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Cost-effectiveness of human papillomavirus testing after treatment for cervical intraepithelial neoplasia

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Objective To compare current cytological follow up of women treated for high-grade cervical intraepithelial neoplasia (CIN) with follow up by high-risk human papillomavirus (HPV) testing together with cytology.

Design A cost-effectiveness modelling study.

Setting Gynaecology clinics in the Netherlands.

Population Women treated for high-grade CIN.

Methods A Markov model was developed to compare six follow-up strategies with HPV testing with current cytological follow up at 6, 12, and 24 months. Model parameter estimation was based on three Dutch follow-up studies and a Dutch population-based screening cohort.

Main outcome measures The number of CIN2/3 cases missed after 5 years follow up, the number of diagnostic procedures, and costs involved.

Results Strategies with adjunct HPV testing were more effective than current follow up (reduction in missed CIN2/3 cases 32–77%, corresponding to a number needed to treat of 192–455) and less inconvenient (reduction in repeat smears 28–65%). A particularly attractive strategy was HPV testing alone at 6 months and both HPV and cytological testing at 24 months after treatment. This strategy yielded a high detection rate of post-treatment CIN, did not lead to an increase in colposcopy rate, and was €49 per woman cheaper than the current strategy.

Conclusions Our model supports the use of high-risk HPV testing for monitoring women treated for high-grade CIN.

Keywords Cervical intraepithelial neoplasia, cost-effectiveness, human papillomavirus, models, post-treatment.

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Introduction

After treatment for high-grade cervical intraepithelial neoplasia (CIN), women are currently invited for repeat cytological testing to check for persistent or recurrent cervical lesions. Recurrence rates of 5–15% have been reported,[1–5] underlining the importance of an appropriate post-treatment management. As women without CIN may present with abnormal cytology,[2,6] current protocols that are based on cytology lead to unnecessary diagnostic procedures (repeat smears and colposcopic examinations). The purpose of this study was to examine whether follow up after treatment can be enhanced by including high-risk human papillomavirus (HPV) testing adjunct to cytological testing. Persistent infection with high-risk HPV is not only a prerequisite for the development and progression of primary CIN lesions[7–9] but also observed in virtually all cases of post-treatment CIN.[10–12] Effective treatment for CIN is assumed to result in eradication of both the lesion and the HPV infection present before treatment.[13] Therefore, testing for the presence of high-risk HPV may contribute to a better risk assessment of post-treatment CIN. In order to compare several different follow-up strategies with HPV and cytological testing, we developed a Markov model. For estimation of the model parameters, we included three cohorts of women treated for CIN2/3.[11,12,14]

Methods

We developed a computer-based mathematical Markov model that simulates the natural history of HPV infections and cervical abnormalities in women treated for CIN2/3. The model contains seven health states among which each woman is allowed to move twice a year.[15] The model was programmed in Microsoft Excel 2000 and is shown in Figure 1.

An important model assumption is that CIN2/3 is preceded by a high-risk HPV infection.[9] Post-treatment CIN is considered to result from incomplete removal of the cervical CIN lesion or from persistent/recurrent HPV infection developing into a new CIN lesion. CIN lesions are considered to regress spontaneously or progress to cervical cancer. In our model, all women start in health state 'treated HPV-positive CIN2/3' (Figure 1). The other six health states are following:

1. Successfully treated and both CIN and high-risk HPV are absent (Figure 1, 'well').
2. Cured from CIN but not from high-risk HPV (Figure 1, 'persistent HPV infection').
3. Unsuccessfully treated for CIN (Figure 1, 'persistent HPV-positive CIN2/3').
4. Recurrently infected with high-risk HPV after successful treatment (Figure 1, 'recurrent HPV infection').
5. Having developed recurrent HPV-positive CIN after successful treatment (Figure 1, 'recurrent HPV-positive CIN2/3').
6. Having developed invasive cancer (Figure 1, 'cervical cancer').

