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
Nine testing strategies for chronic hepatitis C virus (HCV) were examined. The strategies were based on the combination of two tests for antibodies, namely enzyme immunoassay (EIA) and recombinant immunoblot assay (RIBA), and one for viraemia, namely reverse transcription polymerase chain reaction (PCR). The use of optical density (OD) to divide the EIA results into three categories (high positive, low positive, and negative) was also considered. The diagnostic strategies were as follows.

EIA alone.

EIA-RIBA: EIA was followed by RIBA for individuals found to be positive by EIA; RIBA was added to decrease the percentage of false positives.

EIA(OD)-RIBA: EIA was performed first and samples were categorised as antibody positive (signal-to-cutoff ratio > 3.8) or low positive (1.0 =< signal-to-cutoff ratio =< 3.8) or negative (signal-to-cutoff ratio < 1.0); EIA tests that divided OD into three categories were designated as EIA(OD); only samples designated as low antibody positives proceed to RIBA.

EIA(OD)-RIBA-PCR: specimens necessary for EIA(OD), RIBA and PCR were collected; all samples designed antibody-positives or indeterminate on the basis of EIA(OD) and RIBA were tested for viraemia using PCR.

EIA-PCR-RIBA: specimens necessary for EIA, RIBA and PCR were collected; if the EIA signal-to-cutoff ratio was greater than or equal to 1, PCR was performed; if PCR was positive, no further test was performed; if viral RNA was not detected, then a RIBA would be performed to determine antibody status.

EIA-PCR: specimens for EIA and PCR were collected; if the EIA signal-to-cutoff ratio was greater than or equal to 1, PCR was performed.

EIA-RIBA-PCR: this strategy was similar to EIA(OD)-RIBA-PCR but did not allow for a low positive EIA; RIBA was performed when the EIA signal-to-cutoff ratio was greater than or equal to 1.

EIA(OD)-PCR-RIBA: this strategy was similar to EIA(OD)-RIBA-PCR but assessed the impact of reversing the order of RIBA and PCR; PCR was performed when EIA(OD) was either positive or low positive; RIBA was performed only when the PCR was negative following a low-positive EIA.

PCR alone: this strategy tested for viral status, but not antibody status, thus it might be of interest in high-risk groups when only viral status is of interest.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.
Study population
The study population comprised a hypothetical cohort of patients undergoing HCV testing.

Setting
The setting was a laboratory. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data came from studies published between 1994 and 2003. The dates to which data referred were not explicitly reported. The costs were estimated in 2002, which could have been the price year.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and opinions.

Modelling
A decision tree model was constructed for each diagnostic strategy to assess the accuracy and costs. The structure of the tree for the strategy EIA(OD)-RIBA-PCR was reported. It started with individuals who might be HCV positive or negative. No other details were provided.

Outcomes assessed in the review
The outcomes estimated from the literature were HCV prevalence and the sensitivity and specificity of all diagnostic strategies examined in the study.

Study designs and other criteria for inclusion in the review
Prevalence appears to have been derived from studies that were identified selectively. The sensitivity and specificity data came from a review of the literature. However, no details on the primary studies were reported.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
Fifteen primary studies provided clinical evidence.

Methods of combining primary studies
A narrative method appears to have been used to identify the primary estimates.

Investigation of differences between primary studies
Not stated.
Results of the review
Two scenarios for disease prevalence were considered. The proportions of HVC antibody positive were 0.05 and 0.25 (range: 0 - 0.6).

The proportion viraemic was 0.85 (range: 0.65 - 0.95).

The proportion EIA positive when true antibody positive was 0.94 (range: 0.90 - 0.98).

The proportion EIA positive when true antibody negative was 0.0075 (range: 0 - 0.03).

The proportion EIA(OD) high positive when true antibody positive was 0.9276 (range: 0.88 - 0.98).

The proportion EIA(OD) low positive when true antibody positive was 0.0124 (range: 0 - 0.04).

The proportion EIA(OD) high positive when true antibody negative was 0.0010 (range: 0 - 0.02).

The proportion EIA(OD) low positive when true antibody negative was 0.0065 (range: 0 - 0.03).

The proportion RIBA positive when true antibody positive and EIA positive was 0.9772 (range: 0.90 - 1).

