TITLE: Rapid Response Testing for the Detection of *Clostridium difficile*: A Review of the Diagnostic Accuracy

DATE: 28 July 2009

CONTEXT AND POLICY ISSUES:

*Clostridium difficile* (*C. difficile*) is recognized as a major causative agent of antibiotic-associated diarrhea\(^1,2\) and nearly all cases of pseudomembranous colitis.\(^3\) It is estimated that 20% of hospitalized inpatients and 25% to 80% of otherwise healthy newborns and infants test positive for *C. difficile*.\(^4\) Although some *C. difficile*-positive individuals will remain asymptomatic (carriers), others will present with a range of symptoms including diarrhea, fever, abdominal pain, and colitis.\(^1\)

The majority of *C. difficile*-positive cases involved individuals who were recently treated with antibiotics.\(^4\) It has been suggested that antibiotic use may result in a disruption in the normal gut flora and renders the individual susceptible to colonization of *C. difficile* spores.\(^4\) Sources of spores can include contaminated bed rails, toilets, and other surfaces within hospitals and long-term care facilities.\(^4\)

While all *C. difficile* strains express the common antigen glutamate dehydrogenase\(^5\), production of toxins A and B is restricted to toxigenic strains. Both toxin A and toxin B contribute to the pathogenesis of *C. difficile*-associated disease.\(^6\) Diagnosis of *C. difficile* is primarily accomplished by detecting toxins in the stools of individuals with suspected disease.\(^6\) Direct stool toxin assays include the cytotoxin assay (CTA) and enzyme immunoassays.\(^7\) Detection of toxin B through CTAs is considered to be the gold standard for the diagnosis of *C. difficile*.\(^3\) The CTA involves exposing cultured cells to fecal extracts in the presence and absence of anti-toxin. Fecal samples that are *C. difficile*-positive have a cytopathic effect on the cultured cells that have not been treated with anti-toxin.\(^8\)

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**C. difficile** can also be detected by culturing the organism under anaerobic conditions. This method has high sensitivity, but is also time consuming and can require more than three days. In addition, this approach does not distinguish between toxigenic and non-toxigenic strains. Further testing of bacterial culture isolates using EIA is typically performed to identify if the *C. difficile* strain is toxin-producing.

Both the CTA and culturing of *C. difficile* are time-consuming and labour-intensive. A delay in the diagnosis of *C. difficile* could postpone treatment of a *C. difficile*-positive individual. Similarly, a false-positive diagnosis may result in the individual being treated with an antibiotic regimen tailored for *C. difficile* infection. It may also result in an individual falsely diagnosed with *C. difficile* sharing a room with truly *C. difficile*-positive individuals. A rapid and easily-performed assay that has a high sensitivity and specificity is needed. This report will review the available evidence regarding the diagnostic accuracy of rapid response testing for *C. difficile*.

**RESEARCH QUESTION:**

What are the diagnostic accuracies of antigen and toxin detection assays for the detection of *Clostridium difficile*?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID’s Medline, Embase, and Biosis, the Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and June 2009. No filters were applied to limit the retrieval by study type. Internet links were provided, where available.

To be considered for inclusion, the study had to test clinical human stool samples using a rapid antigen test, a rapid polymerase chain reaction test, or a rapid toxin test compared to CTA with or without stool culture for *C. difficile* as the reference standard, and report diagnostic performance measures (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). Studies were excluded if the reviews were not systematic (did not include a search of more than one database and involve article selection by at least two people) and if they did not provide sufficient detail to discern the methods used for testing.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, controlled clinical trials, and observational studies.

**SUMMARY OF FINDINGS:**

One systematic review and six observational studies were identified by the literature search. No health technology assessments, randomized controlled trials, or controlled clinical trials were identified. A table providing the summary statistics from all of the included studies is located in Appendix 1 (Table 1). A narrative summary of the included studies is below and a discussion of the overall study limitations follows later in the report.
Systematic reviews and meta-analyses

A systematic review was published by Planche et al. (2008) in which authors compared the sensitivity and specificity of commonly-used commercial assays for the detection of *C. difficile* toxins A and B. The search of multiple databases was conducted in November 2007 and only articles published after 1994 were considered for inclusion. Studies were eligible if they evaluated one of the following toxin A or B assays: Meridian Premier *C. difficile* Toxin A&B ELISA (enzyme-linked immunosorbent assay), TechLab Tox A/B II (ELISA), TechLab Tox A/B Quik Chek (rapid antigen capture), Remel Xpect (rapid chromatographic immunoassay), BioMérieux VIDAS (enzyme immunoassay [EIA]), and Meridian ImmunoCard (rapid EIA).

