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.

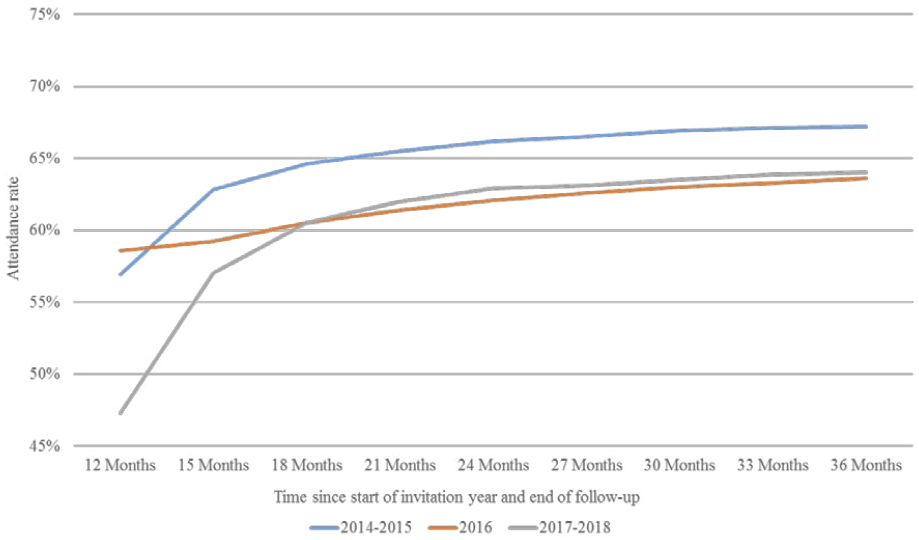

Figure 1: *Attendance rate by increasing inclusion period by year of invitation*
NB. Attendance rates in 2017-18 after 24 months are based only on data from 2017. Last date of screening in the dataset is in November 2019.

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-

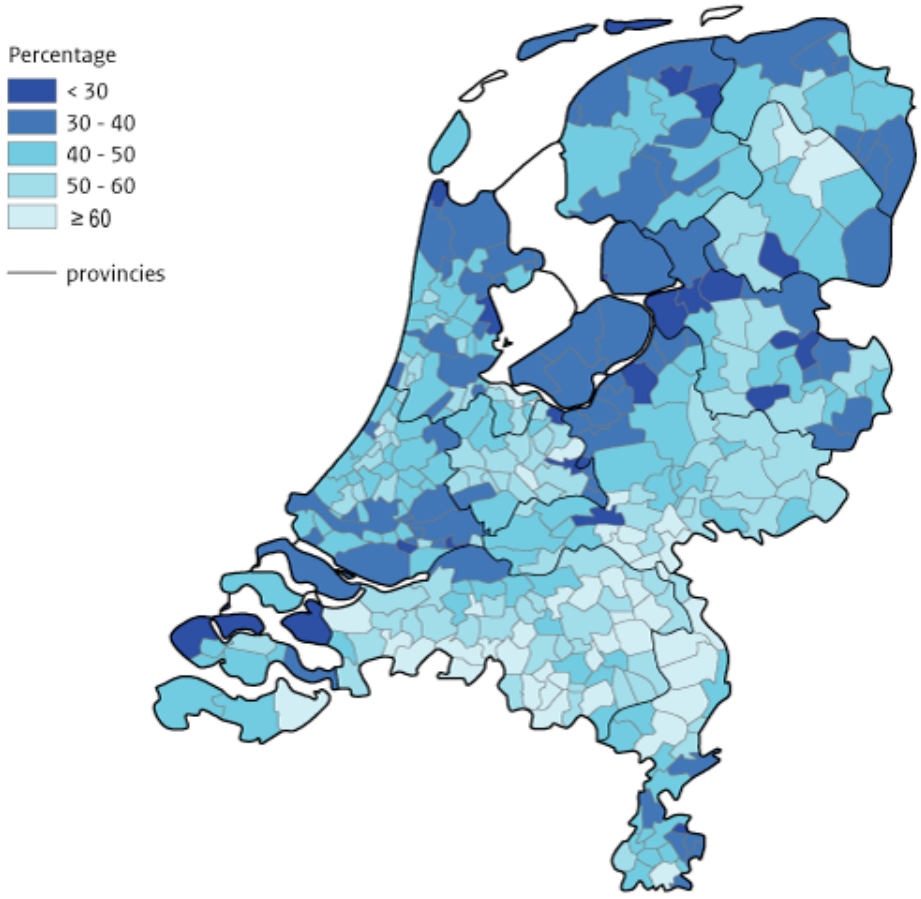

Figure 2: *HPV vaccination coverage, girls in birth cohort 2004, by city council region and province, 2019. Image source: Volksgezondsheidenzorg.info.[46] Data source: RIVM- Dienst Vaccinvoorziening en Preventieprogramma's. Grey lines denote city council regions, black boundaries denote borders of provinces.*

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.

