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

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ABSTRACT

Background

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

Methods

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

Results

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

Conclusions

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

BACKGROUND

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

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

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

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

METHODS

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

MISCAN-Cervix model

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

Disease development

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

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

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

[a] Calibrated in MISCAN-cervix

* Progressive CIN 3/Regressive CIN 3

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

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

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

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

Test characteristics

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

Triage strategies

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

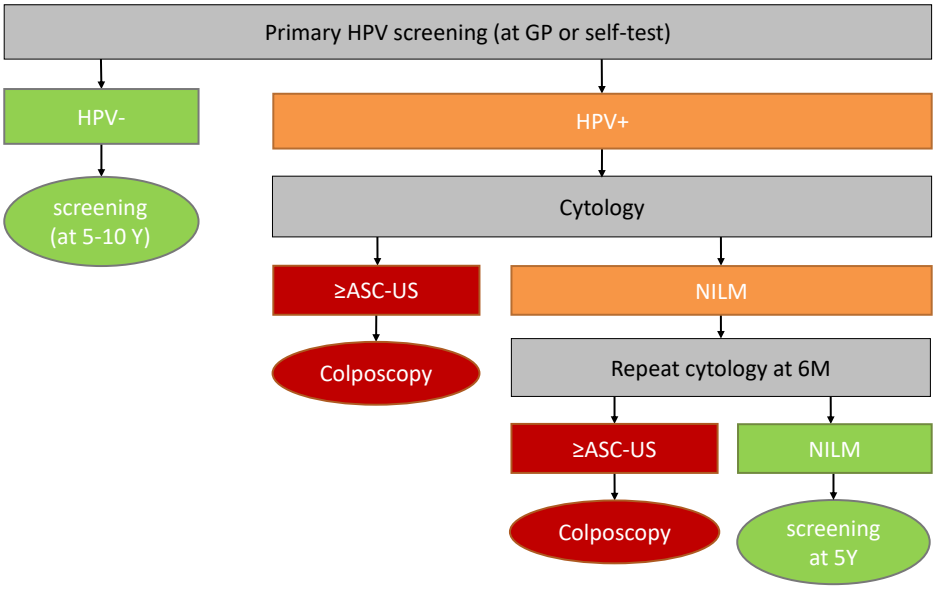

Figure 1: *Current HPV-based screening and triage algorithm.*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: Primary screening could be conducted by a general practitioner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

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

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

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

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

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

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

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

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

Key outcomes

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

Base case analysis

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

Sensitivity analyses

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

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

Patient and public involvement

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

RESULTS

Base case analysis

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

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

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

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

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

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

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

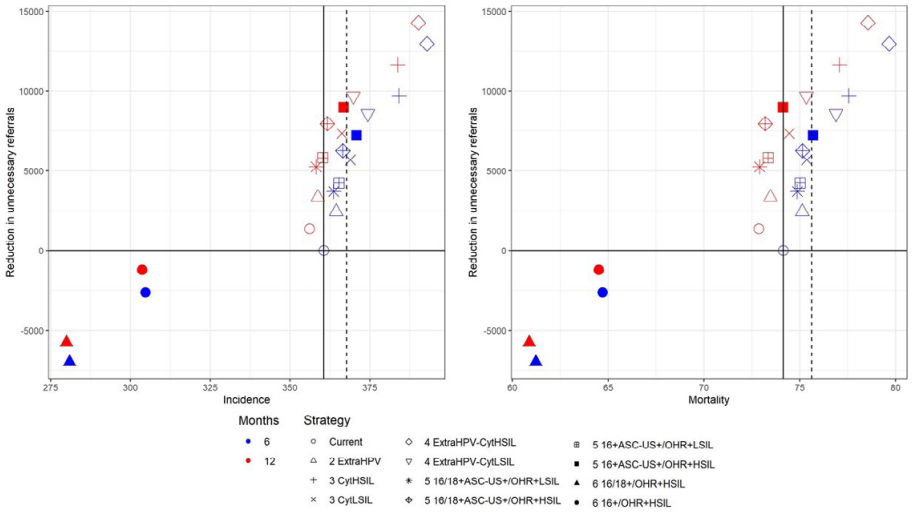

Figure 2: *Reduction in unnecessary referrals plotted against incidence and mortality for all 24 strategies (per 100,000 women).*

