Annex 5.5

PICO 3 - Testing strategies (HBV)

Diagnostic strategies for hepatitis B surface antigen detection: a meta-analysis and review of the literature

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*Co-leaders of this review

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1. Executive study

**Background:** Most individuals with chronic HBV infection are not aware of their serostatus, contributing to delayed diagnosis and complications from advanced disease. Chronic HBV infection, defined as persistence of hepatitis B surface antigen (HBsAg) for at least six months, is a major cause of preventable morbidity and mortality worldwide. Advances in hepatitis B virus (HBV) detection technology create new opportunities for enhancing screening, referral, and treatment. This review will look into what is the best testing strategy (diagnostic accuracy, cost, cost–effectiveness, and other resource utilization) for detection of HBsAg.

**Methods:** A comprehensive literature search algorithm, including Internet searches, using the components hepatitis B, screening, and testing strategies were applied. We reviewed observational and RCT studies that provided original data from patient specimens. Our goal was to compare two broad strategies for HBsAg detection—one-test strategies and two-test strategies.

**Results:** Our search resulted in 3655 literature review references and 7 additional Internet references for PICO 3. Screening of titles/abstracts resulted in 7 selected articles for possible data extraction. None of these 7 articles met all of the data extraction inclusion criteria so no articles were identified as final selection for PICO 3; comparing the diagnostic accuracy, cost, or effectiveness of two different testing algorithms, where possible. These 7 articles are discussed in more detail—4 of the articles provided 3 national HBV algorithms (Australia, UK, US); 1 discussed testing strategies for select populations; 2 provided a look at cost–effectiveness of given testing strategies.

**Conclusions:** No study compared the diagnostic accuracy, cost, or cost–effectiveness of one-versus two-step HBsAg testing strategies. Studies that may provide contextual information about testing strategies were briefly summarized.

2. Background

**Hepatitis B virus**

An estimated 240 million individuals worldwide\(^1\) are chronically infected with hepatitis B virus (HBV) and there are an estimated 4 million acute HBV infections each year. Twenty per cent to 30% of those with chronic hepatitis B infection will develop cirrhosis\(^2\) or hepatocellular carcinoma,\(^3\) leading to approximately 650,000 deaths each year.\(^4\) However, most individuals with chronic HBV infection are not aware of their serostatus, contributing to delayed diagnosis and complications from advanced disease.\(^5\) HBV testing is critically important in order to refer infected individuals to HBV treatment and care, to refer uninfected individuals to vaccination, and to mobilize prevention and control efforts.

In March 2015, the World Health Organization published the first guidelines for the prevention, care, and treatment of individuals with chronic HBV infection.\(^5\) These guidelines focused on assessment for treatment eligibility, initiation of first-line therapies, switching,
monitoring. These initial guidelines did not include recommendations on testing strategies that included what test to use and how to test. Given the large burden of HBV in low- and middle-income settings where there are limited or no existing HBV testing guidelines, there is a substantial need for HBV testing guidelines.

**Description of HBV Ag detection**

Chronic HBV infection is defined as persistence of hepatitis B surface antigen (HBsAg) for at least six months. However, interpretation of HBV serologies is complex (Table 1). The serological markers most frequently used for HBV testing include HBsAg, total anti-HBc, and anti-HBs (Table 1).

**Table 1. Hepatitis B serological marker interpretation**

<table>
<thead>
<tr>
<th>Serological marker</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg (hepatitis B surface antigen)</td>
<td></td>
</tr>
<tr>
<td>Total anti-HBc (antibody to hepatitis B core antigen)</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc (immunoglobulin M to anti-HBc)</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs (antibody to HBsAg)</td>
<td></td>
</tr>
<tr>
<td>Test results</td>
<td></td>
</tr>
<tr>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
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<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>


**One test vs two test serological testing strategy**

The most important marker for the diagnosis of chronic hepatitis B infection requiring further assessment or treatment remains HBsAg. The case definition of chronic hepatitis B is the detection of HBsAg twice six months apart.

