EUCLID: the fuller picture of the incidence of *Clostridium difficile* infection (CDI) across Europe

What is EUCLID?

The **EU**ropean, multi-centre, prospective bi-annual point prevalence study of **CL**ostridium difficile **I**nfection in hospitalised patients with **D**iarrhoea (EUCLID) study is the largest European CDI epidemiology study ever conducted. EUCLID has been designed to determine the underlying incidence of CDI in hospitalised patients with diarrhoea and the magnitude of underdiagnosis. The study was initiated and sponsored by Astellas Pharma Europe Ltd. and endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study group for *Clostridium difficile*.

Why was this study conducted?

Clostridium difficile infection (CDI) is the leading cause of hospital-acquired (nosocomial) diarrhoea in industrialised countries.[1] Hospitalised patients with CDI are up to three times more likely to die in hospital (or within a month of infection) than those without CDI.[2,3] Furthermore, CDI has an enormous impact on healthcare systems as infected patients can stay in hospital an extra 1-3 weeks,[4,5,6] at an additional cost of up to €14,000, compared with patients without CDI.[7] The incidence and severity of CDI continues to increase.[8,9,10,11,12]

A previous epidemiological survey of 106 laboratories from 34 European countries, completed in 2008 (European CDI surveillance: ECDIS), showed high variability of CDI incidence across Europe.[8] The study demonstrated that hospitals with higher CDI testing rates diagnose more cases than hospitals with lower testing rates.[8] This suggests that the number of cases reported doesn't necessarily represent the true incidence of CDI, but reflects the differing levels of clinical awareness of the disease across Europe. Furthermore, a study conducted in the same year across 118 hospitals in Spain (covering 75.4% of the population) suggested that two thirds of patients with CDI were not tested for *C. difficile* at the local hospital or were misdiagnosed.[13]

The variable awareness of CDI across Europe is compounded by a lack of agreement on the optimum diagnostic method, as well as significant variation in the sensitivity and specificity between currently available commercial tests.[1]

As a result of these data, the reported rates of CDI in Europe are widely thought to be under-estimated and there is a need for further research and standardisation (or harmonisation) of surveillance. Therefore in 2012, EUCLID, the largest European epidemiology study to date in this disease, was launched to quantify the anticipated level of underdiagnosis and reporting of CDI cases across Europe. Understanding the true incidence of CDI will allow the appropriate and effective allocation of resources in an effort to control this distressing and sometimes life-threatening infection.

Study outline

EUCLID[14] was conducted in two parts, winter 2012/2013 and summer 2013 and the results were used to assess a number of aspects of CDI:

- Reported incidence
- Rate of underdiagnosis
- Accuracy of testing methods
- Variation in testing methods used
- Prevalence and spread of CDI strains
- Seasonal differences in CDI

Summary of study[14]

20 European countries

482 participating hospitals

Information recorded at participating hospital for each sample and passed to NCL:

- **Whether sample tested for CDI and result**
- **Testing procedure used**
- **Whether test was requested by physician**

1 day winter 2012/2013
1 day summer 2013

7181 faecal samples sent to National Coordinating Laboratory (NCL)

Samples assessed for CDI at NCL

C. difficile ribotype assessed

How was the study conducted?

The study was coordinated out of the University of Leeds, UK, by Professor Mark Wilcox's research group, with support from the study co-chair, Professor Ed Kuijper, and the EUCLID Core Group.

There were 20 participating countries across Europe, each with a central national coordinating laboratory that completed the testing and reported to the core study group. The study involved hospitals at a ratio of one hospital per one million population, to ensure that data was representative of the population size.
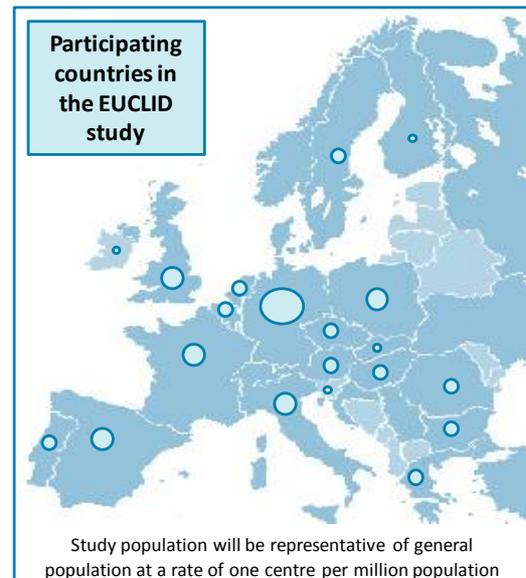
On each of the assigned days, participating hospitals submitted all received samples of un-formed faeces to their national coordinating laboratory. These samples were tested for CDI using an optimised two-stage algorithm for CDI diagnosis: membrane enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH)/ membrane EIA for toxins A and B (the *C. DIFF QUIK CHEK COMPLETE*®, TechLab, USA) assay and any positive results were confirmed using standardised confirmation methods outlined in the study methodology.

