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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 measured incidence 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[3-6].

The most recent European epidemiological survey carried out in 2008 (European CDI surveillance: ECDIS) reported that the CDI incidence in 97 hospitals across 29 countries varied markedly (range 0.0-36.3 per 10,000 patient days per hospital; weighted mean 4.1)[7]. Most notable, however, was the marked variation in testing frequency, and the correlation between testing rate and reported CDI rate (Figure 1.)[7].

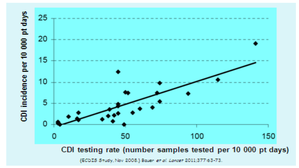

Figure 1. Scatterplot showing correlation between frequency of CDI testing and measured CDI incidence in European countries.[7]

Under-ascertainment has been further investigated in Spain where a recent point prevalence study highlighted that 66% 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%)[8].

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 reported CDI rate.

Samples at PHs

All in-patient diarrhoeal samples submitted to the PHs laboratory on a single day were sent to the EUCLID national coordinating laboratory (NCL), regardless of original test requested. 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 COMPLETE®*, Techlab, USA). The result 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 GDH 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 coordinator. 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.

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 0-19.7%).**

Testing policy

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 faecal in-patient samples. The reported percentage of samples testing by PHs was 16.4% (country range 0-64.35), whilst the percentage of samples submitted to the NCLs that had been tested at the PHs was 60.55 (country range 0-97.3%). The mean number of CDI tests/10,000 patient bed days (PBDs) reported by PHs was 62.3 (country range 4.6-132.5); the mean number of positive CDI cases/10,000 PBDs was 6.6 (country range 0.8-16.2).

Country	CDI tests/10,000 Patient Bed Days	CDI positive cases/10,000 Patient Bed Days
Sweden	98.9	16.2
Ireland	129.3	4.8
Finland	124.3	14.9
Slovakia	16.2	5.3
Spain	57.3	3.5
France	38.2	3.9
UK	132.5	3.8
Bulgaria	4.6	0.8
Greece	29.5	3.4
Germany	70.0	10.2
Belgium	100.2	5.5
Romania	12.3	3.9
Portugal	28.1	2.9
Slovenia	No data	No data
Netherlands	97.3	7.4
Austria	49.1	4.4
Poland	34.4	8.6
Czech Republic	49.1	4.4
Hungary	45.8	12.3
Italy	67.6	9.5
Europe	62.3	6.6

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

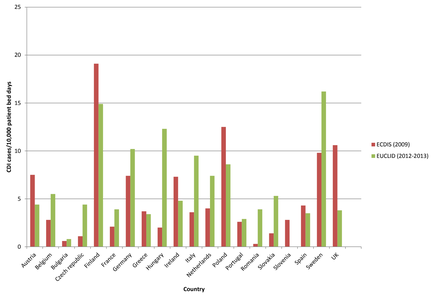

Figure 2. Changing CDI incidence per country from 2008 to 2013

Laboratory diagnostics

Across Europe only 27.4% of PHs used an optimised CDI algorithm for routine testing, although 43.4% used combinations of assays that could detect *C. difficile* toxins in faecal samples and 72% used at least one assay that could detect *C. difficile* toxins in faecal samples. Both Finland and Sweden had >20% of PHs that used a molecular assay alone to diagnose CDI.

Country	No. hospitals	No using optimised algorithm for CDI diagnosis	% using optimised algorithm for CDI diagnosis.	No. using a method to detect C. difficile toxins in faecal samples (although not optimal)	% using a method to detect C. difficile toxins in faecal samples (although not optimal)
Austria	9	1	11.1	6	66.7
Belgium	10	7	70.0	10	100.0
Bulgaria	5	0	0.0	4	80.0
Czech Republic	10	1	10.0	10	100.0
Finland	5	0	0.0	3	60.0
France	70	19	27.1	40	57.1
Germany	87	25	28.7	64	73.6
Greece	11	1	9.1	7	63.6
Hungary	10	9	90.0	10	100.0
Ireland	5	0	0.0	1	20.0
Italy	65	15	23.1	48	73.8
Netherlands	14	0	0.0	10	71.4
Poland	27	6	22.2	27	100.0
Portugal	11	2	18.2	10	90.9
Romania	5	0	0.0	4	80.0
Slovakia	6	0	0.0	6	100.0
Slovenia	2	0	0.0	0	0.0
Spain	51	12	23.5	32	62.7
Sweden	9	0	0.0	3	33.3
UK	56	30	53.6	42	75.0
Europe	468	128	27.4	337	72.0

Table 2. Concordance with optimised CDI diagnostic methods across Europe

Under-diagnosis and misdiagnosis

There were 246 patients on a single day across Europe (6.3%, country range 0-23.0%) that received an incorrect result i.e. false-positive, false-negative, or not tested at PH but found positive at NCL.

The potential **under-diagnosis rate** (no test performed at PH on sample found positive at NCL) was 24.6% (Country range 0-100%); 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 NCLs that did receive a test at the original PH but got an **incorrect negative result** (2.3%, Country range 0-5.9%).

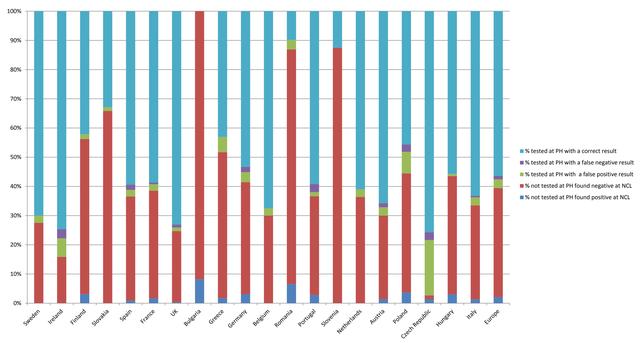

Figure 3. Summary of outcome of all samples by country

Bulgaria did not test any samples at the PHs before they were sent to the NCLs.

The Netherlands and Slovenia did not have any positive samples during the testing period.

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 (52.1) to 62.3 tests/10,000 patient bed days[7].
- There has also been a **marked increase in measured CDI incidence from 4.1 to 6.6 CDI cases/10,000 patent bed days**[7]. It should be noted however that there were only 87 hospitals in the original survey compared to the 482 surveyed here[7].
- Only **10.6% of PHs reported testing all diarrhoeal in-patient 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 survey[7]. Although not optimal, 72% of PHs did use at least one assay to detect *C. difficile* toxin in the faecal sample, which has been shown to correlate more closely with clinical disease severity than detection of toxigenic isolates of *C. difficile* in faecal samples[9].
- The false-positive rate at the PHs across Europe was 5.0% (country range 0-25%), whilst the false-negative rate was 2.3% (country range 0-6.7%). Although these rates appear low, they equate to **166 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 25% of inpatients under-diagnosed in a study in Spain in 2009[8]. Notably, the Spanish study used toxigenic culture for testing at the NCL, whilst this study used the *C.DIFF QUIK CHEK COMPLETE®*[8].
- Across Europe **on a single day 82 CDI patients were missed due to lack of clinical suspicion**. Furthermore, on a single day, there were **246 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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