colposcopy referral rates are relatively low compared to other triage strategies. However, as the performance of the triage strategies and the accepted

balance between safety and screening-related burden varies considerably between countries, different triage strategies might be more suitable in other countries. Moreover, additional research should be performed to evaluate the clinical performance of the currently established triage strategies in the second HPV-based screening round.

5. Adjustment of screening ages and intervals

European guidelines recommend primary HPV testing for women aged 35 years and older.⁵³ Primary HPV testing in women under the age of 30 is not recommended as this is expected to lead to a considerable amount of overdiagnosis and overtreatment of potentially regressive CIN lesions, due to the high prevalence of transient HPV infections in women under 30. Guidelines do not recommend for or against primary HPV testing in women aged 30 to 34, due to a lack of evidence regarding this age category. In the Netherlands, cytology-based screening started at the age of 30. Results from the POBASCAM study showed that the cumulative detection of CIN3+ and CIN2+ over two consecutive HPV-based screening rounds did not differ between women aged 30–34 years and women aged 34 years and older in both study arms (HPV only versus HPV and cytology co-testing), indicating that there was no overdiagnosis in women aged 30–34 compared to women >34 years. Consequently, the starting age of 30 was maintained in the new HPV based screening programme in the Netherlands.

There is no evidence on the most optimal age to stop primary HPV-based screening. European guidelines recommend the same upper age limit as maintained for cytology-based screening (i.e. at age 60 to 65).⁵³ In the previous cytology-based screening programme, last screen was at 60 and this is maintained in the new screening programme. However, a negative HPV test is used as an exit test, meaning that women who test HPV-positive at age 60 are invited for an additional screen at age 65 to minimize the risk of cancer when exiting screening (Table 2). With this addition, the CIN3+ risk for women over 60 years of age is expected to be lower as compared to the previous cytology-based screening programme. Additional research should be performed to develop a potentially more appropriate follow-up and exit scheme for older women.

Long-term follow-up studies of women screened with HPV and cytology showed that HPV-negative women have very low long-term cervical cancer, CIN3+ and CIN2+ risks (Table 3A).⁵⁴⁻⁵⁸ In the POBASCAM cohort, long-term CIN3+ risks in HPV-negative

women aged 40 years and older were 72% lower than in HPV-negative women under 40. These results support an extension of the interval for HPV-negative women aged 40 years and older from five to 10 years. This extension has been included in the new HPV-based screening programme in the Netherlands. For HPV-negative women aged 30 or 35, screening intervals of five years are maintained (Table 2).

Long-term CIN3+ risks of HPV positive women with a negative triage test have been analysed separately (Table 3B). Results show that HPV-positive women with a negative triage test (i.e. cytology combined with HPV16/18-genotyping and/or repeat cytology) remain to have non-negligible long-term CIN3+ risks: ~4% CIN3+ risk after five years follow-up and ~7% CIN3+ risk after 14 years follow-up.^{54,55} Therefore, extension of the screening interval beyond five years cannot be justified, and a five year screening interval is maintained for these women.

Table 3. Long-term cancer, CIN3+ and CIN2+ risks in HPV-negative women (A) and HPV-positive women with negative triage (B).

Cohort	Follow-up period	Cancer risk	CIN3+ risk	CIN2+ risk
A. HPV-negative women				
VUSA-Screen ¹	5 years	-	0.09%	0.21%
POBASCAM ²	14 years	0.09%	0.56%	-
ARTISTIC ³	6 years	-	0.28%	0.87%
Swedescreen ⁴	13 years	-	0.84%	1.74%
Kaiser Permanente ⁵	18 years	-	0.90%	1.85%
B. HPV-positive, triage negative women				
Triage with cytology and repeat cytology				
VUSA-Screen ¹	5 years	-	4.1%	7.0%
POBASCAM ²	14 years	-	~10.4%	-
Triage with cytology and HPV16/18-genotyping				
VUSA-Screen ¹	5 years	-	3.5%	7.9%
POBASCAM ²	14 years	-	~8.7%	-

¹Uijterwaal et al. *Cancer Prev Res* 2015; ²Dijkstra et al. *BMJ* 2016; ³Kitchener et al. *Eur J Cancer* 2011; ⁴Elfstrom et al. *BMJ* 2014; ⁵Castle et al. *J Clin Oncol* 2012.

CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse.

6. Implementation of HPV self-sampling

In the Netherlands, approximately half of the cervical cancer cases occur in women not attending cervical screening.⁵⁹ Studies have shown that offering HPV self-sampling to screening non-attendees increases participation rates.⁶⁰⁻⁶⁶ In Dutch studies, self-sampling attendance rates up to 34% were observed among screening

non-responders.⁶³⁻⁶⁷ Based on these results, self-sampling is available on request in the new Dutch cervical screening programme. However, self-sampling is only recommended for women who do not want to visit their general practitioner (GP) for cervical sampling (Table 2).³⁰

Previous studies evaluating women their preferences indicated that a proportion of women who do normally attend clinician-based sampling for cervical screening would also prefer self-sampling.⁶⁸⁻⁷¹ Moreover, implementation of self-sampling as a primary screening option could reduce the screening-related costs as it would greatly reduce the number of GP visits. However, before HPV self-sampling can be considered as a primary screening option, the clinical performance of HPV testing on self-collected samples as compared to clinician-collected samples needs to be assessed.^{72,73} Previous studies comparing the clinical performance of HPV self-sampling and clinician-based sampling showed substantial variation, most likely due to the use of different self-sampling devices and HPV assays.⁷⁴⁻⁷⁹ A meta-analysis reviewing results of 36 self-sampling studies showed a similar sensitivity between HPV self-sampling and clinician-based HPV testing when a PCR-based HPV assay was used.⁷² Consequently, self-sampling in combination with a PCR-based HPV assay might be considered for routine screening.

The inclusion phase of a randomised paired screen positive non-inferiority trial (i.e. the IMPROVE trial) comparing self-collected versus clinician-collected HPV testing in the Netherlands has recently been completed. Results show that HPV testing using a clinically validated PCR-based assay has similar accuracy for detection of CIN2+ and CIN3+ on self-collected and clinician-collected samples.⁸⁰ These results strongly support the use of HPV self-sampling as a primary screening method in routine screening. Moreover, a recent questionnaire study performed in the context of the IMPROVE trial shows that women from a regular screening population have a positive attitude towards self-sampling, and would prefer self-sampling in future screening.⁸¹ It is expected that, based on these results, primary self-sampling will be introduced in the Netherlands in the near future.

7. Colposcopy and histology

HPV-positive women with a positive triage test are referred to a gynecologist for visual examination of the cervical transformation zone with a colposcope, allowing magnification for more accurate inspection. Application of acetic acid during colposcopy leads to the visible appearance of HPV-induced dysplasia. According to

national guidelines, the colposcopist takes biopsies of all visible abnormalities.⁸² When no abnormalities are visible during colposcopy, it is advised to take two random biopsies in women with worse than BMD cytology, while biopsies can be omitted in women with BMD cytology.

Cervical histology specimens are graded according to the CIN classification⁸³⁻⁸⁵: in CIN1 dysplasia is seen in less than one third of the depth of the epithelium (mild dysplasia); in CIN2 dysplasia is seen in two thirds of the depth of the epithelium (moderate dysplasia); while in CIN3 dysplasia is seen in more than two thirds of the depth of the epithelium (severe dysplasia). When atypical cells invade the basal membrane, the lesion is graded as cervical cancer. All CIN lesions can progress, persist or regress. Treatment of CIN lesions is performed by a large loop excision of the transformation zone (LLETZ), in which the transformation zone and lesion are excised using a loop-shaped electric wire.

