Clostridium difficile Ribotyping Network (CDRN) for England and Northern Ireland

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Published January 2016
PHE publications gateway number: 2015555
# Contents

About Public Health England 2

**Introduction** 4

Accessing the service 5

Enhanced DNA fingerprinting 7

Antibiotic susceptibility testing 8

Electronic requesting and reporting system 8

Results for 2013-2015 9

- Proportion of mandatory CDI reported cases ribotyped 10
- Reasons for sample submission to CDRN Service 11
- *C. difficile* recovery rate 12
- Ribotype distributions 13
- Enhanced fingerprinting 21
- Outcome data 22
- Antibiotic exposure 23
- Metronidazole, vancomycin and fidaxomicin susceptibility 25

Summary 27

References 28

Acknowledgements 30
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 *C. difficile* ribotype 027, which is associated with poor outcome,\(^3\) has declined markedly.

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 eighth year of operation, the CDRN now comprises eight participating regional laboratories (Figure1):

- Leeds (Leeds General Infirmary) [Yorkshire & Humber];
- CDRN Reference Laboratory
- Birmingham (Heartlands Hospital) [West & East Midlands Regions]
- Bristol [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 Hospital *with support from Freeman Hospital*) [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 regional 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 the CDRN service is used by hospitals/infection control teams in England 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
- 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. At present, screen test (eg GDH/NAAT) positive but toxin negative faecal samples are not an indication for CDRN submission.
Figure 1. CDRN Laboratories (2013-2015)
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.\(^4\) MLVA is far superior to most other fingerprinting methods, including pulsed field gel electrophoresis, for analysing closely related *C. difficile* strains.\(^5\) CDRN is planning to move from MLVA to WGS in 2016 (see page 21).

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 regional 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
- a hospital/trusts that is failing to meet its *C. difficile* target trajectory despite implementation and audit of control measures
- a declared outbreak of CDI as agreed with the local Health Protection Unit

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
- 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 of *C. difficile* isolates from CDI cases to treatment antibiotics (metronidazole, vancomycin, fidaxomicin), 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, which includes 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 via: https://cdrn.phe.nhs.uk

Historical data and user guides are available on the PHE webpages at: www.gov.uk/government/collections/clostridium-difficile-ribotyping-network-cdrn-service

The electronic requesting and reporting system is operational in all regions, and most are now completely electronic. The system enables faster reporting of results to assist outbreak investigation, as well as enhanced 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.
Results for 2013-2015

In 2013/14 and 2014/15, CDRN processed 7,208 faecal samples from 139 healthcare facilities, and 8,124 faecal samples from 152 healthcare facilities, respectively. Figures available since 2008 show slight regional differences in the number of samples submitted to the service (Figure 2). On average since 2008, 24, 33, 46, 40, 43, 51, and 53 samples were submitted to CDRN by each participating hospital in 08/09, 10/11, 11/12, 12/13, 13/14, and 14/15, 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 this report we have generally excluded data for 2007/08, due to the relatively small numbers of samples submitted to CDRN in this inaugural year.*

Figure 2. Distribution of CDRN samples submitted to the service (April 2008 – March 2015)

It should be noted that an epidemiological study took place in the North East region during 2009-2011, which accounts for the larger numbers of samples processed here in these years.
Proportion of mandatory CDI reported cases ribotyped

Figure 3 shows the ribotyping sample submission to CDRN by quarter, expressed as the proportion of mandatory *C. difficile* (all reported cases) on the Mandatory HCAI data capture system (DCS) in England from April 2008 to March 2015. The overall average proportion of *C. difficile* reported cases from which samples were sent for ribotyping over the whole analysis period 2008-2015 was 31.3%. Usage of CDRN, expressed both in crude numbers and in terms of the proportion of all reported cases that were referred, has increased markedly since the service was launched. The latest data show that over two thirds of reported CDI cases were ribotyped (67.8% of cases in Jan-Mar 2015 of all *C. difficile* reported cases in England had samples referred to CDRN for ribotyping). There is a caveat here; samples submitted to CDRN on the basis of a positive *C. difficile* screening test (eg GDH) but a negative toxin test will falsely elevate the proportion of all CDI cases assumed to have been examined by CDRN. Current CDRN submission criteria do not include screening test only positive samples.