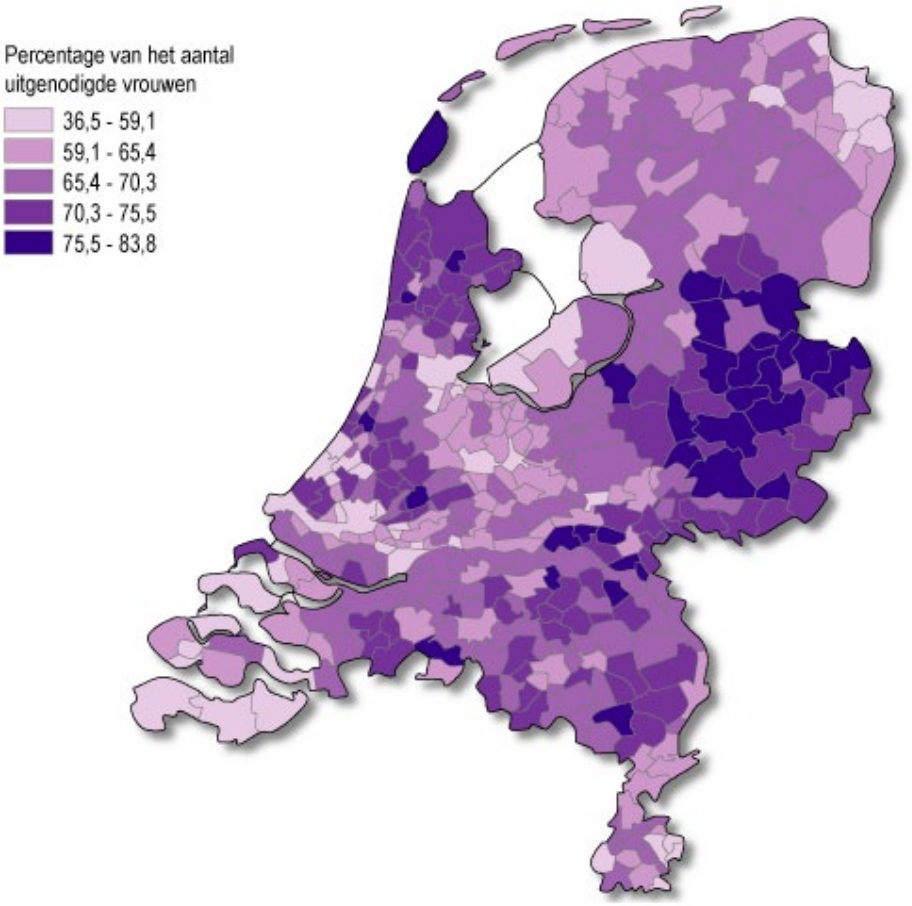

Figure 3: *Participation in the Dutch cervical cancer screening programme by city council region, 2012. Image source: Volksgezondsheidenzorg.info. Data source: Regional screening organisation. Colours denotes the attendance rates within city council regions. Lighter purple denote lower attendance and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

