Estimating the costs and benefits of screening monogamous, heterosexual couples for 
unrecognised infection with herpes simplex virus Type 2

Fisman D N, Hook E W, Goldie S J

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
Three options for screening monogamous heterosexual couples for asymptomatic herpes simplex virus Type 2 (HSV-2) were considered. The options were no screening, universal condom use, and serological screening for HSV-2 with condom use targeted to concordant couples. The screening tests evaluated included Western blot (WB), enzyme-linked immunosorbent assays (ELISA), and WB followed by ELISA.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The hypothetical population comprised 25-year-old heterosexual couples that were about to commence a monogamous relationship with the possibility of pregnancy.

Setting
The setting was primary and secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1983 and 2001. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A Markov model was used to estimate the clinical impact of the screening options and to assess their economic costs. The model comprised three main health states, which were then subdivided to allow for pregnant and non-pregnant states in the female partner. The time horizon of the model was 25 years, with transitions between states on a monthly cycle.

Outcomes assessed in the review
The following model input parameters relating to the clinical impact of screening were identified:
the prevalence of infection amongst men;
the prevalence of infection amongst women;
the probability of infection being passed to the male partner;
the probability of infection being passed to the female partner;
the probability of symptomatic disease amongst infected individuals;
the average future symptom days amongst men with symptomatic disease;
the average future symptom days amongst women with symptomatic disease;
the relative risk of infection with regular condom use;
the sensitivity and specificity of the WB test;
the sensitivity and specificity of the ELISA;
the number of live births per 1,000 women;
the probability of an infant born to an infected mother being infected;
the probability of death in an infected infant;
the probability of long-term sequelae in an infected infant.

Study designs and other criteria for inclusion in the review
None of the study designs included in the review were reported. No inclusion or exclusion criteria were specified.

Sources searched to identify primary studies
MEDLINE and the abstracts from "major scientific meetings" were searched for relevant primary studies.

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
The model input parameters relating to the clinical impact of screening were taken from 34 papers.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.
Results of the review
The model input parameters relating to the clinical impact of screening were as follows:

- The prevalence of infection amongst men was 13%.
- The prevalence of infection amongst women was 23%.
- The annual probability of infection being passed to the male partner was 5%.
- The annual probability of infection being passed to the female partner was 18%.
- The probability of symptomatic disease amongst infected individuals was 40%.
- The average future symptom days amongst men with symptomatic disease was 87.
- The average future symptom days amongst women with symptomatic disease was 66.
- The relative risk of infection transmission with regular condom use was 50%.
- Both the sensitivity and specificity of the WB test were 100%.
- The sensitivity of the ELISA was 96% and the specificity was 97%.
- There were between 53 and 114 live births per 1,000 women.
- The probability of an infant born to an infected mother being infected was 10%.
- The probability of death in an infected infant was 14%; and
- The probability of long-term sequelae in an infected infant was 40%.

Measure of benefits used in the economic analysis
Three measures of benefit were used in the economic analysis. These were adult infections averted, symptom days averted, and neonatal infections averted.

Direct costs
The direct costs of the health care provider were included in this study. All appropriate cost elements appear to have been included. The estimates of resource use were derived from the model that provided the clinical effectiveness evidence. The model input parameters were taken from published studies or assumed by the authors. The unit costs were taken from published studies and all unit costs were reported. No specific price year was reported. The costs were appropriately discounted at a rate of 3% per annum.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The cost of lost wages due to clinic visits and hospitalisation were estimated using the average US hourly wage rate. The paper did not provide a breakdown of this unit cost and the number of hours lost. No specific price year was reported. The costs were appropriately discounted at a rate of 3% per annum.

Currency
Sensitivity analysis
A combination of univariate and bivariate sensitivity analyses were undertaken. These were conducted to establish the impact of variability in the data and the extent of uncertainty around the study's findings, and to assess their generalisability. Plausible ranges were taken from the highest and lowest values and, where available, confidence intervals found in the literature.

Estimated benefits used in the economic analysis
The model estimated that the do nothing strategy resulted in 170 new adult infections, 5,350 symptom days, and 0.2 neonatal infections per 1,000 couples.