The current Dutch guidelines for the follow up of women treated for CIN consist of repeat cytological testing with Papanicolaou (Pap) smears at 6, 12, and 24 months after treatment (current strategy). After three consecutive normal smears, women return to the 5-year cervical screening programme. In case of a cytologically abnormal smear (borderline/mild dyskaryosis or worse), colposcopic examination, followed by biopsy sampling and, if necessary, treatment for post-treatment CIN is performed. Thereafter, follow up is recommenced with cytological testing at 6, 12, and 24 months.

We compared the current strategy of follow up after treatment for CIN2/3 (cytological testing at 6, 12, and 24 months) with plausible strategies that include HPV testing. In Figure 2, flow charts of the current strategy (Figure 2A) and the HPV testing strategies are presented. In the strategies with HPV testing, the follow up consists of either two recalls at 6 and 24 months (Figure 2B) or one recall at 6 or 12 months (Figure 2D). The strategies with two recalls are as follows:

A1. HPV and cytological testing at 6 and 24 months.
A2. Only HPV testing at 6 and 24 months.
A3. A mixed strategy with HPV testing at 6 months and both cytological and HPV testing at 24 months.

For the strategy with cytology and HPV testing at 6 and 24 months, we also considered a variant where at 6 months, a positive colposcopic result is immediately followed by large loop excision of the transformation zone (LLETZ treatment) without histological verification before treatment (Figure 2C, see-and-treat strategy). The strategies with only one recall are as follows:

B1. Both HPV and cytological testing at 6 months.
B2. Both HPV and cytological testing at 12 months.

After obtaining a positive result on at least one of the tests (borderline/mild dyskaryosis or worse and/or HPV positive), colposcopy is performed, followed by biopsy and treatment of CIN2/3.

We compared the different strategies in terms of effectiveness, patient burden, and cost-effectiveness. Effectiveness was measured by the number of missed post-treatment CIN2/3 cases (or invasive cancer) 5 years after treatment of the primary lesion. In addition, the mean duration until detection of post-treatment CIN2/3 was calculated. The patient burden was measured by the number of repeat smears and the colposcopy rate for women without post-treatment CIN2/3 (due to a false-positive test result on cytology and/or HPV). Cost-effectiveness was assessed by comparing the proportion of missed post-treatment CIN2/3 cases of all treated women to the discounted 5-year costs per woman. By one-way sensitivity analyses, the robustness of the proportion of missed post-treatment CIN2/3 cases and average discounted 5-year costs per woman were examined with regard to changes in the performance of HPV testing (analytical sensitivity 90–99% and analytical specificity 97–100%), the performance of conventional cytological testing (sensitivity of cytology for

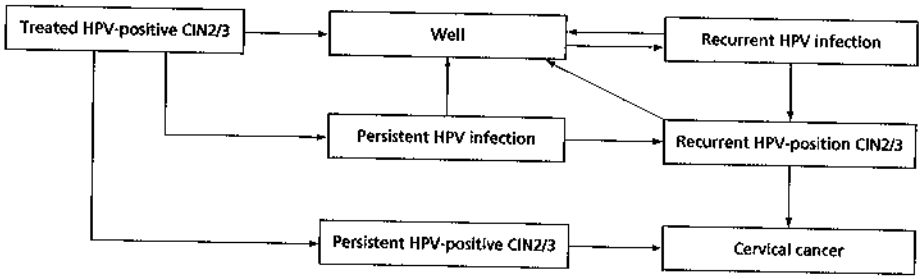

Figure 1. Flow chart representation of the post-treatment model.

