

Surveillance, Diagnosis and Management of *Clostridium difficile* Infection in Ireland

National Clinical Guideline No. 3

National Clinical Effectiveness Committee (NCEC)

The National Clinical Effectiveness Committee (NCEC) was established as part of the Patient Safety First Initiative in September 2010. The NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

National Clinical Guidelines are **“systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and service users’ decisions about appropriate healthcare for specific clinical circumstances across the entire clinical system”**. The implementation of clinical guidelines can improve health outcomes, reduce variation in practice and improve the quality of clinical decisions.

The aim of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence based and consistent care across Irish healthcare services.

The oversight of the National Framework for Clinical Effectiveness is provided by the National Clinical Effectiveness Committee (NCEC). The NCEC is a partnership between key stakeholders in patient safety and its Terms of Reference are to:

- Apply criteria for the prioritisation of clinical guidelines and audit for the Irish health system
- Apply criteria for quality assurance of clinical guidelines and audit for the Irish health system
- Disseminate a template on how a clinical guideline and audit should be structured, how audit will be linked to the clinical guideline and how and with what methodology it should be pursued
- Recommend clinical guidelines and national audit, which have been quality assured against these criteria, for Ministerial endorsement within the Irish health system
- Facilitate with other agencies the dissemination of endorsed clinical guidelines and audit outcomes to front-line staff and to the public in an appropriate format
- Report periodically on the implementation of endorsed clinical guidelines.

It is recognised that the health system as a whole, is likely to be able to effectively implement and monitor only a small number of new National Clinical Guidelines each year. Not all clinical guidelines will be submitted for national endorsement and clinical guideline development groups can continue to develop clinical guidelines using an evidence based methodology in response to the needs of their own organisations.

Information on the NCEC and endorsed National Clinical Guidelines is available on the Patient Safety First website at www.patientsafetyfirst.ie, www.health.gov.ie/patient-safety/ncec

Disclaimer

The Guideline Development Group's expectation is that healthcare staff will use clinical judgement, medical, nursing and clinical knowledge in applying the general principles and recommendations contained in this document. Recommendations may not be appropriate in all circumstances and the decision to adopt specific recommendations should be made by the practitioner taking into account the individual circumstances presented by each patient/resident and available resources. Therapeutic options should be discussed with a clinical microbiologist or infectious disease physician on a case-by-case basis as necessary.

Guideline Development Group

This National Clinical Guideline is an update of the 2008 national *Clostridium difficile* guidelines and was developed by the *Clostridium difficile* subcommittee of the Scientific Advisory Committee of the Health Protection Surveillance Centre (HPSC). (Appendix 1)

Using this National Clinical Guideline

This guideline is intended to be relevant to all healthcare staff involved in the care of patients/residents that may be at risk of or have *Clostridium difficile* infection (referred to as *C. difficile* infection or CDI through this document) in acute hospitals, long-term care facilities, other institutions and in primary care nationally. Patients/residents and members of the public will find these guidelines of relevance as they outline the general and specific measures required to prevent and control CDI, how patients/residents can play a role in CDI prevention and how the recommendations should be incorporated into quality measures to safeguard the quality of patient/resident care.

The Guideline Development Group has provided a number of tools and recommendations to assist healthcare facilities comply with this guideline. (Appendix 2) A summary version of the National Clinical Guideline outlining the recommendations, is available on the website: www.health.gov.ie/patient-safety/ncec

The recommendations align with two of the three main aims of the national clinical programme for the prevention of healthcare-associated infection and antimicrobial resistance (namely hand hygiene by all and using antimicrobials wisely/antimicrobial stewardship). Recommendations are presented with practical guidance. The recommendations are linked to the best available evidence and/or expert opinion using the grades for recommendations outlined in Section 1.8.

The Chair wishes to acknowledge all the Guideline Development Group members (Appendix 1) who gave freely of their time and expertise and Ms. Siobhan Dowling and Ms. Orla Bannon, HPSC. A special word of thanks is expressed to external experts, Prof. Ed Kuijper, Chair, ESCMID study group for *C. difficile* and Prof. Ciarán P. Kelly, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA.



Dr. Fidelma Fitzpatrick, Chair, Guideline Development Group, June 2014

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1 Background

Clostridium difficile is the leading cause of infectious nosocomial diarrhoea in industrialised countries.(1) It is a spore-forming anaerobic bacterium that is widely distributed in soil and the intestinal tracts of animals and is part of the normal gastrointestinal flora in up to 3% of healthy adults, up to 20% of adults on antimicrobial therapy and up to 90% of healthy newborns and infants. The incidence of *C. difficile* colonisation increases with the duration of hospital stay in adult in-patients.(2) Gastrointestinal tract colonisation occurs via the faecal-oral route following environmental exposure to *C. difficile* spores or from contact with an infected person. The spectrum of *C. difficile* infection (CDI) ranges from mild diarrhoea to potentially fatal colitis. Antimicrobials predispose to CDI by disturbing the normal colonic microbiota permitting growth of *C. difficile*.(3)

1.1 Need for revised guideline

The first national *C. difficile* guidelines were published in May 2008.(4) Since publication, there have been new developments in diagnosis and patient management and our understanding of CDI has advanced significantly. With the exception of information on *C. difficile* ribotypes, we now have national information on the burden of CDI from both the mandatory (notifiable) and voluntary (enhanced) surveillance schemes as summarised in Section 1.3 of this guideline. (5) CDI has been increasingly recognised as an important infection in populations not traditionally considered as at risk including community-acquired infection, patients with no previous exposure to antimicrobials, children, pregnant women and patients with inflammatory bowel disease (IBD). New reservoirs such as soil, water, animals, meats and vegetable sources have been reported and potential new treatment strategies developed (3). Accurate, reliable laboratory diagnosis of CDI is a pre-requisite for appropriate patient management, prevention of cross infection and obtaining reliable epidemiological data; however, since 2008 to date, despite numerous publications outlining the problems with current testing algorithms, there is no agreed international consensus or single gold standard reference test.

1.2 Clinical and financial impact of CDI

CDI continues to impose a considerable burden on patients. Patients experience considerable morbidity from debilitating and profuse diarrhoea, require isolation, and supportive therapy in addition to specific anti-CDI therapy. Patients with CDI are twice as likely to be discharged to a long-term care facility (LTCF) rather than to their home.(6) For those patients who develop serious complications, significant morbidity and additional costs arise from the need for surgery and post-operative care. CDI prolongs hospital stay and delays the return to normal activities which has a significant, if not yet measured economic impact on society. CDI is a potentially life-threatening condition, especially among those patients who develop fulminant colitis but also in patients with less severe disease.(7, 8) The overall mortality rate has been reported as 22%, with CDI directly responsible for approximately 2% of all deaths and a contributor to death in a further 7% of cases. (9) These rates are much lower than in the UK where CDI-attributable mortality rates have exceeded 20% for several years.(10) While CDI-attributable mortality rates have historically been less than 2% in North America, rates have increased in the past decade, for example, Canadian data indicate that the 30-day mortality rate may be as high as 37%.(11)

CDI costs money. Patients with CDI spend significantly longer in hospital, on average, an additional one to three weeks which contributes significantly to additional hospital costs.(12) CDI is also associated with an increased risk of hospital readmission.(13) Other costs include additional infection prevention and control measures required for CDI patient management, and when outbreaks occur, cohort isolation and ward closure. (14) A German study reported that patients with CDI had significantly longer hospital stay (median of seven days) and the additional cost of treating CDI per patient episode was from €4,067 to €9,276.(15) A recent US review of 13 studies showed that total costs in 2008 for treating primary CDI ranged from \$9,822 to \$13,854 compared to \$6,950 to \$9,008 for controls.(16) Costs were significantly more in patients with co-morbidity, (e.g., patients with IBD, where costs were \$22,873 per case compared with \$15,762 for non-infected IBD patients). From this review, it was estimated that the attributable healthcare costs of CDI in the US were \$433 to \$797 million per year. These estimates are consistent with other studies.(17) The total costs for recurrent CDI has been shown to be approximately three-fold higher than for a primary episode of CDI.(16) In Europe, estimates suggest that the potential costs associated with the management of CDI are in the region of €3,000 million. This figure is likely to rise in line with an ageing population: by 2050 more than 134 million Europeans will be aged 65 years or older.(14) In the UK, NICE has estimated the impact of a 5%, 10% and 15% reduction in the number of meticillin resistant *Staphylococcus aureus* (MRSA) bacteraemias and *C. difficile* cases. A 5% reduction in MRSA and *C. difficile* cases would reduce national NHS costs by an estimated £4.9 million annually based on 2010/11 data. (18) Table 1, Appendix 11).

See Appendix 3 for details of HIPE analysis and Appendix 11 for more detail regarding the budget impact assessment for this guideline.

1.3 Overview of CDI epidemiology in Ireland

In 2008, the European Centre for Disease Prevention and Control (ECDC) funded a one-month European hospital-based survey comprising a network of 106 laboratories in 34 European countries, which included three Irish tertiary hospitals.(9) The incidence of CDI varied across hospitals with a European weighted mean incidence of 4.1 CDI cases per 10,000 patient days per hospital (range 0.0 to 36.3). The Irish weighted mean incidence of 7.3 CDI cases per 10,000 patient days was higher than the European average.

Prior to 2008, there was very little information regarding the true burden of CDI in Ireland. In May 2008, upon publication of the first national CDI guidelines¹, all new CDI cases became notifiable under the category of 'Acute Infectious Gastroenteritis' (AIG). However, this potentially underestimated the true burden of CDI as recurrent cases were not captured. Recurrent CDI can account for up to 20% of all cases and patients with recurrent CDI also need to be isolated with Contact Precautions and managed appropriately. In January 2012 the AIG category was dissolved and CDI became a notifiable infectious disease in its own right, as new or recurrent CDI. Table 1.1 summarises CDI cases notified to the Computerised Infectious Disease Reporting (CIDR) system from 4th May 2008 to 31st December 2013. The majority of cases were reported from patients aged 65 years or older.

