

### What is already known on this topic

Preterm birth and choriamnionitis are associated with cerebral palsy and infection with neurotropic viruses in neonates and infants can lead to neurological disability, including cerebral palsy

### What this study adds

Stored dried neonatal blood spots, from babies who were diagnosed subsequently to have cerebral palsy, and from control babies, often contain nucleic acids from neurotropic viruses

Herpes group A (including cytomegalovirus) nucleic acids were found more often in neonatal blood spots of preterm control babies than in control babies born at term

Herpes group B nucleic acids were found more often in neonatal blood spots of babies who were diagnosed subsequently to have cerebral palsy than in control babies

The presence of neurotropic viral nucleic acids in the blood of newborns and the subsequent diagnosis of cerebral palsy are significantly associated

thrombophilia and cerebral palsy has been found in our cohort.<sup>9</sup>

### Conclusions

Exposure to viral infection is common in newborn babies in South Australia, especially in preterm babies.

The risk of cerebral palsy is nearly doubled with exposure to herpes group B viruses but may require other factors or clinical events for brain damage and subsequent cerebral palsy to occur. Future studies are planned to investigate these factors.

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## Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: modelling study

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### Abstract

**Objectives** To predict the incremental lifetime effects, costs, and cost effectiveness of using human papillomavirus testing to triage women with borderline or mildly dyskaryotic cervical smear results for immediate colposcopy.

**Design** Modelling study.

**Setting** Three centres participating in NHS pilot studies, United Kingdom.

**Population** Women aged 25-64 with borderline or mildly dyskaryotic cervical smear results.

**Interventions** Screening using conventional cytology, liquid based cytology, and four strategies with different age cut-off points and follow-up times that used combined liquid based cytology and human papillomavirus testing (adjunctive human papillomavirus testing).

**Results** The model predicts that compared with using conventional cytology without testing for human papillomavirus, testing for the virus in conjunction with liquid based cytology for women (aged 35 or more) with borderline or mildly dyskaryotic cervical smear results would cost £3735 (€5528; \$6474) per life year saved. Extending adjunctive human papillomavirus testing in combination with liquid based cytology to include women aged between 25 and 34 costs an additional £4233 per life year saved. Human papillomavirus testing is likely to reduce



People involved in study, table, and figure are on bmj.com



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Editorial by Schiffman and Castle and p 83

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lifetime repeat smears by 52-86% but increase lifetime colposcopies by 64-138%.

**Conclusions** Testing for human papillomavirus to manage all women with borderline or mildly dyskaryotic cervical smear results is likely to be cost effective. The predicted increase in lifetime colposcopies, however, deserves careful consideration.

## Introduction

Human papillomavirus is present in most cases of cervical cancer.<sup>1</sup> Testing for the virus could be incorporated in a cervical cancer screening programme to stratify women with minor cytological abnormalities for immediate colposcopy.<sup>2,3</sup> In the United Kingdom, women with borderline or mild smear results are recalled for repeat smears every six months and only return to routine screening intervals after three consecutive negative test results.

In 2000-1 the Department of Health established a series of pilot sites to assess both liquid based cytology and human papillomavirus testing of women with borderline or mildly dyskaryotic smear results. The clinical and epidemiological outcomes observed at 12 months are presented elsewhere.<sup>4</sup>

We compared the lifetime effects, costs, and cost effectiveness of using cytology alone with using combined cytology and triage on the basis of human papillomavirus testing to manage women with borderline and mildly dyskaryotic smear results in the United Kingdom. We used the current policy of screening women aged 25-49 every three years and women aged 50-64 every five years.

## Methods

We used the final results of the NHS pilot studies. As no long term follow-up data are available, we used a mathematical model to estimate the lifetime effects, costs, and cost effectiveness. We used an adapted version of a prior natural history model.<sup>5</sup> Our model predicted the lifetime costs and effects of alternative strategies for screening from age 15 to death. The analysis was from the health service perspective.