CIN3 has the lowest chance of spontaneous regression and is considered a true premalignant stage, and consequently, is always treated. In contrast, CIN1 is most often the result of a transient HPV infection and has the highest chance of spontaneous regression. Therefore, a wait-and-see policy with follow-up after one year is warranted. The chance of spontaneous regression of a CIN2 lesion is somewhere in between the regression chances of CIN1 and CIN3, however, remains very uncertain. Additionally, the diagnosis CIN2 has a low reproducibility.⁸⁶ Consequently, there is no uniform consensus regarding treatment of CIN2: women are often advised to undergo treatment in order to prevent possible progression to cancer, however, for women in their fertile life phase with a future child wish it can be decided, depending on the size of the lesion and the colposcopic aspect, to follow a wait-and-see policy.⁸² Because of the low reproducibility of CIN2, the WHO has introduced a two-tiered grading system in which lesions are subdivided in high-grade squamous intraepithelial lesions (HSIL; i.e. CIN2 and CIN3) and low-grade squamous intraepithelial neoplasia (LSIL; i.e. CIN1), which has been adopted in the USA.^{87,88} However, as this system leads to a considerable amount of overtreatment of women with regressive HSIL, in most European countries, including the Netherlands, the CIN grading system is still used. Moreover, to minimize the amount of overtreatment when using the CIN grading system, an attempt is made to subdivide CIN2 in CIN1-like (wait-and-see policy) and CIN3-like lesions (need for immediate treatment) with additional immunohistochemical staining (e.g. p16 and/or Ki-67 staining) or biomarker testing (e.g. methylation marker analysis and/or HPV-E4).^{53,86,89,90} At this moment, both the CIN and the HSIL/LSIL grading systems are debatable. It is expected that, in the near future, a new classifying system based on

biomarkers will be developed that better predicts the risk of cancer development and will therefore lead to more personalized treatment and less overtreatment.

8. Cost-effectiveness of the new Dutch screening programme

Several modelling studies showed that implementation of HPV-based cervical screening with cytology triage was likely to be cost-effective in the Netherlands.⁹¹⁻⁹³ Additional support comes from data of a modelling study that was conducted in preparation of the new cervical screening programme.⁹⁴ Results showed that the new HPV-based screening programme is expected to be more effective in preventing cervical cancer and cervical cancer death than the previous cytology-based programme: 100 additional cervical cancer cases and 35 additional cervical cancer related deaths are expected to be prevented annually (Table 2).⁹⁴ The introduction of HPV self-sampling is expected to be a key factor for this higher effectiveness of the new programme as it increases screening participation rates.

The total screening-related costs consist of the following components: primary screening tests, triage tests, colposcopy referrals and CIN treatments, and cervical cancer treatments and palliative care. Table 4 provides an overview of the expected changes in the screening-related costs and the adjustments that lead to these changes in costs.⁹⁴ The costs of the primary screening tests account for >50% of the total costs and therefore greatly impact the total screening-related costs. In the first five years after implementation, the new HPV-based screening programme is expected to be more expensive than cytology-based screening as the increase in the costs of triage tests, colposcopy referrals and CIN treatments, and cervical cancer treatment and palliative care outnumber the decrease in the costs of the primary screening test, resulting in an increase of ~€5 million per year as compared to cytology-based screening. After five years the costs of the primary screening tests will decrease even further due to extension of the screening intervals for HPV-negative women aged 40 and 50, resulting in less screening moments. This decrease in costs outnumbers the increase of the other components, resulting in a total decrease of ~€5 million per year (~11%) as compared to cytology-based screening.

Collectively, the replacement of the cytology-based programme by the new HPV-based cervical screening programme in the Netherlands is expected to be effective and cost-saving.⁹⁴ Whether implementation of HPV-based screening in other countries is cost-effective depends on decisions that will be made with regard to

Table 4. Overview of the expected changes in the screening-related costs and the adjustments that lead to these changes in costs (adapted from Naber et al., 2016).

Yearly costs			Adjustments that lead to an increase/decrease in costs
Cytology-based screening	HPV-based screening first five years* (%)	HPV-based screening after five years (%)	
Primary screening tests	€33.107.879	€26.554.658 (-20%)	€21.017.671 (-37%) Increase in costs due to: 1. Lower costs of the HPV assay as compared to cytology 2. Lower number of primary screening tests from five years after start of the new screening programme due to extension of screening intervals for HPV screen-negative women aged 40 and 50 years old 3. Lower costs of the primary screening test due to implementation of self-sampling for non-attendees, and possible future expansion of self-sampling as a primary screening instrument
Triage tests	€1.797.126	€2.472.471 (+38%)	€2.365.387 (+32%) Increase in costs due to: 1. More triage tests due to the higher sensitivity and lower specificity of the primary screening test 2. More repeat cytology due to the follow-up of HPV-positive women with normal baseline cytology
Colposcopy referrals and CIN treatments	€9.097.185	€18.631.951 (+105%)	€15.159.727 (+67%) Increase in costs due to: 1. More colposcopy referrals and CIN treatments due to the higher sensitivity and lower specificity of the primary screening test
Cervical cancer treatments and palliative care	€1.826.234	€2.537.234 (+39%)	€1.767.761 (-3%) Increase in costs due to: 1. Increased detection of cervical cancer in the first five years after start of the new screening programme due to the higher sensitivity of the primary screening test 2. Increased detection of cervical cancer in the first five years after start of the new screening programme due to implementation of HPV self-sampling for non-attendees
Total screening-related costs	€45.472.383	€50.196.314 (+10%)	€40.310.545 (-11%)

