Diagnostic Accuracy of Real-time Polymerase Chain Reaction in Detection of *Clostridium difficile* in the Stool Samples of Patients With Suspected *Clostridium difficile* Infection: A Meta-Analysis

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**Background.** Current detection methods for *Clostridium difficile* infection (CDI) can be time-consuming and have variable sensitivities. Real-time polymerase chain reaction (PCR) may allow earlier and more accurate diagnosis of CDI than other currently available diagnostic tests. A meta-analysis was performed to determine the diagnostic accuracy of real-time PCR.

**Methods.** We searched MEDLINE (Pubmed/Ovid) and 4 other online electronic databases (1995–2010) to identify diagnostic accuracy studies that compared PCR with cell culture cytotoxicity neutralization assay (CCCNA) or anaerobic toxigenic culture (TC) of *C. difficile*. Screening for inclusion, data extraction, and quality assessment were carried out independently by 2 investigators and disagreements resolved. Data were combined by means of a random-effects model, and summary receiver operating characteristic curves and diagnostic odds ratios were calculated.

**Results.** Nineteen studies (7392 samples) met our inclusion criteria. The overall mean sensitivity of PCR was 90% (95% confidence interval [CI]: 88%–91%), specificity 96% (CI: 96%–97%), positive likelihood ratio 26.89 (CI: 20.81–34.74), negative likelihood ratio 0.11 (CI: .08--.15), diagnostic odds ratio 278.23 (CI: 213.56–362.50), and area under the curve 0.98 (CI: .98–.99). Test accuracy depended on the prevalence of *C. difficile* but not on the reference test used. At *C. difficile* prevalence of <10%, 10%–20% and >20% the positive predictive value and the negative predictive value were 71%, 79%, 93% and 99%, 98% and 96%, respectively.

**Conclusions.** Real-time PCR has a high sensitivity and specificity to confirm CDI. Overall diagnostic accuracy is variable and depends on CDI prevalence.

*Clostridium difficile* is the commonest cause of nosocomial and antibiotic-associated diarrhea in North America and Europe [1]. The hypervirulent BI-NAP1-027 strain has been responsible for causing several epidemics of *C. difficile* infection (CDI) in recent years [1]. Infection with this strain is associated with both a higher incidence and increased severity of disease [2]. Almost all antimicrobials have been associated with CDI including cephalosporins, penicillins, and fluoroquinolones [3, 4]. CDI is suspected in a patient with diarrhea, abdominal pain, and fever with a recent history of hospitalization or antimicrobial use. Current methods available for the diagnosis of CDI include cell culture cytoxicity neutralization assay (CCCNA), anaerobic toxigenic culture (TC), enzyme immunoassay (EIA) for toxin A and B, glutamate dehydrogenase (GDH) EIA, real-time polymerase chain reaction (PCR), and sigmoidoscopy and colonoscopy [5]. CCCNA for detection of toxin B has a sensitivity.
and specificity of \(70\% - 100\%\) and \(90\% - 100\%\), respectively [6]. The anaerobic TC has a sensitivity of \(90\% - 100\%\) and specificity of \(98\% - 100\%\) [4]. Since there is no accepted real gold standard, these 2 tests are often used as reference tests for each other to obtain the reported sensitivities and specificities. Also, both these tests are time-consuming and difficult to perform. Thus, most laboratories use the easier and quicker EIA for toxin A and B detection. EIA has a sensitivity and specificity of \(70\% - 80\%\) and \(98\%\), respectively, when CCCNA and/or anaerobic TC is used as a reference test [5, 7]. Recent studies have reported a lower sensitivity and specificity compared with earlier studies [8]. Real-time PCR detects the chromosomal genes encoding \(C. difficile\) toxin B (tdkB) or the toxin regulatory gene (tdtC) directly from stool samples. There are many in-house and commercial PCR-based amplification methods available for the detection of \(C. difficile\). However, only 4 commercial amplification methods have received Food and Drug Administration (FDA) approval in the United States (BD GeneOhm assay, Prodesse assay, Cepheid Gene Xpert assay, Illumigen assay). These are being implemented in some hospitals to improve the rapidity and detection rates of CDI. Also, the FDA now requires all vendors to include toxigenic culture as a comparator for any new diagnostic test for \(C. difficile\) detection. Two recent systematic reviews evaluated the quality of all currently available diagnostic methodologies including a real-time PCR for \(C. difficile\) toxin B gene for detecting CDI and concluded that none of the current tests were suitable as a stand-alone test to diagnose CDI in endemic populations [7, 9]. UK-based studies have also reported that none of the currently available toxin detecting EIA and membrane-based assays have a high diagnostic accuracy [9, 10]. Infectious Diseases Society of America (IDSA)/Society for Healthcare of America (SHEA) guidelines on diagnostic testing of \(C. difficile\) suggest that more data are needed on nucleic acid amplification tests before it can be implemented for wide-scale use [11]. We undertook a meta-analysis to assess the diagnostic accuracy of real-time PCR in CDI. Our aim was to investigate whether real-time PCR used alone was sufficiently sensitive and specific for the diagnosis of CDI in endemic populations.