REFERENCES

1. Machalek DA, Roberts JM, Garland SM, et al. Routine cervical screening by primary HPV testing: early findings in the renewed National Cervical Screening Program. Med J Aust 2019;**211**(3):113-19.
2. Naber SK, Matthijsse SM, Jansen EEL, et al. Kosten en effectiviteit van het vernieuwd bevolkingsonderzoek baarmoederhalskanker. The Netherlands: Erasmus MC, 2016.
3. Health Council of the Netherlands. Population screening for cervical cancer [in Dutch]. The Hague: Health Council of the Netherlands, 2011.
4. Dijkstra MG, van Zummeren M, Rozendaal L, et al. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. BMJ 2016;**355**:i4924.
5. Gerend MA, Shepherd MA, Kaltz EA, et al. Understanding women's hesitancy to undergo less frequent cervical cancer screening. Prev Med 2017;**95**:96-102.
6. Silver MI, Rositch AF, Burke AE, et al. Patient concerns about human papillomavirus testing and 5-year intervals in routine cervical cancer screening. Obstet Gynecol 2015;**125**(2):317-29.
7. Hawkins NA, Benard VB, Greek A, et al. Patient knowledge and beliefs as barriers to extending cervical cancer screening intervals in Federally Qualified Health Centers. Prev Med 2013;**57**(5):641-5.
8. Scalzo K, Mullins R. The recommended interval for cervical cancer screening: Victorian women's attitudes to an extended interval. Aust N Z J Public Health 2015;**39**(2):153-6.
9. Netherlands Comprehensive Cancer Organisation (IKNL). Monitor bevolkingsonderzoek baarmoederhalskanker 2018: Rijksinstituut voor Volksgezondheid en Milieu, 2019.
10. Leinonen MK, Campbell S, Klungsoyr O, et al. Personal and provider level factors influence participation to cervical cancer screening: A retrospective register-based study of 1.3 million women in Norway. Prev Med 2017;**94**:31-39.
11. Harder E, Juul KE, Jensen SM, et al. Factors associated with non-participation in cervical cancer screening - A nationwide study of nearly half a million women in Denmark. Prev Med 2018;**111**:94-100.
12. Kristensson JH, Sander BB, von Euler-Chelpin M, et al. Predictors of non-participation in cervical screening in Denmark. Cancer Epidemiol 2014;**38**(2):174-80.
13. Leinonen MK, Campbell S, Ursin G, et al. Barriers to cervical cancer screening faced by immigrants: a registry-based study of 1.4 million women in Norway. Eur J Public Health 2017;**27**(5):873-79.
14. Broberg G, Wang J, Ostberg AL, et al. Socio-economic and demographic determinants affecting participation in the Swedish cervical screening program: A population-based case-control study. PLoS One 2018;**13**(1):e0190171.
15. Virtanen A, Anttila A, Luostarinen T, et al. Improving cervical cancer screening attendance in Finland. Int J Cancer 2015;**136**(6):E677-84.
16. Bongaerts TH, Büchner FL, Middelkoop BJ, et al. Determinants of (non-)attendance at the Dutch cancer screening programmes: A systematic review. J Med Screen 2020;**27**(3):121-29.
17. Marlow LAV, Chorley AJ, Haddrell J, et al. Understanding the heterogeneity of cervical cancer screening non-participants: Data from a national sample of British women. Eur J Cancer 2017;**80**:30-38.
18. Korfage IJ, de Kwaadsteniet EW, van Voorst A, et al. Preferences for cervical cancer screening: The role of implicit associations. Patient Educ Couns 2018; **101**(2): 310-317.