Eighteen reports that described 28 comparisons were included in the systematic review. Seven of the publications were peer-reviewed articles (study types were not specified, however, all were prospective in design), while the remaining 11 were conference proceedings. The setting for all of the peer-reviewed publications was in-hospital, while five of the 11 conference proceedings reported on data collected in-hospital. The average number of patients in the peer-reviewed publications was 430. The median prevalence of positive stools across all 18 studies was 15%. The authors did not find a statistically significant difference in the sensitivities and specificities depending on the reference standard used (CTA with or without stool culture), therefore studies were pooled by test type. For each assay the median and interquartile range (IQR) for the sensitivity and specificity were reported.

Diagnostic odds ratios (DORs) were calculated to provide an estimate of overall accuracy. There were no significant differences in DORs between any of the assay evaluated (\(P=0.33\)). Logistic regression analysis was conducted to estimate the effect of test choice on sensitivity. The Meridian Premier *C. difficile* Toxin A&B ELISA had the highest sensitivity at 94.8% (86.4% to 96.8%; \(P<0.0001\)) with a specificity of 97.0% (95.3% to 97.5%; \(P=0.0042\)). The TechLab Tox A/B Quik Chek had the highest specificity at 99.7% (99.4% to 99.8%; \(P<0.0001\)). The authors considered an acceptable test to be one with a sensitivity of at least 90% at the 25th percentile and the false-positive rate below 3% when estimated at the 25th percentile for specificity. None of these tests met these criteria. The authors recommended that a rapid test be used for an initial screen of a stool sample. By this method, most positive results would be identified and authors noted that because all of evaluated tests had sensitivities over 75%, the NPVs would exceed 98%. Confirmation of the rapid test result by CTA could be used to provide a definitive result. The methodological approach to the systematic review was rigorous. Authors declared that they had no conflicts of interest.

Observational studies

Stamper et al. (2009) evaluated the diagnostic performance of BD GeneOhm real-time polymerase chain reaction (PCR) test (that amplifies the toxin B gene). The reference standard was a commercially available CTA (Wampole *C. difficile* Toxin B test). This study was an industry-sponsored Food and Drug Administration trial that took place in a 900-bed tertiary care centre in the United States. A total of 404 samples from 377 individuals were analyzed. Forty positive test results were positive by CTA. The sensitivity of GeneOhm was 83.6% (95% CI: 74.3% to 92.9%) and the specificity was 98.2% (96.8% to 99.6%). The PPV and NPV were 89.5% (81.5% to 97.4%) and 97.1% (95.3% to 98.9%), respectively. In a second analysis, GeneOhm was compared to the anaerobic culture as the reference standard. These data are presented in Table 1, Appendix 1. The procedural time for the GeneOhm test was approximately three hours, while the time for the CTA typically was 24 to 48 hours, and approximately five days for anaerobic culture. Authors concluded that GeneOhm is a rapid and sensitive test for the detection of *C. difficile*. 
An evaluation report was produced by Wilcox and Eastwood (2009) for the UK-based National Health Service-associated Centre for Evidence-based Purchasing. A total of 600 stool samples were tested for the presence of \textit{C. difficile} toxin using nine commercially available toxin detection assays. It was not stated if the stool samples were from individuals within the hospital or community. Tests were excluded from consideration if they did not detect both Toxin A and B. The reference standard used was the CTA either from direct stool samples, or in cases of test discrepancy, by cytotoxigenic culture (testing the ability of cultured isolates to induce a cytopathic effect on cultured cells). The tests included were: Premier Toxin A&B, Vidas \textit{C. difficile} Toxin A&B, GA Clostridium Difficile Antigen, Ridascreen Toxin A/B, TechLab Toxin A/B II, Remel ProSpecT, Remel Xpect, TechLab Tox A/B Quik Chek, and Premier ImmunoCard A+B. Data regarding the comparative sensitivity, specificity, PPV, and NPV were reported. Two tests had sensitivity values over 90%; Premier Toxin A&B (91.7% [95% CI: 84.7% to 96.1%]) and TechLab Toxin A/B II (90.7% [83.6% to 95.5%]). Two different tests had the highest specificities Remel Xpect (98.8% [97.2% to 99.5%] and TechLab Tox A/B Quik Chek (98.6% [96.9% to 99.4%]. The same two tests also had the highest PPVs. The PPV and NPV were estimated when prevalence of \textit{C. difficile} was stated to be 2% (which authors reported represented a rate similar to when testing stool samples from the community) to 10% (similar to a rate observed when testing stool samples from a hospital). The procedural time for each test ranged from 16 minutes (Premier ImmunoCard A+B) to one hour and 45 minutes for Ridascreen Toxin A/B. The authors concluded that no single test was superior with respect to both sensitivity and specificity; however five tests out-performed the others. These five included: Remel Xpect, TechLab Tox A/B Quik Chek, Premier Toxin A&B, Vidas \textit{C. difficile} Toxin A&B, and TechLab Toxin A/B II. The authors concluded that the majority of the PPVs were low and questioned the appropriateness of any of the tests used as a single-agent for the detection of \textit{C. difficile}.