The proportion RIBA indeterminate when true antibody positive and EIA positive was 0.0228 (range: 0 - 0.10).

The proportion RIBA positive when true antibody negative was 0 (range: 0 - 0.02).

The proportion RIBA indeterminate when true antibody negative was 0.08 (range: 0.02 - 0.12).

The proportion PCR positive when viraemic was 0.97 (range: 0.90 - 1).

The proportion PCR positive when not viraemic was 0.02 (range: 0 - 0.05).

Methods used to derive estimates of effectiveness
Some assumptions were also made to derive estimates of effectiveness. Some clinical data came from personal communications.

Estimates of effectiveness and key assumptions
Individuals being tested were not in the acute phase of HCV infection.

Parameters did not vary across testing sites and across sub-groups of individuals.

The results of the tests were independent.

The proportion of RIBA positive when true antibody positive and EIA(OD) low positive was 0.5 (range: 0.25 - 0.75).

The proportion of RIBA indeterminate when true antibody positive and EIA(OD) low positive was 0.5 (range: 0.25 - 0.75).

Measure of benefits used in the economic analysis
The model outputs were viral sensitivity and specificity, antibody sensitivity and specificity, and true positives designated antibody indeterminate. All measures were obtained using the decision model. The number of false positives avoided was used as the summary benefit measure and was combined with the costs.

Direct costs
The perspective adopted in the study was not explicitly stated. Only the direct medical costs associated with the diagnostic tests under examination were included in the analysis. The resource use data was based on the frequency of the tests, which depended on the strategy being evaluated. The costs were estimated from 64 Veteran Affairs (VA) medical centres responding to a VA national survey of HCV testing in 2002. The unit costs were presented separately from the quantities of resources used. The price year was not explicitly stated, although it might have been 2002. Discounting was not relevant because of the short time horizon of the analysis.

**Statistical analysis of costs**

Median values for the costs were used. No statistical analyses of the costs were carried out.

**Indirect Costs**

The indirect costs were not included in the economic evaluation.

**Currency**

US dollars ($).

**Sensitivity analysis**

Univariate sensitivity analyses were carried out to test the robustness of the model results to variations in all model inputs. It was not stated whether the ranges of values used were derived from the literature.

**Estimated benefits used in the economic analysis**

Among strategies that tested only antibody status, the sensitivity was 0.9400 with EIA, 0.9338 with EIA(OD)-RIBA and 0.9186 with EIA-RIBA. The specificity was 0.9925 with EIA, 0.9990 with EIA(OD)-RIBA and 1 with EIA-RIBA.

The rate of true positives designated antibody indeterminate was 0.0062 with EIA(OD)-RIBA and 0.0214 with EIA-RIBA.

The analysis showed that all strategies that test for both antibody and viral status had equal sensitivity and varied only slightly with respect to viral specificity. In particular, among the strategies that tested both antibody and viral status:

- sensitivity and specificity values for viral status were, respectively, 0.9118 and 0.9997 with EIA-PCR,
- 0.9118 and 0.9998 with EIA(OD)-RIBA-PCR,
- 0.9118 and 0.9997 with EIA(OD)-PCR-RIBA,
- 0.9118 and 0.9998 with EIA-RIBA-PCR, and
- 0.9118 and 0.9997 with EIA-PCR-RIBA; and

- sensitivity and specificity values for antibody status were, respectively, 0.9400 and 0.9925 with EIA-PCR,
- 0.9389 and 0.9990 with EIA(OD)-RIBA-PCR,
- 0.9389 and 0.9989 with EIA(OD)-PCR-RIBA,
- 0.9363 and 1 with EIA-RIBA-PCR, and
- 0.9363 and 1 with EIA-RIBA-PCR,
0.9363 and 0.9999 with EIA-PCR-RIBA.

The rate of true positives designated antibody indeterminate was 0.0011 with EIA(OD)-RIBA-PCR and with EIA(OD)-PCR-RIBA, and 0.0037 with EIA-RIBA-PCR and with EIA-PCR-RIBA.

The sensitivity of PCR for viral status was 0.9700 and the specificity was 0.9800.

