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## Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine

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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 human papillomavirus (HPV) 16/18 vaccine in a population with an organised cervical cancer-screening programme. Current screening practice was one of the alternative strategies considered. In addition, a variety of cancer prevention control policies that comprised a primary prevention component (i.e. vaccination) and/or a secondary cervical cancer prevention component (i.e. cervical screening programme starting at a specific age and conducted at a specific frequency) were considered in the analysis. Cervical screening could be performed either with conventional or liquid-based cytology. The authors considered screening intervals of 1 to 5 years and liquid-based cytology initiated at age 18, 21, 25, 30 and 35. When considering all possible combinations of these alternative characteristics for the programme, there were 80 potential cervical cancer prevention strategies.

### Type of intervention

Primary prevention and secondary prevention.

### Economic study type

Cost-utility analysis.

### Study population

The targeted population comprised a hypothetical cohort of females over 12 years old.

### Setting

The authors did not report a specific setting for their analysis. However, as the health technology studied was an intervention added to an existing cervical cancer-screening programme, the setting is likely to have been either primary and/or secondary care. The economic study was conducted in the USA.

### Dates to which data relate

The effectiveness data used to populate the model were selected from papers published between 1968 and 2003. The cost data were collected from papers published between 1998 and 2004, and expressed in 2002 US dollars.

### Source of effectiveness data

The effectiveness data were obtained from a review of completed studies.

### Modelling

The authors developed a Markov Model that was capable of simulating the natural history of HPV infection and cervical carcino-genesis, and incorporating the underlying type-specific HPV distribution within each stage of cervical disease. The time horizon of the analysis was the entire lifetime. The length of the Markov cycles was 6 months. The health states were defined by five general categories of HPV infection, three categories of cervical disease, and three categories of invasive cervical cancer. The HPV infection categories were persistent HPV16/18, persistent high-risk

non-16/18 HPV types, persistent low-risk HPV types, transient low-risk or high-risk HPV types, and no HPV. The cervical disease categories were no neoplasia or cancer, cervical intraepithelial neoplasia (CIN)1 and CIN2,3. The invasive cervical cancer categories were local, regional and distant. The model assumed a cohort of 100,000 adolescent girls subject to age-dependent probabilities of acquiring and clearing HPV infection starting at age 13 years.

### **Outcomes assessed in the review**

The outcomes assessed were:

the incidence and clearance of HPV infection;

the natural history of CIN;

the natural history of invasive cervical cancer (in terms of the probabilities of progression from one stage to the next, and the probabilities of developing symptoms, and of survival at 5 years for each of the stages);

vaccine characteristics (i.e. efficacy, age at vaccination and vaccine coverage);

screening test characteristics (specificity and sensitivity); and

health-related quality of life for the different stages of detected invasive cancer before and after treatment.

Unless stated otherwise, the parameters estimated were reported as 6-month probabilities.

### **Study designs and other criteria for inclusion in the review**

No inclusion or exclusion criteria were explicitly stated, although the authors reported that the values for the sensitivity and specificity of cervical cytologic screening were obtained from large clinical trials and recent comprehensive reviews.

### **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**

In total, 56 studies provided data to populate the model. Thirty-four were used for transition probabilities, 12 for sensitivities and specificities of tests, 2 for vaccine characteristics, 3 for health-related quality of life weights, and 5 were modelling studies.

### **Methods of combining primary studies**

Not reported.

### **Investigation of differences between primary studies**

Not reported.

### Results of the review

The transition probabilities for the incidence and clearance of HPV infection were:

for females who moved from normal to persistent HPV DNA, between 0.010 and 0.030 for age younger than 35 years and between 0.02 and 0.006 for age 35 or older;

for females who moved from normal to transient HPV DNA, between 0.030 and 0.070 for age younger than 35 and between 0.02 and 0.010 for age 35 or older DNA; and

for females who moved from HPV DNA to normal, between 0.100 and 0.460 independent of age.