A study by Alcalá et al. (2008) compared the diagnostic performance of three rapid EIAs: Xpect \textit{Clostridium difficile} Toxin A/B test, Wampole Tox A/B Quik Chek, and ImmunoCard Toxins A&B. The study took place in a 1,750 bed tertiary care centre in Spain. The reference standard was the combination of CTA from stool specimens and CTA from cultured toxigenic isolates from stool samples. The outcomes of interest included sensitivity, specificity, PPV, NPV, and time to complete each test procedure. A total of 367 stool specimens from 305 patients were tested. A positive test result by the reference standard was obtained in 27% of samples. There were no statistically significant differences in the specificity values between the three tests, but the sensitivity of ImmunoCard Toxins A&B was significantly higher than either of the other two tests (66.7% [95% CI: 56.6% to 75.7%]; \(P<0.013\)). ImmunoCard Toxins A&B also had the shortest procedure time with a median time to test five stool samples of approximately 24 minutes. Authors concluded that the ImmunoCard Toxins A&B test was the most sensitive and the fastest EIA evaluated. The authors did not declare a conflict of interest; however, they reported that all supplies for the tests were provided by the manufacturers of the EIAs.

The diagnostic performance of five EIAs for the rapid diagnosis of \textit{C. difficile} were evaluated by Miendje et al. (2008). The study took place in Belgium. The authors compared Biostar OIA CdTOX, ImmunoCard Toxins A&B, Xpect \textit{C. difficile} toxin A/B, \textit{C. difficile} toxin A test, and TOX A/B QUIK CHEK to the reference standard, CTA. A total of 100 stool samples from 91 hospitalized patients suspected to have CDAD were processed. Twenty-three samples were positive for \textit{C. difficile} by CTA. Sensitivity, specificity, PPV, and NPV were measured for all five tests and are reported in Table 1 in the appendix. There were no statistically significant differences in these performance measures between the commercial tests. In addition, the authors reported that the differences between the EIAs and the CTA were not statistically
Musher et al. (2007)\textsuperscript{14} compared the performance of three EIAs (Premier Toxins A&B, TechLab Tox A/B II, and ProSpecT \textit{Clostridium difficile} toxin A/B microplate assay) and one rapid EIA (ImmunoCard). The study took place in US. It was not stated within the article if the stool samples were from hospitalized patients; however, samples were submitted to a hospital laboratory for processing. The reference standard used was a commercially available CTA (CTYA) and was considered to provide true results for the purpose of this study. This study was conducted in two phases. The first phase evaluated the rapid EIA (ImmunoCard) and one EIA (Premier Toxins A&B) in 446 stool samples. This phase was conducted to evaluate if EIA or the rapid EIA could reliably reproduce the results of CTA. The sensitivities of Premier Toxins A&B and ImmunoCard were 98.7% (95% CI 92% to 99%) and 96.1% (95% CI 88% to 91%), respectively. Specificities were 97.3% (95% CI 95% to 98%) and 98.9% (95% CI 97% to 99%), respectively. Study investigators evaluated the three EIAs (not including the rapid EIA ImmunoCard) in subset including 131 fresh stool samples in which 54 were CTA-positive and 77 were CTA-negative. There were no statistically significant differences in the sensitivities between tests (see Table 1, Appendix 1 for data); however the specificity of TechLab Tox A/B II was significantly lower than the other two EIAs ($P=0.04$). The authors did not make any conclusions regarding the comparative performances of tests. They noted that CTA is labour- and time-intensive and requires additional resources such as a cell culture facility and an inverted microscope. They also noted that traditional EIA, such as the three evaluated in their study, was also labour-intensive and required several hours of medical laboratory technology time and an EIA plate reader. The rapid EIA may be more costly on a per test basis; however, this may prove to be an appropriate option for those institutions that process samples on an occasional basis. The authors did not declare a conflict of interest; however, they reported that all supplies for the tests were provided by the manufacturers of the EIAs.