After an initial positive result for HBsAg, supplementary testing can be undertaken in order to facilitate entry into a care pathway. The detection of HBsAg in blood can include rapid diagnostic tests, or enzyme immunoassays. Confirmation of the specificity of a reactive HBsAg first-line test result is usually carried out by either:
i) repeating the HBsAg testing in a different assay of similar sensitivity, or
ii) performing a neutralization test using a specific anti-HBs-containing reagent in the same
first-line assay after appropriate dilution of the specimen under test. Specificity is
confirmed when this reagent abolishes reactivity in the assay.

WHO recommends standardized testing strategies to maximize the accuracy of
hepatitis B and C testing while minimizing cost and increasing simplicity. This PICO question
addresses the issue of whether a positive result from a single HBsAg assay has sufficient
specificity in order to proceed to supplementary testing and/or entry into a care pathway, or
whether confirmatory testing on the same specimen with a different HBsAg assay (or
neutralization), performed sequentially after the first assay is required. This is particularly
relevant in low prevalence settings where more than one assay may be required
to confirm specificity. Two previous reviews\textsuperscript{6,7} on hepatitis testing focused on the test performance but
did not compare testing strategies.

Fig. 1. Options for HBV screening, which may include HBsAg in a one-test strategy (e.g. a
single HBsAg using a rapid diagnostic test [RDT] or enzyme immunoassay [EIA]) and
two-test strategies (second RDT or EIA or neutralization with EIA)
HBsAg testing strategy: Among persons identified for hepatitis B testing, what is the best testing strategy (diagnostic accuracy and other outcomes) for detection of HBsAg? (One-test versus two-test strategy) (Figs 1A, 1B)

<table>
<thead>
<tr>
<th>P</th>
<th>Persons identified for HBV testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>One-test strategy; one HBsAg test (Fig. 1A)</td>
</tr>
<tr>
<td>C</td>
<td>Two-test strategy; two different HBsAg tests (Fig. 1B)</td>
</tr>
<tr>
<td>O</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td></td>
<td>True negatives (TN), who are screen negative, and do not have HBV infection</td>
</tr>
</tbody>
</table>
False negatives (FN), who are screen negative but have HBV infection. These are incorrectly misclassified, and this may result in missed opportunities to recognize and present progression of liver disease.

True positives (TP), who are screen positive and have HBV infection.

False positives (FP), who are screen positive, but do not truly have HBV infection. These will have additional unnecessary tests and evaluation.

Costs (cost of testing strategy, including lab reagents and running costs, cost of further evaluation of a false positive)

Cost–effectiveness

Acceptability to health-care worker and patients

Other outcomes (missed cases of liver disease because of false negative results, unnecessary referral, investigations and/or treatment in false positives)

3. Objectives

- To identify quantitative evidence on the sensitivity and specificity of one-test compared to two-test algorithms for detection of HBsAg
- To evaluate the cost–effectiveness, acceptability, and other outcomes (missed liver disease because of false-negative results, unnecessary referral, investigations) associated with these two types of testing strategies
- To inform models to optimize hepatitis B screening algorithms.

4. Methods

We reviewed observational studies and randomized controlled trials (RCTs) that provided original data from patient specimens. Our goal was to compare two broad strategies for HBsAg detection – one-test strategies and two-test strategies.

Search algorithm

Literature search strategies were developed by a medical librarian with expertise in systematic review searching. Our search algorithm consisted of the following components: hepatitis B, screening, and testing strategies (Annex 1).

We searched MEDLINE (OVID interface, 1946 onwards), EMBASE (OVID interface, 1947 onwards), the Cochrane Central Register of Controlled Trials (Wiley interface, current issue), Science Citation Index Expanded (Web of Science interface, 1970 onwards), Conference Proceedings Citation Index-Science (Web of Science interface, 1990 onwards), SCOPUS (1960 onwards), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) (BIREME interface) and WHO Global Index Medicus. The search was supplemented by searching for ongoing studies in WHO’s International Clinical Trials Registry. The literature search was limited to the English language and human subjects.
We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies. After the MEDLINE strategy was finalized, it was adapted to the syntax and subject headings of the other databases.

In addition to searching databases, we also searched the Internet for any peer-reviewed articles and conference abstracts that might have been missed through our librarian search and also expanded our search to national guidance documents.