### Screening strategies

We compared current screening protocols using conventional cytology with five strategies (box). In all strategies, women with moderate or severe cytology results are referred directly for colposcopy, inadequate cytology results are retested, and women with normal results return to routine screening.

When only cytology was used for repeat testing every six months (strategies A and E and women aged less than 35 in strategy D), women were referred for colposcopy after three borderline or two mildly dyskaryotic smear results. Women only returned to routine screening after three consecutive negative results, again at six month intervals.

When cytology and human papillomavirus tests were used for repeat testing, women were referred for colposcopy if the repeat test was positive for human papillomavirus, or the cytology result was mild dyskaryosis or worse, or both, otherwise they returned to routine screening.

### Alternative strategies for screening women for cervical cancer

#### Strategy A

Liquid based cytology only

#### Strategy B

Combined liquid based cytology and human papillomavirus testing (hybrid capture II assay for human papillomavirus DNA; Digene, Abbott, Maidenhead) for women with borderline or mildly dyskaryotic results. Women who test positive for the virus are referred for immediate colposcopy and women who test negative are recalled at six months for repeat cytology and human papillomavirus testing (this strategy reflects the original pilot protocol)

#### Strategy C

Same as strategy B except that women aged less than 35 who initially tested positive are not referred for colposcopy. Even if repeat tests for these women give negative results, they are recalled for a third combined test at 12 months (this strategy reflects the amended pilot protocol)

#### Strategy D

Combined liquid based cytology and adjunctive human papillomavirus testing (as described in strategy B) for women aged 35 or more, and liquid based cytology only for women under 35 (as described in strategy A)

#### Strategy E

Combined liquid based cytology and adjunctive human papillomavirus testing (as described in strategy B) but no testing for human papillomavirus in repeat tests

### Natural history

From the literature we took the probability of transitions between health states (healthy, human papillomavirus only, cervical intraepithelial neoplasia (CIN) grades 1, CIN-2, or CIN-3, and invasive cancer stages I-IV), and the probability of symptoms in an unscreened population.<sup>5</sup> We chose the natural history model as it has been validated<sup>5</sup> and reflects current scientific understanding of preinvasive disease.

All probabilities of transition were calculated for six months, reflecting the cycle length of the model. We adapted the model for the United Kingdom using local data on survival from invasive cancer<sup>6</sup> and mortality from other causes.<sup>7,8</sup> See [bmj.com](http://bmj.com) for these and other variables in the model.

We assumed that all cases of preinvasive and invasive cervical cancer begin with human papillomavirus infection, that the American categories for low grade and high grade squamous intraepithelial lesions are equivalent to CIN-1 and CIN-2 or CIN-3, and that women who survive after five years have the same life expectancy as women in the general population.<sup>9</sup>

### Attendance and effectiveness of screening

Attendance rates at routine screening were based on the percentage of eligible women who attended at least once over five years.<sup>10</sup> We estimated attendance rates for repeat screening and colposcopy using data from the pilots.<sup>4</sup> We assumed that if women did not attend they would only be recalled for screening at the next screening round.

Estimates of sensitivity and specificity for human papillomavirus using the hybrid capture II assay were

identified from a meta-analysis.<sup>11</sup> These studies followed up women with both positive and negative test results at colposcopy or histology thus minimising verification bias. It is assumed that sensitivity and specificity for human papillomavirus was the same for CIN-1 and human papillomavirus.

At baseline we used estimates of the sensitivity and specificity of conventional cytology from an earlier study.<sup>12</sup> For liquid based cytology, sensitivity estimates for detecting CIN-1 were derived from a recent meta-analysis<sup>13</sup> and the positive predictive values from the pilots were used to estimate the sensitivity of CIN-2 or CIN-3 ranging from 3.6% (95% confidence interval – 1.2% to 5.0%). See [bmj.com](http://bmj.com) for further details of the assumptions used about the effectiveness of screening.