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

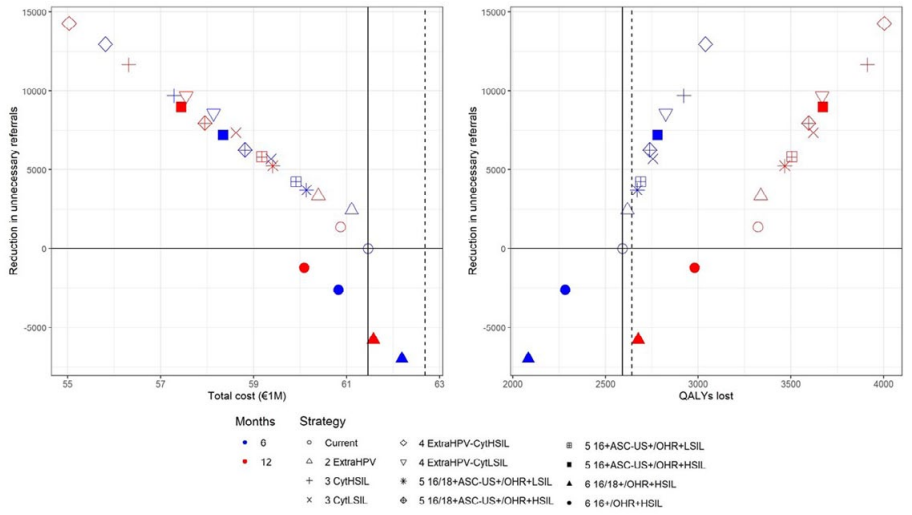

Figure 3: *Reduction in unnecessary referrals plotted against total costs and QALYs lost for all 24 strategies (per 100,000 women).*

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

Sensitivity analysis

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

DECLARATIONS

Conflicts of interests

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

Authors' contributions

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

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Ethics approval

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

Transparency statement

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

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APPENDICES

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

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

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

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

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

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

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

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

hrHPV = high-risk human papillomavirus; CIN = cervical intraepithelial neoplasia; CC = cervical cancer
* CIN 3 lesions can never transition to cervical cancer without an HPV infection

Appendix B Visual representation of triage strategies

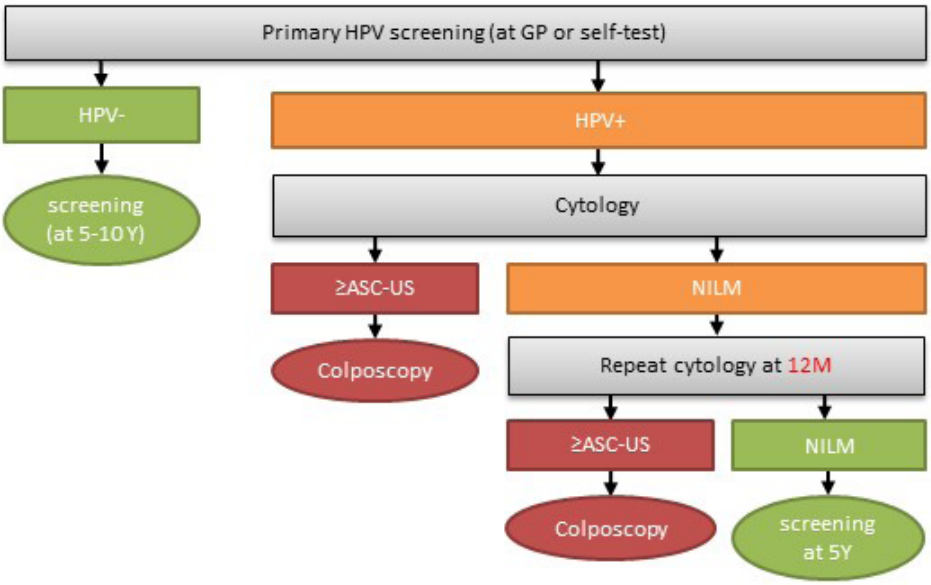

Figure S1: *Category 1 - Extend time to repeat test to 12 months*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed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

