Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of human papillomavirus (HPV) DNA testing in screening programmes for cervical cancer. The first strategy (“HPV triage”) involved cytology throughout a woman's lifetime, using HPV testing as a triage strategy for equivocal cytology results. The second strategy (“combination testing”) involved cytology until the age of 30 years, followed by HPV testing in combination with cytology thereafter.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The hypothetical populations comprised women currently eligible for screening in the UK, The Netherlands, France and Italy.

Setting
The study had a hypothetical community setting in one of the countries studied (the UK, The Netherlands, France, or Italy).

Dates to which data relate
The effectiveness and resource use data referred to 1992 to 2004. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.

Modelling
An existing model was updated to model the natural history of cervical carcinogenesis. The model had four states of cervical health. These were healthy, infection with HPV, Grade 1 cervical intraepithelial neoplasia (CIN) and Grade 2 CIN. The model also contains three further health states relating to local cancer, regional cancer and distant cancer. The model allowed for forward and backward transitions between cervical health states. Women in the model may die from cervical cancer or from other causes. The model was calibrated using country-specific data on the age-specific risk of cervical cancer without screening, which was necessarily based on historical data. The model was then validated by simulating the current cytology screening programme in each country and comparing the model results to recent empiric data from the International Agency for Research on Cancer. Several assumptions were required for the model, and these were presented in full in the paper.
Outcomes assessed in the review
The outcomes assessed included the risk of progressing through the states of cervical health from healthy to HPV infection to CIN Grade 1 then Grade 2 to 3, and from there through the stages of invasive cervical cancer. The review also assessed the sensitivity and specificity of conventional cytology and the HPV DNA test, and the sensitivity and specificity of the two tests in combination.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
At least 30 studies were included in the effectiveness review. The authors presented selected input parameters, which might have been due to space limitations for the article.

Methods of combining primary studies
The authors did not report the methods used to combine the primary studies. It appears that some study results might have been combined for inclusion in the model.

Investigation of differences between primary studies
Not reported.

Results of the review
The monthly probability of HPV infection was estimated to range from 0.00028 to 0.00948 in the UK, France and Italy, and from 0.00028 to 0.01896 in The Netherlands.

The monthly probability of progressing from HPV infection to Grade 1 CIN was 0.0046.

The monthly probability of progressing from Grade 1 CIN to Grade 2 - 3 CIN was between 0.0011 and 0.0039.

The monthly probability of progressing from Grade 2 - 3 CIN to locally invasive cervical cancer was 0.0040.

The sensitivity of HPV DNA testing was 88.4% and the specificity was 94.7%.

In the UK, France and Italy, the sensitivity HPV DNA testing in combination with conventional cytology was 95% and the specificity was 92.9%. In The Netherlands, the sensitivity was 96% and the specificity was 92.9%.

Measure of benefits used in the economic analysis
Life-years saved were used as the primary measure of health benefit in the economic analysis.

**Direct costs**
The study included direct medical costs from a societal perspective. Such costs included the cost of the tests, treatment, staff time and office visits. The cost data were taken from published cost-effectiveness studies and costing studies. The resource use quantities were not reported separately from the costs. A model was used to extrapolate the costs to a lifetime population setting. Future costs were discounted at a rate of 3% per annum. The study reported the total average lifetime costs. The costs from the UK had been updated to 2004 British pounds sterling using the UK Consumer Price Index and then converted to US dollars using the Federal Reserve exchange rate. The costs from the other three countries were updated to 1999 using the Consumer Price Index and then converted to 2004 Euros using Euro/ECU exchange rates. These were then converted to US dollars using the Federal Reserve exchange rate.

**Statistical analysis of costs**
Sampled data were not available for the costs.

**Indirect Costs**
The study included the cost of patient time taken for screening and treatment. The authors did not provide details of how patient time was costed.

**Currency**
US dollars ($). British pounds sterling and Euros were converted from 2004 values to US dollars using the Federal Reserve exchange rate.

**Sensitivity analysis**
The authors undertook extensive one-way sensitivity analyses to explore uncertainty and variability in the data. Among the parameters varied was the frequency of the screening interval, the type of follow-up for HPV DNA positive women, and the type of test used for conventional cytology (to assess the use of liquid-based cytology).

