Clostridium difficile Ribotyping Network (CDRN) for England and Northern Ireland
2011–13 Report
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Introduction

The *Clostridium difficile* Ribotyping Network (CDRN) for England and Northern Ireland has continued to expand and respond to a major public health need, by providing a molecular epidemiological service that enhances our understanding of this pathogen. Since the introduction of CDRN the reports of *C. difficile* in England have fallen markedly.\(^1\) Reports of deaths associated with CDI have also been decreasing since a peak in 2007.\(^2\) It is not possible to determine which interventions have been particularly responsible for this decreased incidence of CDI. However, it is plausible that better access to the ribotyping and enhanced fingerprinting results provided by CDRN may have facilitated better local investigation and control of CDI cases. It is most notable that the epidemic ribotype *C. difficile* 027, which is associated with poor outcome,\(^3\)\(^4\) has declined markedly.\(^5\)

Samples are submitted to CDRN according to local clinical need. We aim to provide results within two weeks of sample receipt. We believe that the timely data provided by CDRN has enabled healthcare institutions to respond to changes in CDI presentation and/or incidence. We encourage all hospitals to consider submitting samples according to the CDRN criteria so that they can be best placed to continue to prevent and control CDI.

In its sixth year of operation, the CDRN now comprises nine participating Public Health/NHS Laboratories (Figure1):

- Leeds (Leeds General Infirmary) [Yorkshire & Humber];
  - CDRN Reference Laboratory
- Birmingham (Heartlands Hospital) [West & East Midlands Regions]
- Bristol (Bristol Royal Infirmary) [South West Region]
- Cambridge (Addenbrooke’s Hospital) [East of England Region]
- London (Barts Health NHS Trust) [London Region]
- Manchester (Manchester Royal Infirmary) [North West Region]
- Newcastle (Royal Victoria Infirmary) [North East Region]
- Southampton (Southampton General Hospital) [South East Region]
- Belfast (Royal Victoria Hospital) [Northern Ireland Region]

Accessing the service

The CDRN laboratories provide access to *C. difficile* culture and ribotyping according to standardised criteria for submission of faecal samples. The number of samples to be submitted to the CDRN per scenario is agreed prospectively with respective Lead Public Health Microbiologists, or a microbiologist from the CDRN laboratory, according to the extent and severity of CDI cases. The CDRN aims to provide timely information to help optimise the management of *C. difficile* at a local level, with a turnaround time of less than
two weeks (this includes the time to culture *C. difficile*). It is recommended that hospitals/infection control teams in England use the CDRN service to investigate the following scenarios:

- increased frequency of cases OR high baseline rates of CDI
- increased severity/complications of cases of CDI
- increased mortality associated with CDI or
- increased recurrence rate of CDI

We believe that the CDRN service can help local teams to meet targets that have been set for reducing the incidence of CDI. Additionally, we collect, via a mandatory request form, antibiotic risk and outcome data that can be used to provide more detailed information about CDI at a national level. We stress that some requests provide few such data, which hinders this aim, and we therefore encourage all users of the CDRN service to submit the data requested.

**Figure 1: CDRN laboratories (2011–2013)**
Enhanced DNA fingerprinting

Since late 2008, CDRN has offered an enhanced DNA fingerprinting (multilocus variable repeat analysis, MLVA) service. This can be used to characterise and improve the understanding of the transmission of epidemic C. difficile strains within healthcare institutions. Importantly, the method can provide a high level of discrimination among epidemic C. difficile ribotypes, including 001, 027 and 106. For example, MLVA can distinguish more than 20 sub-types of C. difficile ribotype 027. MLVA is far superior to most other fingerprinting methods, including pulsed field gel electrophoresis, for analysing closely related C. difficile strains.

Institutions should consider the use of the CDRN MLVA Enhanced Fingerprinting service to optimise the control and prevention of CDI. As with the CDRN ribotyping service, there is currently no charge for the enhanced fingerprinting service for NHS hospitals in England. Access to the service is controlled, in the first instance by Lead Public Health Microbiologists, given its high cost and need to balance availability with the scale of CDI challenge. MLVA is available via the Leeds laboratory (based at Leeds General Infirmary), which acts as the reference laboratory for the CDRN service. In the East and West Midlands, MLVA is available via the Birmingham (Heartlands laboratory).

The criteria used to access the enhanced fingerprinting service are:

- a hospital/trust with a high rate of CDI as identified with local commissioners or
- a hospital/trusts that is failing to meet its C. difficile target trajectory despite implementation and audit of control measures

or

- a declared outbreak of CDI as agreed with the local health protection team.