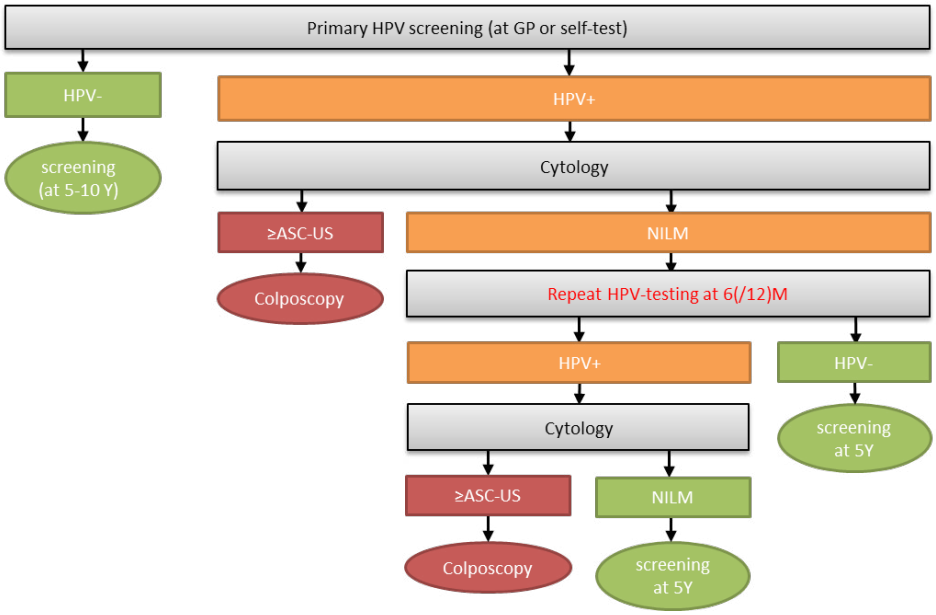

Figure S2: *Category 2 - Add HPV test to repeat test*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has been changed is highlighted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

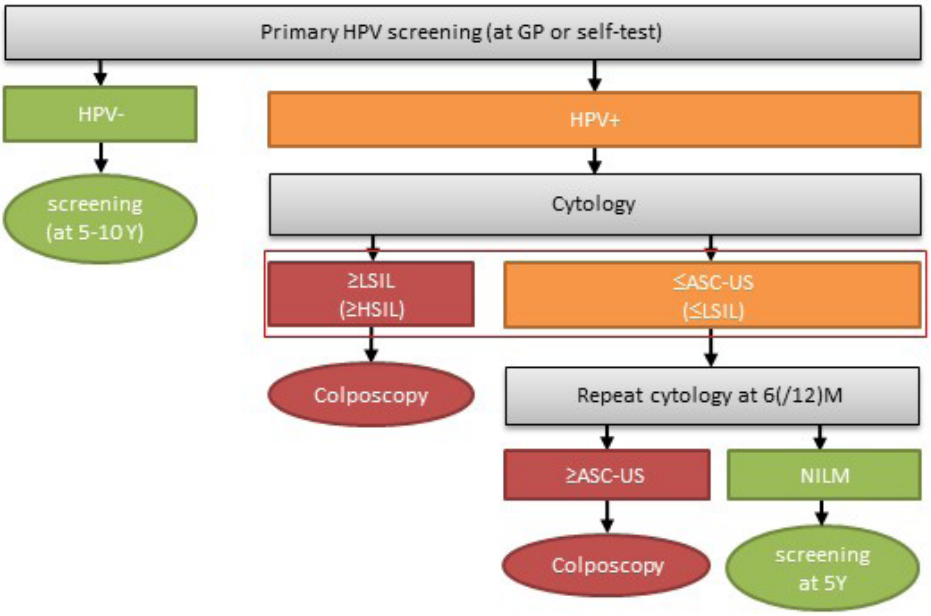

Figure S3: *Category 3 - Increase referral threshold to LSIL/HSIL (two strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm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

