Diagnosis of *Clostridium difficile* infection by toxin detection kits: a systematic review

Tim Planche, Adamma Aghaizu, Richard Holliman, Peter Riley, Jan Poloniecki, Aodhán Breathnach, Sanjeev Krishna

Clostridium difficile **can be a fatal hospital-acquired infection and its prevalence has increased. Accurate diagnosis of *C difficile* is essential for patient management, infection control, and for defining its epidemiology. We did a systematic review of commonly used commercial assays for detection of *C difficile* toxin (CDT) A and B in stool samples. By comparison of detection of CDT in cell culture with or without selective culture for *C difficile*, the median sensitivities and specificities (IQR) were as follows: Meridian Premier 0·95 (0·86–0·97) and 0·97 (0·95–0·98), TechLab Tox A/B II 0·83 (0·82–0·85) and 0·99 (0·98–1·00), TechLab Tox A/B Quik Chek 0·84 (0·81–0·87) and 1·00 (0·99–1·00), Remel Xpect 0·82 (0·75–0·89) and 0·96 (0·95–0·98), Meridian Immunocard 0·90 (0·84–0·92) and 0·99 (0·98–1·00), and BioMérieux VIDAS 0·76 and 0·93. If the prevalence of CDT A and B in stool samples is relatively low (<10%), the positive predictive value of these assays is unacceptably low (eg, <50% in some circumstances) and will vary depending on the assay and number of samples tested. This low positive predictive value impinges on clinical management, outbreaks, and makes epidemiological data unreliable. To improve diagnosis, we suggest a two-stage testing strategy for *C difficile* toxin with an initial highly sensitive rapid screening test to identify positive samples that are then confirmed by a reference method.**

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Introduction

Clostridium difficile-associated diarrhoea (CDAD) is life threatening, with an attributable mortality of 6–15%.[1] CDAD has become more common and may also be increasing in severity.[2] There is an urgent need to control the spread of this infection in hospitals, where it frequently afflicts the most vulnerable patients who receive antibiotic therapies for complicated infections. Public concern about *C difficile* has increased in recent years, and in the UK, national reporting of CDAD is mandatory,[3,4] with a commitment to reduce prevalence of *C difficile* infections being part of government policy.[5] A proportion of funding to acute health-care trusts in England and Wales is dependent on reductions in the number of reported *C difficile* cases according to a standard formula.[6]

Accurate diagnosis of CDAD is crucial in the management of individual patients, in controlling its spread, and in the generation of reliable surveillance data; such data allow reliable tracking of the infection, comparisons between institutions, and assessment of the efficacy of interventions. Intrinsic test limitations can undermine these aims in various ways. Tests of limited sensitivity will obviously miss some patients, who may then receive suboptimum care and be ineffectively isolated, thus leading to further cases of CDAD. The consequences of limitations in specificity are perhaps less well appreciated: less specific tests will generate more false-positive cases in patients, who may subsequently have necessary antibiotics curtailed, and receive unnecessary treatment for CDAD. Such patients might then be nursed in wards or bays with genuine cases, putting them at increased risk of CDAD. Limitations in either sensitivity or specificity may undermine the reliability of surveillance data and their conclusions. An understanding of the performance characteristics of the tests in use should help to inform professionals involved in the management of CDAD, both in terms of patient care and public-health policy.

Since the identification of toxin-producing *C difficile* as a cause of antibiotic-associated diarrhoea in the 1970s, several diagnostic methods have been used to detect infection. Most tests rely on detection of *C difficile* toxin (CDT) A with or without CDT B. The reference method for the detection of *C difficile* is cytotoxicity of stool in cell culture that may be neutralised by antisera.[7,8] This test takes 2–3 days to complete. Some researchers recommend the additional culture of stool for *C difficile* with confirmation of toxin production, because this may improve sensitivity.[1,9]