In addition:

- ribotyping carried out by CDRN must have confirmed the presence of a dominant C. difficile ribotype
- a plan should be in place of how results of C. difficile enhanced fingerprinting will contribute to the control of CDI
- infection control teams/consultant microbiologists will first need to agree with the regional microbiologist that use of the C. difficile enhanced fingerprinting service is merited and
- numbers of samples/isolates to be examined will be agreed with the MLVA laboratory on a case-by-case basis, taking account of the scale of CDI challenge
Antibiotic susceptibility testing

In order to determine the epidemiology of the susceptibility to metronidazole and vancomycin of *C. difficile* isolates from CDI cases, prospective surveillance is performed on strains received by the CDRN Reference Laboratory in Leeds.

Electronic requesting and reporting system

A dedicated electronic requesting and reporting system is now available for NHS trusts to complete electronic request forms and receive test results electronically, as well as access archived historical results. The service is accessible via the NHS N3 secure network and users must securely register on the site before making requests. The service can be accessed at the following web address:

https://nww.cdrn.nhs.uk

A detailed user guide is available to download on the system front page, as well as the dedicated CDRN pages

(http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/LaboratoriesAndReferenceFacilities/ClostridiumDifficileRibotypingNetworkService/) of the main PHE website

www.hpa.org.uk

The electronic requesting and reporting system is operational in all regions; paper requests should not be used. The system enables faster reporting of results to assist outbreak investigation, as well as enhance data analysis capabilities.

We are collaborating with the PHE healthcare-associated infection surveillance team to streamline data collection. The aim is to enable different electronic data collection systems to communicate, and so minimise the duplication of data input by users of the different surveillance schemes.

In addition, functional modifications to the system are being designed up to allow matching to the new NHS organisational structure and bring many of the features of the system up to date.
Results for 2011-2013

In 2011/12 and 2012/13, CDRN processed 5,144 faecal samples from 129 healthcare facilities, and 5,830 faecal samples from 135 healthcare facilities, respectively. Figures available since the service began show slight regional differences in the number of samples submitted to the service (Figure 2). On average since the service began, 15, 24, 33, 46, 40, and 43 samples were submitted to CDRN by each participating hospital in 2007/08, 08/09, 10/11, 11/12, and 12/13, respectively. Despite the decreasing number of reports of *C. difficile* recorded by the mandatory scheme in England (Figure 3), submissions to CDRN have continued to increase over time. In 2012/13, over one-third of the CDI cases reported in England were examined for ribotyping by the CDRN (Figure 3). Males accounted for 40.2% of cases and the age range was 1-101 years, with a mean (median) age of 72 (77) years.

**Figure 2: Regional distribution of CDRN samples submitted to the service (2007–2013)**

It should be noted that an epidemiological study took place in the North East region during 2009-11, which accounts for the larger numbers of samples processed here in these years.
Proportion of mandatory CDI reported cases ribotyped

Figure 3 below shows the ribotyping sample submission to CDRN by quarter year, expressed as the proportion of mandatory *C. difficile* toxin positive reports on the Mandatory HCAI Data Capture System (DCS) in England from 2007 to 2013. The overall average proportion of *C. difficile* reported cases from whom samples were sent for ribotyping over the whole analysis period 2007–13 was 23.4%. Usage of CDRN, expressed both in crude numbers and in terms of the proportion of all reported cases that are referred, has increased markedly since the service was launched. The latest data shows that more than one in three (34.7%) of all *C. difficile* reported cases in England have samples referred to CDRN for ribotyping.

*Figure 3: Proportion of HCAI CDI cases submitted for ribotyping (April 2007–March 2013)*
Reasons for sample submission to CDRN service

In 2011/12 and 2012/13, 5,144 and 5,830 samples were submitted in response to clinical need. The reasons provided for sample submission are shown in Figure 5. The commonest reasons cited for sample submission was clustering of cases (50% of all samples cited this as a reason), followed by unexplained increase in CDI rate (12% of all samples), and severity of symptoms of CDI in the affected patient and in other patients (10% of all samples); 28% of requests either gave an answer of ‘other reason’ or no reason given.

