Supplementary Online Content


eMethods. Literature Search Strategies

eTable 1. Tests for Syphilis

eTable 2. Quality Assessment Criteria

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eTable 4. Quality Assessment of Diagnostic Accuracy Studies

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Literature Search Strategies

Medline
 Database: Ovid MEDLINE(R) without Revisions
 Search Strategy:
--------------------------------------------------------------------------------
1 exp Treponema pallidum/
2 exp Syphilis/ or syphili$.mp.
3 1 or 2
4 exp mass screening/ or screen$.mp.
5 3 and 4
6 limit 5 to english language
7 limit 5 to abstracts
8 6 or 7

Database: Ovid MEDLINE(R) without Revisions
 Search Strategy:
--------------------------------------------------------------------------------
1 exp Treponema pallidum/
2 exp Syphilis/ep, et, pc, px, tm
3 1 or 2
4 exp risk/
5 ((assess$ or stratif$ or quantif$ or identif$) adj7 risk$).mp.
6 4 or 5
7 3 and 6

Database: Ovid MEDLINE(R) without Revisions
 Search Strategy:
--------------------------------------------------------------------------------
1 exp Treponema pallidum/
2 exp Syphilis/di
3 1 or 2
4 exp "Sensitivity and Specificity"/
5 3 and 4
6 exp Diagnostic Errors/
7 3 and 6
8 5 or 7
9 (fals$ adj3 (positiv$ or negativ$)).mp.
10 3 and 9
11 (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12 3 and 11
13 8 or 10 or 12

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**Cochrane Central Register of Controlled Trials**
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 exp Mass Screening/
5 3 or 4
6 1 or 2
7 5 and 6

**Database: EBM Reviews - Cochrane Central Register of Controlled Trials**
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 exp Risk/
5 risk$.mp.
6 4 or 5
7 3 and 6

**Database: EBM Reviews - Cochrane Central Register of Controlled Trials**
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 exp "Sensitivity and Specificity"/
5 exp Diagnostic Errors/
6 (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 (fals$ adj3 (positiv$ or negativ$)).mp.
8 (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9 4 or 5 or 6 or 7 or 8
10 3 and 9

**Cochrane Database of Systematic Reviews**
Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 [exp Mass Screening/]
5 3 or 4
6 1 or 2
7 5 and 6

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 [exp Risk/]
5 risk$.mp.
6 4 or 5
7 3 and 6

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 [exp "Sensitivity and Specificity"/]
5 [exp Diagnostic Errors/]
6 (diagno$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, abstract, full text, keywords, caption text]
7 (fals$ adj3 (positiv$ or negativ$)).mp.
8 (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9 4 or 5 or 6 or 7 or 8
10 3 and 9

Database of Abstracts of Reviews of Effects
Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:
--------------------------------------------------------------------------------
1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 [exp Mass Screening/]
5 3 or 4
6 1 or 2
7 5 and 6

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:
1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 [exp Risk/]
5 risk$.mp.
6 4 or 5
7 3 and 6

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 [exp "Sensitivity and Specificity"/]
5 [exp Diagnostic Errors/]
6 (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, full text, keywords]
7 (fals$ adj3 (positiv$ or negativ$)).mp.
8 (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9 4 or 5 or 6 or 7 or 8
10 3 and 9

NHS Economic Evaluation Database
Database: EBM Reviews - NHS Economic Evaluation Database
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 exp Mass Screening/
5 3 or 4
6 1 or 2
7 5 and 6

Database: EBM Reviews - NHS Economic Evaluation Database
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 exp Risk/
5 risk$.mp.
6 4 or 5
7 3 and 6
Database: EBM Reviews - NHS Economic Evaluation Database
Search Strategy:

1     syphil$.mp.
2     treponema pallidum.mp.
3     1 or 2
4     exp "Sensitivity and Specificity"
5     exp Diagnostic Errors/
6     (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, text, subject heading word]
7     (fals$ adj3 (positiv$ or negativ$)).mp.
8     (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9     4 or 5 or 6 or 7 or 8
10     3 and 9
**eTable 1. Tests for Syphilis**\(^{1-3}\)