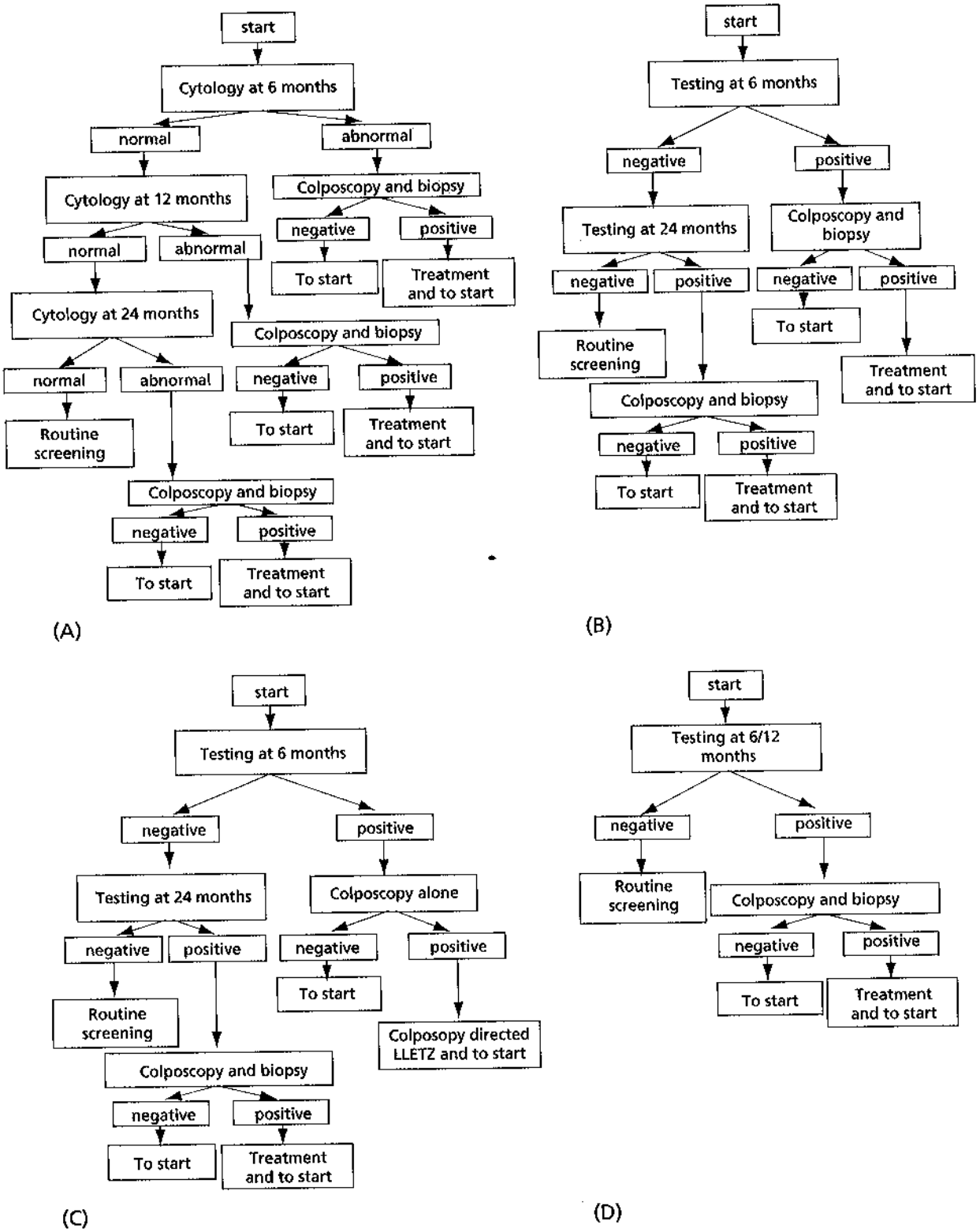

Figure 2. Current and new strategies for follow up after treatment for CIN. (A) The current strategy (cytological testing at 6, 12, and 24 months). (B) Strategies with two recall dates: A1 = cytological and HPV testing at 6 and 24 months, A2 = HPV testing at 6 and 24 months, A3 = HPV testing at 6 months; cytological and HPV testing at 24 months. (C) See-and-treat strategy = cytological and HPV testing at 6 months + see-and-treat; cytological and HPV testing at 24 months. (D) Strategies with one recall date: B1 = cytological and HPV testing at 6 months and B2 = cytological and HPV testing at 24 months.

CIN2/3 60–80% and specificity cytology 90–99%), the laboratory costs of HPV testing (€20 – €40), the costs of treating CIN2/3 (€500–€1100), the costs of treating invasive cervical cancer (€3000–€9000), and the specificity of colposcopy without histological verification before treatment used in the see-and-treat strategy (60–90%).