Figure 4: Reason for sample Submission to CDRN (2008/09 to 2012/13)
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### C. difficile Recovery Rate

Figure 5 shows *C. difficile* recovery rates for samples submitted to the service since 2008/09. These figures exclude samples not processed (not enough sample, duplicates, etc). There was a 29% increase between 2007/08 and 2008/09 in the proportion of (presumed toxin positive at the source laboratory) faecal samples submitted to CDRN that were *C. difficile* culture-negative (i.e. from 9.6% to 12.4%). This change may have reflected more false positive samples, as CDRN examines samples that have tested locally as ‘toxin positive’. Notably, the *C. difficile* recovery rate has progressively increased, which implies that the proportion of samples identified locally as *C. difficile* positive that truly harbour the bacterium is increasing. This observation is consistent with improved diagnosis of CDI. Guidelines for the diagnosis of CDI were issued in 2012.8

**Figure 5: C. difficile recovery rate (2008/09 – 2012/13)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Samples</th>
<th>C. difficile Growth</th>
<th>Recovery Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008/09</td>
<td>4682</td>
<td>4101</td>
<td>87.6%</td>
</tr>
<tr>
<td>2009/10</td>
<td>5720</td>
<td>4995</td>
<td>87.3%</td>
</tr>
<tr>
<td>2010/11</td>
<td>7026</td>
<td>6197</td>
<td>88.2%</td>
</tr>
<tr>
<td>2011/12</td>
<td>5144</td>
<td>4761</td>
<td>92.6%</td>
</tr>
<tr>
<td>2012/13</td>
<td>5830</td>
<td>5523</td>
<td>94.7%</td>
</tr>
</tbody>
</table>

### Ribotype Distribution

#### Changes in ribotype prevalence

Figure 6 demonstrates the marked shifts in ribotype prevalences in the 24 quarters (six years) since CDRN was introduced. There has been a striking decrease in the prevalence of *C. difficile* ribotype 027, and also in ribotypes 001 and 106, with ‘compensatory’ increases in the other types. In general, the pattern of ribotypes in England has become more heterogeneous. This phenomenon may reflect the success of control measures to reduce cross-infection in hospitals caused by former predominant epidemic strains, especially ribotype 027. In some regions, ribotype 027 has almost completely disappeared, according to these CDRN data. With increased sample submission to CDRN, such an effect may be expected to accompany an increase in the relative contribution of other ‘emergent’ *C. difficile* ribotypes to overall disease burden.

The top 14 most prevalent ribotypes are shown, ie those with >2% prevalence in 2008/09. In 2007/08, 2008/09, 2009/10, 2010/11, 2011/12 and 2012/13, 7.2%, 8.1%, 10.9%, 14.9%, 4.7%, and 4.4%, respectively, of all isolates were designated as sporadic, ie these were not one of the commonly recognised ribotypes.
It is notable that one of these ‘emergent’ \textit{C. difficile} ribotypes is 078 (see also Figure 7). Ribotype 078 has caused outbreaks in N. Ireland and has been prevalent in the Netherlands and Scotland.\textsuperscript{9-11} It has been recovered from several animal sources, but there is no definitive evidence to link food sources and human CDI. Other emergent ribotypes include 002, 005, 014/020 and 015.
Figures 7a-i: Distributions *C. difficile* ribotypes within each region in England (April 2007–March 2013)
East Midlands (2007-2013)

London (2007-2013)
A European Centre for Disease Prevention and Control sponsored C. difficile period prevalence study was carried out in 69 hospitals in 28 countries in Europe in the month of November 2008. Ribotypes 001, 002, 012, 014, 015, 018, 027 and 078 predominated. Of these eight types commonly seen across Europe, six featured in the top eight most prevalent ribotypes in England in 2012/13 (the exceptions being ribotypes 012 and 018). The most prominent ribotype that used to be seen in England, but rarely elsewhere, was 106; however, ribotype 106 is no longer among the ten most prevalent types in England.
Enhanced fingerprinting

The Leeds CDRN Reference Laboratory has previously published an analysis of enhanced fingerprinting (MLVA) investigations of potential CDI case clusters/outbreaks in hospitals in England. Notably, despite sharing a common ribotype, 19% of these potential CDI case clusters/outbreaks comprised unrelated isolates, and 34% contained a mixture of highly related and distinct isolates, as shown by MLVA. These findings emphasise the value of enhanced fingerprinting to confirm or refute suspected CDI case clusters. In 2011/12 and 2012/13, Leeds carried out 60 (142 isolates) and 78 (339 isolates) MLVA based investigations, respectively.