5. Results

Study selection

The librarian search resulted in 3655 references for PICO 3. Because of overlap with objectives and search strategies between PICOs 3 and 4, and to expedite the initial screening, PICO 3 references were combined with the 3060 references identified through the librarian search for PICO 4 (HCV); 2388 searches were immediately excluded. The librarian excluded 835 for not being relevant and there were 1553 duplicates. Thus, 4327 remained for screening. Titles/abstracts were screened according to protocol inclusion and exclusion criteria, for both PICOs 3 and 4. Reasons for excluding 4307 reports were noted (Fig. 2).
From the librarian search, no reports were identified for possible data extraction. The Internet searches resulted in 7 additional reports for possible data extraction. Full documents (manuscripts, abstracts, guidelines, etc.) were obtained and assessed against inclusion criteria. Papers were either accepted or rejected and reasons for rejection were explained.

The following inclusion criteria were used to evaluate the final selection: evaluations of HBV testing strategies; evaluations based on human clinical materials. The following exclusion criteria were used: studies focused only on evaluation of single-test assays without a two-test comparator group; studies focused on two-test strategies that include other types of test (e.g. anti-HBsAg) studies with primary aims other than evaluation of testing strategies; studies related to disease prevalence, drug resistance, genotyping, sequencing, or non-diagnostic purposes; articles in languages other than English, conference abstracts.

Data abstraction and data synthesis
Of the 7 selected for possible data extraction, the following variables were collected, when available: first author, title, year, objective, and exclusion criteria (Table 2).
Table 2. Seven reports assessed for eligibility

<table>
<thead>
<tr>
<th>Author or source year</th>
<th>Title</th>
<th>Objective</th>
<th>Exclusion criteria</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fan et al. 2014</td>
<td>Cost-effectiveness of testing hepatitis B-positive pregnant women for hepatitis B e antigen or viral load</td>
<td>To estimate cost-effectiveness of testing with hepatitis B (hepatitis B surface antigen [HBsAg]-positive) for hepatitis B e antigen (HBeAg) or hepatitis B virus (HBV) DNA</td>
<td>Decision tree model to estimate the costs and effects of two sequential testing strategies</td>
<td>Either sequential HBeAg testing or sequential HBV load testing was cost-effective. Sequential HBeAg testing dominated sequential HBV load testing with 1000 QALYs and $6.6 million saved</td>
</tr>
<tr>
<td>2. US Preventive Services Task Force, 2014</td>
<td>Hepatitis B, non-pregnant adolescents and adults: screening. May 2014</td>
<td>To recommend screening for hepatitis B virus (HBV) infection in persons at high risk for infection</td>
<td>No data/not a study. USPSTF makes recommendations about the effectiveness of specific clinical preventive services for patients without related signs or symptoms.</td>
<td>Document makes screening recommendation; not relevant to data synthesis for this report</td>
</tr>
<tr>
<td>3. Prepared for the US Preventive Services Task Force by Peter W. Pendergrass and Carolyn DiGuiseppi (Texas Dept State Health and Univ. Colorado), 2014</td>
<td>Screening for hepatitis B virus infection</td>
<td>To develop recommendations for USPSTF</td>
<td>No data/not a study</td>
<td>Document makes screening recommendation; not relevant to data synthesis for this report</td>
</tr>
<tr>
<td>4. Chen et al. 2015</td>
<td>Cost-effectiveness of augmenting universal hepatitis B vaccination with immunoglobin treatment</td>
<td>To compare the cost-effectiveness of hepatitis B virus (HBV) control strategies combining universal vaccination</td>
<td>Not testing strategies – vaccination strategies</td>
<td>Universal vaccination plus screening for hepatitis B surface antigen (HBsAg) and HBIG treatment for HBsAg-positive mothers’ neonates averted the most infections</td>
</tr>
</tbody>
</table>
Public Health England (PHE), National Health Service (NHS), 2014

UK Standards for Microbiology Investigations

To develop a set of standards for hepatitis B diagnostic serology in the immunocompetent (including hepatitis B in pregnancy)

No data/not a study

No conclusions

Australian Government, 2012

National HBV Testing Strategy

To provide diagnostic strategies for HBV

No data/not a study

No conclusions

Peng et al. 2011

Development of an economic and efficient strategy to detect HBsAg: Application of “grey-zones” in ELISA and combined use of several detection assays

To thoroughly assess the performance of the HBsAg assays and testing algorithm currently used in clinical settings

Does not compare strategies

Combined use of “grey-zones” in ELISA and several different detection assays can significantly increase the efficiency of HBsAg detection

References found in Annex 2.
None of the reports compared the cost or effectiveness of two different testing algorithms. Of the 13 documents selected, 4 referenced algorithms and are therefore shown in Table 3. Types of tests performed and exclusion criteria are also included.