For the estimation of the probabilities of moving between health states, we used three Dutch cohort studies[11,12,14] and estimates retrieved from a previously developed cervical screening model.[16] The estimates are presented in Table 1. The performance of cytology in women treated for CIN2/3 was estimated from a Dutch cohort study[11] in which cytological follow up was based on the conventional Pap smear. Cervical smears were read according to the CISOE-A classification[20] and interpreted as normal (Pap1), borderline dyskaryosis (Pap2), mild dyskaryosis (Pap3a1), moderate dyskaryosis (Pap3a2), severe dyskaryosis (Pap3b), suspicion of carcinoma *in situ* (Pap4), or suspicion of carcinoma

Table 1. Model assumptions: disease parameters, test characteristics, and costs

Disease parameters			
From	**To**	**6-month transition probability (%)***	**References**
Treated HPV-positive CIN2/3	Well	83	Chua and Hjerpe[11], Zielinski *et al.*[12] and Hogewoning *et al.*[14]
	Persistent HPV infection	7	
	Persistent HPV-positive CIN2/3	10	
Well	Well	99	Bulkmans *et al.*[17] and Berkhof *et al.*[24]
	Recurrent HPV infection	1	
Persistent HPV infection	Well	33	Nobbenhuis *et al.*[11]
	Persistent HPV infection	50	
	Recurrent HPV-positive CIN2/3	17	
Recurrent HPV infection	Well	42	Bulkmans *et al.*[17] and Berkhof *et al.*[24]
	Recurrent HPV infection	52	
	Recurrent HPV-positive CIN2/3	6	
Recurrent HPV-positive CIN2/3	Well	30	Bulkmans *et al.*[17] and Berkhof *et al.*[24]
	Recurrent HPV-positive CIN2/3	60.6	
	Cervical cancer	9.4	
Persistent HPV-positive CIN2/3	Persistent HPV-positive CIN2/3	90.6	Bulkmans *et al.*[17] and Berkhof *et al.*[24]
	Cervical cancer	9.4	
Cervical cancer	Cervical cancer	100	Bulkmans *et al.*[17] and Berkhof *et al.*[24]
Test	**Test characteristics**	**Accuracy (%)**	
HPV testing by GP5+/6+	Analytical sensitivity	95	Jacobs *et al.*[21]
	Analytical specificity	100	Snijders *et al.*[18]
Conventional cytological testing	Specificity at first recall after 6 months	91	Nobbenhuis *et al.*[11] and Berkhof *et al.*[24]
	Specificity at second recall	97	
	Sensitivity	70	
Colposcopy	Specificity	70	Mitchell *et al.*[19]
Procedure	**Details**	**Cost (€) (2004)**	
Conventional cytology (including visit and indirect costs)		100	Berkhof *et al.*[24]
HPV testing	Laboratory costs GP5+6+	27	Berkhof *et al.*[24]
Colposcopy (including visit and indirect costs)	Colposcopically directed biopsy	233	Oostenbrink *et al.*[26]
	Colposcopy alone	168	
Treatment of recurrent CIN2/3 (including hospitalization and indirect costs)	75% LLETZ, 25% cone biopsy	695	Oostenbrink *et al.*[26]
	Colposcopically guided LLETZ	745	
Treatment Figo Ia (including hospitalization and indirect costs)		5629	Berkhof *et al.*[24] and van Ballegooijen *et al.*[25]

*The transition probabilities sum to 100% for each health state under the column head From.

(Pap5). A translation into the Bethesda 2001 classification is available.[20] The specificity of conventional cytology was assumed to improve with time after treatment. The rationale for this is that the treated cervix is likely to show transient cytological abnormalities related to the healing process. The HPV test used in two of three cohort studies as well as in the screening trial was the GP5+6+ polymerase chain reaction–enzyme immunoassay test.[21] The performance of this test is similar to that of the Hybrid Capture II HPV test (HCII) test in both screening[22] and follow up after treatment.[23] Notably, the sensitivity and specificity of the HPV test are the analytical sensitivity and specificity for detecting the presence of the virus in the cervix (Table 1).