Figure 3. Proportion of HCAI CDI Cases Submitted for Ribotyping to All Reported Cases of CDI to Public Health England (April 2008 – March 2015)
Reasons for sample submission to CDRN service

In 2013/14 and 2014/15, 7,208 and 8,124 samples were submitted in response to clinical need. The reasons provided for sample submission are shown in Figure 4. The commonest reasons cited for sample submission was clustering of cases (49.5% of all samples cited this as a reason), followed by unexplained increase in CDI rate (18.6% of all samples), and severity of symptoms of CDI in the affected patient and in other patients (12.5% of all samples); 19.4% of requests either gave an answer of ‘other reason’ or no reason given.

Figure 4. Reason for Sample Submission to CDRN (2008/09 to 2014/15)
**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 or rejected (not enough sample, duplicates, etc). The *C. difficile* recovery rate progressively increased, and has then stabilised at about 94%. This implies that the proportion of samples identified locally as *C. difficile* positive that truly harbour the bacterium increased and is now stable. These data are consistent with improved diagnosis of CDI. Guidelines for the diagnosis of CDI were issued in 2012.6

### Table 1. *C. difficile* recovery rate (2008/09 – 2014/15)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Samples</th>
<th><em>C. difficile</em> Growth</th>
<th>Recovery Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008/09</td>
<td>4774</td>
<td>4175</td>
<td>87.5%</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>6202</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>
<tr>
<td>2013/14</td>
<td>7208</td>
<td>6781</td>
<td>94.1%</td>
</tr>
<tr>
<td>2014/15</td>
<td>8124</td>
<td>7609</td>
<td>93.7%</td>
</tr>
</tbody>
</table>
Ribotype distributions

Changes in ribotype prevalences

Figure 5 demonstrates the marked shifts in England in ribotype prevalences in the 32 quarters (six years) since 2008/09. There has been a striking decrease in the prevalence of *C. difficile* ribotype 027 (Figure 6), 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 disappeared, according to these CDRN data (Figure 7). The North-West is an outlier in this respect, with about 10% of typed case still due to ribotype 027. 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 most prevalent ribotypes are shown in Figure 5 ie those with an overall minimum of >2% prevalence in all regions for all years between 2008/09 and 2014/15 (n=47). In 2008/09, 2009/10, 2010/11, 2011/12, 2012/13, 2013/14 and 2014/15, 7.9%, 12.5%, 14.9%, 7.1%, 5.6%, 6.6% and 9.0%, 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’ C. difficile ribotypes is 078 (see also Figure 6,7). Ribotype 078 has caused outbreaks in N. Ireland and has been prevalent in the Netherlands and Scotland.7-9 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.
Figure 6. Overall average prevalence of ribotype 027 in England by financial year
Figures 7a-i. Distributions C. difficile ribotypes within each region in England (April 2008-March 2015)
A pan-European CDI prevalence survey (EUCLID) was carried out in almost 500 hospitals in 20 countries in winter 2012-13 and summer 2013. Of over 1200 *C. difficile* isolates, the ten most common ribotypes detected were (in rank order) ribotypes 027, 001/072, 014, 002, 140, 010, 020, 018, 015 and 005. Of these ten types commonly seen across Europe, seven featured in the top ten most prevalent ribotypes in England in 2013/15 (the exceptions being ribotypes 140, 010 and 018). The most prominent ribotypes that were seen in England, but uncommonly elsewhere were 078 and 023.
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 2013-14 Leeds carried out 80 (339 isolates) MLVA based investigations. 23% of investigations comprised unrelated isolates and 23% were made up of a mixture of highly related and distinct isolates. In 2014-15 Leeds performed 88 (207 isolates) MLVA based investigations. 34% of investigations comprised unrelated isolates and 11% were made up of a mixture of highly related and distinct isolates. In 2013-14 Birmingham carried out 25 (63 isolates) MLVA based investigations. 48% of investigations comprised unrelated isolates and 8% were made up of a mixture of highly related and distinct isolates. In 2014-15 Birmingham performed 62 (199 isolates) MLVA based investigations. 40% of investigations comprised unrelated isolates and 18% were made up of a mixture of highly related and distinct isolates.