We have been examining the utility of whole genome sequencing in comparison with MLVA for the examination of case clusters. This project is part of a UK-wide consortium (Modernising Medical Microbiology), funded by the Wellcome Trust and MRC, between the University of Oxford, PHE and the Wellcome Trust Sanger Institute, to establish how revolutionary new technologies can be optimally integrated into medical microbiology. We have examined *C. difficile* isolates from 61 adults with on-going/recurrent CDI and 17 asymptomatic carriage episodes in children (201 samples), and from 61 suspected outbreaks affecting 2–41 patients in 31 UK hospitals (300 samples) using both 7-locus MLVA and WGS. Conclusions on whether potential outbreaks were confirmed were concordant in 58/61 (95%) of investigations. Overall findings using MLVA and WGS were very similar, despite these techniques analysing different parts of the bacterial genome. With improvements in WGS technology, it is likely MLVA loci data will be available from WGS in the near future. Additionally, WGS provides additional data, such as antimicrobial susceptibility genotype and the presence/absence of virulence genes. We will be transitioning to using WGS instead of MLVA for the enhanced fingerprinting and investigation of *C. difficile*. 
Outcome Data

In 2011/12 and 2012/13, respondents provided responses to at least one clinical question in ~44% and ~50% of cases, respectively. Clinical follow-up data are shown in Figure 9 (these are for all referred cases, regardless of culture result); the data should be interpreted with caution given the partial response rate.

Figure 9: Outcome data provided at the time of CDRN request submission (2007/08–2012/13)
A detailed analysis of risk factors associated with CDI, outcomes and specific ribotypes was presented in the 2009-10 CDRN report (www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1296681523205). Further detailed information can also be found in two recent publications.\textsuperscript{4,5}
Antibiotic Exposure

The interpretation of data on CDI risk associated with individual antibiotics is extremely difficult as commonly used agents may be reported as being associated with CDI those rarely prescribed antimicrobials, data often do not take into account duration of exposure or polypharmacy, and may be confounded by other risks (patient age, co-morbidities, etc). Thus, the data in the following paragraphs needs to be interpreted with caution; notably, the data should not be considered to be indicative of which agents caused CDI.

The most commonly reported antibiotics in 2011/12 and 2012/13 were piperacillin-tazobactam (n=750, 718) and co-amoxiclav (n=835, 749) (Figures 10a and 10b). It is noticeable that the most commonly recorded antibiotics have changed markedly over the six-year period that CDRN has been in existence. In 2007/08, cephalosporins were the most commonly cited agents, whereas these were uncommonly cited in subsequent reporting periods, and indeed have been numerically superseded by co-amoxiclav and piperacillin-tazobactam from 2008/09 onwards. This data likely reflects real changes in prescribing of systemic antibiotics as one of the control measures for CDI.

The antibiotics most frequently reported for CDI cases referred to CDRN have changed. The previous preponderance of cephalosporins or fluoroquinolnes associated with CDI cases has been replaced by co-amoxiclav and piperacillin-tazobactam. The markedly decreased usage in England of cephalosporins and fluoroquinolnes, their replacement by co-amoxiclav and piperacillin-tazobactam as the most often used broad spectrum antibiotics, the frequent receipt of multiple agents, alongside other potential confounding factors, makes it difficult to determine the relative risk of CDI for individual antimicrobial agents.

It is also noteworthy that there appears to have been a shift in the prescribing of CDI treatment antibiotics from metronidazole in favour of vancomycin (Figure 10). Such data is consistent with possible greater adherence to guidelines that advocate the choice of treatment agent according to severity of CDI.
Figure 10a: Specific antibiotics reported (2007/08 to 2012/13)

Figure 10b: Specific antibiotics reported as a proportion of respondents reporting at least one antibiotic (2007/08 to 2012/13)
Metronidazole and vancomycin susceptibility

Previously, targeted surveillance, based on investigation of cases suspected to represent cross-infection, has identified reduced metronidazole and vancomycin susceptibility amongst epidemic ribotypes.\textsuperscript{16,17} Epidemic ribotypes with reduced metronidazole or vancomycin susceptibility were associated with location clusters, as determined by MLVA. This may indicate expansion or selection of strains with reduced susceptibility within epidemic ribotypes.

Two hundred and forty three \textit{C. difficile} isolates (comprising 28 PCR ribotypes) submitted to CDRN Leeds from the centres around the UK between July 2011–June 2012 were tested for their susceptibility to metronidazole, vancomycin and fidaxomicin. Note that this testing period pre-dates the introduction of fidaxomicin to the UK market. The MIC\textsubscript{90} (range) of metronidazole, vancomycin and fidaxomicin for these strains was 2 mg/L (<0.125-8), 1 mg/L (0.125-2) and 0.125 mg/L (0.001-0.25), respectively.