¹ <http://www.hpsc.ie/A-Z/Gastroenteric/Clostridiumdifficile/Publications/>

Table 1.1: CDI cases notified via CIDR May 2008 to December 2013 (Source: HPSC)

	2008 (Wks19-53)	2009	2010	2011	2012	2013
CIDR notifications						
AIQ cases	4,169	4,357	4,290	4,387	N/A	N/A
Total cases, of which:	1,609	1,900	1,693	1,848	1,828	1,839
• New	1,609	1,900	1,693	1,848	1,624	1,643
• Recurrent					179	151
• Unknown					25	45
CDI Rate per 100,000 pop/n	57.5	41.4	36.9	40.3	35.4	35.8

* 2008 rate calculated using the 2006 census; 2009-2013 rates calculated using the 2011 census

** 2008 rate adjusted for year

*** In 2012, both new and recurrent cases of *C. difficile* became notifiable

Since new cases of CDI became notifiable in May 2008, the HPSC has issued a weekly report of CDI notifications via the CIDR system. A weekly outbreak report is also issued by HPSC. CDI case notifications via CIDR are collated to calculate an annual crude incidence rate (CIR) of CDI cases per 100,000 population (using latest available census data) and published in the HPSC annual report.

1.3.1 CDI enhanced surveillance data

Although notifiable CDI data provided important preliminary information on the burden of new cases in Ireland, it represents an underestimate of the true burden of CDI, as recurrent CDI cases were not notifiable until January 2012. Also, the current notification system does not capture information on CDI origin or onset. In an effort to gather further information regarding the epidemiology of CDI in Ireland, a national voluntary *C. difficile* enhanced surveillance scheme commenced in August 2009. Information on case type, origin, onset and severity of CDI is collected using ECDC case definitions.⁽¹⁴⁾ Participants submit data to HPSC on a quarterly basis. New and recurrent CDI cases that originated in the participating healthcare facility are used to calculate the quarterly national CDI rate, the rate stratified by healthcare facility type and the local CDI rate for each participating healthcare facility. The CDI rate is expressed as CDI cases per 10,000 bed days used (BDU).

Participating hospitals are issued with both local and national quarterly reports, national quarterly reports are published⁴ by the HPSC and enhanced surveillance data incorporated also into the HPSC annual reports.⁵ Figure 1.1 and Table 1.2 summarise data from the enhanced CDI surveillance scheme from 2009 to 2013. Over this period, there was a decrease in the proportion of patients with CDI symptom onset in a healthcare facility (73% to 59%). Conversely, there was an increase in the proportion of patients with symptom onset in the community (27% to 30%) and those with unknown location of symptom onset.

² <http://www.hpsc.ie/hpsc/NotifiableDiseases/WeeklyIDReports/>

³ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/AnnualReports/>

⁴ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/CdifficileEnhancedSurveillance/Reports/>

⁵ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/AnnualReports/>

Figure 1.1: Quarterly national rate of healthcare-associated CDI (new and recurrent) 2009-2013. (Source: HPSC)

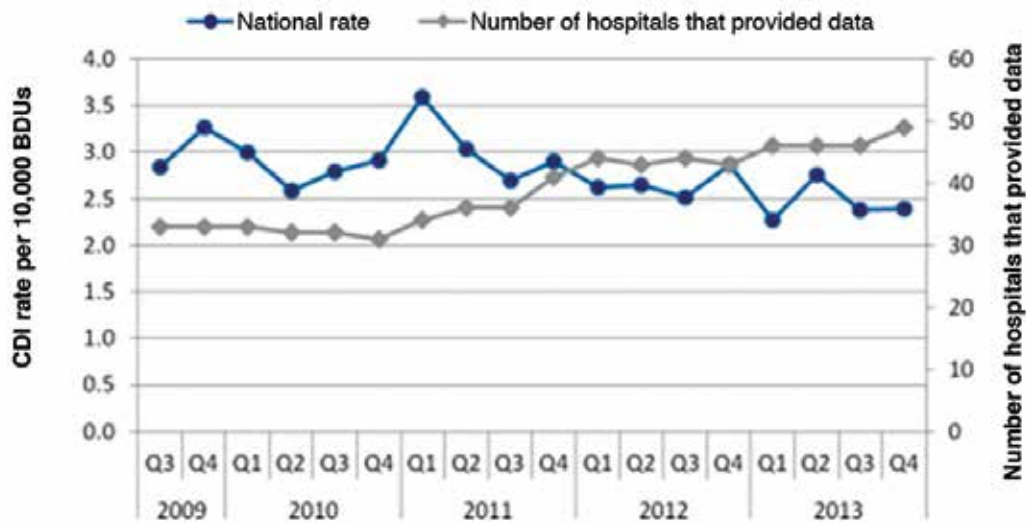


Table 1.2: National CDI rates and breakdown by origin and onset of cases, 2009-2013.
(Source: HPSC)

	2009	2010	2011	2012	2013**
Numbers of participating hospitals ^a	33	32	37	44	47
Total CDI cases reported nationally	522	1187	1511	1735	1742
Cases known to have originated in a hospital ^b	336	726	862	894	838
National CDI rate ^c	3.1	2.8	3.0	2.7	2.4
National median rate	2.7	2.3	2.2	1.7	1.8
Case Type					
% New cases	85%	92%	92%	86%	84%
% Recurrent cases	14%	8%	7%	9%	9%
% Unknown	1%	0%	1%	4%	7%
New CDI rate per 10,000 BDUs	2.7	2.6	2.8	2.4	2.2
Recurrent CDI rate per 10,000 BDUs	0.4	0.2	0.2	0.2	0.2
Age/Sex					
% >65	73%	71%	69%	66%	69%
% M	42%	44%	39%	41%	38%
%F	58%	56%	61%	59%	62%
Origin					
Healthcare-associated	83%	77%	74%	68%	63%
<i>Breakdown of those that were healthcare associated:</i>					
<i>Within reporting hospital</i>	78%	80%	78%	76%	77%
<i>Other Hospital</i>	10%	7%	8%	6%	4%
<i>Nursing Home/LTCF</i>	10%	10%	13%	15%	17%
<i>Unknown</i>	2%	2%	1%	3%	1%
Community-associated	13%	20%	20%	17%	18%
Discharged 4-12 wks from healthcare facility	0%	0%	3%	5%	5%
Unknown	4%	3%	4%	10%	14%
Onset					
Healthcare-onset	76%	73%	71%	64%	59%
<i>Breakdown of those that were healthcare-onset</i>					
<i>Within reporting hospital</i>	81%	82%	78%	77%	76%
<i>Other Hospital</i>	9%	5%	6%	3%	2%
<i>Nursing Home/LTCF</i>	9%	10%	14%	16%	18%
<i>Unknown</i>	1%	2%	1%	3%	3%
Community-onset	23%	27%	27%	30%	30%
Unknown	1%	0%	2%	6%	11%
Severity					
% Severe cases	1.0%	1.4%	1.4%	1.5%	1.8%

^a The number of participating hospitals varied quarterly therefore an annual average is presented above.

^b CDI cases that were healthcare-associated and originated within the reporting hospital.

^c The CDI rate is the number of CDI cases (both new and recurrent) originating within the participating hospital - per 10,000 bed days used (BDUs).

** Data for 2013 is provisional**

1.3.2 C.difficile ribotyping

There is a strong focus on performing PCR ribotyping of *C. difficile* isolates in other jurisdictions. England and Northern Ireland have a well established *C. difficile* ribotyping network (CDRN) which comprises designated regional laboratories for ribotyping isolates from all microbiology laboratories since 2007. In 2010/11, 7,026 faecal specimens were submitted to CDRN and 6,197 were successfully cultured for *C. difficile*, giving a recovery rate of 89.9%.⁽¹⁹⁾ Case clustering was the referral indication for 50%, unexplained increase in CDI cases accounted for 12% and CDI symptom severity accounted for 10% of referrals. ⁽¹⁹⁾ There was a marked change in the ribotype prevalence reported by CDRN between 2007 and 2011. In particular, a 42.9% reduction in ribotype 027 was observed over this period.⁽¹⁹⁾

There is no *C. difficile* reference laboratory in Ireland for ribotyping or antimicrobial susceptibility testing of *C. difficile* isolates. In March 2009, a one-month national CDI surveillance and ribotyping project was performed in Ireland. ⁽²⁰⁾ Thirty-three healthcare facilities, representing all regions of Ireland, submitted 211 faecal specimens with corresponding clinical details. Table 1.3 illustrates the distribution of PCR ribotypes in recent studies conducted in Europe, US and Canada and England in comparison with the 2009 Irish study. ^(9, 19-21)

Table 1.3: Rank order of *C. difficile* PCR ribotypes detected in recent research studies

Study	Rank order of <i>C. difficile</i> PCR ribotypes identified				
	1st	2nd	3rd	4th	5th
EU 2008 (9)	014/020 (16%)	001 (9%)	078 (8%)	027 (5%)	
US and Canada 2008-9 (21)	027 (38%)	002 (7%)	106 (7%)	017 (6%)	078 (6%)
Ireland 2009 (20)	027 (19%)	001 (16%)	106 (13%)	078 (10%)	014 (8%)
England 2010/11 (19)	027 (12.4%)	015 (7.7%)	002 (7.5%)	106 (7.3%)	001 (6.8%)

A 2005 survey of laboratory *C. difficile* testing practices in Ireland found that none of the laboratories surveyed routinely requested ribotyping of *C. difficile* isolates and only 28% requested ribotyping in the setting of a suspected CDI outbreak.⁽²²⁾ This survey was repeated in 2011 as part of the guideline review process and 24 of 33 (73%) laboratories performing *C. difficile* testing reported having referred toxin-positive faecal specimens or isolates to a reference laboratory abroad for ribotyping. The criteria for referral varied between laboratories with 15 (62.5%) doing so in the event of an outbreak, 11 (46%) upon request and nine for severe infection (38%). Only four of 24 (17%) laboratories responding to the 2011 survey reported routine referral of specimens abroad for PCR ribotyping [Data courtesy of HPSC].

1.4 Aims of this guideline

The purpose of this guideline is to enhance the safety and quality of patient/resident care by reducing healthcare-associated infection, specifically infection caused by *C. difficile*, through a series of recommendations that reflect best evidence and international practice. Comprehensive implementation of this guideline in all Irish healthcare settings as part of an integrated infection prevention and control and patient safety strategy will ensure that patients/residents with CDI are detected in a timely fashion, managed optimally and that cross infection to other patients/residents is minimised.

