Survey of English NHS laboratory testing methods for *Clostridium difficile* reveals widespread suboptimal practice

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Introduction

Recent studies have shown poor performance of commonly used toxin Enzyme Immunoassays (EIAs) for laboratory testing for *Clostridium difficile.* The current 'gold' standard is the cell cytotoxin neutralisation assay (CTN), however most clinical laboratories no longer have the facilities or expertise to perform this test which can take up to 72 hours for a resut. Furthermore CTN itself is poorly standardised and may produce false negatives in some patients with obvious clinical disease.

In March 2009 the UK Health Protection Agency (HPA) advised that laboratories should not rely on EIAs as single tests. In 2010 ESCMID published a review on the subject and recommended a two-step protocol for diagnosing CDI, screening with one method and confirming with another. Shortly after this SHEA and IDSA jointly produced updated clinical practice guidelines for CDI diagnosis and management; these stated that EIA testing for toxins A and B is suboptimal and also recommended a two-step testing algorithm.

More than one year after the HPA had published guidance on testing for CDI, we surveyed current testing practices and *C. difficile* positivity rates in clinical laboratories in English NHS Acute Trusts.

Methods

170 English Acute NHS Trusts were asked for details of their *C. difficile* testing procedures. Specifically they were asked whether testing was available routinely seven days per week, whether there was a specific written Standard Operating Procedure (SOP) for testing, the total number of tests performed (including repeats on the same patient) and the number positive for January to December 2008 and 2009, and the exact laboratory method/s being used on the day of the survey (21st April 2010).

Results

Complete or partial responses were received form 168/170 Trusts (a 99% response rate). Two Trusts gave no response and a further two were unwilling to disclose the exact testing procedure 'for commercial reasons', although they confirmed that they used an EIA for toxins A/B.

15 (9%) of laboratories were not able to offer routine testing 7 days per week. 3 laboratories (1.8%) did not have a written SOP.

The majority (117, 70%) used an EIA for detection of toxins A and B as a stand-alone method, 64% using a well type device and 6% lateral flow. Only 6 laboratories (3.6%) offered CTN assay and only one laboratory used PCR as a single stage test. 35 (19%) laboratories were using a two-step testing algorithm, performing the second stage only if the first step (or a component) was positive. The common combinations were toxin A/B EIA or GDH EIA followed by PCR, however 8 (5%) laboratories were using two toxin EIAs together. 8 (5%) laboratories were using a commercial kit that performed EIAs for GDH and toxin simultaneously.

Table 1.

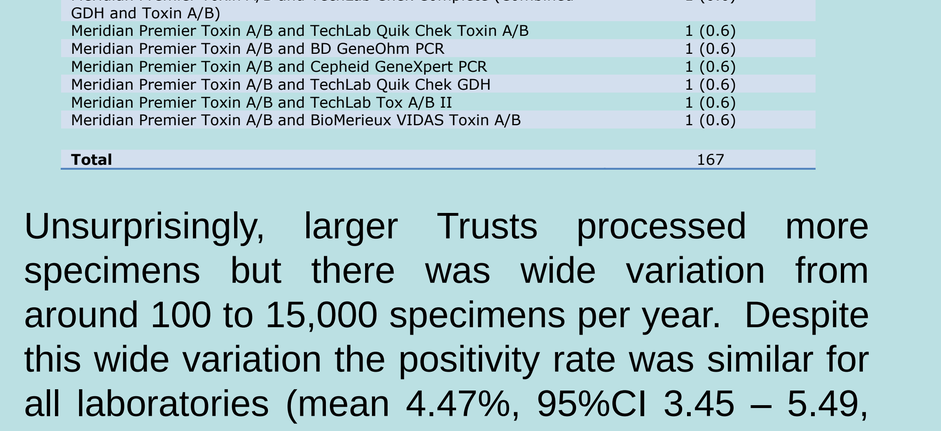
Distribution of English NHS laboratory methods used for detection of *C. difficile*