**METHODS**

This review was performed with a standardized written protocol that followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines [12].

**Search Strategy**

We systematically searched the literature using the following predetermined inclusion criteria. Studies evaluating real-time PCR as a diagnostic test for CDI were eligible for inclusion if the studies (1) described original research; (2) performed stool specimen analyses from inpatients or outpatients; (3) compared PCR to a reference method—either CCCNA or anaerobic TC; (4) reported total number of patients tested and positive/negative results that allow calculation of true positives (TP), true negatives (TN), false positives (FP), false negatives (FN); and (5) were published between 1995 and 2010 in any language. We excluded studies if (1) all samples were not tested by at least 1 reference test, that is, CCCNA or anaerobic TC; (2) if the reference test was performed only on a subset of samples, that is, only positives, negatives, or those that were discordant; (3) the reference test was a combination of >1 diagnostic test; (4) tests involved animal studies or laboratory cultures of \(C. difficile\); and (5) studies that focused on detecting virulence of different \(C. difficile\) ribotypes using real-time PCR. In the excluded studies, real-time PCR tests were confirmed using other diagnostic tests but not CCCNA or anaerobic TC. We also excluded combination reference tests because we wanted to individually calculate the diagnostic accuracy of real-time PCR vis-à-vis the 2 most accepted reference standards.

This search was performed in September 2010 and included articles published from January 1995. The following databases were searched: PubMed (1995–2010), Ovid (1995–2010), Web of Science (1995–2010), CINAHL (1995–2010), Cochrane Library, and SCOPUS (1995–2010). In addition, we reviewed the reference lists of several previously published reviews on \(C. difficile\) diagnostic testing. Search terms included “\(Clostridium\) difficile, \(C.\) diff, \(C.\) difficile, CDAD, CDI, real-time polymerase chain reaction, rt-PCR, real-time PCR analysis, TaqMan, BD GeneOhm, Prodesse, Xpert Cepheid, sensitivity, specificity, screening, false positives, false negatives, accuracy, predictive value, diagnostic test, diagnosis.” Reference lists from included studies were also searched. In addition, experts and commercial PCR manufacturers for \(C. difficile\) diagnosis were contacted for additional studies. The electronic search strategy of PubMed is available in Supplementary Appendix 1.

**Study Selection**

A list of retrieved articles was reviewed independently by 2 investigators (V. P. and A. D.) in order to choose potentially relevant articles, and disagreements about particular studies were discussed and resolved. When multiple articles for a single study had been published by the same authors, we used the most relevant publication and supplemented it, if necessary, with data from other publications. Authors of studies were contacted when the information was not available in the published study.

**Data Extraction**

Two investigators (A. D. and V. P.) independently extracted data from full text of the included studies, and disagreements were discussed and resolved. All studies evaluated the diagnostic accuracy of real-time PCR on a per-sample basis.
Assessment of Study Quality
The methodological quality for each paper was assessed independently by 2 investigators (A. D. and V. P.) using the QUADAS criteria [13]. The study quality criteria are available in Supplementary Appendix 2. For most studies interpretation of the index test and reference test were not performed independently as the aim of the studies was to compare the diagnostic accuracy of real-time PCR to the reference tests. Also, because real-time PCR was not FDA approved for clinical diagnosis at the time when many of the studies were done, clinical data were not available for test result confirmation.

Data Synthesis and Meta-Analysis
TP, FP, TN, and FN were taken directly from the source papers. Where this information was not available, the values were calculated from the data that were provided in the article. In some cases the corresponding authors of the article were contacted to provide information for creating the 2 × 2 table. Data were analyzed using the freeware program Meta-DiSC (version 1.4) and were pooled using the DerSimonian-Laird random effects model [14]. The random effects model is more suited for this study than the fixed effects model because it also takes into consideration within-study variability (random error) and between-study variability (heterogeneity).