Specifically this guideline:

1. Updates the 2008 guidance for the surveillance, diagnosis, prevention and control, and treatment of CDI in Ireland.
2. Provides appropriate audit and other tools for healthcare staff/healthcare facilities to monitor implementation of the recommendations.
3. Complies with the requirements for guidelines published by the Department of Health (DoH) National Clinical Effectiveness Committee in early 2012.

1.5 Scope of the National Clinical Guideline

This guideline is intended to be relevant to all healthcare staff involved in the care of patients/residents that may be at risk of or have CDI in acute hospitals, long-term care facilities, other institutions and in primary care nationally. Patients/residents and members of the public will find this guideline of relevance as it outlines the general and specific measures required to prevent and control CDI, how patients/residents can play a role in CDI prevention and how the recommendations should be incorporated into quality measures to safeguard the quality of patient/resident care.

This updated guideline acknowledges changes in CDI epidemiology, new developments in diagnostics, new therapeutic approaches and provide audit measures such as those outlined in Appendix 2 to ensure that elements of this guideline are implemented.

This full version of the National Clinical Guideline in addition to the summary document, which provides more detail on the National Clinical Guideline are available at www.health.gov.ie/patient-safety/ncec. Further information on *C. difficile* in Ireland is available at: www.hpsc.ie

1.6 Guideline Development Group: The HPSC *C. difficile* subcommittee

Members of the multidisciplinary 2008 *C. difficile* subcommittee were invited to join the guideline development group. Additional representation was sought from the Irish Patients Association, long-term care (Nursing Homes Ireland), the Irish Antimicrobial Pharmacists' Group (IAPG) and the Irish Society of Gastroenterologists. Efforts were made to ensure that all the relevant professional groups and patients were represented and that the background of those involved included patient representatives, the acute hospital healthcare setting, long-term care and community care. The Guideline Development Group members' names, areas of the document they were primarily responsible for drafting and any potential conflicts of interest are outlined in Appendix 1. Membership of the Guideline Development Group was voluntary, no member was paid a fee for his/her contribution, and the input of members, in general, was done out-of hours, e.g. during evenings and at their own expense, e.g. using their own personal computer. The work was not funded by any public or private agency but did receive administrative support for meetings from the HPSC.

1.7 Methodology and literature review

The recommendations update and expand on the Irish guidelines published in 2008, where relevant, and incorporate other international guidelines, relevant published literature and the consensus expert opinion of the guideline development group.

The Guideline Development Group first met in October 2011 and meet on a number of occasions thereafter up to December 2012, with teleconferencing facilities available to assist those contributing from outside Dublin. The recommendations are divided into eight sections. Guideline Development Group members took the lead for certain sections as outlined in Appendix 1 according to their expertise and were responsible for the literature review of this section, presenting the initial drafts to the Guideline Development Group for discussion at each meeting and redrafting this section

as appropriate after discussion. Draft sections were forwarded to the chair and circulated to the entire Guideline Development Group in advance of each meeting. The chair then incorporated them into one overall document after each meeting, managed the reference manager and incorporated the changes after these meetings and after the consultation process into a revised document.

Recommendations were graded as outlined in Section 1.8. All available evidence was reviewed after the literature review as outlined in Appendix 4, however, evidence was weighted according to the grading. For example, a randomised controlled trial was judged as better quality evidence than an expert report – therefore, the relevant recommendation was drafted accordingly.

The work was carried out at the meetings in HPSC and also by email with the exchange of draft documents, comments and opinions on issues as they arose. All the recommendations and those areas where no recommendations were made were agreed to by all members of the Guideline Development Group. Potential conflicts of interest, as outlined in Appendix 1, did not impact on agreeing what was or was not appropriate to recommend. There were processes in place for the management of potential conflicts of interest. The reference section of this guideline outlines the breadth of the literature review that took place as part of the guideline update process.

The consultation exercise, which involved the active soliciting of feedback from professional groups and from patients (Appendix 5), was designed to be comprehensive and to ensure that any gaps in representation on the Guideline Development Group were compensated for by as wide a range of professional groups, healthcare managers, healthcare agencies, patient groups and experts from abroad. Submissions made during the consultation process were discussed at the Guideline Development Group's final meeting in December 2012 and incorporated as appropriate into the final document submitted to the Scientific Advisory Committee (SAC) of the HSE-HPSC in January 2013. The guideline was approved by the SAC, placed on the HPSC website and forwarded to the NCEC in March 2013. Notification of the updated guideline occurred widely through the various patient representative, professional and healthcare groups as was the case during the consultation process. This notification highlighted where new recommendations were made and where the updated guideline differs significantly from the 2008 guideline. Tools for monitoring implementation were re-iterated and the need for local educational sessions will be highlighted as part of this process.

After feedback from the NCEC review, the document was revised accordingly. A Guideline Development Group review of the recommendations and the summary document was conducted in January and April 2014.

A separate guidance document for primary care management of CDI was produced in conjunction with the Irish College of General Practitioners (ICGP) Quality in Practice Committee and placed on the HPSC website in November 2013. This document was also included in the update antimicrobial prescribing guidelines for primary care (www.antibioticprescribing.ie) in January 2014.

1.8 Grading of recommendations

The recommendations are followed by a grade. This is a consensus grade agreed by the CDI Guideline Development Group. It reflects the strength of the evidence supporting the recommendation and discussion of the evidence amongst the CDI Guideline Development Group.

The grades used throughout the guideline are as follows;

- **Legal requirement** (e.g., in the case of the notifiable infectious diseases legislation).
- **Grade A.** Evidence from a meta-analysis/systematic review of RCTs or from at least one RCT.
- **Grade B.** Evidence based on one controlled trial without randomisation (e.g., cohort study) a quasi-experimental study, or extrapolated from RCT.
- **Grade C.** Evidence from comparative studies, correlation studies, case control studies or extrapolated from category A or B.
- **Grade D.** Evidence from expert committees, reports or opinions, the clinical experience of respected authorities, and the conclusions of the Guideline Development Group.
- **No recommendation**

1.9 External review

The Guideline Development Group was extremely fortunate that two of the world experts in *C. difficile* agreed to review this guideline with no payment or gratuity.

The consultation document was forwarded to Professor Ed Kuijper, Chair, ESCMID study group for *C. difficile* Executive Committee and Department of Medical Microbiology, Leids Universitair Medisch Centrum, Leiden, The Netherlands in October 2012. The Guideline Development Group is very grateful to Professor Kuijper and appreciate the time commitment that was involved for him to review the entire consultation document.

Professor Ciarán P. Kelly, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA, reviewed recommendations 51-66, treatment of CDI in December 2012 after redrafting following the consultation process.

The Guideline Development Group wishes to thank both Professor Kuiper and Professor Kelly for their generosity in sharing their expertise and giving of their time so freely.

1.10 Procedure for update of guideline

The Guideline Development Group is a subcommittee of Scientific Advisory Committee (SAC) of the HSE- HPSC. It was agreed by the SAC in October 2008 that the SAC will review its publications on a three-yearly basis and update as appropriate. Therefore, this guideline will be reviewed again in 2017.

1.11 Implementation of guideline

For full implementation of this National Clinical Guideline, it is essential that all healthcare staff understand and appreciate that they are responsible for the prevention and control of HCAI which includes CDI in all areas of their responsibility. This must be supported by clear lines of accountability which include systems that can detect and correct lapses in infection prevention and control practice on a timely basis and increases in CDI incidence as outlined in this guideline. Patients/residents can also play a role, expecting the highest standards of healthcare quality and safety and ensuring that healthcare facilities assure them that there is an effective CDI control programme in place.

Many recommendations in this guideline represent a re-iteration of previous guidelines and are therefore cost neutral. However, the Guideline Development Group wishes to highlight the areas that require improvement to ensure full implementation of the updated guidance. Details of this budget impact assessment are in Appendix 11.

1.12 Roles and responsibilities

Each healthcare staff member has a role to play in the prevention and control of HCAI, which includes CDI by adhering to best practice as outlined in this guideline. This guideline should be reviewed by the healthcare facilities senior management teams in conjunction with the relevant specialists to plan implementation of the recommendations. This will enable the facility to ensure that the prevention and control of CDI is a key patient/resident safety issue for the facility.

Organisational responsibility: Within each healthcare facility the CEO/General Manager has corporate responsibility for implementation of the National Clinical Guideline.

All healthcare staff should:

- Comply with this National Clinical Guideline and related policies, procedures and protocols
- Adhere to their code of conduct and scope of practice guidelines as appropriate to their role and responsibilities
- Maintain competency in the prevention and control of CDI
- In using this guideline be aware of the role of appropriate delegation

1.13 Audit criteria

To ensure that this guideline positively impacts on patient care, it is important that implementation is audited. Audit is recommended to support continuous quality improvement in relation to the implementation of the National Clinical Guideline – CDI.

The following are examples of audit criteria which are consistent with HIQA *National Standards for the Prevention and Control of Healthcare Associated Infections (2009)*:

1.13.1 Number of new cases of CDI acquired in the healthcare facility per reporting time period (e.g., month or quarter)

- Hospitals: per 1,000 patient admissions and per 10,000 patient days (or bed days used)
- Long-term care facilities: per 10,000 resident days

1.13.2 Antimicrobial consumption data

- Hospital antimicrobial consumption (Defined daily doses/100 bed days used)
- Antimicrobial use audits assessing compliance with local antimicrobial prescribing guidelines

1.13.3 Hand hygiene compliance score (%)

- Overall and per each of the WHO 5 moments of hand hygiene
- By staff group
- By ward or unit

1.13.4 Compliance with Contact Precautions

- Number of observed patient care episodes in which contact precautions are appropriately implemented/number of observed patient care episodes in which contact precautions are indicated x 100

1.13.5 Compliance with environmental and patient care equipment cleaning/disinfection

This can include:

- Hygiene audit scores
- Patient care equipment decontamination audit
- Sluice room audit.