Screening with ELISA followed by a WB test resulted in 132 new adult infections, 4,040 symptom days, and 0.096 neonatal infections per 1,000 couples.

Screening with ELISA alone resulted in 133 new adult infections, 4,080 symptom days, and 0.099 neonatal infections per 1,000 couples.

Screening with the WB test alone and universal condom use resulted in 130 new adult infections, 3,990 symptom days, and 0.091 neonatal infections per 1,000 couples.

These estimated benefits relate to a period of 25 years.

Cost results
The total costs for 1,000 couples were:

for the do nothing strategy, $175,000;

for screening with ELISA followed by a WB test, $495,000;

for screening with ELISA alone, $506,000;

screening with the WB test alone, $590,000; and

for universal condom use, $981,000.

Synthesis of costs and benefits
The incremental cost-effectiveness ratios for screening with ELISA followed by the WB test over the do nothing strategy were:

$8,200 per adult infect averted;

$240 per symptom-free day; and

$3,075,000 per neonatal infection averted.

The incremental cost-effectiveness ratios for screening with the WB test alone over the do nothing strategy were:

$63,600 per adult infect averted;

$6,400 per symptom free-day; and

$19,080,000 per neonatal infection averted.
On all measures of benefit, universal condom use and use of ELISA alone were dominated.

The sensitivity analysis showed that the rank order of the screening strategies remained the same except when the sensitivity of the ELISA was varied. When the sensitivity of the ELISA reached 99%, the option of screening with ELISA followed by the WB test no longer dominated screening with ELISA alone. The cost-effectiveness of screening with ELISA followed by the WB test was sensitive to condom efficacy, condom costs and compliance with use of condoms, baseline prevalence of the virus, and the assumption of monogamy.

**Authors' conclusions**
Serological screening for asymptomatic herpes simplex virus Type 2 (HSV-2) in asymptomatic, monogamous heterosexual couples reduces the incidence of infections in adults and newborns, although it does increase health care costs.

**CRD COMMENTARY - Selection of comparators**
No specific justification was reported for the options considered in this study. Although they appear to have been viable options, it is unclear whether they include all available options. You should consider how the options assessed in this study relate to your own setting prior to applying the results of this study.

**Validity of estimate of measure of effectiveness**
The model input parameters were derived from published studies. The authors reported the key words used for searching and the sources searched. Although a comprehensive search appears to have been undertaken, the authors did not state that it was systematic. In addition, they did not report any inclusion criteria, quality assessment, or assessment of the impact of differences between the primary studies. It is unclear if the results of the studies were combined. However, if this was the case, there was no information on how data from the primary studies were combined to arrive at a single estimate for each model parameter. These factors limit the reliability and validity of the clinical effectiveness evidence.

**Validity of estimate of measure of benefit**
The estimates of benefit used in the economic analysis were taken directly from the model. No rationale for the choice of benefit measures was reported, but the authors highlighted some of the difficulties in obtaining preference-based measures of health gain in this type of scenario.

**Validity of estimate of costs**
The authors reported that a societal perspective was adopted and, as such, all appropriate costs appear to have been included. While the unit costs were reported separately, the resource use data were not reported comprehensively. The authors stated that they included productivity losses, but did not report this in detail. The sensitivity analysis, which used appropriate ranges to assess variability in the data, was thorough. The unit costs were taken from a number of published studies, but no reflation to a single price year was reported in the paper. If this has not been done it could create inconsistencies within the study, thus making it difficult to interpret the results of the study and limiting its generalisability. The costs were appropriately discounted.

**Other issues**
The authors did not compare their study findings with other work, nor consider how their results could be generalised to other settings. They appeared to have presented their results in a comprehensive manner and their conclusion reflected their analysis.

**Implications of the study**
The authors recommended that clinical studies to quantify the impact of HSV-2 on health-related quality of life should
be given the highest priority. In addition, for those couples that choose to be screened, they recommended the use of a two-step strategy including initial ELISA followed by a confirmatory WB test for positive ELISA results.

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