Table 3. Four reports that examined testing strategies

<table>
<thead>
<tr>
<th>References</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Test 4</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fan et al.</td>
<td>Sequential HBeAg</td>
<td></td>
<td></td>
<td>Decision tree model to estimate the costs and effects of two sequential testing strategies</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>Sequential HBV load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2*</td>
<td>Public Health England (PHE), National Health Service (NHS), 2014</td>
<td>HBsAg</td>
<td>Repeat HBsAg</td>
<td>Confirm by neutralization</td>
<td>No data/not a study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBsAg</td>
<td>Repeat HBsAg</td>
<td>Anti-HBc</td>
<td>HBV DNA or IgM</td>
</tr>
<tr>
<td>3*</td>
<td>Australian Government, 2012</td>
<td>HBsAg</td>
<td>Anti-HBs</td>
<td>Anti-HBc</td>
<td>No data/not a study</td>
</tr>
<tr>
<td>4*</td>
<td>Peng et al.</td>
<td>ELISA</td>
<td>ELISA</td>
<td>CMIA</td>
<td>Confirm by HBsAg</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td></td>
<td></td>
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</table>

* Algorithm schematics attached (Annex 3)

Extensive review of the literature found no articles, reports, etc. that met all of the eligibility criteria for data extraction to be used to address this question. Most of the literature focused on screening blood donations.

Seven reports were identified that might be useful for modelling exercises to address this PICO question. This short narrative will provide an overview of these 7 articles, also drawing on other informative reviews and personal communications.

Cost

Fan et al. (2014) examined the cost–effectiveness of testing hepatitis B-positive pregnant women for hepatitis B e antigen or viral load. In this select population of mothers of a neonate birth cohort, either sequential HBeAg testing or sequential HBV load testing was found cost–effective. Sequential HBeAg testing dominated sequential HBV load testing with 1000 QALYs
and $6.6 million saved. It is important to note that this study used a decision tree model to estimate the costs and effects of two sequential testing strategies.

Chen et al. (2015) also examined cost–effectiveness of three strategies using a cohort of hospital patients in China. In this case, costing was not related to testing strategies but vaccination strategies, specifically universal HBV vaccination with immunoglobulin treatment. Their study found that while screening tests may be cost–effective, they require more infrastructure than is needed for vaccination, including laboratory services and adequate numbers of medical professionals to interpret test results and administer HBIG. As previously mentioned, it appears that vaccination should strongly be taken into account with considering HBV testing strategies.

Quality assessment

Study quality was not evaluated using the QUADAS-2 tool and the STARD checklist, as it was not applicable since none of the studies met inclusion criteria.

6. Discussion

Testing strategies

Although four of the seven reports identified provided national testing algorithms for Australia and the UK, none published data on supporting evidence. This has been confirmed by personal communications.

In general, HBV screening typically includes HBsAg in both the one-test (e.g. HBsAg) and two-test strategies. Beyond this it is unclear how to select other tests. This may depend on findings from PICO 1 to better understand the performance characteristics of HBV tests, and from this to model various testing strategies for feasibility and utility. The “simplest” testing strategies seemed to include all 3 tests below (as seen in the US and Australia algorithms).

- hepatitis B surface antigen (HBsAg)
- hepatitis B core antigen (anti-HBc)
- hepatitis B surface antibody (anti-HBs)

Public Health England (PHE) provides testing strategies to confirm HBsAg by an alternative assay or neutralization. Without much other evidence to support this, it seems as though confirming with an alternative assay might be a simple, cost–effective approach. It is also important to note that almost all reports reviewed also discussed comparing cost of screening and a testing strategy to cost of vaccination.

Testing recommended for select populations

During domestic medical examination of refugees, CDC screens using the above tests for chronic HBV (HBsAg) for all persons from countries with intermediate (≥2%–7%) or high (≥8%)
prevalence of chronic HBV infection. The only exception would be if a negative HBsAg test result is documented on their medical form.