### Costs

We used data from the pilot sites to calculate the unit costs of liquid based cytology, conventional cytology, and human papillomavirus testing. Staff time was estimated from record sheets sent to a random sample of smear takers and all smear readers at the laboratories. We obtained costs of conventional cytology equipment and consumables from the laboratory; estimates of the indicative market price for liquid based cytology and human papillomavirus equipment were made in consultation with the NHS Purchasing and Supplies Agency. Unit costs for primary care were taken from the literature and laboratory staff costs estimated using the mid-point of staff salaries.<sup>14</sup> We adjusted the costs for cytology to incorporate the cost of cytology results that were inadequate (that is, where slides were non-interpretable for technical reasons).<sup>4</sup> All costs are converted to 2001-2 prices using the NHS Health and Community Price Index and are reported in sterling.

We used a detailed patient audit of the costs of invasive cancer over five years, including treatment and palliative care.<sup>15</sup> We also used audit data on costs associated with cervical intraepithelial neoplasia, including initial diagnosis at colposcopy, management, and any subsequent colposcopy follow-up (including adverse events).<sup>15</sup> A single outpatient attendance was used as a proxy cost for a colposcopy when there was no cervical intraepithelial neoplasia.<sup>16</sup>

### Analysis

We discounted future costs and future benefits at 3.5% for the first 30 years and 3% thereafter.<sup>17</sup> To estimate the comparative cost effectiveness between the strategies, we first ranked the strategies in ascending order of effectiveness. We excluded options that were dominated (less effective and more costly than an alternative) and strategies that were extended dominated (inside the cost effectiveness frontier). For the remaining strategies we calculated the incremental costs, effects, and cost effectiveness ratios.

To test the effect of uncertainty about a variable, we carried out one way and probabilistic sensitivity analyses. In the one way sensitivity analysis we used the minimum and maximum estimates for each variable. As the data for estimating the sensitivity of conventional cytology were based on one UK study, we used additional data from the international literature to test uncertainty around these estimates. We carried out a random effects meta-analysis to synthesise the result of a systematic review.<sup>18</sup> The combined estimate of sensitivity to detect CIN-1 was 0.46 (95% confidence

Estimates of average lifetime resource use, risk of treatment for invasive cancer, and mortality

Lifetime resource use	Strategy				
	A	B	C	D	E
Average No of routine smears	9.4	9.4	9.4	9.4	9.4
Average No of smears in surveillance	0.77	0.11	0.24	0.37	0.30
Average No of human papillomavirus tests after initial routine smear	0.00	0.42	0.43	0.25	0.40
Average No of human papillomavirus tests in surveillance	0.00	0.11	0.21	0.08	0.00
Average No of colposcopies	0.21	0.41	0.40	0.31	0.35
Average lifetime probability of treatment for invasive cancer	0.02	0.017	0.013	0.013	0.013
Lifetime risk of death from invasive cancer	0.0049	0.0045	0.0046	0.0046	0.0045

interval 0.29 to 0.72) and to detect CIN-2 or CIN-3 was 0.84 (0.75 to 0.94).

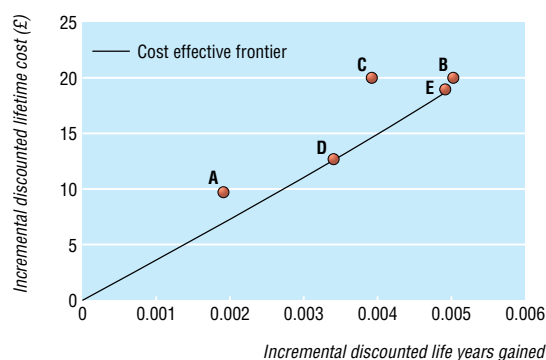
For the probabilistic sensitivity analysis,<sup>19</sup> we used simulation to generate a series of estimates for the costs and effects of each strategy by sampling from the distribution of each model variable. We then used a net benefit framework to plot cost effectiveness acceptability curves showing optimal strategies at different values that society would be willing to pay for a gain in life years (see [bmj.com](http://bmj.com)).<sup>20</sup>

