First report from European, multi-centre, prospective bi-annual point prevalence study of *Clostridium difficile* Infection in hospitalised patients with Diarrhoea

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INTRODUCTION

*Clostridium difficile* is still the major cause of nosocomial diarrhoea in the developed world and rapid and accurate diagnosis is paramount for patient care and infection prevention.1 There has been an increase in the prevalence of *C. difficile* infection (CDI) in countries with active surveillance programmes, and a marked shift in epidemiology over the last decade.2 Sub-optimal case ascertainment, either due to inadequate laboratory diagnosis or lack of clinical suspicion means that the true burden of CDI remains unclear.3

The most recent European epidemiological survey carried out in 2008 (European CDI surveillance: ECDC) reported that the CDI incidence in 97 hospitals across 29 countries varied markedly (range 0.5-15,000 per 10,000 patient bed days, weighted mean 4.1).4 Most notably, however, was the marked variation in testing frequency, and the correlation between testing rate and reported CDI rate (Figure 1).5

**Figure 1.** Scatterplot showing correlation between frequency of CDI testing and measured CDI incidence in European countries.

Under-ascertainment has been further investigated in Spain where a recent point prevalence study highlighted that 46% of *CDI* patients on a single day (June 2008) were undiagnosed or misdiagnosed, due either to lack of clinical suspicion (47%) or inadequate laboratory diagnostics (19%).6

This study aims to measure the extent of under-testing and under-detection of CDI across 20 countries in Europe.

METHODS

Study design

To determine the true incidence of CDI in hospitals in 20 European countries, participating hospitals submitted diarrhoeal faecal samples collected on one day (Dec 2012 or Jan 2013) to the national coordinating laboratory for their country, regardless of the original tests requested. The target number of participating hospitals (PHs) to recruit was determined by country population (1 PH per 1 million people).

Initial study questionnaire

Data were collected from PHs on local policy for CDI testing and reporting, laboratory methods used for CDI diagnosis, local rates of testing and the local laboratory methods used for CDI diagnosis.

Samples at PHs

All in-patient diarrhoeal samples submitted to the PHs on a single day were sent to the EUCLID national coordinating laboratory (NCL), regardless of original test requisition. Sample forms were completed for each sample by the PH recording patient’s age, gender and clinical specialty of the patient location, whether the sample was tested for CDI and if so what was the result.

Samples at NCLs

Samples were tested using an optimised 2-stage algorithm for CDI diagnosis: membrane enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH/membrane EIA for toxins A & B (C.DIFF QUIK CHEK COMPLETER). The results for each sample at the PH and NCL were compared. Confirmation assays (either culture/PCR for toxin genes or cytotoxigenic culture) were performed on all screening test positive or indeterminate samples (eg. GDH positive/toxin positive or ODH positive/toxin negative).

Data analysis

All data were uploaded to the EUCLID web-based data management system. The database was locked once data querying and cleaning were completed. Data analyses were carried out by the EUCLID European co-ordinator. Local testing rates and CDI positive reporting rates were compared for each country. Results were compared for each submitted sample and the original PH result were determined to be correct, false positive, false negative or not tested. The mean CDI positivity rate at the NCL was 8.8% (country range 0.1-19.7%).

RESULTS

There were 482 PHs from 20 European countries participating in the study. The PHs submitted 3920 faecal samples to NCLs (mean 8.2, range 5.3-13.5 per hospital). The mean CDI positivity rate at the NCL was 8.8% (country range 0.1-19.7%).

CDI diagnostics were performed at 468/482 (97%) of the PHs. 242/468 (51.7%) tested for CDI only on physician request and across Europe only 10.6% tested all diarrhoeal faeces in patient samples. The reported percentage of samples testing by PHs was 16.4% (country range 0.6-64.3%), whilst the percentage of samples submitted to the NCLs that had been tested at the PHs was 60.55% (country range 0.4-97.3%). The mean number of CDI tests/10,000 patient bed days (PPDs) was 62.3 (country range 4.6-132.5); the mean number of positive CDI cases/10,000 PPDs was 6.6 (country range 0.8-16.2).

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**Figure 2.** Changing CDI incidence per country from 2008 to 2013

Under-diagnosis and misdiagnosis

There were 244 patients on a single day across Europe (6.3%, country range 0.2-23.0%) that received an incorrect result i.e. false-positive, false-negative, or not tested at PH but found positive at NCL.

**Figure 3.** Summary of outcome of all samples by country

The potential under-diagnosis rate (no test performed at PH on sample found positive at NCL) was 24.6% (country range 0.1-100%) in total on a single day 82 patients across Europe with CDI were not diagnosed due to lack of clinical suspicion. There were 47 patients found to be positive for CDI at NCL that did not receive a test at the original PH but got an incorrect negative result (2.2%, Country range 0.5-9%).

**Table 1.** CDI testing and positive case rates reported by PHs per country

**Table 2.** Concordance with optimised CDI diagnostic methods across Europe

**Figure 3.** Summary of outcome of all samples by country

DISCUSSION

• This is the largest study of CDI incidence across Europe to date, involving 482 hospitals in 20 countries.

• The reported CDI testing frequency has increased from that recorded in 2008 [22.1% to 62.3%].

• There has also been a marked increase in measured CDI incidence from 4.1 to 6.6 CDI cases/10,000 patient bed days.7 It should be noted however that there were only 87 hospitals within the original survey compared to the 482 surveyed here.

• Only 10.6% of PHs reported testing all diarrhoeal patients faecal samples, and 51.7% tested only on physician request. The actual PH testing rate of the samples sent to the NCLs was however much higher at 60.5%, possibly indicating accurate clinical suspicion.

• Only 27.4% of PHs used optimised laboratory diagnostic methods for the diagnosis of CDI, which is very similar to the 29% found in a recent survey6. Although not optimal, 72% of PHs did use at least one assay to detect C. difficile toxin in faecal samples, which has shown to be more closely with clinical disease severity than detection of toxicigenic isolates of C. difficile in faecal samples.2

• The false-positive rate at the PHs across Europe was 0.5% (country range 0.2-5%), whilst the false-negative rate was 2.3% (country range 0.4-6.7%). Although these rates appear low, they equate to 164 patients with a misdiagnosis.

• The rate of under-diagnosis (samples tested positive at NCL but no original test performed at PH) was 24.6%. This is similar to the 23% of inpatients under-diagnosed in a study in Spain in 200910. Notably, the Spanish study used toxigenic culture for testing at the NCL whilst this study used the C.DIFF QUIK CHEK COMPLETE®.

• Across Europe on a single day 82 CDI patients were missed due to lack of clinical suspicion. Furthermore, on a single day, there were 244 patients across Europe that received an incorrect result (false-positive, false-negative, or not tested at the original PH).

CONCLUSIONS

Under-testing (not testing all samples) and under-detection (inadequate laboratory diagnostics) likely account for a large disparity between the reported and actual rates of CDI across Europe. Potentially wrong diagnoses in up to 23% of patients may lead to inappropriate or inadequate treatment of patients and inadequate infection control measures.

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