We have been examining the utility of whole genome sequencing (WGS) in comparison with MLVA for the examination of case clusters. This project is part of a UK-wide consortium, funded by the Wellcome Trust and MRC, between the University of Oxford, Public Health England 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.

A PHE funded project is underway at Leeds (CD-LINK) to determine the proportions of linked and unlinked CDI cases within five geographically-distinct hospitals in England over a 12-month period (n=~1000 isolates) using WGS. Currently, WGS is being performed in parallel with MLVA investigations to validate the planned replacement in 2016 of MLVA with WGS for CDRN enhanced fingerprinting services.
Outcome data

In 2013/14 and 2014/15, clinical follow-up data were available for ~44% and ~50% of cases, respectively, although some follow-up data (eg mortality) was provided more commonly (39% of cases). Clinical follow-up data are shown in Figure 8 (these are for all referred cases, regardless of culture result); the data should be interpreted with caution given the partial response rate.

Figure. Outcome data provided at the time of CDRN request submission (Apr 2008 – Mar 2015)

A detailed analysis of risk factors associated with CDI, outcomes and specific ribotypes was presented in the 2009-10 CDRN report (www.gov.uk/government/publications/clostridium-difficile-ribotyping-network-cdrn-report). Further detailed information can also be found in two peer reviewed reports.\textsuperscript{13,14}
Antibiotic exposure

The interpretation of data on CDI risk associated with individual antibiotics is extremely difficult. Commonly used agents are potentially more likely to be reported as being associated with CDI, compared with rarely prescribed antimicrobials. Reports often do not take into account duration of exposure or polypharmacy. Furthermore, associations may be confounded by other risks (patient age, co-morbidities, etc). Thus, the data in the following paragraphs need 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 2013/14 and 2014/15 were piperacillin-tazobactam (n=1004, 1136) and co-amoxiclav (n=864, 890) (Figure 9). It is noticeable that the most commonly recorded antibiotics have changed markedly over the eight-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 were numerically superseded by co-amoxiclav and piperacillin-tazobactam from 2008/09 onwards. These data likely reflect real changes in prescribing of systemic antibiotics as one of the control measures for CDI.

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 (Figures 9a and 9b). Such data are consistent with possible greater adherence to guidelines that advocate the choice of treatment agent according to severity of CDI. CDRN data on the prescribing of fidaxomicin for CDI treatment are not currently available.
Figure 9a. Specific Antibiotics Reported (2008/09 to 2014/15 FY)

Figure 9b. Specific Antibiotics Reported as a Proportion of CDRN Respondents Reporting at Least One Antibiotic (2008/09 to 2014/15 FY)
Metronidazole, vancomycin and fidaxomicin 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} 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 \emph{C. difficile} isolates (comprising 32 PCR ribotypes) submitted to CDRN Leeds from UK centres were tested for susceptibility to metronidazole, vancomycin and fidaxomicin (Table 2).

\textbf{Table 2.} \emph{C. difficile} susceptibility to metronidazole, vancomycin and fidaxomicin (2008/09 – 2014/15)

<table>
<thead>
<tr>
<th>mg/L</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>Fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC\textsubscript{50}</td>
<td>0.25</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>MIC\textsubscript{90}</td>
<td>0.5</td>
<td>1</td>
<td>0.125</td>
</tr>
<tr>
<td>Geometric mean MIC</td>
<td>0.26</td>
<td>0.75</td>
<td>0.06</td>
</tr>
<tr>
<td>range</td>
<td>&lt;0.12-4</td>
<td>0.5-4</td>
<td>0.015-0.125</td>
</tr>
</tbody>
</table>

MIC data for ribotypes containing n=5 or more isolates (ribotypes 002, 005, 015, 020, 014, 078, 023, 001, 027, 026, 106) are shown in Table 3.