We calculated several diagnostic accuracy measures per study. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratios (DOR), and 95% confidence intervals (CI) were calculated. The data were displayed graphically on Forest plots and summary receiver operating characteristic (SROC) plots. The SROC curve was fitted using the Littenberg-Moses method. The definition and significance of other statistical parameters is shown in Supplementary Appendix 3. We adopted Planche et al’s definition of an acceptable test criteria of sensitivity >90% (when estimated at its 25th centile) and a false positive rate of <3% (estimated at its 25th centile for specificity) [9].

Investigations of Heterogeneity
Exploring heterogeneity is a critical issue to (1) understand the possible factors that influence accuracy estimates and (2) to evaluate the appropriateness of statistical pooling of accuracy estimates from various studies [15]. Subgroup analyses were therefore performed by type of reference test (CCCNA vs. TC) and estimated prevalence of C. difficile (<10%, 10%–20%, and >20%). The percentage positivity expected in C. difficile samples being tested using real-time PCR in a hospitalized setting ranges from 7% to 11% [4], and therefore the cutoff values for subgroup analyses were chosen as <10%, 10%–20%, and >20%.

RESULTS
Study Characteristics
Of the 141 references identified, 88 potentially relevant citations were selected based on relevance to the study topic. After screening all the titles and abstracts, 67 articles were selected for full-text review (Figure 1). Nineteen studies that...
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Reference test</th>
<th>Total no of samples</th>
<th>Prev. CDI (%)</th>
<th>Extraction/PCR</th>
<th>Target gene</th>
<th>Assay design</th>
<th>FDA approved</th>
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<tr>
<td>Tenover FC [16]</td>
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<td>tcdB</td>
<td>Xpert Cepheid</td>
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<td>CCCNA</td>
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<td>10.06</td>
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<td>tcdA and tcdB</td>
<td>Applied Biosystems</td>
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<td>89</td>
<td>28.08</td>
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<td>tcdA</td>
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<td>No</td>
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Abbreviations: CCCNA, cell culture cytotoxicity neutralization assay; TC, toxigenic culture.
reported the sensitivity and specificity of real-time PCR on stool samples for the diagnosis of *C. difficile*, published between 1995 and 2010, were included in the meta-analysis. Forty-eight articles were excluded (reasons for exclusion in Figure 1).

Table 1 summarizes the main characteristics of the included studies. In total, 7392 stool samples from patients at risk of CDI were included in the meta-analysis. The prevalence of CDI across all studies ranged from 3% to 52%. PCR was used for diagnostic purposes in all the studies and not for screening patients. Details of the PCR methodology used are summarized in Table 1. Five variations in the PCR technique were used including studies that used laboratory developed/non FDA approved PCR (Table 1). The quality of studies as assessed by the QUADAS tool was generally high, with all studies meeting 8 or more of the criteria (Figure 2). Four studies [20, 23–25] used both CCCNA and anaerobic TC as a reference test.)

**Figure 2.** Study quality according to QUADAS guidelines.

**Figure 3.** Forest plot estimates of the pooled sensitivity.

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*Clostridium difficile* Infection Diagnosis Using Real-time PCR • *CID* 2011:53 (1 October) • e85
separately for the same stool samples. These studies were analyzed separately for subgroup analysis (based on the type of reference test and calculated prevalence), thereby contributing to a total of 23 studies.

Meta-Analysis
Results are given as values (95% CI). The overall sensitivity was 90% (88%–91%), specificity 96% (96%–97%), PLR 26.89 (20.81–34.74), NLR 0.11 (.08–.15), DOR 278.23 (213.56–362.50), Q 0.94 and AUC 0.98 (.98–.99) (Figures 3, 4, 5). There was considerable heterogeneity (I² >50%) for all the statistical measures except the DOR, which had an I² of 2.3%.

Subgroup Analysis by Reference Test
With anaerobic TC as the reference test (8 studies, 4833 samples) the results were as follows: sensitivity 90% (88%–92%), specificity 96% (95%–96%), PLR 32.35 (20.85–50.21), NLR 0.12 (.08–.17), DOR 271.17 (196–375.17), Q 0.94 and AUC 0.98 (.98–.99) (Supplementary Figure 1). There was considerable heterogeneity (I² >50%) for all the statistical measures except the DOR, which had an I² of 0%.