The transition probabilities for the natural history of CIN were:

for females who moved from HPV DNA to CIN1, between 0.030 and 0.060 for age younger than 35 and between 0.007 and 0.015 for age 35 or older;

for females who moved from HPV DNA to CIN2,3, between 0.001 and 0.006 for age younger than 35 and between 0.004 and 0.025 for age 35 or older;

for females who moved from CIN1 to CIN2,3, between 0.008 and 0.050 for age younger than 35 and between 0.037 and 0.220 for age 35 or older; and

for females who moved from CIN2,3 to invasive cancer, between 0.001 and 0.002 for age younger than 35, between 0.006 and 0.012 for 35- to 64-years-old, and between 0.001 and 0.020 for age 65 or older.

Independent of age, the probability of a female changing from CIN1 to HPV was between 0.440 and 0.540;

from CIN1 to normal, between 0.110 and 0.540;

from CIN2,3 to HPV, between 0.010 and 0.030; and

from CIN2,3 to normal, between 0.001 and 0.003.

The transition probabilities for the natural history of invasive cervical cancer were:

1.1500 (range: 0.1125 - 0.1875) for progression from Stage I to Stage II;

0.1600 (range: 0.1200 - 0.2000) for progression from Stage II to Stage III;

0.2252 (range: 0.16 - 0.2815) for progression from Stage III to Stage IV;

0.0750 (range: 0.0563 - 0.0938) for developing symptoms in Stage I;

0.1125 (range: 0.0844 - 0.1406) for developing symptoms in Stage II;

0.3000 (range: 0.2250 - 0.3750) for developing symptoms in Stage III; and

0.4500 (range: 0.3375 - 0.5625) for developing symptoms in Stage IV.

The probability of survival at 5 years was:

0.84 (range: 0.63 - 0.98) for Stage I;

0.66 (range: 0.49 - 0.83) for Stage II;

0.38 (range: 0.28 - 0.48) for Stage III; and

0.11 (range: 0.08 - 0.14) for Stage IV.

Vaccine efficacy was 90% (range: 50 - 100), age at vaccination was 12 years (range: 12 - 15), and vaccine coverage was 100% (range: 50 - 100).

The sensitivity of liquid-based cytology was 84% (range: 69 - 88) and the specificity was 88% (range: 77 - 93).

The sensitivity of conventional cytology was 66% (range: 34 - 86) and the specificity was 97% (range: 88 - 99).

The utility weights associated with health-related quality of life were:

0.65 (range: 0.49 - 0.81) for detected invasive cancer Stage I;

0.56 (range: 0.42 - 0.70) for Stage II;

0.56 (range: 0.42 - 0.70) for Stage III;

0.48 (range: 0.36 - 0.60) for Stage IV;

0.97 (range: 0.73 - 0.99) after treatment for invasive cancer Stage I;

0.90 (range: 0.68 - 0.98) after treatment for invasive cancer Stage II;

0.90 (range: 0.68 - 0.98) after treatment for invasive cancer Stage III; and

0.62 (range: 0.47 - 0.78) after treatment for invasive cancer Stage IV.

### **Methods used to derive estimates of effectiveness**

Some assumptions were formulated in order to obtain some of the estimates of effectiveness.

### **Estimates of effectiveness and key assumptions**

The authors assumed that:

colposcopy and biopsy examinations would accurately identify the true underlying histology of the cervix;

all the cohort of girls would be successfully vaccinated at the age of 12 years before their first exposure, and would be fully immunised at 13; and

the probability of acquiring persistent infection with HPV16/18 vaccine would be reduced by 90%.

### **Measure of benefits used in the economic analysis**

The measure of benefits used was the quality-adjusted life-years (QALYs). The authors also reported the reduction in the lifetime risk of cancer. The quality weights for the time spent in cancer health states were derived from utility estimates by the Committee to Study Priorities for Vaccine Development (Institute of Medicine; Stratton et al. 2000, see 'Other Publications of Related Interest' below, for bibliographic details) and varied with the disease stage. Age-specific QALY weights were used for non-cancer states. The methods used to develop the QALY weights were not reported. The QALYs were discounted at an annual rate of 3%.