Peng et al. (2011) examined novel strategies to detect HBsAg using ELISA “grey-zones”, in combination with other detection assays. As noted, clinical HBV detection methods differ between countries with high and low levels of endemic HBV infection. This study focused on a select population to test the algorithm currently used in clinical settings in China, specifically assessing the performance of the KHB (Kehua Bio-engineering Co. Ltd., Shanghai, China) and CMIA (Chemiluminescent Microparticle Immunoassay) HBsAg tests. While KHB is one of the most commonly used kits in China, this was a major limitation for the purposes of this systematic review. Yet, they presented a novel approach of combining strategies using ELISA “grey-zones”, which was found to significantly increase the efficiency of HBsAg detection. Although this approach “broadened the range” to allow for increased sensitivity, it may prove to be rather complicated requiring the establishment of numerous population-specific “grey-zones” and complex interpretations.

Again, almost all reports discussed testing based on select populations but this study did not focus on identifying algorithms to be used on select populations.

The choice between a one-test versus two-test strategy depends on the diagnostic accuracy of HBsAg tests. Results from a systematic review of the diagnostic accuracy of HBsAg tests (PICO 1) across 21 studies that evaluated 25 brands of RDTs using 15 EIA reference assays, with 36,919 total samples, including serum, plasma, venous and capillary whole blood, showed that the overall pooled clinical sensitivity and specificity of rapid HBsAg tests were 90.0% (95% CI: 89.1, 90.8) and 99.5% (95% CI: 99.4, 99.5), respectively, compared to laboratory-based immunoassay reference standards. Sensitivities ranged from 50% to 100% with overall pooled sensitivity of 90.0% (95% CI: 89.1, 90.8). Specificities ranged from 69% to 100%, with overall pooled specificity of 99.5% (95% CI: 99.4, 99.5). Pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 117.5 (95% CI: 67.7, 204.1) and 0.095 (95% CI 0.067, 0.136), respectively, with tau-square 3.89, 1.72, respectively, suggestive of significant heterogeneity between studies.

Pooled sensitivity in studies of HIV-positive persons was lower than in known HIV-negative patients; 72.3% (95% CI: 67.9, 76.4) compared to 92.6% (95% CI: 89.8, 94.8), respectively. Pooled sensitivity and specificity in blood donors were 91.6% (95% CI: 90.1, 92.9) and 99.5% (95% CI: 99.5, 99.9), respectively. Samples using whole blood specimens (venous or capillary) were 91.7% (95% CI: 89.1, 93.9) and 99.9% (95% CI: 99.8, 99.9) sensitive and specific compared to serum. The overall pooled clinical sensitivity and specificity of laboratory-based HBsAg tests were 88.9% (95% CI: 87.0, 90.6) and 98.4% (95% CI: 97.8, 98.8) sensitivity and specificity, respectively, compared to state-of-the-art chemiluminescent microparticle enzyme immunoassays.

Although these tests appeared to have excellent specificity and would have required a 2-test strategy, in a low-prevalence setting, even tests that have excellent specificities may produce false-positive results. This would then require the use of a second test to reduce the number of false-positive results. This can be illustrated as follows:
In a hypothetical population of 1000 people where the HBV prevalence is 2%, a test with a sensitivity of 100% and a specificity of 99% may lead to 10 false-positive and 20 true-positive results. This means that 1 in 3 positive results may be a false-positive result.

Table 4. Diagnostic accuracy in a low-prevalence setting example

<table>
<thead>
<tr>
<th></th>
<th>Reference test</th>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Index test +</td>
<td>20</td>
</tr>
<tr>
<td>Index test –</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
</tr>
</tbody>
</table>

Sensitivity = 20/20 = 100%; Specificity = 970/980 = 99%; PPV = 20/30 = 67%; NPV = 970/970 = 100%.

The systematic review also showed that HBsAg tests have a lower sensitivity in HIV-positive individuals. A second test may be useful for increasing the performance of testing overall.