Over the past two decades, more rapid detection methods have been developed for the detection of CDT, although early tests detected CDT A only. However, after the recognition that some isolates only produce CDT B, combined assays were introduced, and most currently available commercial assays detect both toxins. Other detection methods for *C difficile*, such as PCR,[10,11] or detection of the presence of glutamate dehydrogenase,[11–13] are also available. Current UK guidance recommends that laboratories should test specimens by either an enzyme immunoassay (EIA) that detects both CDT A and B, or by a neutralised cell cytotoxicity assay.[14] New guidance in the UK is currently under consultation, but testing strategies have not changed.[15] The current EIAs used for surveillance in the UK are thought to provide satisfactory sensitivity and specificity, provided that an assay that detects both CDT A and B is used.[14] However, no review of performance characteristics of these tests has been done, although the performance characteristics of assays in general has been extensively reviewed elsewhere.[16]

We assessed the value and limitations of several widely used commercially available kits for diagnosis of CDAD (for CDT A and B) in the UK, with particular respect to

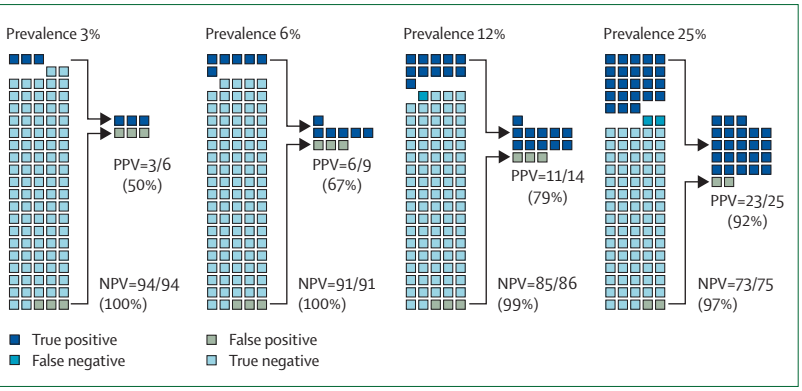

Figure 1: **Effect of varying prevalence on the PPV and NPV of a theoretical *Clostridium difficile* toxin assay with a sensitivity of 92% and a specificity of 97%**
NPV=negative predictive value. PPV=positive predictive value.

the diagnosis of nosocomial disease. This analysis was designed to compare the sensitivity and specificity of these immunoassays.

Methods

Performance characteristics of tests

The properties of a test independent of the prevalence of a condition are its sensitivity (true positives/[true positives+false negatives]) and specificity (true negatives/[true negatives+false positives]). Because the chance of misidentifying negative cases as false positives increases with a decline in specificity, it is often useful to consider false positivity (1–specificity). For example, a test with a specificity of 97% (false positivity of 3%) will wrongly identify 30 false-positive cases for every 1000 negative cases tested. If an assay gives a numerical value, as do most EIAs, a cut-off value is used to distinguish between positive and negative results. A low cut-off means that more true positives are detected at the expense of also detecting more false positives. Conversely, a high cut-off detects fewer false positives at the expense of detecting fewer true positives. For any given detection method, selection of a particular cut-off can increase sensitivity at the expense of specificity, or vice versa.

Unlike sensitivity and specificity, the positive predictive value (PPV; true positives/[true positives+false positives]) and negative predictive value (NPV; true negatives/[true negatives+false negatives]) vary depending on the prevalence of the condition being detected (figure 1). For example, a 22% absolute fall from 25% to 3% in the prevalence of a condition results in a 42% fall in PPV from 92% to 50% (see figure 1). Clearly, if testing for a condition with a low prevalence, such as screening for HIV infection, a high specificity is required: for example, a test with a specificity of less than 99·5% will have an unacceptably low PPV. For these reasons, we defined an acceptable test as one that would have a sensitivity of at least 90% (when estimated at its 25% centile) and a false-positive rate of 3% or less (estimated at the 25% centile for specificity).