1.14 Tools to assist in implementation of National Clinical Guideline (Appendix 2)

Relevant links available at:

<http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/Publications/>

2 National Clinical Guideline recommendations

This guideline updates the HPSC 2008 guideline, acknowledges changes in CDI epidemiology, new developments in diagnostics, new therapeutic approaches and provides audit measures to support implementation of recommendations. The recommendations align with two of the three main aims of the national clinical programme for the prevention of healthcare-associated infection and antimicrobial resistance (hand hygiene by all and using antimicrobials wisely/antimicrobial stewardship).

The following areas have been specifically updated and contain new recommendations from the 2008 guidelines;

- **Essential elements of a CDI prevention and control programme:** New section
- **Prevention of CDI:** Update on 2008 recommendations including incorporation of antimicrobial stewardship recommendations
- **Surveillance:** Update of 2008 recommendations – recommended denominators for LTCF
- **Laboratory diagnosis:** Updated two step laboratory testing recommendations
- **Management of patients/residents with suspected/confirmed CDI:** New sections on management of patients/residents with potentially infectious diarrhoea, management of Glutamase dehydrogenase(GDH)/Nucleic acid amplification test (NAAT) positive: toxin negative patients/residents
- **Treatment of CDI:** Update on patient/resident management, new section on patients/residents with IBD, surgical management of CDI and new drugs/non-pharmacological options
- **Management of outbreaks and clusters:** No change.

Recommendations are divided into eight sections as follows:

Section	Subsection	Recommendation Number
National recommendations	• Designation of an Irish reference laboratory	1
	• Establishment of a single national CDI surveillance system	2
	• Improvement of access to infection specialists for non-acute services	3
	• Management of bed spacing	4
	• Newly built inpatient accommodation	5
Essential elements of CDI	• Governance structures	6
	• Standard Precautions	7
	• Standard operating procedures for a positive <i>C. difficile</i> result	8, 9
	• CDI clusters/outbreak review	10
	• CDI testing essentials	11,12
Prevention of CDI	• Antimicrobial stewardship	13,14
	• Proton pump inhibitor use	15
	• Education for staff and patients	16,17
	• Management of asymptomatic carriers	18
Surveillance	• Surveillance - when and who	19,21
	• Surveillance in children <2 years	20
	• Case definitions	22,23
Laboratory diagnosis	• Who should be tested	24
	• Type of specimen to be tested	25-27
	• Repeat testing for CDI	28-31
	• Testing strategy for CDI diagnosis	32-34
	• Susceptibility testing and molecular typing	35-38
Management of suspected/confirmed CDI	• Management of patients/residents with potential CDI	39,40
	• Informing patients/residents that they have CDI	41
	• Management of cases of confirmed CDI	42-44
	• Discontinuation of Contact Precautions	45
	• Transfer and discharge of patients	46-49
	• Management of patients/residents at home	50
Treatment of CDI	• Treatment of first CDI episode	51-53
	• Anti-motility agent use	54,55
	• CDI and surgical review	56,57
	• Role of fidaxomicin	58
	• Treatment of first CDI recurrence	59
	• Treatment of second and subsequent CDI recurrence	60
	• Role of probiotics	61
	• Managing patients with IBD and CDI	62
	• Role of combination antimicrobial/adjuvant therapy in CDI	63-66
	Management of outbreaks and clusters	• Recognising a cluster/potential cluster of CDI
• Membership of the Outbreak Control Team		70
• Key implementation measures in an outbreak		71-73

2.1 National recommendations

Recommendations 1-5 are high level national recommendations which have implications across a number of services. Responsibility for implementation of these recommendations lies at corporate HSE level.

Recommendations 1-3 require a full business case and cost analysis to assess the savings, costs and clinical advantages associated with their implementation in the Irish healthcare system. This will facilitate the most appropriate approach for implementation of these recommendations.

- **Designation of an Irish reference laboratory**

Recommendation 1

An Irish reference laboratory for *Clostridium difficile* should be designated. Pending designation, specimens should be sent to an international reference laboratory. Isolates collected as part of national surveillance should be compared with isolates from other countries to determine evolutionary trends and the emergence of virulent strains. This should occur in conjunction with laboratories abroad and as part of an international laboratories network. **Grade D**

- **Establishment of a single national CDI surveillance system**

Recommendation 2

A single national surveillance system for CDI surveillance should be established. This should incorporate typing and antimicrobial susceptibility data as relevant and be capable of linking with healthcare facility performance management systems. **Grade D**

- **Improvement of access to infection specialists for non-acute services**

Recommendation 3

Non-acute services should have access to infection specialist expertise as appropriate. **Grade D** (For example, a microbiologist and infection control nurses)

- **Management of bed spacing**

Recommendation 4

Bed spacing should be planned and managed in a way that minimises the risk of spread of CDI as outlined by HIQA (2009) *National Standards for the Prevention and Control of Healthcare Associated Infections*.⁶ **Grade D**

- **Newly built inpatient accommodation**

Recommendation 5

Newly built acute hospital inpatient accommodation should comprise 100% single rooms with ensuite shower and toilet facilities and clinical hand-washing sink as outlined in the *National Standards for Prevention and Control of Healthcare Associated Infections* (2009) and *Infection Prevention and Control: Building Guidelines for Acute Hospitals in Ireland* (2009) HPSC.⁷ **Grade C**

⁶ <http://www.hiqa.ie/publications/national-standards-safer-better-healthcare>

⁷ <http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,3439,en.pdf>

2.2 Essential elements of a CDI prevention and control programme

2.2.1. Governance structures and standard precautions

The following are responsible for implementation of **recommendation 6:**
CEO/General Manager of healthcare facility.

- **Governance structures**

Recommendation 6

Healthcare services should ensure that they have strong governance structures with clear accountability, responsibility and authority for:

- The prevention and control of CDI
- Active CDI surveillance and antimicrobial stewardship programmes
- Timely CDI laboratory diagnosis
- Adherence to appropriate infection prevention and control measures
- Timely management of CDI cases as outlined in this guideline. **Grade D**

Practical Guidance

As healthcare facilities develop patient safety statements⁸ appropriate HCAI indicators including CDI surveillance data should be incorporated to facilitate timely CDI management.

The following are responsible for implementation of **recommendation 7:**
Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance) and all healthcare staff.

- **Standard Precautions**

Recommendation 7

Standard Precautions should be used at all times by all healthcare staff when caring for patients/residents. **Grade B**

Practical Guidance

Standard Precautions are a group of infection prevention and control practices and measures that apply to all patients/residents at all times regardless of suspected, confirmed or presumed infectious status, in any setting in which healthcare is delivered. Standard Precautions include:

1. Occupational Health Programme
2. Patient/resident placement
3. Hand hygiene
4. Personal Protective Equipment (PPE) for staff
5. Patient-care equipment/instruments/devices
6. Environmental decontamination
7. Management of dishes and eating utensils
8. Management of spillages
9. Management of needle stick injuries and blood and body fluid exposure
10. Management of healthcare waste including sharps
11. Management of laundry and linen
12. Respiratory hygiene and cough etiquette
13. Safe injection practice and aseptic technique
14. Infection control practices for special lumbar puncture procedures.

When Standard Precautions are consistently implemented, the risk of transmission of infectious agents to healthcare workers and patients/residents is minimised.

⁸ http://www.dohc.ie/publications/pdf/portlaoise_perinatal_deaths.pdf?direct=1

Control of CDI requires rapid instigation of measures to prevent cross infection to other patients/residents. This usually involves a combination of infection prevention and control measures as outlined in this guideline including early isolation of patients/residents with contact precautions, education of staff and patients/residents/visitors, environmental and equipment decontamination and optimising hand hygiene by all. However, the effectiveness of each individual measure has not been determined as most studies and reports use a combination of different measures.(23)

Sufficient numbers of staff should be rostered to provide nursing care commensurate with infection prevention and control practices. The Stoke Mandeville inquiry found that levels of staffing made it particularly difficult for nurses to find the time to practice control of infection effectively.(24) A higher bed-occupancy rate means that there is less time for thorough cleaning between patients/residents and a higher probability of transmission of infection between patients/residents. This was cited as a contributory factor in the Maidstone outbreak.(25) Managers of healthcare facilities need to be aware of these risk management issues in meeting other targets. One of the factors which contributed to the second hospital-wide outbreak in the Stoke Mandeville hospital was the national policy of penalising Emergency Departments that exceeded a four hour maximum waiting time for patients, resulting in the inappropriate use of single rooms. (24) Performance targets (e.g., waiting times in the Emergency Department) should not compromise the appropriate care and isolation of patients with CDI. This is particularly important in an outbreak setting where a ward/unit may need to suspend admissions on a temporary basis.

Standard and Transmission-based Precautions are the basic principles of infection prevention and control. Standard Precautions are based on the principle that all blood, body fluids, secretions, excretions (except sweat), non-intact skin and mucous membranes may contain transmissible infectious agents. The purpose of Standard Precautions is to break the chain of infection focusing particularly but not exclusively on the mode of transmission, portal of entry and susceptible host sections of the chain. Standard Precautions should be used at all times by all healthcare staff when caring for patients/residents. When Standard Precautions are consistently implemented, the risk of transmission of infectious agents to healthcare workers and patients/residents is minimised. Healthcare facilities should ensure that the resources necessary to implement standard and transmission-based precautions are provided, including but not limited to:

- Ensuring that infection prevention and control is incorporated into the decision-making, service planning, performance management, project management and other related processes.
- Risk assessment for all healthcare activities to ensure quality and safe care for patients, healthcare staff, visitors and the general public.
- A qualified and competent infection prevention and control team commensurate with the size and complexity of the service and internationally accepted norms.
- Ensuring access to an occupational health service and implementation of occupational health recommendations to protect staff and patients/residents. Where staff are employed by an agency, the agency must ensure that equivalent services are available.
- An infection prevention and control induction and ongoing education programme for all staff.
- Adequate staffing levels within the facility.
- Provision of appropriate equipment to facilitate compliance with Standard and Transmission-based Precautions (e.g., hand hygiene facilities, personal protective equipment, cleaning equipment).
- Ensuring that the physical infrastructure (e.g., isolation rooms, hand wash sinks) is appropriate for the needs of the patient/resident population.
- Developing quality improvement plans to address any non-compliance with Standard and Transmission-based Precautions identified by regular monitoring and audits.