## Results

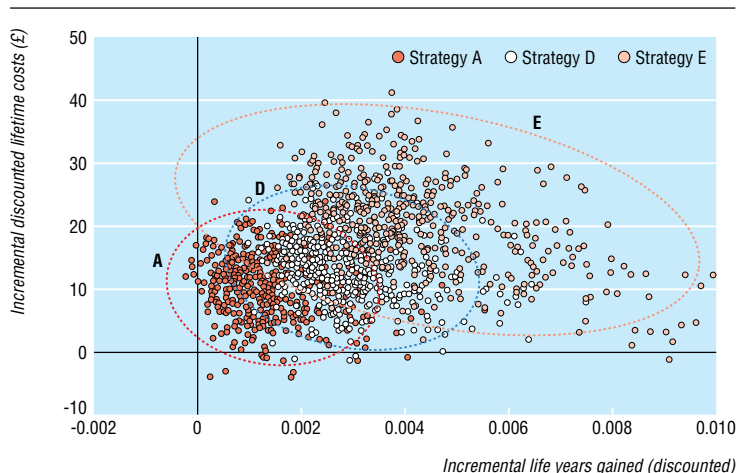
Our model predicted a peak prevalence for human papillomavirus at age 22, tailing off significantly after age 30. The prevalence for CIN-1 peaks at age 25. The rates of human papillomavirus for women aged 30-60 are consistent with UK data on prevalence of the virus.<sup>21</sup> Allowing for death from other causes, the model predicts a lifetime risk of death from invasive cancer of 1.4% in the absence of screening.

Compared with screening using conventional cytology, the next most cost effective strategy seems to be combined liquid based cytology and human papillomavirus testing to prioritise women aged 35 or more with borderline or mildly dyskaryotic smear results for immediate colposcopy (strategy D; fig 1). Although liquid based cytology alone (strategy A) is cheaper than strategy D, it also seems less effective and has a higher cost effectiveness ratio. Therefore it is likely to be more cost effective to use strategy D.

Strategies B, C, and E provide additional health gain compared with strategy D but are also more expensive. Strategy C is inside the cost effectiveness frontier and is likely to be dominated (fig 1). These



**Fig 1** Incremental discounted lifetime costs and effects of alternative screening strategies for cervical cancer compared with screening using conventional cytology only



**Fig 2** Results of probabilistic sensitivity analysis. Ellipses show 95% confidence interval for each strategy

results suggest that strategy E may save slightly fewer life years but is slightly less expensive than strategy B.

**Lifetime resource use and invasive cancer mortality**

The table reports estimated lifetime use of resources and mortality from invasive cancer. Compared with screening using only liquid based cytology, there is a 52-86% reduction in the number of surveillance smears required with the four strategies using human papillomavirus testing. With such strategies, however, the average number of lifetime colposcopies is increased by between 64% and 138%. This increase is lowest when only women aged more than 35 are tested for human papillomavirus.

The baseline model predicts a 0.49% lifetime risk of death with liquid based cytology, which compares with current UK data of a 0.56% lifetime risk of death from invasive cancer.<sup>7</sup> The model predicts that for women with a borderline result from a routine smear test, 67% aged less than 35 and 50% aged 35 or more would test positive for human papillomavirus, and that for women with a mild test result, 81% aged less than 35 and 67% aged 35 or more would test positive.

**Sensitivity analyses**

In the one way sensitivity analysis the ranking of the strategies remained similar. The costs associated with liquid based cytology, human papillomavirus testing, and colposcopy had a significant influence on overall costs.