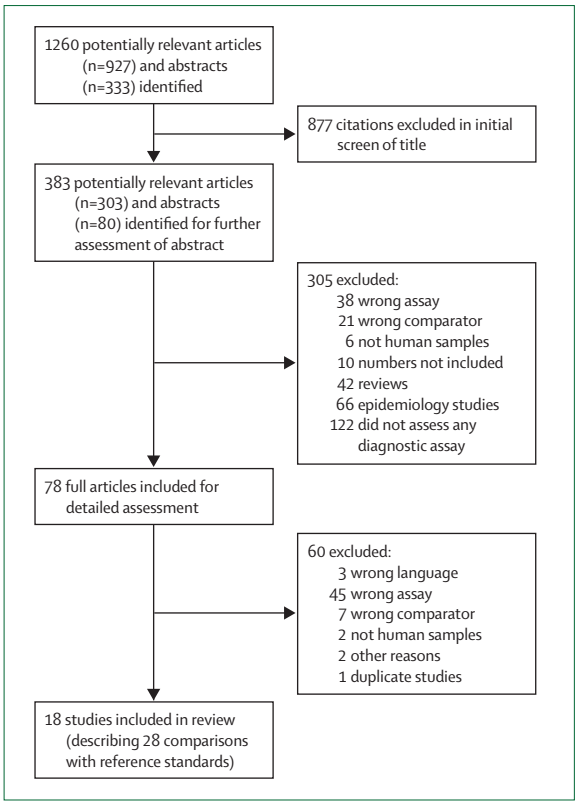

Figure 2: **Summary of selection process and reasons for exclusion of studies**

Data source

The analysis conformed to guidelines given by the Cochrane Collaboration.[17] Searches were done in Medline and EmBase with "*Clostridium difficile*" combined with the following subject headings: "diagnostic accuracy", "enzyme immunoassay", "enzyme linked immunosorbent assay", "faeces analysis", "*Clostridium difficile* toxin A", "*Clostridium difficile* toxin B", and "intermethod comparison". Further searches were done with the names of the manufacturers or tests "Remel", "Meridian", "VIDAS", and "TechLab" as textword searches.

Databases from the American Society for Microbiology and the European Congress of Clinical Microbiology and Infectious Diseases conferences were checked by electronic search for relevant abstracts, and any references identified in reference lists were also obtained. This search was done in November, 2007, and only articles published after 1994 were considered, because these assays were unavailable before that time. No language restrictions were used in the initial data search.

Study eligibility

The following assays, which detect CDT A and B, were considered: Meridian Premier (enzyme-linked immunosorbent assay [ELISA]; Meridian Bioscience Inc, Cincinnati, OH, USA), TechLab Tox A/B II (ELISA; TechLab, Blacksburg, VA, USA), TechLab Tox A/B Quik

Chek (rapid antigen capture; TechLab), Remel Xpect (rapid chromatographic immunoassay; Remel, Lenexa, KS, USA), BioMérieux VIDAS (EIA; BioMérieux, Marcy l'Etoile, France), and Meridian Immunocard (rapid EIA; Meridian Bioscience Inc). Only articles in English, French, and Spanish were reviewed further, because these languages are spoken by the reviewers.

Abstracts were initially checked for relevance. All the following inclusion criteria needed to be fulfilled before a study was included in analysis: tests were done on clinical human stool specimens; a reference method comparator was used for detection of neutralisable CDT in cell culture with or without stool culture for *C difficile*; and the total number of patients tested, and numbers of positive and negative cases were provided. Studies were excluded if they were part of a training set used to define a cut-off for an assay. Full articles of selected publications were obtained, if available, and the stated criteria confirmed.

Data extraction and quality assessment

Source data were reviewed (by TP) and two-by-two tables were constructed for each study. Study investigators were contacted by telephone if further details were needed. The type of reference method used was recorded, but no demographic data were abstracted. Data were only accepted if reference method diagnosis was done on all samples, and not only on positive samples (to exclude partial verification bias). Studies that used nucleic acid amplification techniques or detection of glutamate dehydrogenase were not included in the analysis.

