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.