Analysis of the extent of under-diagnosis as well as the sensitivity of different testing methods was supported by the collection of additional data. Each sample that was sent to the national coordinating laboratory was submitted with further data including:

1. whether a CDI test was requested for that patient
2. which test was used
3. whether the test was positive

Participating hospitals also provided data from the previous year including the total number of CDI tests performed and how many of these tests were positive.

The national coordinating laboratories collated all CDI samples and sent them to the European coordinator for their strain type to be determined.

Participating countries in the EUCLID study

Study population will be representative of general population at a rate of one centre per million population

Results[14]

The initial set of data,[15] from the winter testing day, was released at ECCMID in 2013 and the main findings showed that:

- infection rates had increased substantially compared with the 2008 data,[8] from 4.1 to 6.8 cases per 10,000 patient-bed days
- identification of cases that had not been picked up at the participating hospital showed that 82 patients with CDI were not diagnosed across Europe on a single day

The full data from both days of the study have been released at ECCMID 2014.

Key findings

In winter:
- More than 1 in 4 of the CDI positive patients had been missed due to inaccurate diagnosis
    - 82 patients not diagnosed due to lack of local CDI request
    - 46 patients due to false negative test at local hospital

In summer:
- More than 1 in 5 of the CDI positive patients had been missed
    - 67 patients not diagnosed due to lack of a local CDI test request
    - 22 patients due to false negative test at local hospital

> **"This equates to more than 39,000 missed diagnoses across Europe each year"**
>
> **Professor Mark Wilcox**
> Professor of Medical Microbiology,
> Leeds Teaching Hospitals & University of Leeds

Reported annual incidence of CDI increased even further:
- 6.8 per 10,000 patient-bed days from the winter study (Sept 2011 – Aug 2012)
- 7.9 per 10,000 patient bed days from the summer study (Sept 2012 – Aug 2013)

Analysis of the PCR-ribotype profiles of the collected isolates showed a high diversity of strains across Europe, with the hypervirulent PCR-ribotype 027 being the single most prevalent strain identified (18.4%),[16] a marked increase from the 5% reported in 2008.[8] Those countries with the highest rates of CDI testing had the lowest rates of ribotype 027.[17]

> **"Increased awareness, using optimal testing policies and methodologies can reduce the prevalence of epidemic strains"**
>
> **Professor Mark Wilcox**
> Professor of Medical Microbiology,
> Leeds Teaching Hospitals & University of Leeds

The average CDI positive rate for the winter collection day was 8.8%, compared to 9.2% on the summer day, showing no evidence of seasonal difference in CDI cases.

There was a large variation across the centres in testing policy. 32 of the hospitals stated that their testing policy had changed between the two study dates[17] with most becoming more comprehensive.

Although the use of optimised methods for CDI diagnosis increased between the two study days (32.5% in the first day versus 47.0% in the second day), still less than half of the participating hospitals used the optimised methods and over half of the hospitals only tested stools when specifically requested by a physician.

Overall, false-positive rates were less than 5%, and were even lower in those countries where the testing methodology had improved between study days.[17]

Summary of data presented at ECCMID 2014

Second report from the EUropean, multi-centre, prospective bi-annual point prevalence study of *CLostridium difficile* Infection in hospitalised patients with Diarrhoea (EUCLID)[14]

Summary
Analysis of the full study comprising the winter and summer study days.