	Country	Source	Setting	Patients	Consecutive selection	Prospective data collection	Patients (n)	Reference method	Prevalence of positive stools	Sensitivity	Specificity
Meridian Premier											
Van den Berg et al (2007)[10]	Netherlands	PRA	Hospital	All	Yes	Yes	540	TD	0·06	0·97	0·94
Leeming et al (2006)[19]	UK	CP	Hospital	Adults	Yes	Yes	332	TD	0·21	0·99	0·95
Miendje et al (2005)[20]	Belgium	CP	Hospital	All	Yes	Yes	234	T&C	0·11	0·88	0·98
Benavente et al (2002)[21]	..	CP	..	All	..	..	114	T&C	0·25	0·86	0·95
Gleaves et al (2000)[22]	..	CP	Hospital	..	..	..	573	T&C	0·17	0·95	0·97
Gleaves et al (2001)[23]	..	CP	..	Children	..	..	264	TD	0·11	0·96	0·94
Summers et al (2006)[24]	..	CP	..	All	.	Yes	188	TD	0·12	0·86	0·97
O'Connor et al (2001)[25]	Ireland	PRA	Hospital	Adults	Yes	Yes	200	TD	0·31	0·80	0·99
Musher et al (2007)[26]	USA	PRA	Hospital	All	Yes	Yes	446	TD	0·17	0·99	0·97
TechLab Tox A/B II											
Snell et al (2004)[13]	Canada	PRA	Hospital	All	Yes	Yes	497	T&C	0·10	0·85	0·98
Leeming et al (2006)[19]	UK	CP	Hospital	Adults	Yes	Yes	332	TD	0·21	0·81	0·92
Summers et al (2006)[24]	..	CP	..	All	..	Yes	187	TD	0·11	0·86	1·00
O'Connor et al (2001)[25]	Ireland	PRA	Hospital	Adults	Yes	Yes	200	TD	0·31	0·82	0·99
Massey et al (2003)[27]	Canada	PRA	Hospital	Adults	..	Yes	559	TD	0·26	0·75	0·98
Russmann et al (2007)[28]	Germany	PRA	Hospital	All	Yes	Yes	383	T&C	0·16	0·88	1·00
TechLab Tox A/B Quik Chek											
Reyes et al (2007)[12]	Canada	PRA	Hospital	All	Yes	Yes	387	T&C	0·12	0·80	1·00
Leeming et al (2006)[19]	UK	CP	Hospital	Adults	Yes	Yes	332	TD	0·21	0·81	0·98
Summers et al (2006)[24]	..	CP	..	All	..	Yes	188	TD	0·12	0·86	1·00
Greene et al (2006)[29]	..	CP	..	..	..	..	400	TD	0·14	0·89	1·00
Remel Xpect											
Leeming et al (2006)[19]	UK	CP	Hospital	Adults	Yes	Yes	332	TD	0·21	0·69	1·00
Summers et al (2006)[24]	..	CP	..	All	..	Yes	188	TD	0·12	0·95	0·93
Meridian Immunocard											
Leeming et al (2006)[19]	UK	CP	Hospital	Adults	Yes	Yes	332	TD	0·21	0·87	0·98
Miendje et al (2005)[20]	Belgium	CP	Hospital	All	Yes	Yes	234	T&C	0·11	0·92	1·00
Benavente et al (2002)[21]	..	CP	..	All	..	..	114	T&C	0·25	0·75	1·00
Van Broeck et al (2005)[30]	Belgium	CP	Hospital	All	..	..	533	T&C	0·09	0·88	0·99
Berg et al (2005)[31]	..	CP	Hospital	All	Yes	Yes	369	TD	0·06	0·91	0·96
Sliwinski et al (2005)[32]	..	CP	..	..	..	No	400	TD	0·11	0·98	0·99
BioMérieux VIDAS											
Carricajo et al (2005)[33]	..	CP	..	..	Yes	Yes	62	T&C	0·53	0·76	0·93

CP=conference proceeding. PRA=peer-reviewed article. TD=toxin detection by cell-culture cytotoxicity assay. T&C=culture of *C difficile* with toxin detection by cell-culture cytotoxicity assay. ..=not known.