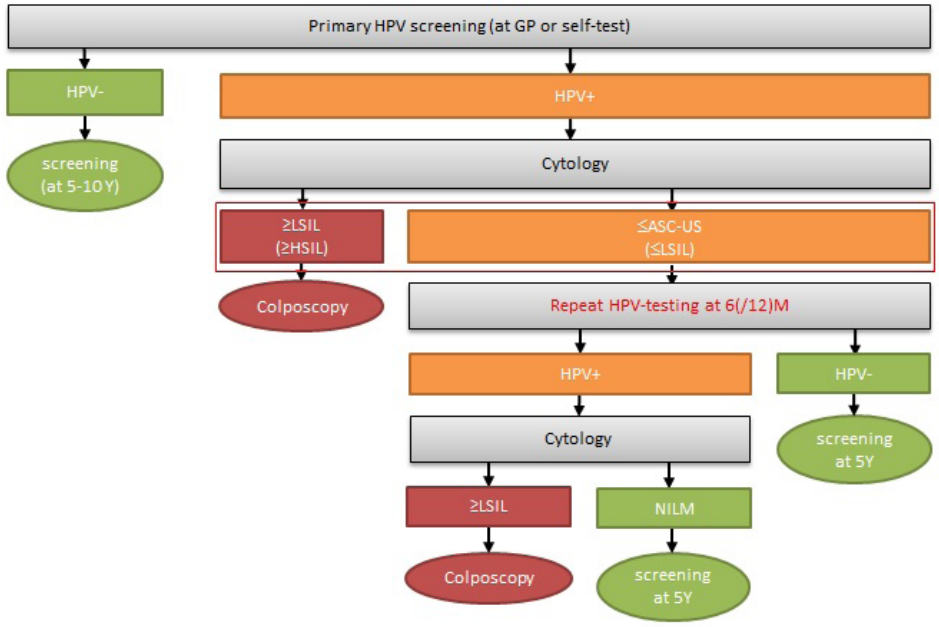

Figure S4: *Category 4 - Combination of categories 2 and 3 (two strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has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

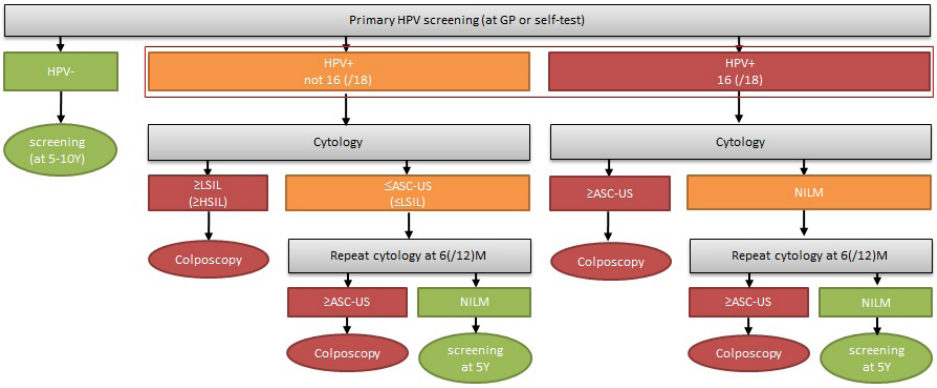

Figure S5: *Category 5 - HPV genotyping and increase referral threshold to LSIL/HSIL (four strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the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

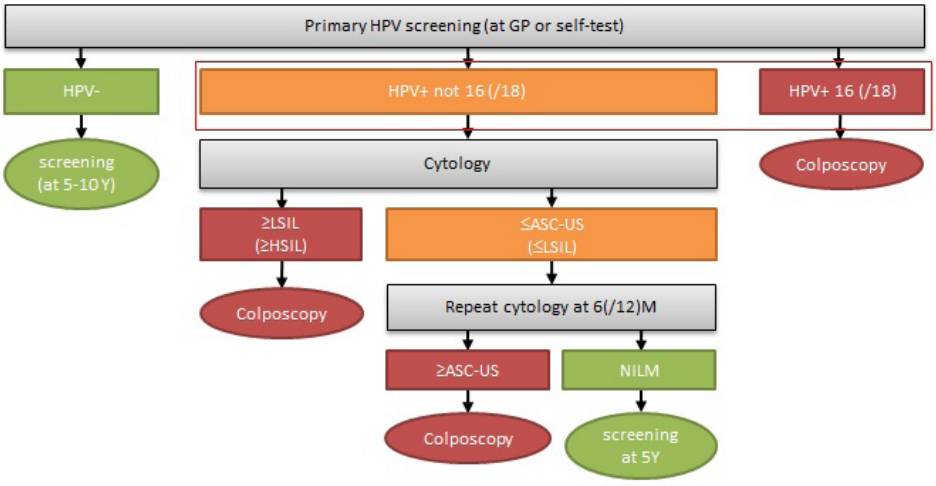

Figure S6: *Category 6 - HPV genotyping and direct referral (two strategies)*
HPV-/+: negative/positive result of HPV test
ASC-US: Atypical squamous cells of undetermined significance
NILM: Negative for intraepithelial lesion or malignancy
M/Y: months/years
NB: The part of the triage algorithm that has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

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

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

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

* Costs are included in treatment

Appendix D: Assumptions for attendance and adherence in sensitivity analyses

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

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

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

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

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

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

Appendix E: Results from sensitivity analyses

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

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

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

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

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

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

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

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

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