Cost results
With disease prevalence set at 5%, the mean cost per individual tested was:

- $7.38 with EIA,
- $7.97 with EIA(OD)-RIBA,
- $12.09 with EIA-RIBA,
- $10.90 with EIA-PCR,
- $11.12 with EIA(OD)-RIBA-PCR,
- $11.43 with EIA(OD)-PCR-RIBA,
- $15.18 with EIA-RIBA-PCR,
- $12.21 with EIA-PCR-RIBA, and
- $65 with PCR.

With disease prevalence set at 25%, the mean cost per individual tested was:

- $8.68 with EIA,
- $9.38 with EIA(OD)-RIBA,
- $29.62 with EIA-RIBA,
- $24.33 with EIA-PCR,
- $24.73 with EIA(OD)-RIBA-PCR,
- $24.79 with EIA(OD)-PCR-RIBA,
- $44.92 with EIA-RIBA-PCR,
- $28.33 with EIA-PCR-RIBA, and
- $65 with PCR.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the alternative diagnostic options.

The analysis revealed that strategies that did not include PCR were among the weakest strategies. EIA(OD)-PCR-RIBA was dominated by EIA(OD)-RIBA-PCR.
The incremental cost per false positive avoided with EIA(OD)-RIBA-PCR over EIA-PCR was $36 with prevalence at 5%, $83 with prevalence at 25%, and $193 with prevalence at 50%.

The incremental cost per false positive avoided with EIA-PCR-RIBA over EIA(OD)-RIBA-PCR was $1,335 with prevalence at 5%, $5,585 with prevalence at 25%, and $15,680 with prevalence at 50%.

The incremental cost per false positive avoided with EIA-RIBA-PCR over EIA-PCR-RIBA was $22,654 with prevalence at 5% and $160,305 with prevalence at 25%.

Using EIA(OD)-RIBA-PCR rather than EIA-PCR resulted in 112 false antibody positives avoided for every true antibody positive missed with prevalence at 5%, 18 false antibody positives avoided with prevalence at 25%, and 6 false antibody positives avoided with prevalence at 50%.

The sensitivity analysis showed that the relative standing of the strategies that tested for antibody and viral status did not change.

Authors' conclusions
The strategy of enzyme immunoassay (optical density)-recombinant immunoblot assay-polymerase chain reaction (EIA(OD)-RIBA-PCR) should be used for the diagnosis of hepatitis C virus (HCV) infection in settings with a prevalence rate lower than 20%, while EIA-PCR should be recommended for higher prevalence rates (high-risk settings). The authors added that from a clinical standpoint, strategies that do not include PCR should not be used because they do not determine viral status. These conclusions were not substantially affected by variations in the costs or in the performance of individual laboratories (in terms of sensitivity and specificity). The study showed the difficulties of making decisions among techniques with similar accuracy.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators, which were widely used or strongly recommended by several agencies and organisations in the USA. They went on to state that second- rather than third-generation EIA was used because it is most commonly used in the USA. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from published studies, and a review of the literature was undertaken to assess accuracy data. However, it was not stated whether the review was systematic and details of the design of the primary studies and patient samples were not reported. Thus it was difficult to assess the validity of the primary sources of clinical evidence. Differences between the primary studies were not investigated and a narrative approach was used to combine the primary estimates. All the clinical data were extensively varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It is not comparable with the benefits of other health care interventions.

Validity of estimate of costs
Limited information on the cost analysis was provided. For example, the perspective adopted in the study was not explicitly stated and only the costs of the diagnostic tests were included. The unit costs were reported, while the quantities of resources used depended on the frequency of the diagnostic tests. The costs came from a national health plan (VA) and the impact of using alternative cost estimates was tested in the sensitivity analysis. These showed that the base-case results did not change substantially. The price year was not explicitly reported, which limits the possibility of performing reflation exercises.
Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They did not explicitly address the issue of the generalisability of the study results to other settings. The external validity of the analysis was enhanced by the use of sensitivity analyses, which were carried out on all inputs. However, the results of the sensitivity analysis were not reported. The authors noted that the development of more accurate diagnostic tests would affect the conclusions of the current analysis. Further, it was noted that the analysis did not assess the impact of the diagnostic options on the costs associated with false positives and false negatives.

Implications of the study
The study results supported the use of EIA(OD)-RIBA-PCR for the diagnosis of viral and antibody status in patients with suspected HCV infection. However, in high-risk settings, EIA-PCR should be used.

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