Table 1: **Summary of characteristics of all studies included, by detection assay**

	Studies (n)	Cases (n)	Sensitivity				Specificity			
			Median (IQR)	OR (95% CI)*	p value	Manufacturer's value (95% CI)	Median (IQR)	OR (95% CI)*	p value	Manufacturer's value (95% CI)
TechLab Tox A/B II[13,19,24,25,27,28]	6	2158	0·833 (0·816–0·854)	1·0	..	0·92 (0·87–0·96)	0·987 (0·977–0·998)	1·0	..	1·0 (0·99–1·0)
Meridian Premier[10,19–26]	9	2891	0·948 (0·864–0·968)	3·11 (2·00–4·83)	<0·0001	0·95 (0·88–0·98)	0·970 (0·953–0·975)	0·60 (0·41–0·88)	0·0042	0·97 (0·95–0·99)
TechLab Tox A/B Quik Chek[12,19,24,29]	4	1307	0·839 (0·812–0·870)	1·24 (0·79–1·96)	0·9668	0·90 (0·84–0·94)	0·997 (0·994–0·998)	4·32 (1·82–10·2)	<0·0001	1·0 (0·99–1·0)
Remel Xpect[19,24]	2	520	0·820 (0·753–0·887)	0·71 (0·42–1·21)	0·0106	..	0·962 (0·945–0·979)	0·75 (0·40–1·41)	0·2967	..
Meridian Immunocard[19–21,30–32]	6	1982	0·896 (0·874–0·918)	1·87 (1·167–2·99)	0·0373	0·97 (0·90–1·00)	0·993 (0·981–0·999)	1·61 (0·97–2·66)	0·0347	0·99 (0·96–1·0)
BioMérieux VIDAS[33]	1	62	0·757	0·74 (0·32–1·71)	0·1315	0·88	0·931	0·32 (0·07–1·37)	0·0628	1·0

*From logistic regression analysis. OR=odds ratio.

Table 2: **Summary of sensitivity and specificity values of the assays**

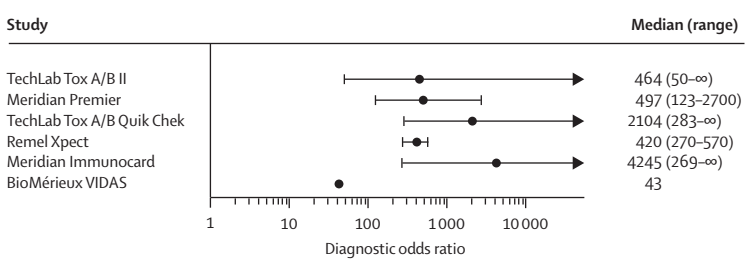

Figure 3: **Diagnostic odds ratio of the assays**
Medians (ranges) are shown. Upper limit extends to ∞ because several studies reported specificities of 1·0. Only one study was available for the VIDAS assay so no range is shown for this.

Statistical analysis

Data were analysed with SAS version 9. For each study, sensitivity and specificity were calculated. Estimates of these variables were regarded as univariate because cut-off thresholds for positivity had been set by the individual manufacturers and did not vary between studies. Heterogeneity of sensitivity and specificity were assessed with the χ^2 test.

The effects of different reference methods (both culture and cell-culture cytotoxicity, or cell-culture cytotoxicity alone) were examined by the Wilcoxon rank sum test. The diagnostic odds ratio (DOR) was used to provide an overall measure of accuracy.[18] The DOR is defined as (sensitivity/[1–sensitivity])/([1–specificity]/specificity) and represents the ratio of the odds of a positive result in a stool sample with CDT compared with a specimen without CDT. DORs were compared between commercial assay kits by the Kruskal-Wallis test. Logistic regression was used to estimate the effect of choice of commercial assay on sensitivity. The logistic regression contained only a single fixed factor for commercial assay type and not for any other factors. Manufacturers' data were excluded.

Results

The results of the two searches (articles and abstracts) are summarised in figure 2. Some of the included studies compared more than one assay with a reference standard, giving a total of 28 comparisons of toxin detection kits with reference standards. Summaries of the studies included are shown in table 1.