*Average costs in the first five years after implementation of the new HPV-based screening programme; (%) difference as compared to cytology-based screening.

triage strategy, adjustment of screening ages and intervals, and implementation of self-sampling.

9. Conclusion

The Netherlands is one of the first countries worldwide to implement nationwide HPV-based screening and therefore may provide guidance to other countries. In this manuscript we discussed the rationale of the new Dutch cervical screening programme by reviewing the scientific evidence that contributed to the design of the new screening algorithm.

HPV-based screening was implemented in the Netherlands in 2017, as it has been shown to provide better protection against cervical precancer and cancer than cytology. Triage testing of HPV-positive women is required to identify HPV-positive women with underlying high-grade CIN. In the Netherlands, HPV-positive women are triaged with cytology and repeat cytology after 6 months. Screening intervals for HPV-negative women aged 40 years and older are extended from five to 10 years as HPV-negative women have very low long-term CIN3+ risks. For women under 40 and for HPV-positive women with negative triage, regular five-year screening intervals will be maintained. HPV self-sampling is implemented for screening non-responders, since this has been shown to be an effective strategy to attract non-attendees into screening.

The new screening algorithm is expected to annually prevent 100 additional cervical cancer cases and 35 additional cervical cancer related deaths as compared to the previous cytology-based screening programme. Implementation of the new HPV-based screening programme will result in an increase in costs during the first five years, but costs are expected to be lower as compared to cytology-based screening from five years after implementation of the new programme.

10. Future perspectives

Several other countries are expected to implement HPV-based screening in the coming years. The recent results of the IMPROVE trial, showing that HPV testing using a clinically validated PCR-based assay has similar accuracy for detection of CIN2+ and CIN3+ on self-collected and clinician-collected samples, are likely to

enlarge role of self-sampling in cervical screening, making screening more accessible to women and increasing its efficiency.

Future research should focus on the development of more objective triage tests. Two promising techniques that have been investigated extensively are p16/Ki-67 dual-stained cytology (CINtec PLUS [Roche mtm laboratories AG, Mannheim, Germany]) and host cell DNA methylation marker analysis (QIASure [Qiagen, Hilden, Germany] and PreCursor-M [Self Screen B.V., Amsterdam, The Netherlands]). Several studies have shown the value of p16/Ki-67 dual-stained cytology for triage of HPV-positive women. However, the threshold for positivity of the assay is the presence of one single p16/Ki-67 positive cell, which demands the presence of sufficient intact cervical cells in a sample.⁹⁵⁻¹⁰³ Consequently, p16/Ki-67 dual-stained cytology cannot be applied to self-samples. Although the research regarding methylation marker analysis for triage of HPV-positive women is ongoing, results up to now have proven that this technique is applicable on both self-collected and clinician collected samples, opening the way to full molecular screening.¹⁰⁴⁻¹¹⁰ Finally, monitoring of screening programmes remains of great importance, and linkage of HPV vaccination and screening registries will provide relevant information for further improvement of cervical screening. In the Netherlands, HPV vaccination has been introduced in 2009 for girls aged 12, with a catch-up programme for girls aged 13 to 16 (born in 1996 to 1993). These vaccinated girls will reach the screening starting age in 2023. However, also after 2023 screening will remain necessary as HPV vaccination uptake in the Netherlands is approximately 55% and is declining in the last years. The effectivity of the HPV vaccines is currently being evaluated. Depending on the results, especially those concerning cross-protection and herd immunity, adapted screening algorithms may be developed.

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