<table>
<thead>
<tr>
<th>Test</th>
<th>Use</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Nontreponemal Antibody Tests:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR)</td>
<td>To evaluate disease activity; guide treatment; VDRL used to detect neurosyphilis</td>
<td>Highly <em>sensitive</em>; positive results must be confirmed with treponemal antibody test because it can be positive in other conditions. Nontreponemal antibodies generally disappear with treatment after 3 years.</td>
</tr>
<tr>
<td><em>Treponemal Antibody Tests:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescent treponemal antibody absorbed (FTA-ABS), <em>T. pallidum</em> particle agglutination (TPPA), enzyme immunoassay (EIA), chemiluminescence immunoassay (CIA), Multiplex flow immunoassay (MFI), Syphilis Health Check</td>
<td>Screen or confirm a positive non-treponemal antibody test</td>
<td>Highly <em>specific</em>; positive results must be followed by nontreponemal antibody test to differentiate between active and past infection. Treponemal antibodies remain positive for life even after treatment.</td>
</tr>
<tr>
<td><strong>Direct detection methods (less common)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic Exam, Darkfield Exam: sample from chancre is placed on a slide and examined with a special microscope</td>
<td>Diagnose syphilis in primary stage.</td>
<td>Syphilis is diagnosed if bacteria are seen.</td>
</tr>
<tr>
<td><em>Polymerase chain reaction (PCR)</em></td>
<td>Detects genetic material of bacteria in chancre, blood, or CSF.</td>
<td>Positive test result indicates presence of <em>T. pallidum</em> nucleic acid</td>
</tr>
</tbody>
</table>

Abbreviations: CIA= chemiluminescence immunoassay; CSF= cerebrospinal fluid; EIA= enzyme immunoassay; FTA-ABS= fluorescent treponemal antibody absorption assay; MFI= Multiplex flow immunoassay PCR= polymerase chain reaction; RPR= rapid plasma reagin; TPPA, *T. pallidum* particle agglutination; VDRL= Venereal Disease Research Laboratory
### eTable 2. Quality Assessment Criteria

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Adapted Quality Criteria</th>
</tr>
</thead>
</table>
| **Cohort Studies, adapted from the U.S. Preventive Services Task Force methods**<sup>4</sup> | - Initial assembly of comparable groups: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts  
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)  
- Important differential loss to follow-up or overall high loss to follow-up  
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)  
- Clear definition of interventions  
- Important outcomes considered  
- Analysis: adjustment for potential confounders for cohort studies. |
| **Diagnostic Accuracy Studies, adapted from the U.S. Preventive Services Task Force methods**<sup>4</sup> | - Screening test relevant, available for primary care, adequately described  
- Study uses a credible reference standard, performed regardless of test results  
- Reference standard interpreted independently of screening test  
- Handles indeterminate results in a reasonable manner  
- Spectrum of patients included in study  
- Sample size  
- Administration of reliable screening test |

Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus.
### eTable 3. Quality Assessment of Cohort Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria?</th>
<th>Were the groups comparable at baseline?</th>
<th>Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?</th>
<th>Were outcome assessors and/or data analysts blinded to treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bissessor, et al., 2010*</td>
<td>Yes—consecutive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cohen, et al., 2005*</td>
<td>Yes—consecutive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Zou, et al., 2013*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bissessor, et al., 2011*</td>
<td>Yes—consecutive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
### eTable 3. Quality Assessment of Cohort Studies, continued

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the article report attrition?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>Is there important differential loss to follow-up or overall high loss to follow-up?</th>
<th>Were outcomes pre-specified and defined, and ascertained using accurate methods?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bissessor, et al., 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Cohen, et al., 2005&lt;sup&gt;6&lt;/sup&gt;</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Zou, et al., 2013&lt;sup&gt;7&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Bissessor, et al., 2011&lt;sup&gt;8&lt;/sup&gt;</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: KQ= Key question
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Representative spectrum</th>
<th>Random or consecutive sample</th>
<th>Screening test adequately described</th>
<th>Screening cutoffs predefined</th>
<th>Credible reference standard</th>
<th>Reference standard applied to and analysis includes all patients, or a random subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binnicker, Jespersen, and Rollins, 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Juárez-Figueroa, et al., 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Study, year</td>
<td>Same reference standard applied to all patients</td>
<td>Reference standard and screening examination interpreted independently</td>
<td>High rate of uninterpretable results or non-compliance with screening test</td>
<td>Analysis includes patients with uninterpretable results or non-compliance</td>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
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<td>Yes</td>
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References