No significant difference in sensitivity or specificity was attributable to the reference method used in the study (sensitivity p=0·45, specificity p=0·36), and therefore studies were combined for further analysis irrespective of the reference method used. A χ^2 test showed that the sensitivity and specificity were significantly heterogeneous for the studies reported for each commercial assay except the TechLab Quik Chek assay (sensitivity p=0·27, specificity p=0·08) and VITEK (one study only). In view of this heterogeneity, formal meta-analytic methods were not used to derive pooled estimates of sensitivity, specificity, or DOR. Medians and IQRs for sensitivity and specificity are given for each assay. The reported sensitivities of these tests were 0·69–0·99 and reported specificities were 0·92–1·00 (table 1). Results of the analyses are summarised in table 2. Some assessments (ie, Remel Xpect and BioMérieux VIDAS) included relatively small numbers of patients and estimates for these tests are less certain.

There was a large range of DORs (figure 3), because several studies reported specificities of 1·0 (table 1), giving an infinite value for the DOR. There was no evidence for a significant difference in DOR between any of the commercial assay methods (p=0·33). Although the overall test performances were similar, as shown by the DORs, there were significant differences between sensitivity and specificity estimates for the commercial assays as demonstrated by the logistic regression (table 2). For example, the Meridian Premier was most likely to give a positive result if the sample were a true positive

and the Techlab Quik Chek was most likely to give a negative result when the samples were negative.

Figure 4 shows the combined PPVs for the assays. None of the tests met our criteria for an acceptable test (IQRs for sensitivity above 90% and for false positivity below 3%).

Discussion

Because there was heterogeneity in sensitivity and specificity of data in these studies, we are unable to provide mean estimates for sensitivity and specificity. Nevertheless, reasons for this heterogeneity are of interest and could include geographic variation either in patient populations or in *C difficile* isolates that give rise to observed differences in assessment of diagnostic performance of these assays. There may also be differences in the laboratory processing of samples during these studies. Other pitfalls of comparative studies of diagnostic methods include substantial modifications to the manufacturer's instructions (eg, not following manufacturers' protocols by changing cut-offs, altering dilutions, or changing the wavelength for measuring absorbance), improper sample storage, or lack of reference standards. Studies of the detection of CDT, for example, lack standardised methods.[1] Cell lines and antisera used, time of specimen storage, and the dilution of stool specimens can all vary. Variation in reference methods for the detection of CDT in stool samples underscores the need for further standardisation in methods for *C difficile* culture and cell-culture cytotoxicity assays. Assessments of diagnostic assays in one centre may have inherent limitations because of the particular reference method used.

Despite the heterogeneity of these data, several important conclusions are apparent. First, there were no significant differences detected in DOR between the commercial assays, implying no difference in their overall diagnostic performance. Second, there were differences in the performance characteristics of assays, with most having higher specificities than sensitivities. One test (Meridian Premier) had a higher sensitivity and lower specificity. These differences between tests are likely to result from differences in the threshold cut-off selected for each assay. Finally, no assay reliably fulfilled the criteria we preset for an acceptable single test to detect CDT. Newer detection methods, such as nucleic acid amplification tests, may prove acceptable as a single test.

In recent years, there has been a trend, particularly in the UK, to test greater numbers of cases of diarrhoea for CDT. For surveillance purposes, microbiology laboratories have been advised to test diarrhoeal specimens for evidence of CDAD in all patients aged over 65 years who have not been diagnosed with CDAD in the preceding 4 weeks.[14] Apart from age, this recommendation is made irrespective of the presence or absence of any specific risk factors.[14] The inclusion of patients without risk factors for CDAD is likely to lower the prevalence of the condition in the population tested, and is thus likely to lead to an increased proportion of false-positive results. The exact proportion of stool samples positive for CDT from this population across the UK is unknown. However, with increased testing and increasingly effective infection control measures, the proportion of stool samples positive for CDT will decrease.