With CCCNA as the reference test (15 studies, 4098 samples), the results were as follows: sensitivity 90% (88%–92%), specificity 97% (96%–98%), PLR 24.67 (17.16–35.46), NLR 0.10 (0.06–0.16), DOR 323.65 (190.24–550.64), Q 0.95 and AUC 0.99 (0.98–1.00) (Supplementary Figure 2).

Subgroup Analysis by CDI Prevalence
At a prevalence of <10% (6 studies, 2262 samples) the sensitivity was 93% (88%–96%), specificity 97% (96%–98%), PPV 71% (64%–77%), NPV 99% (98.9%–99.7%), DOR 378.50 (149.05–961.16), Q 0.95, and AUC 0.99 (.96–1.01) (Supplementary Figure 3). The observed heterogeneity among the measures was varied: Sensitivity and NLR had an I² of 0%, whereas specificity and PLR had an I² >50%.

At a prevalence between 10% and 20% (10 studies, 5645 samples) the sensitivity was 89% (87%–91%), specificity 96% (CI: 95%–96%), PPV 79% (77%–82%), NPV 98% (97.5%–98.4%), DOR 243.40 (181.15–327.03), Q 0.94, and AUC 0.99 (.98–1.00) (Supplementary Figure 4).

Finally, at a prevalence of >20% (7 studies, 1009 samples) the sensitivity was 91% (87%–94%), specificity 97% (96%–98%), PPV 93% (89%–96%), NPV 96% (95%–98%), DOR 520.34 (222.92–1214.58), Q 0.96, and AUC 0.99 (0.98–1.00) (Supplementary Figure 5).

Theoretical values of PPV and NPV were calculated using the pooled sensitivity (90%) and specificity (96%) values and plotted against increasing CDI prevalence. The PPV values correlated positively with increasing CDI prevalence, whereas NPV remained almost the same (Figure 6).

DISCUSSION
Real-time PCR for the diagnosis of CDI has a high sensitivity and specificity. However, the overall diagnostic accuracy is variable and depends on CDI prevalence. In settings where C. difficile prevalence is <10%, the PPV for an accurate diagnosis is low. The positive and negative likelihood ratios demonstrate that real-time PCR may serve as a suitable method.
for either confirming or excluding CDI. We observed no differences in diagnostic accuracy by the type of reference standard used, that is, CCCNA or anaerobic TC.

We anticipated some degree of heterogeneity of diagnostic measures across studies because differences in sample size, reference tests, and CDI prevalences were observed. We found high heterogeneity among studies (as defined by the I² statistic) for all measures except DOR when the studies were pooled together. We therefore performed prespecified subgroup analyses to investigate potential sources of the observed between-study heterogeneity. We assumed the disparity was likely to result from the differences in the type of reference test used. Thus, it is possible that when evaluating real-time PCR assays using a less sensitive reference standard can lead to overestimation of the assay’s sensitivity and underestimation of the true prevalence of toxigenic Clostridium difficile. However, when the 2 reference standards (CCCNA and anaerobic TC) were individually compared with real-time PCR, we observed no significant differences in sensitivities and specificities between the 2 types of reference tests.

Differences in CDI prevalence across studies was another potential source of observed heterogeneity. Sensitivity and
specificity do not take into account the different prevalences of \textit{C. difficile} in the tested population (Table 2). Therefore, we calculated the prevalences from different studies and subgrouped the studies based on their calculated prevalences. We found that the PPV of the test was higher at \textit{C. difficile} prevalences of \(>20\%\), and there was no significant change in NPV with a change in \textit{C. difficile} prevalence. With a \textit{C. difficile} prevalence of \(<10\%\), the sensitivity and specificity was 93\% and 97\%, respectively, and the PPV at this prevalence was only 71\%. Clinically, a 71\% PPV for a diagnostic assay is highly desirable [7], particularly if a false positive result may lead to unnecessary initiation of antimicrobial treatment, discontinuation of offending antimicrobials, and unnecessary isolation of the patient. However, at a \textit{C. difficile} prevalence of \(>20\%\), the PPV is 93\%, which is within acceptable limits. Therefore, real-time PCR is an ideal diagnostic assay in epidemic conditions with higher \textit{C. difficile} prevalence but might not be the best diagnostic test in endemic situations with lower \textit{C. difficile} prevalence. Also, at a calculated prevalence of \(<10\%\), the NPV is 99\% and does not change significantly even at prevalences \(>20\%\). Since the NPV of real-time PCR is acceptable at \textit{C. difficile} prevalence of \(<10\%\), this suggests that real-time PCR may possibly serve as a more effective screening test in endemic situations, with emphasis on a negative test result.