2.2.2 Review of positive *C. difficile* results, surveillance and feedback, systems analysis

The following are responsible for implementation of **recommendations 8-10**:

Healthcare facility Senior Management Team, Clinical Director, Clinicians, Infection Prevention and Control and Antimicrobial Stewardship Teams

- **Standard operating procedures for a positive *Clostridium difficile* result**

Recommendation 8

Each healthcare facility should have an up-to-date documented standard operating procedure to be followed in the event of a positive *Clostridium difficile* laboratory result from a patient/resident.

Grade D

Recommendation 9

- Each healthcare facility should have a system in place to ensure frequent review of positive *Clostridium difficile* results to designate CDI cases in order to ensure prompt identification of potential clustering of CDI cases. **Grade D**
- Once a case is identified, CDI data should be reviewed at ward/unit, directorate and healthcare facility management level on a regular basis, at a minimum of every 4 weeks depending on ward/patient activity and more often in an outbreak situation. This review should be carried out in conjunction with other relevant indicators to include antibiotic consumption data, hand hygiene, environment and equipment decontamination audits. **Grade D**

Practical Guidance

- Appendix 2 summarises tools and indicators that will assist healthcare facilities in the implementation of recommendations 8-10.

- **CDI cluster/outbreak review**

Recommendation 10

- At a minimum, each episode of severe CDI and all CDI cases associated with clusters/outbreaks should have a systems analysis performed by the clinical team in conjunction with the infection prevention and control team, risk management and patient safety and quality teams to identify potential precipitating factors and systems should be put in place to reduce the risk of recurrence. **Grade D**
- All healthcare facilities should formally review their management of clusters/outbreaks as a matter of routine, to identify precipitating factors and systems should be put in place to reduce the risk of recurrence. Learning from these incidents should be shared across healthcare facilities. **Grade D**

Practical Guidance

- System analysis is a retrospective review of a patient safety incident undertaken in order to identify what, how and why it happened. In the case of CDI, this process is to identify potentially preventable predisposing factors and prevent further recurrence of CDI in other patients/residents.
- The term 'system' analysis/investigation has replaced 'root cause' analysis/investigation as there is rarely one 'root cause' for any incident.
- The systems analysis process itself should ideally be led by the consultant caring for the patient with the relevant clinical nurse manager, with the full support of the infection prevention and control team, risk management and patient safety and quality specialists. However, while this process is being established in a healthcare facility, teams will need more support and leadership from relevant experts such as the infection prevention and control team, patient safety and risk management.

Patients/residents and members of the public need to be assured that a healthcare facility can detect CDI in a timely fashion, can manage the patient/resident's condition appropriately and prevent further cross infection, thus protecting the other patient/resident's from acquiring CDI. Surveillance (underpinned by appropriate laboratory support for diagnosis) will detect CDI cases, any increases in incidence or severity at an early stage including variations between different ward/unit settings that require interventions and identify potentially modifiable or preventable risk factors for CDI acquisition. *C. difficile* data should be reviewed at ward/unit, directorate and healthcare facility management level in conjunction with other relevant indicators to include antimicrobial consumption data, hand hygiene, environment hygiene, sluice room, equipment and other relevant audit results. Infection prevention and control procedures as outlined in this guideline will prevent further cross-infection and keep other patients/residents safe.

The *National Standards for Safer Better Healthcare* (HIQA, 2012) provide a strategic approach to improving safety, quality and reliability in our health services. The elements of a CDI control programme to ensure that patient/resident care is reliable, designed to keep patients/residents safe and of high quality in line with the National Standards is outlined in Table 2.1.

The Guideline Development Group has provided a number of tools and indicators (Appendix 2) that healthcare facilities may wish to use/adapt. National antimicrobial stewardship guidelines were published in December 2009 and specify the minimisation of CDI as a key part of the programme.(26) Core, high-impact, interventions for antimicrobial stewardship were proposed for hospitals and recommendations were also provided for non-acute residential healthcare facilities. The Guideline Development Group recommends that all healthcare facilities have an implementation plan for antimicrobial stewardship as part of their CDI control programme. The Guideline Development Group recommends that at a minimum, all patients/residents with healthcare-facility severe CDI and all cases associated with CDI clusters/outbreaks should have a systems analysis performed by the clinical and nursing team in conjunction with the infection prevention and control team. This is to identify potentially preventable predisposing factors and prevent further recurrence or CDI in other patients/residents. Staff will require support/training and education to implement this tool, specifically in non-acute settings where there tends to be less risk management expertise available.

A threshold incidence (CDI trigger) should be defined locally that would trigger implementation of additional control interventions.(23)

A CDI trigger is:

- A point at which the clinical team on a ward/unit in conjunction with the infection prevention and control team (IPCT) investigate if infection prevention and control systems on that ward/unit are making patients/residents more vulnerable to CDI.
- Is usually set by the IPCT using local CDI surveillance data for that healthcare facility. Public health specialists are also involved in determining CDI triggers e.g., in long-term care facilities.
- Means that the number of new CDI cases over a defined period of time in a specific ward/unit area has increased and may be of concern.
- Is not synonymous with the term outbreak. A trigger is a more sensitive point at which the IPCT becomes concerned that there may be the possibility of deteriorations in systems causing an increase in cases and decides intervention is necessary to ensure patient safety.

A CDI trigger should be set for all clinical areas (including long-term care facilities) and all staff should be aware of what the trigger is. For example, a healthcare facility could have two separate triggers, one for the entire facility and the other for a particular ward/unit. A trigger may be reached as a consequence of either natural variation in the number of CDI cases or because of a breakdown in infection prevention and control systems (e.g., poor hand hygiene compliance, suboptimal environmental decontamination) or poor antimicrobial prescribing on that ward/unit/hospital. Only by investigating CDI triggers can it be determined if best practice has not been followed and systems should be changed. The Guideline Development Group has provided an

example of a CDI trigger tool as outlined in Appendix 2 that healthcare facilities may wish to use/adapt for investigation of CDI triggers.

Statistical Process Control Charts (SPCs) may be a useful method of presenting healthcare-associated CDI cases and setting threshold limits/triggers.(27) SPCs show data chronologically and describe it as either natural or unnatural variation. They contain three main parameters; the centre line, which in the context of CDI is the average number of healthcare facility-acquired cases per month, the trigger line/warning limit (i.e., needs investigation for possible problems) and the upper control limit (UCL) which is the limit of natural variation (i.e., all results should be below the UCL and any result above is considered unnatural variation and out of statistical control). The rationale behind these lines is that if infection prevention and control practices and antimicrobial prescribing is stable, the environmental cleanliness level does not change and there are sufficient staff who follow procedures correctly, then the number of new patients/residents with acquired CDI will be stable and fall within predicted limits (i.e., below the UCL). If the number of new cases exceeds the UCL, this suggests that the increase is likely to be due to a breakdown in infection prevention and control/antimicrobial stewardship procedures and this needs to be investigated and rectified as appropriate. Further detail on how SPC charts can be used can be found on the website of Health Protection Scotland.(27)

Table 2.1: Elements of a CDI control programme to ensure that patient/resident care is reliable, designed to keep patients/residents safe and of high quality

Quality	Element
Patient/resident-centred care	Prevention and control of <i>C. difficile</i> is a key priority for all healthcare providers. Patient/resident information on CDI prevention and control. Governance and reporting systems to provide assurance. Implementation of National standards in Infection Prevention and Control (IPC).
Effective care	Systems and controls in place to: <ul style="list-style-type: none"> - Monitor outcomes in terms of CDI data. - Monitor compliance with National IPC standards and other national standards relevant to this area. - Analyse and learn from CDI incidents when they occur – dissemination of learning and institution of controls to prevent recurrence.
Safe care	Implementation of national CDI, antimicrobial stewardship and hand hygiene guidelines. Audits and assessment of guideline compliance.
Better health and well being	Healthcare provider education re prevention of HCAI and AMR including CDI Patient/resident education re prevention of CDI.
System design elements	
Governance, leadership and management	Accountability and responsibility for CDI clearly defined. Performance monitoring is undertaken and regularly reviewed. Cluster/outbreak management. Communication regarding CDI with other healthcare providers /patients/residents/public. Microbiological services to support CDI prevention are appropriate. HCAI (including CDI) and AMR surveillance are key components of the system. Antimicrobial stewardship is a key component of safe and effective care.
Workforce	Skills and competencies are defined. Education and training.
Use of resources	Strategies to prevent CDI are cost-effective. Strategies to promote appropriate antimicrobial use are cost-effective. HCAI Education.
Use of information	System so that CDI surveillance, in conjunction with other relevant indicators to include antimicrobial consumption data, hand hygiene, environment hygiene, sluice room, equipment and other relevant audit results, is fed back, reviewed and monitored.

All healthcare facilities should formally review their management of clusters/outbreaks as a matter of routine, to identify precipitating factors and systems put in place to prevent this happening again. Learning from these incidents should be shared across healthcare facilities. However, the majority of nursing homes in the private and voluntary sector operate as sole traders and are therefore not part of a shared governance structure which would enable the sharing of information in respect of the management of clusters/outbreaks of infection. Private and voluntary nursing homes notify HIQA as required under the Health Act (Care and Welfare of Residents in Designated Centres for Older People in Ireland) Regulations 2009 (as amended). Medical practitioners and clinical directors of diagnostic laboratories are required to notify unusual clusters or changing patterns of illness to the Medical Officer of Health (MOH) (who is the local Director of Public Health or the

designated Specialist in Public Health Medicine (SPHM).(28) There is need to develop an initiative to assist in the sharing of learning about HCAI incidents, including clusters and outbreaks of CDI for all healthcare facilities in all healthcare settings.

2.2.2.i Do targets reduce CDI work?

There is a lack of high quality data to support the use of targets to reduce CDI, but targets can highlight an area of priority, giving those responsible a goal to achieve. Although targets may be set at local or regional levels, most familiarity with targets is with those set by governments or national bodies.