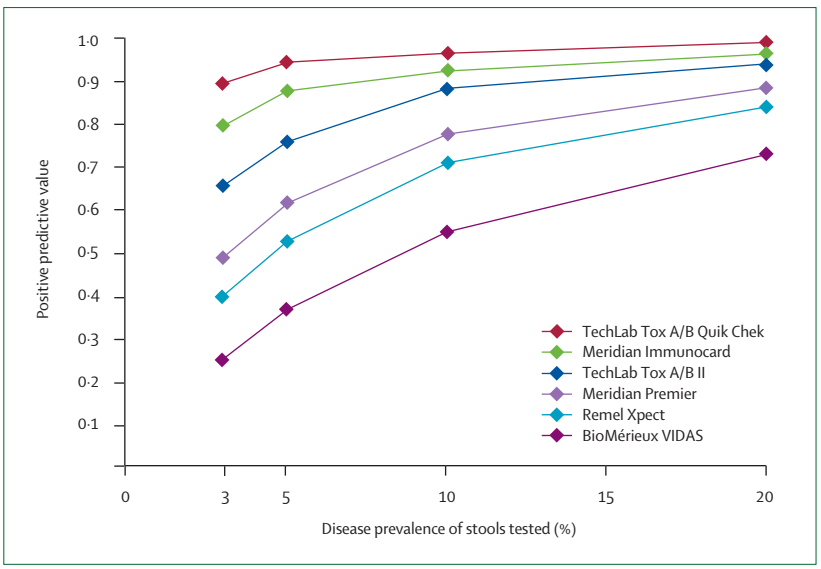

***Figure 4*: Estimated positive predictive values of the assays, by disease prevalence of stools tested**
Median values for specificity and sensitivity were used to calculate these values.

The prevalence of CDAD is often quoted to be 15–25% of cases of antibiotic-associated diarrhoea.[1] However, these prevalence estimates come from studies over 20 years old and may not truly indicate the current situation.[10,29,30,34,35] Additionally, the percentage of CDT-positive samples received by a laboratory determines the PPV and NPV of these assays, and not the percentage of antibiotic-associated diarrhoea cases that are CDAD. Studies published in the past 5 years from Europe and the USA report that only 5–10% of samples submitted to laboratories are CDT positive.[10,29,30,34,35] In the absence of UK national data, this increase in testing and fall in prevalence is indicated in data available from our microbiology laboratory. In the 6 months between March and August, 2007, a mean of 453 samples were tested per month, of which 11% were EIA positive. This compares with a similar period in 2001, when a mean of 255 samples were tested monthly, of which 22·2% tested positive.

The current EIA used in our laboratory is the Meridian Premier test. With the observed prevalence of 11% in our laboratory and assuming the sensitivity and specificity of this test (table 1) are 95% and 97%, respectively, the PPV of this test is only 75% (figure 4). Moreover, the estimated proportion of samples truly positive for CDT is 9%. Clinically, such a PPV for an assay is highly undesirable, particularly if a false-positive result may mean that a patient starts metronidazole, stops other antibiotics, and

is made to share a room with patients who do have *C difficile* infection.

The number of positive cases detected by an assay depends not only on the number of positive samples tested, but also on the number of negative cases tested and the assay used. This makes even simple comparisons of *C difficile* infections between sites more problematic. Even detection rates at the same site may alter substantially if the assay is changed or the number of cases assayed is greatly increased. For example, if we apply the underlying sample prevalence of our data from 2007 (9%), then the number of cases detected per month would vary between 31 and 53 positive samples depending on the assay used. Consequently, direct comparison of CDAD incidence between different institutions without knowledge of the numbers of tests done and the type of assays used is not possible.