Laboratory Method	Number (%) of Laboratories
Toxin EIA (Well type)	**107 (64.1)**
Meridian Premier Toxin A/B	53 (31.8)
TechLab Tox A/B II	32 (19.2)
BioMerieux VIDAS Toxin A/B	20 (12)
Undisclosed Toxin A/B	2 (1.2)
Toxin EIA (Lateral Flow Type)	**10 (6.0)**
Meridian Immunocard A/B	6 (3.6)
TechLab Quik Chek Toxin A/B	4 (2.4)
TechLab C Diff Quik Chek Complete (Combined GDH/Toxin EIA)	**8 (4.8)**
BD GeneOhm Polymerase Chain Reaction (PCR)	**1 (0.6)**
Cell Cytotoxin Neutralisation Assay	**6 (3.6)**
Two Stage Testing procedures	**35 (21.0)**
TechLab Chek 60 (GDH) and TechLab C Diff Quik Chek (Toxin A/B)	4 (2.4)
TechLab Chek 60 (GDH) and Meridian Premier Toxin A/B	2 (1.2)
TechLab Chek 60 (GDH) and TechLab Tox A/B II	1 (0.6)
TechLab Chek 60 (GDH) and Cell Cytotoxin Neutralisation Assay	1 (0.6)
TechLab Chek 60 (GDH) and Cepheid GeneXpert PCR	1 (0.6)
TechLab Chek Complete (Combined GDH and Toxin A/B) and Cepheid GeneXpert PCR	3 (1.8)
TechLab Chek Complete (Combined GDH and Toxin A/B) andTechLab Leuko EZ Vue (Lactoferrin)	1 (0.6)
TechLab Chek Complete (Combined GDH and Toxin A/B) and BioMerieux VIDAS Toxin A/B	1 (0.6)
TechLab Quik Chek Toxin A/B and BioMerieux VIDAS Toxin A/B	1 (0.6)
TechLab Tox A/B II and TechLab Chek Complete (Combined GDH and Toxin A/B)	1 (0.6)
TechLab Tox A/B II and BioMerieux VIDAS Toxin A/B	1 (0.6)
BioMerieux VIDAS Toxin A/B and TechLab Quik Chek Toxin A/B	3 (1.8)
BioMerieux VIDAS Toxin A/B and TechLab Chek Complete (Combined GDH and Toxin A/B)	2 (1.2)
BioMerieux VIDAS Toxin A/B and Cell Cytotoxin Neutralisation Assay	1 (0.6)
BioMerieux VIDAS Toxin A/B and Cepheid GeneXpert PCR	1 (0.6)
Meridian Immunocard Toxin A/B and TechLab Chek Complete (Combined GDH and Toxin A/B)	2 (1.2)
Meridian Immunocard Toxin A/B and Cepheid GeneXpert PCR	1 (0.6)
Meridian Premier Toxin A/B and Cell Cytotoxin Neutralisation Assay	1 (0.6)
Meridian Premier Toxin A/B and TechLab Chek Complete (Combined GDH and Toxin A/B)	1 (0.6)
Meridian Premier Toxin A/B and TechLab Quik Chek Toxin A/B	1 (0.6)
Meridian Premier Toxin A/B and BD GeneOhm PCR	1 (0.6)
Meridian Premier Toxin A/B and Cepheid GeneXpert PCR	1 (0.6)
Meridian Premier Toxin A/B and TechLab Quik Chek GDH	1 (0.6)
Meridian Premier Toxin A/B and TechLab Tox A/B II	1 (0.6)
Meridian Premier Toxin A/B and BioMerieux VIDAS Toxin A/B	1 (0.6)
Total	167

Unsurprisingly, larger Trusts processed more specimens but there was wide variation from around 100 to 15,000 specimens per year. Despite this wide variation the positivity rate was similar for all laboratories (mean 4.47%, 95%CI 3.45 – 5.49, range 0.79% - 19.49%).

The mean number of samples processed remained stable over the past two years (means of 4208 and 4241 for 2008 and 2009 respectively. However the prevalence of positive samples decreased from a men of 6.45% to 4.47%.

Figure 1. Total specimens processed and positivity rate

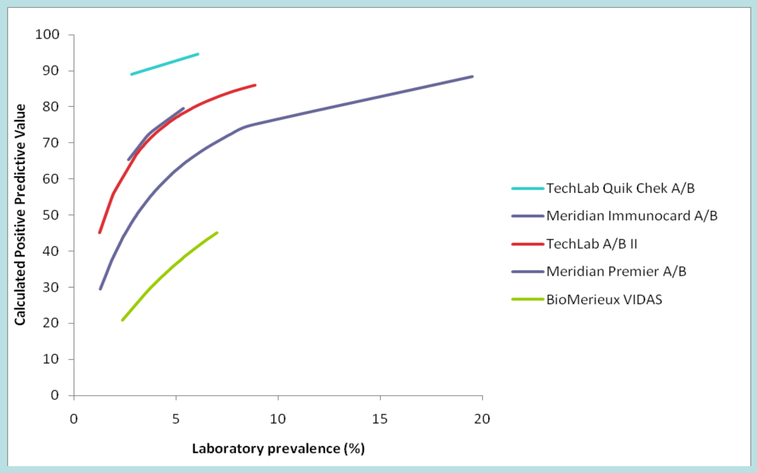


Average sensitivity and specificity data were used from a previously published systematic review to calculate the estimated positive and negative predictive values for each laboratory prevalence for each of the commonly used toxin EIA test. This showed a large range from as low as 20% for laboratories with a prevalence of 2.5%. Of the 108 laboratories using a toxin EIA as a single method, 39 (36%) were operating at an estimated PPV of less than 50%

Test	Mean PPV (Range)	95% Confidence Interval for the mean
BioMerieux VIDAS Toxin A/B	35 (21 – 45)	32 – 38
Meridian Premier Toxin A/B	56 (30 – 88)	53 – 59
Meridian Imunocard A/B	71 (65 – 80)	67 - 75
TechLab Tox A/B II	74 (45 – 86)	58 – 90
TechLab Quik Chek Toxin A/B	91 (89 – 95)	4 - 100

Table 2

Mean (Range) Positive Predictive Values (PPV's) for each Toxin EIA test calculated from individual laboratory data based on sensitivities and specificities published in a systematic review (Planche)



Discussion

The present survey provides the most complete data on laboratory testing methods for diagnosing CDI in English NHS Trusts and clearly demonstrates widespread suboptimal testing practice.

Despite warnings about the poor performance of toxin EIA test and national and international recommendations to confirm results using another method, 70% of laboratories continue to use a single toxin EIA.

Many NHS Trusts may be averse to changing to better performing diagnostic methods. Reasons for this may include organisational change, increased costs and additional training requirements. However, there may also be a perception that a better performing test would adversely affect rates reported under the mandatory reporting scheme and possible lead to financial penalties and unfavourable publicity. The mandatory reporting scheme may therefore be a perverse disincentive for Trusts to change to improved testing methods.