Worked example to illustrate the effect of prevalence on predictive values for the two different testing strategies

Assuming the following assay performance characteristics:
If Assay 1 has sensitivity of 99% and specificity of 98%
If Assay 2 has sensitivity of 99.4 and specificity of 99.5%

Table 5. Effect of prevalence on predictive values for the two different testing strategies

<table>
<thead>
<tr>
<th>Prevalence of analyte</th>
<th>0.1%</th>
<th>1%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay 1</td>
<td>4.7%</td>
<td>33.3%</td>
<td>84.6%</td>
</tr>
<tr>
<td>Assay 1 + Assay 2 (serial)</td>
<td>90.7%</td>
<td>99%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Negative predictive values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay 1</td>
<td>99.9%</td>
<td>99.99%</td>
<td>99.99%</td>
</tr>
</tbody>
</table>

Using the following equation for PPV and NPV that incorporates prevalence more correctly,

7. Conclusions

No study compared diagnostic accuracy, cost, cost–effectiveness of one- vs two-step testing strategies for the detection of HBsAg. Diagnosis of HBV is very complex and there may not be simple algorithms that will cover all settings. All PICOs related to HBV will need to be looked at together to address PICO 3.

The decision tree model described by Fan et al. may prove to be useful for modelling costs of testing strategies. Vaccination strategies should also be taken into account.

References

Appendices

Appendix 1. Librarian search

1. Hepatitis, Viral, Human/
2. Hepatitis Viruses/
3. Hepatitis Antibodies/
4. exp Hepadnaviridae Infections/
5. Hepatitis B Antibodies/
6. Hepatitis B virus/
7. Hepadnaviridae/
8. Hepatitis B Surface Antigens/
9. (hepatitis-b or hep-b or (hepatitis adj5 b) or (hep adj5 b) or hbv).ti,ab.
10. hbsag.ti,ab.
11. exp Hepatitis C/
12. Hepacivirus/
13. Hepatitis C Antibodies/
14. (hepatitis-c or hep-c or (hepatitis adj5 c) or (hep adj5 c) or hcv or aghcv or hepacivirus*).ti,ab.
15. hcvab.ti,ab.
16. or/1-15 [HEP B or HEP C]
17. exp Mass Screening/
18. screen*.ti,ab.
19. 17 or 18 [MASS SCREENING]
20. (one-test* or two-test*).ti,ab.
21. ("1-test*" or "2-test*").ti,ab.
22. ((one or two or "1" or "2" or strateg* or algorithm* or approach or procedure* or system*) adj5 (test or tests or testing or detect* or diagnos* or kit or kits or assay* or device*)).ti,ab.
23. or/20-22 [TESTING STRATEGIES]
24. 16 and 19 and 23
25. Humans/
26. Animals/
27. 25 and 26
28. 26 not 27
29. 24 not 28
30. Limit 29 to English language
Appendix 2. Seven full text articles assessed for eligibility (comparing algorithms, including costing)


Appendix 3. Testing schematics

Public Health England, 2014: hepatitis B virus serology – HBsAg confirmation by alternative assay

Public Health England 2014: hepatitis B surface antigen (HBsAg) confirmation by neutralization

Test to be ordered:
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core total antibody (anti-HBc)
- Hepatitis B core IgM antibody (IgM anti-HBc)

Results:
- HBsAg positive
- anti-HBc positive
- IgM anti-HBc positive [high titre] *

SeroLOGY INTERPRETATION:
- Acute infection

Follow up:
- Assess disease severity and monitor the clinical status of the patient.
- Follow up as appropriate to confirm acute or to exclude chronic infection (HBsAg positive > 6 months)

Australia Government, 2012: suspected acute HBV
Australia Government 2012: suspected chronic HBV

Peng et al. 2011

Detection of HBV serum markers by KHB assays

161,426 subjects between Nov 2006 and Dec 2008

<table>
<thead>
<tr>
<th>HBsAg S/CO</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.20</td>
<td>137a</td>
</tr>
<tr>
<td>0.20-0.99</td>
<td>103</td>
</tr>
<tr>
<td>≥1.00</td>
<td>258b</td>
</tr>
</tbody>
</table>

137a subjects were subjected to quantitative testing with a known positive serum sample.

498 subjects had HBsAg levels ≥0.21.

Of these 498 subjects, 331 were quantitatively reactive.

55 subjects had HBsAg levels ≥0.21 with a S/CO value <1.00 by KHB HBsAg assay.

Detection of HBV DNA
(Roche LightCycler 1.2, PG Biotech)