**Estimated benefits used in the economic analysis**
The status quo in the UK was estimated to have a total discounted life expectancy of 28.7132 years. HPV triage with the same screening intervals as conventional cytology in the UK was estimated to have a total discounted life expectancy of 28.7149. Combination testing with the same screening intervals as conventional cytology in the UK was estimated to have a total discounted life expectancy of 28.7256.

Based on the same screening interval, conventional cytology in The Netherlands was associated with a life expectancy of 28.8318 years, compared with 28.8322 years for HPV triage and 28.8402 years for combination testing.

Based on the same screening interval, conventional cytology in France was associated with a life expectancy of 29.1255 years, compared with 29.1254 years for HPV triage and 29.1317 years for combination testing.

Based on the same screening interval, conventional cytology in Italy was associated with a life expectancy of 29.0804 years, compared with 29.0802 years for HPV triage and 29.0889 years for combination testing.

The health benefits were discounted at a rate of 3% per annum.

**Cost results**
The costs were discounted at a rate of 3% per annum. The status quo in the UK was estimated to have a total average per woman lifetime cost of $313. HPV triage with the same screening intervals as conventional cytology in the UK was
estimated to have a total average lifetime cost of $306. Combination testing with the same screening intervals as conventional cytology in the UK was estimated to have a total average lifetime cost of $498.

Based on the same screening interval, conventional cytology in The Netherlands was associated with a total average lifetime cost of $236, compared with $228 for HPV triage and $372 for combination testing.

Based on the same screening interval, conventional cytology in France was associated with a total average lifetime cost of $146, compared with $136 for HPV triage and $303 for combination testing.

Based on the same screening interval, conventional cytology in Italy was associated with a total average lifetime cost of $202, compared with $190 for HPV triage and $359 for combination testing.

**Synthesis of costs and benefits**

The costs and benefits were combined to calculate the cost per life-year saved. Cost-effectiveness ratios were calculated and strategies were eliminated according to the conventional rules of dominance and extended dominance. The remaining strategies were considered cost-effective if the incremental cost-effectiveness ratio was less than three times the country-specific gross domestic product per capita.

The preferred strategy in every country was estimated to be combination testing at 3-year intervals. The country-specific incremental cost-effectiveness ratios for this strategy were $75,900 per life-year saved in the UK, $37,400 in The Netherlands, $26,300 in France and $25,600 in Italy. The authors stated that the results were most sensitive to changes in the relative performance and costs of the different screening tests. If the sensitivity of combination testing fell below 65%, it would not be considered cost-effective in any of the four countries examined.

**Authors’ conclusions**

The inclusion of human papillomavirus (HPV) DNA testing may be more cost-effective than conventional cytology screening for cervical cancer.

**CRD COMMENTARY - Selection of comparators**

The comparators were chosen to represent current practice in the countries examined in the study. You must decide the relevance of these screening programmes to your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review had been undertaken. They also did not provide much detail of the methods used to identify the primary studies. Consequently, it is not possible to comment on the quality of the review, the quality of the included studies, and the methods used to combine the data from the primary studies. This increases the uncertainty in the study results. The omission of this further detail might have been due to space limitations for this extensive article.

**Validity of estimate of measure of benefit**

A model was used to estimate life expectancy as the measure of health benefit. The authors calibrated the model to country-specific data, and validated the model using data on conventional cytology in each country. The type of model used to estimate life expectancy was appropriate.

**Validity of estimate of costs**

The authors stated that the study was conducted from a societal perspective, and they appropriately included the patients’ time costs in the analysis. However, the methods used to cost patient time were not reported, which increases the uncertainty in the study results. Other direct medical costs were derived from published studies. Again, the methods used to identify these primary studies were inadequately reported, which increases the uncertainty in the model results.
The costs and the quantities were not reported separately. Given the complex nature of the model used to estimate costs for each of the four countries, it is unlikely that additional information on the costs and quantities would have helped readers generalise the results to their own setting. The omission of further detail might have been due to space limitations for this article. Several one-way sensitivity analyses were conducted to explore variations in resource use and cost. These were not reported in detail, also possibly because of space constraints.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies. The study was designed to compare the cost-effectiveness of HPV DNA testing in four countries, thus generalisability to other settings was well addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported that the lack of country-specific data on certain model parameters and the lack of data on the cost and quality of life decrement associated with informing women that they have high-risk HPV infection represent limitations in their analysis. They also stated that they limited their analysis to tested strategies for which data were available.

**Implications of the study**
The authors suggested that the results of studies like theirs should be used in policy-making.

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