For the calculation of the unit costs, we took a societal perspective and included costs of travelling and production loss. Future costs were discounted at a rate of 3% per year. Unit costs in Euros were taken from previous Dutch studies[24,25] or from the *Dutch Handbook for Economic Evaluations*[26] (Table 1). All unit costs were converted to 2004 prices using the consumer price index. Concerning the costs of treatment for persistent/recurrent CIN, we assumed that 75% of the women were treated by LLETZ and 25% by cone biopsy. Treatment with cone biopsy is prone to lead to complications, such as cervical stenosis and infertility. The costs of treating cervical stenosis were incorporated (assuming a 25% complication rate for which 50% requires operative treatment), but treatment for infertility was not included as an expense. The costs of screening 5 years after initial treatment were not taken into account. However, the costs of treating missed CIN2/3 lesions or missed cancer cases, detected at screening, were incorporated.

Results

The simulation results are shown in Table 2. The strategies with (adjunct) HPV testing had a lower proportion of women with missed post-treatment CIN2/3 than the current strategy of repeated cytological testing (at 6, 12, and 24 months). The largest reduction was observed for combined testing (cytology and HPV testing) at 6 and 24 months (Table 2, A1 and see-and-treat). Replacing the current strategy by combined testing at 6 and 24 months would spare one missed CIN2/3 case per 192 women treated for CIN2/3. This figure corresponds to a reduction of 26 missed CIN2/3 cases in the Netherlands where roughly 5000 women are annually treated for CIN2/3. Apart from a reduction in the proportion of missed CIN2/3 cases, a reduction was also observed for the mean duration until detection of post-treatment CIN2/3 except for the combined testing strategy with only one recall at 12 months (Table 2, B2).

Regarding the patient burden, the number of repeat smears was lower for the HPV testing strategies than for the current strategy. The colposcopy rate for women without post-treatment CIN2/3 (but with false-positive test results on cytology and/or HPV) was reduced for the strategy of HPV testing at 6 and 24 months (Table 2, A2) and the strategy of combined testing at 12 months only (Table 2, B2) but was elevated for strategies with HPV testing that include cytological testing at

Table 2. Simulation predictions for the current strategy of follow up after treatment for CIN2/3 (cytology at 6, 12, and 24 months) and six follow up strategies with adjunct HPV testing: A1 = cytological and HPV testing at 6 and 24 months, A2 = HPV testing at 6 and 24 months, A3 = HPV testing at 6 months; cytological and HPV testing at 24 months, see-and-treat = cytological and HPV testing at 6 months + see-and-treat; cytological and HPV testing at 24 months, B1 = cytological and HPV testing at 6 months, and B2 = cytological and HPV testing at 24 months. Calculations are for conventional Pap and GP5+6+ polymerase chain reaction–enzyme immunoassay and costs discounted at 3% per year

Screening strategy	Missed CIN2/3 or cancer (% total number treated)*	Number needed to treat**	Mean duration until detection of post-treatment CIN (months)	Colposcopy rate for women without post-treatment CIN (%)	Mean number of repeat smears	Discounted 5-year cost per woman (€)		
						Follow up	Treatment	Total
Current	0.69		8.2	16	3.42	350	122	472
A1	0.17	192	5.7	25	2.46	351	127	478
A2	0.21	208	6.3	13	2.32***	271	115	386
A3	0.18	196	6.3	16	2.37	303	120	423
See-and-treat	0.17	192	5.6	22	2.28	310	155	465
B1	0.47	455	5.5	19	1.35	222	106	328
B2	0.42	370	10.7	8	1.21	178	103	281

*Post-treatment CIN2/3 rate is estimated at 12.96 %.

**With respect to the current strategy.

***The number of HPV tests.

6 months (Table 2, A1, B1, and see-and-treat). Furthermore, the see-and-treat strategy also led to unnecessary treatments (colposcopically directed LLETZ) in 2.9% of women without post-treatment CIN.