### **Direct costs**

The direct costs included were those of the health service and the patient. Vaccination, screening and treatment costs were considered.

The costs of vaccination included three brief clinic visits, surveillance and educational costs, patient (or parent) time

costs, and a 10-minutes pre-vaccination counselling session with a registered nurse or nurse practitioner. Data from the US Bureau of Labour Statistics were used to assign a cost for the time required from each provider. The direct medical costs of screening included the costs of either conventional or liquid-based cytology, the costs of HPV DNA tests, office visits and patient time costs. The costs of treatment were for colposcopy and biopsy, the treatment of CIN1 and CIN2,3 patients, and costs related to each of the cancer stages (I to IV). The direct medical costs for screening and treatment were derived from published data. The time spent undergoing screening was derived from a prospective study of time costs associated with cervical cancer screening (Shireman et al. 2001, see 'Other Publications of Related Interest' below, for bibliographic details).

Overall, the costs were estimated on the basis of actual data, supplemented with some authors' assumptions about health care resource use. The costs were converted into 2002 US dollars using the medical care component of the Consumer Price Index. Discounting was carried out at an annual rate of 3%.

### **Statistical analysis of costs**

The costs and resource use were treated deterministically.

### **Indirect Costs**

Although the authors reported that a societal perspective was adopted, the indirect costs associated with the lost productivity due to the disease were not considered in the analysis.

### **Currency**

US dollars (\$).

### **Sensitivity analysis**

The authors presented various scenarios with combinations for vaccine efficacy, cytology type, age at screening and screening interval to allow for uncertainty. An extensive one-way sensitivity analysis was carried out on other variables (i.e. costs, natural history parameters) to allow for parameter uncertainty. Parameter value ranges for the sensitivity analysis were derived from the literature. Published data incorporating transportation costs associated with cervical cancer screening were also used in the sensitivity analysis.

### **Estimated benefits used in the economic analysis**

Initially, the authors obtained results for the introduction of a type-specific HPV vaccine (for 70, 80, 90 and 100% vaccination efficacy) to current cervical cancer screening practice in their setting. They also compared the 80 potential cervical cancer prevention strategies (which combined vaccination and-or screening, cytology type, age at screening initiation and screening interval).

The health benefit results for life time duration in the base-case analysis were:

25.9815 QALYs for the current screening programme,

25.9907 QALYs for vaccination at 70% efficacy,

25.9921 QALYs for vaccination at 80% efficacy,

25.9934 QALYs for vaccination at 90% efficacy, and

25.9948 QALYs for vaccination at 100% efficacy.

The lifetime risk of cancer was:

0.86 for the current screening programme,

0.47 for vaccination at 70% efficacy,

0.41 for vaccination at 80% efficacy,

0.36 for vaccination at 90% efficacy, and

0.30 for vaccination at 100% efficacy.

For the comparison of the 80 potential screening strategies, the authors reported results for the 14 potential cervical cancer prevention strategies that were not dominated (i.e. those strategies with higher costs and lower health benefits when compared with any other were excluded). These were as follows:

- 1) no intervention;
- 2) screening only, conventional cytology type, age 35 at screening initiation, 5-year screening interval;
- 3) screening only, conventional cytology type, age 30 at screening initiation, 5-year screening interval;
- 4) screening only, conventional cytology type, age 25 at screening initiation, 5-year screening interval;
- 5) screening/vaccine, conventional cytology type, age 30 at screening initiation, 5-year screening interval;
- 6) screening/vaccine, conventional cytology type, age 25 at screening initiation, 5-year screening interval;
- 7) screening/vaccine, conventional cytology type, age 21 at screening initiation, 5-year screening interval;
- 8) screening/vaccine, conventional cytology type, age 25 at screening initiation, 3-year screening interval;
- 9) screening/vaccine, conventional cytology type, age 21 at screening initiation, 3-year screening interval;
- 10) screening/vaccine, conventional cytology type, age 21 at screening initiation, 2-year screening interval;
- 11) screening/vaccine, conventional cytology type, age 18 at screening initiation, 2-year screening interval;
- 12) screening/vaccine, liquid-based cytology type, age 18 at screening initiation, 2-year screening interval;
- 13) screening/vaccine, conventional cytology type, age 18 at screening initiation, 1-year screening interval;
- 14) screening/vaccine, liquid-based cytology type, age 18 at screening initiation, 1-year screening interval.