\textbf{Table 3.} \emph{C. difficile} susceptibility to metronidazole, vancomycin and fidaxomicin for most common ribotypes (2008/09 – 2014/15)

<table>
<thead>
<tr>
<th>Ribotype</th>
<th>Geometric mean MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td>002</td>
<td>0.20</td>
</tr>
<tr>
<td>005</td>
<td>0.17</td>
</tr>
<tr>
<td>015</td>
<td>0.17</td>
</tr>
<tr>
<td>020</td>
<td>0.30</td>
</tr>
<tr>
<td>014</td>
<td>0.27</td>
</tr>
<tr>
<td>078</td>
<td>0.21</td>
</tr>
</tbody>
</table>
### Geometric mean MIC (mg/L)

<table>
<thead>
<tr>
<th>Ribotype</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>Fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>023</td>
<td>0.23</td>
<td>0.86</td>
<td>0.09</td>
</tr>
<tr>
<td>001</td>
<td>0.28</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>027</td>
<td>2.00</td>
<td>0.67</td>
<td>0.05</td>
</tr>
<tr>
<td>026</td>
<td>0.23</td>
<td>0.83</td>
<td>0.06</td>
</tr>
<tr>
<td>106</td>
<td>0.44</td>
<td>0.76</td>
<td>0.08</td>
</tr>
<tr>
<td>All isolates</td>
<td>0.26</td>
<td>0.75</td>
<td>0.06</td>
</tr>
</tbody>
</table>

#### Metronidazole

Geometric mean metronidazole MICs were elevated in ribotype 027 (2.00 vs 0.26 mg/L for all isolates), which reflects published data.\(^{17}\) Four isolates showed reduced susceptibility (>4 mg/L), three of which were ribotype 027. The remaining isolate was ribotype 106, which has also previously been associated with reduced metronidazole susceptibility.

#### Vancomycin

There was little evidence of elevated geometric mean vancomycin MICs. Only one PCR-ribotype 001 isolate showed reduced vancomycin susceptibility (MIC ≥4 mg/L).

#### Fidaxomicin

All isolates were susceptible to fidaxomicin. There was no evidence of elevated fidaxomicin MICs among the ribotype 027 isolates tested here (n=12). Ribotype 001 isolates exhibited lower fidaxomicin MICs, in agreement with previous observations.\(^{18}\) The highest geometric mean fidaxomicin MICs were observed in ribotype 023 (0.09 mg/L), but this was less than 2-fold higher than the geometric mean fidaxomicin MIC for all isolates (0.06 mg/L).
Summary

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. The number of CDI cases in England for which samples are submitted to CDRN has continued to increase (despite falling incidence), and now equates to over half of all reported episodes. 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 the year after CDRN commenced, which could be due to enhanced control of the epidemic ribotype *C. difficile* 027. The prevalence of *C. difficile* 027 has continued to fall to <5%; it is reassuring that a formerly epidemic strain is no longer a prominent cause of CDI in England. We believe that the timely data provided by CDRN has enabled healthcare institutions to respond to changes in CDI presentation and/or incidence.

We note that has been evidence of a plateau effect for the incidence of CDI reports, but most recently there has been a small increase in rates.¹ There is no evidence that this increase is associated with the emergence of a new *C. difficile* ribotype or expansion of one or more clones. We encourage all hospitals to submit samples, according to the CDRN criteria, so that they can be best placed to continue to prevent and control CDI. Furthermore, systematic referrals to CDRN will increase the chance of identifying new or emergent *C. difficile* ribotypes and associated changes in clinical presentation. Use of enhanced fingerprinted is recommended to optimise the control and prevention of CDI, and we envisage switching to whole genome sequencing shortly as the method of choice for obtaining additional knowledge about *C. difficile*. In particular, this method will allow us to identify more easily if common or closely related *C. difficile* clones are present in England.
References


11. Fawley WN, Wilcox MH; on behalf of the *Clostridium difficile* Ribotyping Network for England and N. Ireland (CDRN). An enhanced DNA fingerprinting service to investigate...


Acknowledgements

We thank everyone who has contributed to the successful development of the CDRN. A full list of contributors is shown below. Report written by Professor Mark Wilcox (mark.wilcox@nhs.net) with considerable help from Mike Shemko on behalf of:

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