The discounted 5-year costs of combined testing at 6 and 24 months (Table 2, A1 and see-and-treat) were similar to the costs of repeated cytological testing. For the other strategies with HPV testing, the discounted 5-year costs were lower than the costs of repeated cytological testing (reduction range €7–€191 per woman). The reduction was largest for combined testing at 12 months only (Table 2, B2).

When considering effectiveness, patient burden, and costs simultaneously, the strategies with HPV testing at 6 months and either combined testing at 24 months (Table 2, A2) or HPV testing at 24 months (Table 2: A3) are particularly interesting. They outperformed the current strategy on all three criteria as they led to a lower proportion of missed CIN2/3 cases (effectiveness), a lower colposcopy rate for women without post-treatment CIN, less repeat smears (burden) and lower discounted 5-year follow up costs per woman (costs).

The cost-effectiveness results are presented in Figure 3, which shows the proportion of missed CIN2/3 lesions plotted against the discounted 5-year follow up costs per woman. The curve in Figure 3 connects strategies of increasing costs that are more effective than those lying below the curve. Compared with the current strategy, all HPV testing strategies were cost-effective because they cost less and led to a reduction in missed CIN2/3. Combined testing at 6 months and combined testing at 6 and 24 months were dominated by the other strategies with HPV testing.

In Figure 4, the effect of varying the analytical sensitivity of the HPV test on the proportion of missed post-treatment CIN2/3 lesions is presented for the strategies with testing at 6 and 24 months (Figure 4, A1, A2, and A3) and for the strategy with combined testing at 12 months (Figure 4, B2). Combined testing at 6 and 24 months (Figure 4, A1) as well as HPV testing at 6 months and combined testing at 6 and 24 months (Figure 4, A3) was very robust against a change in the sensitivity of the HPV test as their curves in Figure 4 are nearly horizontal. Combined testing at 12 months (Figure 4, B2) was sensitive to the performance of the HPV test, but this strategy became inferior to the current strategy only when the sensitivity of the HPV test dropped below 88%. The results for the strategies with HPV testing were robust against changes in the sensitivity of cytology. Compared with the current strategy, all strategies with HPV testing resulted in fewer missed CIN2/3 cases even when the sensitivity of cytology was set at 95%. The cost savings obtained when replacing the current strategy by a strategy with HPV testing strategies were robust against the sensitivity of conventional cytology and the HPV test, the HPV evaluation costs, the costs of treating cervical lesions, and the post-treatment CIN2/3 rate. The cost savings were sensitive to the specificity of cytology, but the HPV testing strategies were nearly always less expensive than the current strategy. Finally, for the see-and-treat strategy, the specificity of colposcopy was varied between 60 and 90%, which had only a slight effect on the costs. The corresponding number of unnecessary CIN treatments ranged from 1 to 3.3%.

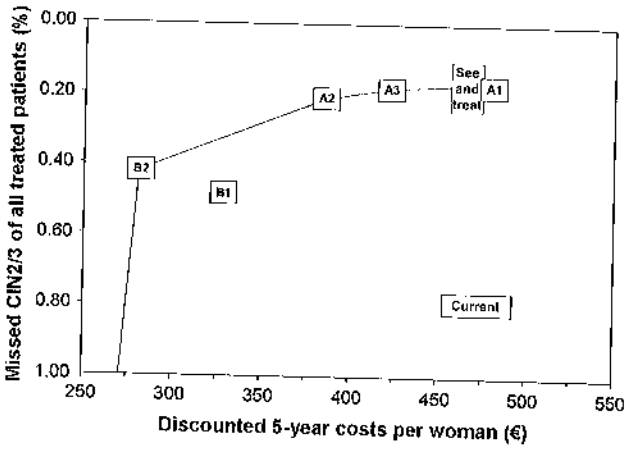

Figure 3. Cost-effectiveness plane for the current strategy (cytological testing at 6, 12, and 24 months) and six follow-up strategies with adjunct HPV testing: A1 = cytological and HPV testing at 6 and 24 months, A2 = HPV testing at 6 and 24 months, A3 = HPV testing at 6 months; cytological and HPV testing at 24 months, see-and-treat = cytological and HPV testing at 6 months + see-and-treat; cytological and HPV testing at 24 months, B1 = cytological and HPV testing at 6 months, and B2 = cytological and HPV testing at 24 months. The *x*-axis represents 5-year discounted costs per woman. The *y*-axis represents the proportion of women treated for CIN2/3 who have a persistent or recurrent CIN2/3 lesion that remains undetected in the follow up.