Results

- The average CDI positive rate for the winter collection day was 8.8%, compared to 9.2% on the summer day, showing no evidence of seasonal difference in CDI cases
- Frequency of testing for CDI has increased between the two 12 month periods spanning September 2011-August 2012 and September 2012-August 2013, from 67.1 to 77.4 tests per 10,000 patient bed days
- There has been an increase in the incidence of CDI to 7.9 cases per 10,000 patient bed days, measured in this study, up from 4.1/10,000 measured in 2008 in a previous study[8]
- More than half of all hospitals only tested for CDI if the physician requested it
- The rate of underdiagnosis – samples that tested positive in the study but had not been tested at the participating hospital – was 21.8% on the summer test day and 24.6% on the winter test day
- The false-negative rate was slightly lower on the summer test day compared to the winter (reduced from 2.3% to 1.0%) and although these rates appear low, they still mean that an average of 152 patients with CDI are misdiagnosed on any one day
- Across Europe, on a single day, an average of 109 patients with CDI were missed due to lack of clinical suspicion or suboptimal testing, meaning that more than 39,000 cases are potentially missed each year

Optimised diagnosis of *Clostridium difficile* infection; is there still room for improvement? Results of a European point prevalence study of *C. difficile* infection (EUCLID)[18]

Summary

This part of the study compared the performance of two types of enzyme immunoassay for laboratory diagnosis of CDI – a 'membrane-based' EIA and a 'well-based' EIA with a neutralised cytotoxin assay.

Results

Both types of assay had more than 99% specificity, but the sensitivity was less than optimal at only 67-72%. This suggests that some cases are being missed and that improved toxin detection methods are needed.

Increased diversity of *C. difficile* PCR-ribotypes across European countries and disparity of 027 prevalence; Results of the European, multi-centre, prospective bi-annual point prevalence study of *Clostridium difficile* infection in hospitalised patients with diarrhoea (EUCLID)[16]

Summary

All *C. difficile* isolates were sent to the European coordinating laboratory (ECL) for PCR-ribotyping. This identifies the strain of the infecting bacteria, which is important for monitoring the epidemiology of the disease, understanding emergence and spread of potentially hypervirulent strains and detection of outbreaks or epidemics.

Results

There were 1,211 *C. difficile* isolates – 633 during winter and 578 during summer. In these samples, 138 different PCR-ribotypes were identified from the 20 countries, with no single strain dominating in the majority of the countries (14/20). This is a marked increase since 2008 when 65 different PCR-ribotypes were identified across 26 countries.[8]

However, the hypervirulent PCR-ribotype 027 was the most commonly isolated (18.4%) and 88.8% of these were found in just four countries, Germany, Hungary, Poland and Romania.

There is a clear difference between European zones, the 027 rates (as a percentage of the total isolates in that zone) were as follows: north 1.6%, south 6.0%, west 17.9% and east 37.3%. Testing rates per 10,000 patient beds was highest in the north (121.25) and lowest in the east (29.24).

The prevalence of PCR-ribotype 027 appears to correlate inversely with the level of CDI testing performed, which suggests that those countries with increased awareness of CDI may have been able to reduce or limit outbreaks associated with 027.

Analysis of actual *Clostridium difficile* epidemiology in Germany based on a multi-centre bi-annual point prevalence study in European countries (EUCLID)[19]

Summary

The EUCLID study was the base for the first prospective evaluation of CDI in hospitalised patients in Germany.

Results

2,057 samples were investigated and CDI was confirmed in 426 cases. The most frequently isolated ribotype was the hypervirulent 027 (21.7%), while other ribotypes with the features of hypervirulence (presence of toxin A and B and binary toxin genes) were newly identified. The geographical distribution of 027 shows it spreading across the country from west to east.

The emergence of the hypervirulent strain 027 presents a threatening scenario in Germany and underlines the need for comprehensive prevention and surveillance strategies.

Italian preliminary data obtained from the EUropean, multi-centre, prospective bi-annual point prevalence study of *CLostridium difficile* Infection in hospitalised patients with Diarrhoea (EUCLID)[20]

Summary

This part of the study looked specifically at the situation in Italy.

Results

710 samples were collected, of which 151 were found to be positive for CDI. Among the samples, 16% were underdiagnosed and 3% wrongly analysed as negative.

These results showed a CDI rate of 9.5/10,000 and 8.3/10,000 patient bed days for the 12 month periods 2011-12 and 2012-13, which is a higher rate than previous studies have indicated (3.6/10,000 patient bed days[8]).

These results underline the need for an increased awareness of CDI in Italy.

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