When a CDAD outbreak is recognised, multiple interventions are often undertaken, including changes in antibiotic policies, enhanced cleaning of wards, or cohorting of affected cases. There may also be changes to the testing of stool samples, possibly using less sensitive or more specific rapid assays, and careful selection of which samples to test. Recognition that changing the testing policy affects detection rates for CDAD is essential to understanding the effective control of *C difficile* outbreaks. Not all these considerations apply to the detection methods and reporting of results for all microbes. For example, data on blood-borne meticillin-resistant *Staphylococcus aureus* infections are centrally collected and monitored in the UK. The test method is by culture of the organism, and this method is also used as the reference method for detection of the organism. The specificity of these tests is assumed to be 100% and issues relating to variability in specificity do not apply. UK government guidance accepts that sample selection will alter the performance of a test and suggests the following standardisation of selection criteria for stools for assay: "it would seem sensible to begin with the assumption that the presence of CDT is only of clinical relevance in patients with diarrhoea, and to restrict testing to diarrhoeal stools; a diarrhoeal stool is conventionally defined as a specimen that takes up the shape of its container".[14] From the results in this analysis and the prevalence of positive tests likely to result from these selection criteria, one-stage testing procedures are difficult to justify.

Depending on the purpose for which data are required, there are several estimates that can be used to improve comparability of *C difficile* diagnoses between institutions, as long as the number of tests done and the type of assay used are known. These approaches would allow comparison of CDAD rates between different institutions, but provide no information for individual patients. Requesting stool samples for repeat assays on patients with initially negative samples improves the sensitivity of an assay. However, this solution is cumbersome and repeat testing reduces the specificity of most tests to unacceptable levels. There is also the possibility of discounting rapid assays to detect CDT and only using the reference method of detection of neutralisable CDT in cell culture with or without culture for *C difficile*. However, this approach would take 3–5 days, increasing turnaround time, expense, and risk of transmission.

Clinical assessment for a more directed testing protocol could reduce the number of negative stool samples being assayed, and thus increase the PPV of the assay. However, clinical assessment is not a reliable way of excluding *C difficile* infection,[1] stool consistency may change ex vivo, and often the details of samples received by a laboratory are insufficient to select stools that are to be tested. Additionally, limiting the number of stools that are assayed may lead to an unacceptable decline in the detection of cases of *C difficile* without a marked improvement in PPV of the assay.

Testing for an infection with a low prevalence in a population is a common requirement in virology clinics. In this context, to screen for several possible rare causes of illness, a supplementary assay is used to confirm the diagnosis and improve the overall precision of testing. We recommend the use of such a supplementary assay to identify true-positive samples initially detected by a positive CDT screening assay. An initial, rapid, highly sensitive screening assay done on the day of the receipt of the sample would detect all (or nearly all) positives and mean that confirmed negative results are issued promptly. This screening test can either detect CDT or glutamate dehydrogenase, both of which have a high sensitivity but low specificity.[1,36] Some commercial kits detect both CDT and glutamate dehydrogenase.[27,37,38] Samples testing positive in this initial assay can be reported as provisionally positive (at high risk of having CDAD). Patients with a provisional positive test can be immediately managed as if they have CDAD with immediate isolation measures and therapy. Because the sensitivities of these assays are over 75%, the NPVs for these assays will be over 98%, allowing most results to be issued the same day with a high degree of diagnostic certainty. A confirmatory test that uses the reference method assay of detection of neutralisable CDT in cell culture (with or without culture) can then be used to provide a definitive result within 2–5 days. We are currently evaluating such a testing scheme in our department.

Several reports have suggested two-stage or three-stage testing protocols for CDT similar to the protocols suggested above.[36,38–40] In cases in which confirmatory testing has been done, the PPV of an initial EIA has been shown to be as low as 45%.[36] Some investigators have suggested using an EIA for detection as a confirmatory assay for stool samples positive by glutamate dehydrogenase assay.[41] Although this is a rapid method, limitations with these EIAs mean that, if they are used as confirmatory assays, the overall sensitivity and specificity

Search strategy and selection criteria

These are described in detail in the Methods section.

of the testing algorithm remains low.[41] Although there are cost implications for performing additional assays, the use of a screening assay reduces the number of time-consuming reference method assays that become necessary. We estimate that we will need to do approximately 500 additional cell-culture cytotoxicity assays annually at total cost of £10 000–30 000 per year. However, we predict that the savings in antibiotic costs, the enhanced use of isolation facilities, reduced burden on infection control, and reduced cases of CDAD across the hospital will offset these additional laboratory expenditures.

Conflicts of interest

We declare that we have no conflicts of interest.

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