In 2007, due to the increasing numbers of healthcare-associated infections (HCAI) in Ireland, the HSE set targets to reduce meticillin resistant *Staphylococcus aureus* (MRSA) infections by 30% and HCAI by 20% within five years. Specific recommendations for CDI could not be made at this time as new CDI cases only became notifiable in May 2008. By 2011, the number of MRSA bloodstream infections fell from 592 in 2006 to 264 in 2011, representing a reduction of 55%.(26)

In 2004 in the UK, rates of MRSA bloodstream infection became a core performance indicator for NHS hospital trusts. An ambitious national government target was set to halve the rate of MRSA bloodstream infections within four years.(29) By 2008, the targets had been reached with a 56% reduction in the rates of these infections.(30) After a series of tragic outbreaks of CDI, the UK government set targets in 2007 to reduce the rates of CDI by 30% by 2011. By June 2009, the CDI rate had already fallen by 35% and by 2010 it had fallen by 54%.(31) Although the introduction of targets in the UK and Ireland appear to have resulted in a reduction of MRSA infection rates, there is no strong evidence to support that this was due to the setting of targets alone. A fall in the incidence of MRSA infections during these times was observed in some European countries which did not set targets.(29) The control of HCAI is multifactorial, and it is likely that reductions observed were due to the introduction of numerous control measures, which may or may not have been introduced as a result of national targets.

Targets help to focus the attention of all relevant stakeholders and may help to prioritise timely introduction of useful infection prevention and control strategies. Traditionally, infection prevention and control was generally considered to be the sole domain of the microbiologist and infection prevention and control team. However, clinicians, managers at all levels in the healthcare system, and healthcare policy makers also have a responsibility.(32, 33) Clinicians are responsible for the safe care of the patient through diagnosis, treatment, and prevention and control. Managers need to provide a safe environment to make infection prevention and control effective. Policy makers are responsible for setting standards, ensuring that HCAs are a priority, and monitoring outcomes. With the threat of financial punishment or exposure in league tables, reaching infection prevention and control targets becomes an institutional focus.

It has been suggested that the setting of targets places enormous pressure on hospitals. Millar *et al.* argues that the use of targets for MRSA bloodstream infections in the UK forced NHS trusts to prioritise an infection that only accounts for 2% of HCAI.(34) Concurrent with the target successes in the UK, an increased number of bloodstream infections due to other organisms were reported, as well as increased antimicrobial resistance, surgical site infections and hospital-acquired pneumonias.(35) As discussed by the Guideline Development Group, if a target is being met, there may be less incentive for management to introduce new and better evidence based-systems, especially if expenditure is required. Lastly, if targets are not being met, this finding does not provide information on process failure.(36)

2.2.2.ii Surveillance and targets

Adequate surveillance structures need to be in place to accurately measure the burden of infection before any target can be set. If a target is set, it is important that infection definitions and surveillance methods are standardised.(37, 38)

Standardisation from one year to the next may be impossible to achieve with implications for any institution attempting to reach targets. For example, the introduction of the very sensitive NAAT tests in a laboratory may result in a rise in the number of CDI cases reported even if the true incidence has remained static or has fallen. In Ireland, the reporting of recurrent CDI cases, in addition to the reporting of new cases, became mandatory in January 2012 so the overall number of CDI cases in 2012 would not be comparable with previous years. Surveillance bias has the potential to pose harm as clinicians will not know if the quality of care is improving.(38)

Finally, if the absolute numbers of a particular infection in an individual unit with adequate surveillance are low, the rates can be subject to random variation and regression to the mean. (37, 39) Such units may never reach a target level of reduction from baseline and could potentially be penalised for it.

In summary, although high quality evidence to support the use of targets is lacking, they may serve to focus attention and allow for accountable practise where clinicians, managers, and policy makers have responsibility in achieving the set goal. The introduction of targets requires adequate and standardised surveillance and a mechanism for not punishing already high-performing units.

2.2.2.iii How do laboratory testing protocols impact on CDI rates - Is it possible for healthcare facilities to benchmark themselves?

The following are responsible for implementation of **recommendation 11**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance) and Microbiology Laboratories.

- **CDI testing essentials**

Recommendation 11

Healthcare facilities should ensure that the frequency of CDI laboratory testing provides for results to be available in a timely basis to ensure appropriate management of patients/residents with *Clostridium difficile*. **Grade D**

The following are responsible for implementation of **recommendation 12**:

Microbiology Laboratories.

Recommendation 12

All microbiology laboratories should have a standardised CDI specimen testing strategy and testing methodology. Where hospitals are served by laboratories using the same CDI testing algorithm, then inter-hospital comparison is possible. **Grade D**

Twenty-five of 29 Irish microbiology laboratories responding to a 2006 laboratory survey on *C. difficile* detection practices performed on-site testing for *C. difficile* and all 25 reported use of an enzyme immunoassay (EIA) for toxin detection. (22) In all but one laboratory, the assay in use detected both toxin A and toxin B. (22)

Changes in the recommended *C. difficile* testing practice were proposed in 2009 and 2010 by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the United Kingdom (UK) National Health Service (NHS). (1, 40) An electronic survey of 122 NHS diagnostic laboratories conducted in March 2010 reported that only 29 (24%) had changed laboratory testing

procedures following revised testing guidance and responses indicated considerable variation in CDI diagnostic practices between NHS laboratories. (41)

The Irish laboratory survey was repeated in 2011 by the Guideline Development Group as part of the current guideline review process. Of the 37 laboratories responding, 33 performed on-site testing for *C. difficile* and 58% reported a change to their testing algorithm in the previous two years. The majority of laboratories reporting changed testing had moved from a one-step to a two-step testing algorithm (74%). Seventeen (52%) continued to use a one-step test, whilst 16 (48%) used a two-step testing algorithm. For two-step algorithms, a variety of testing methodologies were in use (Table 2.2). [Data source: HPSC]

Table 2.2: Two-step testing algorithms in use in Irish microbiology laboratories – 2011

Step One	Step Two	Number of Laboratories
GDH	Toxin EIA	11
GDH	Toxin gene PCR	4
Toxin EIA	Toxigenic culture	1

In Ireland, *C. difficile* infection rates are calculated based on data submitted to the voluntary national enhanced surveillance scheme. (Section 1.3.1) Owing to the considerable variation in current laboratory *C. difficile* testing methodologies, inter-hospital comparison of CDI rates is not recommended as the data in the national quarterly enhanced surveillance reports are not adjusted for differences in the sensitivities of the different diagnostic methodologies used across the different laboratories. At the time of writing this guideline, the impact of changed testing methodologies on Irish CDI rates is not well understood. The success of recruitment of additional hospitals to the voluntary enhanced surveillance scheme has also impacted on the ability to interpret the national CDI rates over the time period since enhanced surveillance began. The Guideline Development Group recommends that all Irish microbiology laboratories move towards a standardised CDI specimen testing strategy and testing methodology. Where hospitals are served by laboratories using the same CDI testing algorithm, then inter-hospital comparison should be possible.

2.3 Prevention of CDI

2.3.1 What antimicrobial stewardship measures should be implemented as part of a CDI prevention and control programme?

The following are responsible for implementation of **recommendation 13**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Antimicrobial Stewardship Teams, Infection Prevention and Control Team and Clinicians.

Recommendation 13

All healthcare facilities should have an active antimicrobial stewardship programme as outlined in *Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) 2009*.⁹ **Grade B**

⁹ Health Protection Surveillance Centre. *Guidelines for antimicrobial stewardship in Hospitals in Ireland*, 2012.

Practical Guidance

- Hospitals should implement the core, high-impact, interventions for antimicrobial stewardship as outlined in *The Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) 2009*, with appropriately staffed antimicrobial stewardship teams.
- An active antimicrobial stewardship programme should include local antimicrobial prescribing guidelines, a restrictive antimicrobial list and efforts to minimise the frequency, duration and number of antimicrobial agents prescribed.
- High impact interventions for antimicrobial stewardship include clinical review and direct prescriber feedback, antimicrobial surveillance and audit, restricted availability of antimicrobials and pre-authorisation.

The use of broad spectrum antimicrobials such as the fluoroquinolones, cephalosporins and clindamycin can place patients at increased risk of acquiring CDI. (42-44) The number of antimicrobials administered, the dose and duration of therapy have also been identified as risk factors for CDI. (45-47) A link between time interval after exposure to antimicrobial therapy and increased risk of CDI has also been reported. This study concluded that the risk for CDI increases during therapy and in the first three months after cessation of antimicrobial therapy.(43) Since the publication of the 2008 Irish *C. difficile* guidelines, there have been a number of developments in antimicrobial stewardship. National standards for the prevention and control of HCAs were published in May 2009 (48) and national antimicrobial stewardship guidelines in December 2009.(49) The antimicrobial stewardship guidelines specify minimisation of CDI as a key part of the programme and proposed core, high-impact, interventions for antimicrobial stewardship. Recommendations were also provided for non-acute residential healthcare facilities.

CDI reduction is a key performance indicator for antimicrobial stewardship in all Scottish hospitals. (50) In 2008, the Scottish Antimicrobial Prescribing Group (SAPG) issued national guidance on restriction of antimicrobials associated with high risk of CDI within antimicrobial prescribing policies. (51) In 2009, the Scottish Government introduced a target for a 50% reduction in CDI by 2011 (52) and SAPG developed and implemented the following quality indicators to support achievement of this target:

- a) Indication recorded and empirical antimicrobial choice compliant with local policy. Target $\geq 95\%$ compliance.
- b) Duration of surgical prophylaxis < 24 hours and choice compliant with local policy. Target $\geq 95\%$ compliance.

By March 2011, CDI rates in Scotland had reduced by 77%. (50) For indicator 'a' above, in acute admission units, median compliance was 93% for indication documented and 83% for compliance with local policy. For indicator 'b' compliance was $> 90\%$ in a variety of surgical specialties. The authors concluded that prescribing indicators are an effective means of improving antimicrobial prescribing.

In the US, the introduction of an electronic medical record system was shown to decrease the rate of CDI by 18.7%. Antimicrobial stewardship pharmacists reviewed prescriptions daily and made recommendations that were acted upon rapidly.(53) The rate of nosocomial CDI was found to correlate with the use of cephalosporins and to a lesser extent quinolones.

Talpaert *et al.* investigated the impact of the introduction of guidelines and enhanced antimicrobial stewardship on reducing broad spectrum antimicrobial use and the incidence of CDI.(44) The study found that there was a significant reduction in CDI when policies were introduced that restricted the use of fluoroquinolone and cephalosporin antimicrobial therapy. Overall antimicrobial use did not decrease, but a change in prescribing trends was observed.