MIC data for PCR ribotypes containing n=5 or more isolates was further examined (PCR ribotypes 027, 001/072, 078, 002, 020, 015, 023, 106, 005, 026, 014). Regarding metronidazole, as in previous years, PCR ribotype 027 showed the highest geometric mean MIC (almost three times greater than the geometric mean MIC for all strains; 1.20 vs 0.41 mg/L, respectively). Examples of PCR ribotypes 027 and 106 (n=2 and 1 respectively) had reduced susceptibility to metronidazole (MIC \textgreater 4 mg/L). There was no evidence of reduced susceptibility to vancomycin among all isolates tested (MICs \textless 2 mg/L). PCR ribotype 106 had the highest geometric vancomycin MIC (0.94 mg/L). Reduced susceptibility to vancomycin has previously been observed only in this PCR ribotype,\textsuperscript{16,17} but not in this cohort of isolates. All isolates were uniformly susceptible to fidaxomicin, no clear association between geometric mean MIC and ribotype. The data provides a baseline against which to compare future susceptibility data.

Two hundred \textit{C. difficile} isolates (comprising 28 PCR ribotypes) submitted to CDRN Leeds between November 2012 and April 2013 from UK centres for PCR ribotyping or MLVA investigation were also tested as above. PCR ribotype 027 again had the highest geometric mean MIC of metronidazole, at almost four times the geometric mean MIC for all strains (2.78 vs 0.57 mg/L, respectively). Geometric mean metronidazole MIC for PCR ribotype 001/072 was also higher than geometric mean MIC for all isolates (0.92 mg/L). Examples of PCR ribotypes 027 and 106 (n=2 and 1, respectively) had reduced susceptibility to metronidazole (MIC \textgreater 4 mg/L). These data are consistent with previous observations of reduced susceptibility to metronidazole among \textit{C. difficile} PCR ribotypes of historical epidemiological significance.\textsuperscript{16,17} A single PCR ribotype 018 isolate was found to have reduced susceptibility to vancomycin (4 mg/L). This has previously been observed in PCR ribotype 018 isolates from Italy.\textsuperscript{18} In the UK, CDRN has previously noted reduced susceptibility to vancomycin most commonly in PCR ribotype 106 isolates.\textsuperscript{16,17} All isolates were uniformly susceptible to fidaxomicin (geometric mean MIC = 0.06 mg/L), with little variation in geometric mean MICs among PCR ribotypes.
Summary

The *Clostridium difficile* Ribotyping Network (CDRN) for England and Northern Ireland has continued to provide a public health service enabling infection control teams to determine the prevalent ribotypes, including whether strains with epidemic potential are present, and if cases clustering/outbreaks are occurring. The rate of referral of CDI cases to CDRN, as a proportion of all *C. difficile* episodes reported in England, has continued to increase; approximately 35% of all reported episodes are now referred for ribotyping.

Since the introduction of CDRN the reports of *C. difficile* in England have fallen markedly. Reports of deaths associated with CDI also started to decrease in the year after CDRN commenced, which could be due to enhanced control of the epidemic ribotype *C. difficile* 027. Indeed, there is data to show that ribotype 027 (and 078) strains are associated with significantly increased mortality.\(^4,9\) Successful control of the epidemic 027 strain in England has occurred coincident with a reduction both in the incidence of CDI and in *C. difficile* associated mortality.\(^1,2\) We believe that the timely data provided by CDRN has enabled healthcare institutions to respond to changes in CDI presentation and/or incidence.

The antibiotics most frequently reported for CDI cases referred to CDRN have changed. The previous preponderance of cases associated with cephalosporins or fluoroquinolones has changed, to be replaced by co-amoxiclav and piperacillin-tazobactam as the antibiotics most frequently received by patients who develop CDI. The markedly decreased usage in England of cephalosporins and fluoroquinolones, their replacement by co-amoxiclav and piperacillin-tazobactam as the most often used broad spectrum antibiotics, the frequent receipt of multiple agents, alongside other potential confounding factors, makes it difficult to determine the relative risk of CDI for individual antimicrobial agents.

The incidence of CDI reports continues to decrease, albeit at a reduced rate.\(^1\) Whilst there is emerging evidence that case-case transmission is not the most common way that *C. difficile* is transmitted in hospitals,\(^19\) we encourage all hospitals to consider submitting samples according to the CDRN criteria so that they can be best placed to continue to prevent and control CDI. Use of enhanced fingerprinted is recommended to optimise the control and prevention of CDI. Continued referral to CDRN will also afford the greatest chance of identifying emergent *C. difficile* ribotypes. Lastly, CDRN (Leeds) now has *C. difficile* whole genome sequencing capability; this technology will allow new ways to investigate CDI.\(^15,19\)
References


15. Eyre DW, Fawley WN, Best EL, Griffiths D, Stoesser NE, Crook DW, Peto T, Walker AS, Wilcox MH. Comparison of multilocus variable number tandem repeat analysis and whole genome


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