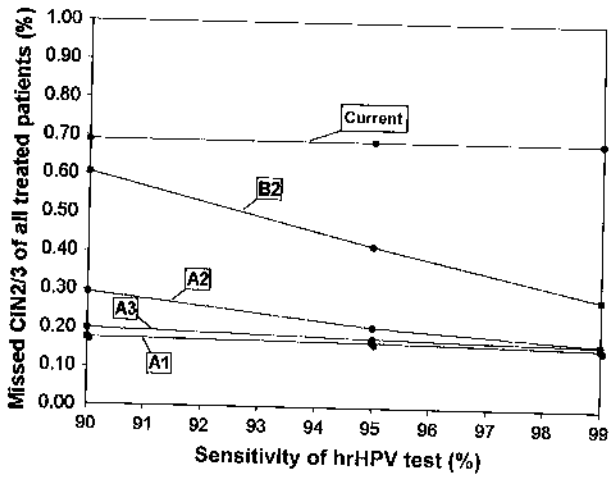

Figure 4. Proportion of missed CIN2/3 lesions against analytical sensitivity of HPV test for the current strategy (cytological testing at 6, 12, and 24 months), A1 = cytological and HPV testing at 6 and 24 months, A2 = HPV testing at 6 and 24 months, A3 = HPV testing at 6 months; cytological and HPV testing at 24 months, and B2 = cytological and HPV testing at 24 months. hrHPV = high-risk HPV.

Discussion and conclusions

Follow up after treatment for CIN2/3 is currently based on repeated cytological testing at 6, 12, and 24 months. We studied, by means of simulation modelling, whether this strategy can be improved by HPV testing. Our model predicted reductions in the number of missed post-treatment CIN2/3 ranging from 32 to 77% when including HPV testing in the follow up. With regard to the follow-up burden, our model suggested that HPV testing can be introduced in order to decrease the number of repeat smears without an increase in colposcopy rate. The low patient burden of strategies with HPV testing was reflected in the costs, which were lower for HPV testing strategies than for the current follow-up strategy.

The highest detection rate of post-treatment CIN was found for the strategies of combined testing (cytology and HPV testing) at 6 and 24 months. By sensitivity analyses, we showed that the reduction in missed CIN2/3 cases was robust against the sensitivity of the HPV test. This suggests that the number of recall dates can be safely reduced from three to two when including HPV testing. Even when follow-up testing was performed at only one recall date (cytological and HPV testing at either 6 or 12 months), the model predicted a reduction in the number of missed CIN2/3 cases compared with cytological follow up. However, the results from strategies with a single recall date relied strongly on the (high) sensitivity of the HPV test. Although the high sensitivity of the HPV test has been established in several studies,[27–29] we tend to favour strategies with two recall dates at 6 and 24 months. An additional argument for 'double recall' is that a single recall at 6 or 12 months may be too early in time to detect recurrent CIN2/3 lesions developed by re-infection of the cervical epithelium.

Unnecessary colposcopies, i.e. examinations that do not lead to detection of CIN2/3, were most common for HPV strategies with cytological testing at 6 months. This probably results from the established difficulty in interpreting cervical smears in recently treated women.[30] In order to limit the number of colposcopies, an attractive strategy would be to perform HPV testing alone at 6 months and both HPV and cytological testing at 24 months. This strategy yielded the same number of unnecessary colposcopies as the current strategy.