There are very few studies available that demonstrate antimicrobial stewardship alone as an effective preventative strategy for the development of CDI. Many describe multiple infection prevention and control and antimicrobial stewardship practices that are combined in a CDI preventative programme. A 2005 Cochrane review evaluated the impact of interventions to improve antimicrobial prescribing practices in hospitals on the incidence of CDI.(54) The review identified five studies, four showed a significant reduction in CDI incidence, which was associated with the intervention under investigation and one demonstrated a non-significant reduction of CDI. The interventions that led to a reduction in CDI were all aimed at the curtailment of the use of cephalosporins and clindamycin. Four additional studies were identified by the Agency for Healthcare Research and Quality.(55) These studies reported that changes in antimicrobial education and policies which result in a reduction in 'high-risk' antimicrobials are associated with a decrease in CDI incidence.(56-59) Changing prescribing guidelines for the treatment of commonly occurring infections (from cephalosporins to agents thought to be less likely to cause CDI), in conjunction with a prescriber education and feedback, resulted in a decrease in the relative risk of CDI.(57) Likewise, a controlled interrupted time series investigating the effects of reinforcing a narrow-spectrum antimicrobial policy on antimicrobial prescription and CDI rates by feedback to prescribers, resulted in a reduction in the use of all targeted broad spectrum antimicrobials (cephalosporins and amoxicillin/clavulanate), an increase in narrow spectrum agents (benzylpenicillin, amoxicillin and trimethoprim) and a significant reduction in CDI.(58) It is likely that the number of CDI cases in a ward in one month is influenced by the number of cases in previous months, so these observations are dependent on one another. These results provide support for antimicrobial policies that minimise the use of broad-spectrum penicillins (co-amoxiclav and piperacillin/tazobactam), cephalosporins and fluoroquinolones.(60)

A study investigating the association between the duration of surgical antimicrobial prophylaxis (≤ 48 hours) and CDI identified prolonged hospital stay, use of third generation cephalosporins and beta-lactam-beta-lactamase inhibitor combinations as independent predictors for CDI.(61) However, this study found no association between the duration of surgical prophylaxis and CDI. A Canadian study reported that the risk of CDI was significantly higher among patients who received a combination of perioperative antibacterial prophylaxis plus a therapeutic course of antimicrobials compared with those who received prophylaxis alone. In the group of patients that did not receive prophylaxis, there were no cases of CDI. The authors concluded that when antimicrobial prophylaxis is being used to prevent infrequent and mild infection, the risk of CDI may outweigh the benefits of the use of surgical prophylaxis particularly in the elderly age group.

2.3.1.i Antimicrobial stewardship outside the hospital setting

Antimicrobial stewardship programmes in the community should focus on public and prescriber education. The national quality standards for residential care setting for older people in Ireland specify that the 'person in charge' must ensure that there is a medication safety policy and procedures that accord with legislation and professional regulatory requirements or guidance.(62) The Pharmaceutical Society of Ireland (PSI) issued guidance that community pharmacists should participate in the review of each patient on long-term medication, at least on a three-monthly basis.(63) Pharmacists should actively participate in the development of medicines management policies in residential homes and advise prescribers and other members of the care team on the safe and rational use of medicines. Records of these visits to patients and interventions to pharmaceutical care made by the pharmacist should be retained and be available for review in the pharmacy and in the residential home. Antimicrobial stewardship strategies for community hospitals have been recently reviewed.(64)

A recent Irish study of community antimicrobial prescribing reported that broad spectrum antimicrobials may be prescribed unnecessarily in Ireland and that public awareness campaigns may help ease patient pressure on GPs to prescribe antimicrobials.(65) In Ireland, public information campaigns have been linked to the annual European Antibiotic Awareness Day (www.hse.ie/go/antibiotics). In the UK, there have been several efforts to increase public awareness of the

appropriate use of antimicrobials.(66) The first campaign 'Andybiotic' began in 1999 and was repeated in 2000, 2002, 2003 and 2006. The impact of the campaign was assessed before and after it was run. There was a small increase in the overall antimicrobial awareness and a reduction in patients' expectations of an antimicrobial prescription for 'sore throats', colds and 'flu'.

2.3.2 What patients/residents are at risk of CDI and what CDI risk factors are modifiable?

The following are responsible for implementation of **recommendation 14**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Antimicrobial Stewardship Teams, Infection Prevention and Control Team and Clinicians.

Recommendation 14

Clinicians should be knowledgeable of intrinsic CDI risk factors prompting increased attention to antimicrobial stewardship and infection prevention and control in 'at-risk' individuals. **Grade C**

Practical Guidance

- Knowledge of intrinsic risk factors should prompt more careful attention to antimicrobial stewardship and infection prevention and control in 'at-risk' individuals. Intrinsic risk factors for CDI include increasing age, severity of underlying disease, co-morbidity, immunosuppression, cognitive and functional impairment.
- Review of potentially modifiable risk factors at an institutional/ward level and in 'at-risk' individuals may reduce the risk of CDI. These risk factors include the use of antimicrobials, length of hospitalisation, receipt of gastro-intestinal procedures and surgery, tube-feeding and acid-suppressant medication, cancer chemotherapy agents, laxatives or stool softener use. Environmental risk factors include high *Clostridium difficile* burden on a ward/unit, high frequency of admissions and discharges to LTCF, residence in close or shared quarters, use of shared toilet facilities and limited ability to isolate infected patients/residents.

Risk factors for CDI include: older age; severity of underlying disease(67); increased co-morbidities (partly through the association with greater healthcare contact and need for hospitalisation); cognitive and functional impairment, poor host immunity to *C. difficile*; antimicrobial use (recent, prolonged and/or multiple antibiotic use); gastrointestinal surgery and nasogastric intubation; length of hospital stay, contact with healthcare facilities and, exposure to other patients with CDI. (68)

Other risk factors include:

- Acid suppressing medications. (Section 2.3.3)
- Cancer chemotherapy – several chemotherapeutic agents have antimicrobial activity, but also risk could be related to the immunosuppressive effect of neutropaenia.(69)
- HIV infection - recent US evidence suggests *C. difficile* has become important pathogen causing bacterial diarrhoea in patients infected with HIV. Specific increased risk due to number of factors, i.e., underlying immunosuppression, exposure to antimicrobials, and exposure to healthcare settings.(70)

Collini *et al.* reviewed experimental and epidemiological literature on CDI in three immunocompromised groups, HIV seropositive patients, haematological stem cell or bone marrow recipients and solid organ transplant recipients. Epidemiological studies consistently show increased rates of CDI in these groups, and CDI rates are higher in those with greater degree of immunocompromise. The data was less consistent with regard to the impact of immunocompromisation on rates of severe, recurrent or complicated CDI.(71)

Geographical clustering of CDI outbreaks has been demonstrated in the US though the reasons behind this were unclear.(72) Hospitals with complex services, such as transplant programmes, are more likely to have a high CDI burden than those with less complex services. A recent study found a significant association between the hospital burden of CDI and both admissions from and discharges to LTCFs after adjustment for patient/resident health status (e.g., case complexity, age, etc.).(73) The authors pointed out that prevention strategies would benefit from better information about transmission patterns both within and between healthcare facilities.

Rates of CDI in populations previously considered low risk have increased in the past decade.(74) Cases in peripartum women have been documented. This may reflect the overall increase of CDI in the population, the emergence of hyper virulent strains and greater use of antimicrobials in the peripartum period.(75) *C. difficile* is thought to colonise patients with inflammatory bowel disease (IBD) more frequently than other patients. (Section 2.7.9) Recent papers have suggested a significant burden of CDI in the community.(76, 77) Community-associated CDI rates are generally much lower than health-care associated rates, accounting for 27% of all CDI cases but are also increasing.(78) However, the source of *C. difficile* responsible for cases of CDI in the community is not well understood. Nested case controlled study shows that community-associated-CDI is occurring among populations not traditionally considered 'high risk' for the disease, i.e., younger people, people without underlying illness, people not exposed to hospitals or antimicrobials.(79) However, this study still attributed antimicrobial use as a major risk factor for community-associated CDI and that this risk persisted over a long period (up to 150 days prior to disease onset).

A number of US studies report an apparent increase in CDI among infants and children.(80-82) In contrast to recent epidemiology among adults, this apparent increase in the incidence of infection in children was not accompanied by an increase in severity of infections or complications. (80) CDI in children has been linked with immunosuppression, bowel disorders and other co-morbidities. Hirschsprung's disease is associated with prolonged carriage as well as increased severity of disease. Studies have shown that CDI can worsen symptoms in patients with IBD. Numerous studies have found an association between CDI and haematology/oncology patients. The combination of broad-spectrum antimicrobials use and chemotherapy can cause damage to the intestinal mucosa resulting in subsequent colonisation and infection. However, the true extent and significance of the apparent changes in epidemiology of CDI remains unclear.(83) In many paediatric cases, additional potential diarrhoeal pathogens were isolated along with *C. difficile*.(81) These studies suggest that infection occurs in young infants and children and in the community without preceding antimicrobial exposure. Despite the absence of traditional risk factors such as preceding antimicrobial and/or hospital exposure in some paediatric cases, judicious antimicrobial use remains paramount.(74, 81) While similarly detailed, age-related epidemiologic data is lacking for Ireland, anecdotal experience and existing evidence does not suggest an increase in paediatric CDI here. Clearly, before firm conclusions can be drawn, more detailed local epidemiological data are required. However, cases may be undiagnosed because of difficulty in differentiating asymptomatic carriage from infection and reluctance to test in the paediatric population.

Recent studies indicate that asymptomatic infants, even in the community, can act as a reservoir for adult infectious strains of *C. difficile*.(84) The literature is inconclusive with regard to the impact of prior antimicrobial treatment on the rate of CDI. Outside the neonatal age group, prior antimicrobial therapy is a commonly associated risk factor in children up to 18 years. A recent review in this group found that the association of prior antimicrobial exposure and CDI can range from 50% to 94%, depending on the design of the study, with some suggestion that there may not be a link at the younger end of this spectrum.(85) Clinicians should consider the possibility and test for CDI in infants and young children with severe unexplained diarrhoea, or previously considered to be at low risk of infection. Where doubt exists regarding the benefits and rational use of testing, interpretation of results, or need for treatment infectious diseases, microbiology opinion should be sought.