The QALYs for strategies 1 to 14 were, in order, 25.9112, 25.9607, 25.9696, 25.9765, 25.9893, 25.9919, 25.9930, 25.9953, 25.9967, 25.9986, 25.9990, 26.0002, 26.0006 and 26.0009.

The reductions in lifetime cancer risk for strategies 2 to 14 were, in order, 67.4%, 71.4%, 73.9%, 88.9%, 89.8%, 89.7%, 94.0%, 95.4%, 96.6%, 96.8%, 98.0%, 98.5% and 99.0%.

### **Cost results**

The lifetime costs results for the base-case were:

\$1,111 for the current screening programme,

\$1,421 for vaccination at 70% efficacy,

\$1,409 for vaccination at 80% efficacy,

\$1,400 for vaccination at 90% efficacy, and

\$1,384 for vaccination at 100% efficacy.

For the 14 non-dominated potential cervical cancer prevention strategies, the average per woman lifetime costs results were, in order (strategies 1 - 14), \$235, \$386, \$443, \$526, \$748, \$828, \$896, \$1,030, \$1,144, \$1,450, \$1,581, \$2,314, \$2,581 and \$3,992.

### **Synthesis of costs and benefits**

The authors combined the benefits and costs using incremental cost-effectiveness ratios (ICERs). These were estimated as the incremental cost per additional QALY gained when two competing strategies were compared. The ICER results in 2002 US dollars versus the current screening programme were:

\$33,700 per additional QALY for vaccination at 70% efficacy,

\$28,100 per additional QALY for vaccination at 80% efficacy,

\$24,300 per gained QALY for vaccination at 90% efficacy, and

\$20,600 per gained QALY for vaccination at 100% efficacy.

For the 14 non-dominated potential cervical cancer prevention strategies, the ICER for each strategy versus the next most effective strategy were, in order (strategies 2 - 14), \$3,100, \$6,400, \$12,100, \$17,200, \$31,200, \$57,400, \$58,500, \$83,000, \$164,400, \$280,200, \$617,900, \$771,300 and \$3,867,500.

The results were most sensitive to alternative assumptions about the duration of vaccine efficacy, the proportion of persistent HPV in women older than 30 years that was attributable to newly acquired HPV infection versus reactivation of infection acquired in early adulthood, and the underlying frequency of cervical cancer screening, age at which screening is initiated, and cost of following women with atypical cytology screening results and low-grade lesions. The results were less sensitive to plausible changes in the natural history parameters, screening test characteristics, cervical cancer mortality and costs. The cost-effectiveness results were stable for a wide range of vaccination costs. However, when the total per person vaccination costs exceeded \$1,000, strategies that combined vaccination with screening were dominated by strategies that relied on screening alone.

### **Authors' conclusions**

The authors concluded that their model predicted that a vaccine that prevented persistent human papillomavirus (HPV) 16/18 infection would reduce the incidence of HPV 16/18-associated cervical cancer, even in a setting of cytologic screening, and had the potential to be cost-effective. A programme of vaccination that permitted a later age of screening initiation and a less frequent screening interval would be likely to be a cost-effective use of health care resources.