19. Marlow LAV, Chorley AJ, Rockliffe L, et al. Decision-making about cervical screening in a heterogeneous sample of nonparticipants: A qualitative interview study. Psychooncology 2018;**27**(10):2488-93.
20. Bosgraaf RP, Ketelaars PJ, Verhoef VM, et al. Reasons for non-attendance to cervical screening and preferences for HPV self-sampling in Dutch women. Prev Med 2014;**64**:108-13.
21. Sheeran P, Webb TL. The Intention–Behavior Gap. Social and Personality Psychology Compass 2016;**10**(9):503-18.
22. Ryan M, Waller J, Marlow LA. Could changing invitation and booking processes help women translate their cervical screening intentions into action? A population-based survey of women's preferences in Great Britain. BMJ Open 2019;**9**(7):e028134.
23. Bennett KF, Waller J, Chorley AJ, et al. Barriers to cervical screening and interest in self-sampling among women who actively decline screening. J Med Screen 2018;**25**(4):211-17.
24. Oscarsson MG, Wijma BE, Benzein EG. 'I do not need to... I do not want to... I do not give it priority...'--why women choose not to attend cervical cancer screening. Health Expect 2008;**11**(1):26-34.
25. Gok M, Heideman DA, van Kemenade FJ, et al. HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. BMJ 2010;**340**:c1040.
26. Campbell HE, Gray AM, Watson J, et al. Preferences for interventions designed to increase cervical screening uptake in non-attending young women: How findings from a discrete choice experiment compare with observed behaviours in a trial. Health Expect 2020; **23**: 202– 211.
27. Nickerson RS. Confirmation Bias: A Ubiquitous Phenomenon in Many Guises. Review of General Psychology 1998;**2**(2):175-220.
28. Demarco M, Hyun N, Carter-Pokras O, et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. EClinicalMedicine 2020;**22**:100293.
29. Patadji S, Li Z, Pradhan D, et al. Significance of high-risk HPV detection in women with atypical glandular cells on Pap testing: Analysis of 1857 cases from an academic institution. Cancer Cytopathology 2017;**125**(3):205-11.
30. Polman NJ, Ebisch RMF, Heideman DAM, et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. The Lancet Oncology 2019; **20**(2): 229-238.
31. Ketelaars PJW, Bosgraaf RP, Siebers AG, et al. High-risk human papillomavirus detection in self-sampling compared to physician-taken smear in a responder population of the Dutch cervical screening: Results of the VERA study. Preventive Medicine 2017;**101**:96-101.
32. Erasmus MC, PALGA. Monitor 2017: RIVM; 2018 [Available from: https://www.rivm.nl/sites/default/files/2018-11/LEBAmon2017-def.pdf.]
33. Rozemeijer K, de Kok IM, Naber SK, et al. Offering Self-Sampling to Non-Attendees of Organized Primary HPV Screening: When Do Harms Outweigh the Benefits? Cancer Epidemiol Biomarkers Prev 2015;**24**(5):773-82.
34. Team Geboortezorg en Gynaecologie. Verbetersignalement Baarmoederhalsafwijking CIN. Zinnige Zorg. Diemen: Zorginstituut Nederland, 2019.
35. Loopik DL, Koenjer LM, Siebers AG, et al. Benefit and burden in the Dutch cytology-based versus high-risk human papillomavirus-based cervical cancer screening program. American Journal of Obstetrics and Gynecology 2020, Epub ahead of print.

36. Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-Time Monitoring of Results During First Year of Dutch Colorectal Cancer Screening Program and Optimization by Altering Fecal Immunochemical Test Cut-Off Levels. Gastroenterology 2017;**152**(4):767-75 e2.
37. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 2012;**13**(1):78-88.
38. Rozemeijer K, Naber SK, Penning C, et al. Cervical cancer incidence after normal cytological sample in routine screening using SurePath, ThinPrep, and conventional cytology: population based study. BMJ 2017;**356**:j504.
39. Palmer T, Wallace L, Pollock KG, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ 2019;**365**:l1161.
40. Lei J, Ploner A, Elfström KM, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. New England Journal of Medicine 2020;**383**(14):1340-48.
41. Naber SK, Matthijsse SM, Rozemeijer K, et al. Cervical Cancer Screening in Partly HPV Vaccinated Cohorts - A Cost-Effectiveness Analysis. PLoS One 2016;**11**(1):e0145548.
42. World Health Organisation. Draft Global Strategy towards the Elimination of Cervical Cancer as a Public Health Problem; April 2020 [Available from: https://www.who.int/publications/m/item/draft-global-strategy-towards-eliminating-cervical-cancer-as-a-public-health-problem].
43. Rijksinstituut voor Volksgezondheid en Milieu. Vaccinatiegraad en jaarverslag: Rijksvaccinatieprogramma Nederland 2018. In: Centrum Infectieziektebestrijding, ed. Bilthoven, the Netherlands: RIVM, 2018.
44. Brisson M, Kim JJ, Canfell K, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet 2020; **395**(10224): 575-590.
45. Steens A, Wielders CC, Bogaards JA, et al. Association between human papillomavirus vaccine uptake and cervical cancer screening in the Netherlands: implications for future impact on prevention. Int J Cancer 2013;**132**(4):932-43.
46. Volksgezondheidenzorg.nl. HPV-vaccinaties per gemeente: Rijksinstituut voor Volksgezondsheid en Milieu; 2019 [Available from: https://www.volksgezondheidenzorg.info/onderwerp/vaccinaties/regionaal-internationaal/adolescenten#!node-hpv-vaccinaties-gemeente].
47. Gefenaite G, Smit M, Nijman HW, et al. Comparatively low attendance during Human Papillomavirus catch-up vaccination among teenage girls in the Netherlands: Insights from a behavioral survey among parents. BMC Public Health 2012;**12**:498.
48. Rondy M, van Lier A, van de Kassteele J, et al. Determinants for HPV vaccine uptake in the Netherlands: A multilevel study. Vaccine 2010;**28**(9):2070-5.