A prospective multi-centre study was published by van den Berg et al. (2005).\textsuperscript{15} The authors of the Netherlands-based study compared a rapid single-test EIA (ImmunoCard Toxins A&B) to an in-house CTA for the detection of \textit{C. difficile}. The authors also compared the performance of ImmunoCard to an in-house real-time PCR protocol for the detection of the toxin B gene; however, given that the PCR test is not commercially available, results from it will not be discussed in the current HTIS report. A total of 367 samples from 300 hospitalized patients were evaluated. Twenty-three samples were positive by CTA. When compared to CTA, the sensitivity and specificity of ImmunoCard were 91.3% and 97.4%, respectively (95% CI not reported). The PPV and NPV were 70.0% and 99.4%, respectively. Any discrepancies between CTA and ImmunoCard results were resolved by culturing toxigenic \textit{C. difficile} from fecal samples. Thirty-three of 40 samples analyzed by culture were positive. Using the results from the discrepancy analysis the authors re-calculated sensitivity, specificity, PPV, and NPV of ImmunoCard; they are as follows: 79%, 99%, 90%, and 98%. Authors concluded that the traditional gold-standard of CTA has some limitations in its diagnostic performance. Authors further concluded that the rapid single-test EIA, ImmunoCard, had excellent sensitivity and NPV and with a rapid turn-around time of approximately 20 minutes, this test may wish to be considered as a first-round screening tool for \textit{C. difficile}. Authors did not declare any conflicts of interest.

**Limitations**

This report has several limitations. The literature search timeframe was limited to the last five years. It is possible that some studies were not included because they did not meet the date restriction. Also, this report limited the inclusion of studies to those that used CTA with or
without *C. difficile* culture as the reference standard. Therefore, studies that used culture alone were not included.

The evaluation of the performance characteristics of rapid tests for the detection of *C. difficile* can be affected by a number of factors including how the test was administered. Some of the tests, in particular the EIAs may require trained laboratory personnel to perform.\(^{11}\) It is possible that differences in laboratory processing of samples influenced the test results. Most of the studies reported that a proportion of stool samples were processed fresh when received, while the remaining were stored at 4°C or frozen and later thawed for processing. It was not always stated that manufacturers’ instructions were followed; therefore any modifications to the intended protocol may have influenced test results. The reference standard for all of the included studies was CTA with or without culture. Some of the studies performed an in-house CTA, while others used a commercially-available kit. All studies differed in their CTA protocol and some studies differed in what was considered to be a cytopathic effect induced by toxins. These differences may have affected the reported test results. The accuracy of the reference standard will have an impact on the performance of the rapid tests.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The evidence in this report suggests that the rapid tests designed to detect *C. difficile* have lower sensitivity and PPV than the reference standard evaluated in this report, CTA with or without anaerobic culture. Those rapid tests that had favourable diagnostic performance characteristics compared to other rapid tests included the Meridian Premier *C. difficile* Toxin A+B ELISA, TechLab Tox A/B Quik Chek, TechLab Toxin A/B II, and ImmunoCard Toxin A&B. The ImmunoCard Toxin A&B test had the shortest procedural time reported in two studies to be 16 and 24 minutes. In addition, this test is a single-test EIA and may be useful in facilities where testing is done on an occasional basis. Several of the other rapid tests evaluated required additional components such as automatic plate reader instruments, plate washers, centrifuges, or consumables such sample preparation kits that are not included in the detection test kits.