### **CRD COMMENTARY - Selection of comparators**

The authors provided a justification for the comparators used in the analysis. For the first part of the analysis, they used current screening practice as the comparator. For the second, given that they considered that recommendations for cervical cancer screening were likely to be modified in the next several years as enhanced cytological methods evolve and new technology is developed, they explored a variety of hypothetical cervical cancer control policies consisting of primary prevention with vaccination and/or secondary prevention with screening. You should decide if these might be widely used technologies in your own setting.

### **Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken. A systematic review is the best means of ensuring that the best available data are used in the model. However, the authors stated that they calibrated the model with the best available data (i.e. age-specific HPV infection, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, and cancer). Moreover, model corroboration was assessed by comparing the

predicted outcomes with those of other published analyses. Estimates of important parameters, such as the sensitivity and specificity of cervical cytology screening, were obtained from large clinical trials and recent comprehensive reviews. The authors considered a wide range of values derived from the literature for the parameters in the sensitivity analysis.

### **Validity of estimate of measure of benefit**

The authors used a single measure of benefits in the economic analysis, QALYs. They did not state if the methods used to derive quality of life weights were calculated using preference-based methods. However, they did report that these weights and their associated ranges of variation were derived from utility estimates in the literature.

### **Validity of estimate of costs**

Although the authors reported that the study had been conducted from a societal perspective, no indirect costs were reported and no justification was provided for their exclusion. All the categories of costs relevant to the health service appear to have been included in the analysis. The authors mentioned the aggregated categories of costs included in the analysis and derived direct medical costs from the literature. However, they did not present all the resource use quantities and unit costs separately. This means that it may be difficult to rework the analysis in other settings. The costs were treated deterministically, but extensive sensitivity analyses were conducted to assess the robustness of the estimates used. Appropriate currency conversions and discounting were performed.

### **Other issues**

The authors compared their findings with those from other studies. In general, their findings were in agreement with the findings of other studies, providing that screening may be initiated at a later age and conducted less frequently. The issue of generalisability of the results to other settings was not addressed. The authors presented their model results selectively for the second part of the analysis and justified this approach: they presented results for those strategies that were not dominated by other strategies. The authors stated some limitations of their analysis. For example, the model cannot be used to assess the impact of HPV vaccination of both men and women on the dynamics of viral transmission and will, therefore, underestimate the impact of factors such as herd immunity. In addition, long-term vaccine efficacy is uncertain, and there are heterogeneities in vaccine response that the authors could not include in the absence of empiric data.

### **Implications of the study**

A combined programme of vaccination and screening that permits a later age of screening initiation and a less frequent screening interval is likely to be a cost-effective use of limited health care resources. As the authors reported, further research is needed to gather reliable data around patient and family preferences, the likelihood of vaccine acceptability, and behavioural response to an intervention that is partially protective against cervical cancer.

### **Source of funding**

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### **Bibliographic details**

Goldie S J, Kohli M, Grima D, Weinstein M C, Wright T C, Bosch F X, Franco E. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *Journal of the National Cancer Institute* 2004; 96(8): 604-615

### **PubMedID**

15100338

### **Other publications of related interest**

Shireman TI, Tsevat J, Goldie SJ. Time costs associated with cervical cancer screening. *Intl J Technol Assess Health*



Care 2001;17:146-52.

Straton K, Durch J, Lawrence R, eds. Vaccines for 21st century, a tool for decision making. Washington (DC): National Academy Press; 2000.

Wolfson MC. Health-adjusted life expectancy. Health Rep 1996;8:41-6.

### **Indexing Status**

Subject indexing assigned by NLM

### **MeSH**

Adult; Aged; Computer Simulation; Cost-Benefit Analysis; Decision Support Techniques; Female; Humans; Incidence; Markov Chains; Mass Screening /standards; Middle Aged; Papillomaviridae; Papillomavirus Infections /complications /economics /prevention & control; Papillomavirus Vaccines; Tumor Virus Infections /complications /economics /prevention & control; United States /epidemiology; Uterine Cervical Neoplasms /economics /epidemiology /mortality /prevention & control /virology; Viral Vaccines /economics /therapeutic use

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