The duration of hospital stay for patients infected with \textit{C. difficile} is believed to be the most influential contributor to increased hospital costs [35]. Therefore, early and accurate detection of CDI using sensitive methods is important to ensure that the patient receives appropriate therapy and spends less time in the hospital [36]. With accurate diagnosis, infection control measures can be initiated to interrupt \textit{C. difficile} transmission to other patients and may result in additional health-care cost savings. While real-time PCR has a quick turnaround time, hospital laboratories will need to adopt this new technology [5]. Several institutions in the United States including our institution (Cleveland Clinic, Geisinger Medical Center) have already switched to real-time PCR as a stand-alone test for diagnosing CDI [37–39].

There are some potential limitations of using real-time PCR as a diagnostic tool. The assay very specifically detects the \textit{tcdB/tcdC} gene encoding the toxin and not the toxin itself. Therefore, hospitalized patients who may be asymptomatic \textit{C. difficile} carriers can be misdiagnosed as having active disease. Also, 50\%–70\% of healthy neonates are said to be colonized with toxigenic \textit{C. difficile}, and testing in this population will give false positive results [40, 41]. Also, it is possible that over time the organism may evolve and/or a genetic drift of the \textit{tcdB/tcdC} gene may occur. In this scenario the assay will be unable to detect toxigenic \textit{C. difficile} and lead to a false negative result. Lastly, because all results are contingent on the unknown diagnostic properties of the current reference tests, and because there is no accepted real gold standard, the diagnostic properties of real-time PCR remain unknown.

Our study has some limitations. First, our meta-analysis did not adjust for differences in patient populations, study variables, physician experience and training, and institutional characteristics. For example, it has been observed that commercial CCCNA is much less sensitive than a well-performed anaerobic TC [25, 27]. Therefore, with this type of analysis and the degree of heterogeneity found among the studies, inaccurate conclusions may be drawn. However, we have performed a limited number of subgroup analyses by reference test and by CDI prevalence to reduce the degree of study heterogeneity. Second, significant heterogeneity of diagnostic accuracy measures was expected and was found among studies and the random effects model partially accounted for the between-study heterogeneity. Third, we did not formally evaluate the level of publication bias in our study. However, we reduced the risk of publication bias by not restricting the search to any particular language. Also, we contacted experts for additional studies, and we used several search engines that were able to identify any unpublished studies in the form of conference abstracts or proceedings.

Despite these limitations, real-time PCR is one of the best tests available for a rapid diagnosis of CDI. Several conclusions can be drawn from our meta-analysis. First, there were no significant differences detected in the sensitivity and specificity

<table>
<thead>
<tr>
<th>Reference test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood ratio</th>
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<tbody>
<tr>
<td>Anaerobic TC</td>
<td>271.17 (196.00–375.1)</td>
<td>0.90 (0.88–0.92)</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>CCCNA</td>
<td>323.65 (190.24–550.64)</td>
<td>0.89 (0.87–0.92)</td>
<td>0.97 (0.96–0.97)</td>
</tr>
<tr>
<td>CDI Prevalence</td>
<td>DOR (95% CI)</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>378.50 (149.05–961.16)</td>
<td>0.93 (0.88–0.96)</td>
<td>0.97 (0.96–0.98)</td>
</tr>
<tr>
<td>10–20%</td>
<td>243.40 (181.15–327.03)</td>
<td>0.89 (0.87–0.91)</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>520.34 (222.92–1214.58)</td>
<td>0.91 (0.87–0.94)</td>
<td>0.97 (0.96–0.98)</td>
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</table>

Abbreviations: CCCNA, cell culture cytotoxicity neutralization assay; CDI, \textit{Clostridium difficile} infection; CI: confidence interval; DOR, diagnostic odds ratio; TC, toxigenic culture.
between the 2 reference standards (CCCNLA and anaerobic TC). Second, real-time PCR has a high sensitivity and specificity in the confirmation of CDI. Lastly, overall diagnostic accuracy is variable and is dependent on CDI prevalence.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copied. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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References