The majority of the studies highlighted the need for confirmation of rapid test results by a more rigorous method such as CTA or anaerobic culture. Further, it was suggested that rapid tests could be used as a preliminary screening approach to identify potentially *C. difficile*-positive individuals. The use of a rapid test would decrease the delay in detecting a *C. difficile* infection.

Overall, the decision to use rapid tests in the detection of *C. difficile* and the type of test used may depend on the cost of the test, the need for additional equipment or training to perform the test, the requirement of a short turn-around time for test completion, the number of samples that are typically processed by the laboratory, the level of laboratory skill of the person performing the test, and the capacity to perform confirmatory tests by either CTA or anaerobic culture.

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APPENDIX 1: Summary of Included Studies

Table 1. Summary Statistics for Included Studies

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Type of C. difficile test evaluated</th>
<th>Comparator</th>
<th>Results: diagnostic performance (95% CI)</th>
</tr>
</thead>
</table>
| Planche et al. (2008)⁹       | Premier C. difficile Toxin A&B (ELISA) | CTA with or without stool culture for all tests | Se: 94.8% (86.4% to 96.8%)  
Sp: 97.0% (95.3% to 97.5%)  
Se: 83.3% (81.6% to 85.4%)  
Sp: 98.7% (97.7% to 99.8%)  
Se: 83.9% (81.2% to 87.0%)  
Sp: 99.7% (99.4% to 99.8%)  
Se: 82.0% (75.3% to 88.7%)  
Sp: 96.2% (94.5% to 97.9%) |
|                              | TechLab Tox A/B II (ELISA)          |            |                                        |
|                              | TechLab Tox A/B Quik Chek (rapid antigen capture) |            |                                        |
|                              | Remel Xpect (rapid chromatographic immunoassay) |            |                                        |
|                              | BioMérieux VIDAS (EIA)              |            |                                        |
|                              | Meridian ImmunoCard (single-test EIA) |            |                                        |
| Stamper et al. (2009)¹⁰      | BD GeneOhm                         | CTA        | Se: 83.6% (74.3% to 92.9%)  
Sp: 98.2% (96.8% to 99.6%)  
PPV: 89.5% (81.5% to 97.4%)  
NPV: 97.1% (95.3% to 98.9%)  
Se: 67.2% (55.4% to 79.0%)  
Sp: 99.1% (98.1% to 100%)  
PPV: 93.2% (85.7% to 99.9%)  
NPV: 94.4% (92.0% to 96.8%) |
|                              | TechLab Wampole TOX-B Cellular Neutralization Assay | Anaerobic culture |                                        |
| Wilcox and Eastwood (2009)¹¹ | Premier Toxin A+B (well-type EIA)  | CTA for all tests | Se: 91.7% (84.7% to 96.1%)  
Sp: 97.1% (95.1% to 98.4%)  
PPV: 78  
NPV: 99.1 |
<p>|                              | Vidas C. difficile Toxin A &amp; B (automated immunoassay) |            |                                        |
|                              | GA Clostridium difficile Antigen (well-type EIA) |            |                                        |
|                              | Ridascreen toxin A/B (well-type EIA) |            |                                        |</p>
<table>
<thead>
<tr>
<th>Author and year</th>
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<th>Results: diagnostic performance (95% CI)</th>
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<tr>
<td></td>
<td>TechLab Toxin A/B II (well-type EIA)</td>
<td>NPV: 96.3</td>
<td>Se: 90.7% (83.6% to 95.5%)&lt;br&gt;Sp: 95.7% (93.4% to 97.3%)&lt;br&gt;PPV: 70.1&lt;br&gt;NPV: 98.9</td>
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<td></td>
<td>Remel ProSpecT (well-type EIA)</td>
<td></td>
<td>Se: 89.8% (82.5% to 94.8%)&lt;br&gt;Sp: 92.6% (89.8% to 94.7%)&lt;br&gt;PPV: 57.5&lt;br&gt;NPV: 98.8</td>