Our model showed that HPV testing did not lead to an increase in costs as the number of repeat smears is reduced by one or two. Cost savings were achieved for all strategies except for the strategy of combined testing at 6 and 24 months, which showed a small increase in costs. The reduction in costs was only substantial for strategies with one recall date, but as mentioned earlier, the calculations for those strategies relied heavily on the sensitivity of the HPV test. The model also predicted that the costs per woman did not substantially decrease when implementing a see-and-treat strategy. A drawback of the 'see-and-treat' strategy is the treatment of women without post-treatment CIN. In our study, the percentage of unnecessarily treated women was predicted at 2.9%. Therefore, we would favour a strategy where treatment is applied after histological verification of the lesion.

Integrating results for costs, detection of post-treatment CIN, and patient burden, a strategy consisting of HPV testing alone at 6 months and both HPV and cytological testing at 24 months is particularly interesting. For this strategy, our model predicted a nearly optimal detection rate of post-treatment CIN, an unchanged number of unnecessary colposcopies, and cost savings of €49 per woman compared with current follow up of cytological testing at 6, 12, and 24 months.

Post-treatment CIN2/3 rates may vary across patient populations, and figures ranging from 5 to 15% have been reported.[1–5] In our model, we varied the post-treatment CIN2/3 rate from 5 to 15%, but this did not lead to different cost-effectiveness outcomes. Other important model parameters that may affect the outcomes are the performances of cytology and the HPV test. We found that the HPV testing strategies performed well and led to fewer missed CIN2/3 cases than current follow up, even for a sensitivity of cytology of 90%. In the literature, sensitivities are much lower than 90%, both for conventional[27,28,31] and liquid-based cytology[32–34] Regarding the performance of the HPV test, we considered ranges of values for the analytical sensitivity and specificity that are in agreement with the internationally observed clinical sensitivities and specificities of both HCII and GP5+/6+.[22] Again, cost-effectiveness results were not substantially affected. For the costs of treatment for post-treatment CIN, we assumed that 75% of the women were treated by LLETZ and 25% by cone biopsy. Because information about the actual treatment of post-treatment CIN is limited, we varied post-treatment costs from the costs of LLETZ only (€500) to the costs of cone biopsy only (€1100). However, cost-effectiveness results were not affected. Therefore, we believe that the recommendations made on the basis of the cost-effectiveness calculations are also applicable to countries with different test accuracies, post-treatment CIN2/3 rates, and management of recurrent CIN.

In most western European countries, follow up after treatment for high-grade CIN is based on the 'current' strategy in this study (cytology at 6, 12, and 24 months with referral to the population cervical screening programme after three negative smears). The NHS guidelines adhered to in the UK differ from this strategy as annual cytological follow up for at least 8 years is recommended after three negative smears. Because our model showed that by adding HPV testing, the number of smears can be safely reduced from three to two, the 12 month follow-up date can be omitted. Furthermore, because the percentage of missed CIN2/3 for strategies with combined HPV and cytological testing was predicted to be very low, annual cytological follow up after three negative smears, as

is practised in the UK, may be replaced by postponing retesting to 3 years after the double-negative smear.[35]

A limitation inherent to a modelling study is the fact that the model is based on structural and parametric assumptions that may not fully capture the complexity of clinical reality. However, our model was firmly based on clinical observations, as various sources of longitudinal information about high-risk HPV presence and cytological testing after treatment for CIN2 and CIN3 lesions were used[11,12,14], and the results were robust against changes in the model parameters. In addition to the cost-effectiveness results, it may still be sensible to verify whether HPV testing also leads to earlier detection of high-grade CIN by means of a prospective trial. A possible design is a two-armed trial in which cytological testing at 6 months is compared with HPV testing at 6 months. Under the assumption of a post-treatment CIN2/3 rate of 10% at 6 months, about 2500 women will be needed in each arm of the trial to achieve a power of 80% to detect a difference in CIN2/3 detection rate at 6 months.

The results of this study support the use of high-risk HPV testing in monitoring women after treatment for CIN2 and CIN3 lesions. The clinical value of adding HPV testing has been shown before by several authors.[11,12,23,36] In addition to previous clinical evidence, our cost-effectiveness results show that HPV testing is also justified from an economic perspective: implementation can be achieved without increasing costs or patient burden by reducing the number of repeat smears from three to two, provided that only HPV testing is performed at the first follow-up date.

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