Considerable uncertainty surrounds both the incremental costs and incremental gains that would accrue from using human papillomavirus testing as a triage for women with borderline or mildly dyskaryotic results (fig 2). A negative correlation also exists in the human papillomavirus triage strategies between costs and effects. Finally, the cost effectiveness acceptability frontier shows that if a decision maker is willing to pay between £7500 (€11 100; \$13 000) and £30 000 per life year gained, strategies when human papillomavirus testing is added to liquid based cytology screening to prioritise all women with borderline or mild dyskaryotic smear results for immediate colposcopy give the greatest net health benefit (see bmj.com).

**Discussion**

Using human papillomavirus testing to triage women with borderline or mild cervical smear results is more expensive than repeat cytology but saves slightly more lives. This gain in life expectancy is related to referring women earlier to colposcopy and to minimising loss to follow-up after the initial smear result. Our study provides further analysis of alternative strategies for adding human papillomavirus testing. It suggests that the most likely strategy to be cost effective (if society is willing to pay between £7500 and £30 000 per life year) uses human papillomavirus testing to triage all women with an initial borderline or mild smear result, using cytology to follow up only women with a negative test result for human papillomavirus.

Our findings are consistent with previous modelling exercises, which indicate that human papillomavirus triage potentially saves slightly more lives than repeat testing.<sup>22 23</sup> In this paper we also explored the uncertainty in the model's variables using a probabilistic sensitivity analysis. Although we have explored a range of screening strategies, further potential options exist such as referring all mild cytology results directly to colposcopy or primary human papillomavirus testing.

The predicted substantial increase in lifetime referral for colposcopy with human papillomavirus testing is of concern (table). Nevertheless our conclusions on the cost effectiveness of human papillomavirus testing are robust in the sensitivity analyses when the estimates for cost and effectiveness of colposcopy are varied.

Finally, this study is limited by the lack of data on the quality of life implications and societal costs of using human papillomavirus testing to triage women compared with repeat testing. A trade-off exists between the predicted potential gains in life expectancy and reduction in surveillance smears (52-86%)

**What is already known on this topic**

Previous models indicate that testing for human papillomavirus to triage women with borderline smear results saves slightly more lives than repeat testing

However, conclusions on the cost implications differ between studies

**What this study adds**

Testing for human papillomavirus in women with low grade cytological abnormalities is likely to be cost effective under current UK screening protocols

New cost, epidemiological, and clinical data collected during a large pilot study were used to estimate cost effectiveness

A trade-off exists between the predicted benefits of a small potential gain in life expectancy and reduced surveillance smears from human papillomavirus testing, and the negative implications of an increase in lifetime referrals for colposcopy

using human papillomavirus testing, and the negative implications for women of increased lifetime colposcopies (64-138%).

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## Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study

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### Abstract

**Objective** To assess the effect of introducing testing for human papillomavirus combined with liquid based cytology in women with low grade cytological abnormalities.

**Design** Observational before and after study.

**Setting** Three cervical screening laboratories, England.

**Participants** 5654 women aged 20-64 with low grade cytological abnormalities found at routine cervical screening in a pilot; 5254 similar women in the period before the pilot.

**Interventions** Human papillomavirus testing combined with liquid based cytology in the management of women with borderline or mildly dyskaryotic cervical smear results compared with conventional smear tests, with immediate referral to

colposcopy of women positive for human papillomavirus.

**Results** 57.9% (3187/5506) of women tested in the pilot were positive for human papillomavirus. The rate of repeat smears fell by 74%, but the rate of referral to colposcopy for low grade cytological abnormalities more than doubled. The estimated negative predictive value of human papillomavirus testing varied between 93.8% and 99.7%.

**Conclusion** The addition of testing for human papillomavirus in women with low grade cytological abnormalities resulted in a reduction in the rate of repeat smears, but an increase in rates of referral to colposcopy.



Members of the pilot studies group are on bmj.com

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Editorial by Schiffman and Castle and p 79

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