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<td></td>
<td>Remel Xpect (membrane assay)</td>
<td></td>
<td>Se: 77.8% (68.8% to 85.2%)&lt;br&gt;Sp: 98.8% (97.2% to 99.5%)&lt;br&gt;PPV: 87.5&lt;br&gt;NPV: 97.6</td>
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<tr>
<td></td>
<td>TechLab Tox A/B Quik Chek (membrane assay)</td>
<td></td>
<td>Se: 84.3% (76.0% to 90.6%)&lt;br&gt;Sp: 98.6% (96.9% to 99.4%)&lt;br&gt;PPV: 86.8&lt;br&gt;NPV: 98.3</td>
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<tr>
<td></td>
<td>Premier ImmunoCard A+B (membrane assay)</td>
<td></td>
<td>Se: 77.8% (68.8% to 85.2%)&lt;br&gt;Sp: 92.8% (91.1% to 94.9%)&lt;br&gt;PPV: 54.7&lt;br&gt;NPV: 97.4</td>
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<tr>
<td>Alcalá et al. (2008)</td>
<td>Xpect Clostridium difficile Toxin A/B</td>
<td>CTA for all tests</td>
<td>Se: 49.0% (39.0% to 59.1%)&lt;br&gt;Sp: 95.8% (92.7% to 97.9%)&lt;br&gt;PPV: 82.0% (70.0% to 90.6%)&lt;br&gt;NPV: 83.0% (78.3% to 87.0%)</td>
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<tr>
<td></td>
<td>Wampole Tox A/B Quik Chek</td>
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<td>Se: 54.9% (44.7% to 64.8%)&lt;br&gt;Sp: 95.5% (92.2% to 97.6%)&lt;br&gt;PPV: 82.4% (71.2% to 90.5%)&lt;br&gt;NPV: 84.6% (80.0% to 88.5%)</td>
</tr>
<tr>
<td></td>
<td>ImmunoCard Toxins A&amp;B</td>
<td></td>
<td>Se: 66.7% (56.5% to 75.7%)&lt;br&gt;Sp: 95.1% (91.8% to 97.4%)&lt;br&gt;PPV: 84.0% (74.1% to 91.1%)&lt;br&gt;NPV: 88.1% (83.8% to 91.6%)</td>
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<tr>
<td>Miendje et al. (2008)</td>
<td>Biostar OIA CdTox AB</td>
<td>CTA for all tests</td>
<td>Se: 87% (CIs not reported)&lt;br&gt;Sp: 100%&lt;br&gt;PPV: 100%&lt;br&gt;NPV: 96.3%</td>
</tr>
<tr>
<td></td>
<td>ImmunoCard Toxins A&amp;B</td>
<td></td>
<td>Se: 91.3%&lt;br&gt;Sp: 100%&lt;br&gt;PPV: 100%&lt;br&gt;NPV: 97.5%</td>
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<tr>
<td>Author and year</td>
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<td>Results: diagnostic performance (95% CI)</td>
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</table>
| Xpect          | C. difficile toxin A/B        |            | Se: 91.3%  
|                | C. difficile toxin A test     |            | Sp: 100%  
|                | Tox A/B Quik Chek            |            | PPV: 100%  
|                |                              |            | NPV: 97.5%  |
| Musher et al. (2007) | First phase of study | CTA (C. difficile toxin A/B detection kit; Diagnostic Hybrids) for all tests and both phases | Se: 98.7% (92% to 99%)  
|                | Premier Toxin A&B:           |            | Sp: 97.3% (95% to 98%)  
|                | ImmunoCard                   |            | PPV: 88.2% (79% to 94%)  
|                | Second phase of study        |            | NPV: 99.2% (97% to 99%)  
|                | Premier Toxins A&B          |            | Se: 96.1% (88% to 91%)  
|                | TechLab Tox A/B II          |            | Sp: 98.9% (97% to 99%)  
|                | ProSpecT Clostridium difficile tox A/B assay |            | PPV: (94.8% (87% to 98%)  
|                | ImmunoCard was not evaluated in the second phase of the study |            | NPV: (99.2% 97% to 99%)  |
| van den Berg et al (2005) | ImmunoCard | CTA for all tests | Se: 91.3% (CIs not reported)  
|                |                              |            | Sp: 97.4%  
|                |                              |            | PPV: 70.0%  
|                |                              |            | NPV: 99.4%  |

CI=confidence interval; C. difficile=Clostridium difficile; CTA=cytotoxin assay; EIA=enzyme immunoassay; ELISA=enzyme-linked immunosorbent assay; Se=sensitivity; Sp=specificity; NPV=negative predictive value; PPV=positive predictive value.