2.3.3 Do proton pump inhibitors (PPIs) increase the risk of CDI?

The following are responsible for implementation of **recommendation 15**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Pharmacists.

Recommendation 15

PPIs should only be prescribed where there is a clear indication for their use. **Grade D**

Practical Guidance

- Available data are inadequate to establish a causal relationship between acid suppressant medicines and CDI; however, evidence available from systematic reviews/meta analyses supports a positive association between acid suppression medication and CDI. **Grade C**

Several studies have explored the association between acid suppression medication and the incidence of CDI. These studies have a number of limitations and a causal link has not been established. However, there is significant evidence to suggest an association exists and it is probably stronger for proton pump inhibitors (PPIs) than for histamine receptor antagonists (H₂RAs). Some studies suggest that patients on PPI therapy have twice the risk of developing CDI as non-users. (86-88) A 2012 meta-analysis focussed on the association between PPIs and CDI.(89) The majority of studies found a statistically significant association. One study looked at PPI and H₂RA use according to 'intensity' of prescription, i.e., daily versus more frequent use.(90) The authors suggest that one additional case of CDI may be expected for every 533 patients who receive a daily PPI. The mechanism by which acid suppression medication may cause CDI remains unclear. Several mechanisms have been suggested.(91, 92) The US Food and Drugs Administration (FDA) recommend that CDI be considered as a diagnosis for patients on PPIs with persistent diarrhoea.(93) A recent meta-analysis reviewed 42 studies and recommended that PPI therapy is discontinued in patients with CDI. (94) Available data are inadequate to establish a causal relationship between acid suppressant medicines and CDI; however, evidence available from systematic reviews/meta analyses supports a positive association between acid suppression medication and CDI. In conclusion, PPIs should only be prescribed where there is a clear indication for their use.

2.3.4 Who needs to receive education regarding CDI prevention?

The following are responsible for implementation of **recommendations 16-17**:

Healthcare Facility Senior Management team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director, Director of Finance), Antimicrobial Stewardship Teams, Infection Prevention and Control Team and Clinicians.

Recommendation 16

Staff education and training on infection prevention and control issues with an emphasis on transmission routes is mandatory for all staff and attendance should be monitored by healthcare facility managers. It should be delivered during orientation/induction, with regular updates and be job/role specific. **Grade D**

Recommendation 17

Patients/residents with CDI and their visitors/carers should be given information on CDI and CDI prevention and shown how to carry out hand hygiene. **Grade D**

Practical Guidance

- All persons that enter the room of a patient/resident with CDI should receive education about the clinical features, transmission and epidemiology of CDI.
- Patients/residents prescribed antibiotics by their GP and patients/residents being discharged on antibiotics should receive appropriate information on their antibiotic to include the importance of taking the antibiotic for the correct duration and at the appropriate dose. The Guideline Development Group has drafted a sample information leaflet that may be useful in this regard.¹⁰

A fundamental requirement of effective infection prevention and control and antimicrobial stewardship practices is an educated workforce. Education of staff is one of the most effective measures of limiting the spread of CDI.(23) All healthcare staff caring for patients/residents with CDI should receive both theoretical and practical education that includes basic pathogenic mechanisms, potential reservoirs, routes of transmission, and Contact Precautions in particular, glove use, hand hygiene and optimal environmental decontamination.(23) Staff education and training on infection prevention and control issues with an emphasis on transmission routes should be mandatory for all HCWs and should be delivered during orientation/induction, with regular updates and be job/role specific. Education updates should include feedback of local and national surveillance data of CDI rates. Training of staff should not only include medical and nursing staff, but also allied healthcare professionals and support staff (e.g., cleaning staff, portering staff, administrative staff, etc..) (48, 95)

Education of patients/residents and visitors/carers about hand hygiene and Contact Precautions is also important to prevent further spread. Visitors suffering from acute diarrhoea should be informed that they should not visit hospital.

2.3.5 What is the role of asymptomatic carriers in transmission of Clostridium difficile in healthcare facilities?

The following are responsible for implementation of **recommendation 18**:

Healthcare Facility Senior Management team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director, Director of Finance), Antimicrobial Stewardship Teams, Infection Prevention and Control Team and Clinicians.

Recommendation 18

Routine placement of asymptomatic *Clostridium difficile* carriers into single rooms **Grade D** and treatment of asymptomatic carriers of *Clostridium difficile*, **Grade A**, are NOT recommended.

The reported prevalence of asymptomatic colonisation with *C. difficile* in hospitalised patients and long-term care residents is 4-20% in non-outbreak settings, (96-98) and may reach 51-85% in the context of outbreaks.(2, 99, 100) Asymptomatic carriers have been identified as potential sources of transmission of epidemic and non-epidemic *C. difficile* strains by horizontal transfer via the environment or the hands of healthcare workers.(99) Skin contamination and environmental shedding have been shown to persist at the time of resolution of diarrhoeal symptoms and recurrent shedding is common one to four weeks after CDI treatment.(101-103) It has been suggested that continuing Contact Precautions until hospital discharge, or until one month after completion of therapy in the case of long-term care facility-associated CDI, should be considered if rates of CDI remain high despite implementation of infection prevention and control measures.(101, 103, 104) However, there is insufficient evidence to support the routine placement of asymptomatic carriers into single rooms.

¹⁰ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/Factsheets/>

A number of studies have evaluated the impact of treating asymptomatic carriers in order to control the horizontal spread of *C. difficile*. Only one prospective study, in a leukaemia unit, demonstrated a significant reduction in the frequency of CDI (from 16.6% to 3.6%) after initiating treatment of asymptomatically colonised patients with oral vancomycin, in combination with renovation and decontamination of the environment. (105) Metronidazole did not reduce the incidence of CDI when administered to *C. difficile* carriers in two studies. (106, 107) A randomised, placebo-controlled study comparing oral vancomycin (125mg four times per day), oral metronidazole (500mg twice per day) and placebo (3 times per day) showed that rates of *C. difficile* carriage immediately after treatment were 10% in the vancomycin group, 70% in the metronidazole group and 80% in the placebo group. (108) However, in the vancomycin group, excretion recurred in eight of nine patients, who were initially negative on completion of therapy, at a mean duration of 20 +/- 8 days. At the end of the two-month follow-up period, six of nine patients treated with vancomycin remained *C. difficile* culture positive, compared with only two of ten patients who received placebo (P<0.05). On the basis of limited available evidence, the treatment of asymptomatic carriers of *C. difficile* is not recommended.

2.3.6 Are healthcare workers (HCWs) at risk of getting CDI?

Practical Guidance

- The risk to healthy HCWs of acquiring CDI is thought to be low. Adherence to infection prevention and control precautions and good standards of personal hygiene as outlined in this guideline is recommended to minimise the risk of HCWs acquiring CDI.
- There is very little evidence to suggest, and no international guidelines have recommended, that HCWs on antibiotics should not be caring for CDI patients/residents. Rather, it is recommended that HCWs pay careful attention to hand hygiene during and after antibiotic therapy and after contact with any patient with diarrhoea.

The majority of healthcare workers (HCWs) are healthy adults, with few risk factors for CDI. Healthy adults can resist colonisation of *C. difficile* because of their mature colonic bacterial flora. (109) Despite the large potential for exposure to *C. difficile*, reporting of CDI in HCWs is uncommon.

Earlier studies anecdotally reported *C. difficile* as an occupational risk in HCWs who provided direct bedside care to patients/residents. Strimling *et al.* reported probable transmission of *C. difficile* from a patient to three healthy nurses, all of whom developed diarrhoea with positive *C. difficile* toxin assays. None of these nurses had taken antibiotic treatment. (110) Boaz *et al.* reported a severe case of pseudomembranous colitis complicated by ascites in a previously healthy nurse that occurred after she received oral clindamycin therapy for a dental infection. (111) Kaplan *et al.* also reported probable transmission in a HCW with CDI, who worked in close contact with two patients with CDI in a surgical ward. The HCW had received oral amoxicillin for a respiratory infection prior to developing CDI. (112) In 2003, Arfons *et al.* reported a further four cases of CDI in HCWs, which were suggested to be linked to cross transmission from patient to HCW. (113) These cases were in HCWs (a physician, a medical student, a nurse and an X-ray technician) who all had preceding antibiotic treatment. No typing studies were performed in any of the above studies; therefore transmission from patient to HCW could not be definitively established.

Recently, though, cases have been described that were more suggestive of cross transmission between HCW and patient. Bouza *et al.* described two cases of transmission of *C. difficile* PCR ribotype O27 from a patient's specimen to a laboratory worker. Both cases involved healthy young women who were working in the microbiology laboratory with the ribotype O27 strain. The first laboratory worker had no history of antibiotic treatment. The second laboratory worker, who was 12 weeks pregnant, had recently taken a dose of fosfomycin to treat a urinary tract infection. In both cases, the *C. difficile* isolate was found to be the same ribotype O27 strain that both laboratory workers had previously worked with.(114) Hell *et al.* reported a case of patient care-associated CDI in a 24-year old female nurse working in an oncology ward. Following antibiotic therapy for root canal treatment, CDI due to *C. difficile* ribotype O53 developed, a strain that was indistinguishable from two of the symptomatic CDI patients the nurse had cared for.(115)

2.3.6.i *C. difficile* colonisation in HCWs

Although cases have been reported of nosocomial acquisition of *C. difficile* by HCWs, studies suggest that there is only a very low risk. In an early one-year prospective case-control study in Minneapolis, in which 149 patients were identified to have CDI, only one HCW out of 68 (1.5%; 54 nurses and 14 physicians) was colonised with *C. difficile*.(116) In another US-based study, Cohen *et al.* reported a colonisation rate of 1.7% among medical house staff.(117) This same study suggested that faecal carriage of *C. difficile* was not important in hospital-acquired *C. difficile* in HCWs. More recent studies show variable rates of *C. difficile* carriage in HCWs. In 2009, in a study in the Netherlands of 30 asymptomatic HCWs (13 were working on a ward with patients who had symptomatic CDI, 17 were working on a ward without patients that had *C. difficile*) four HCWs (7.5%) were carriers of toxigenic *C. difficile*. As the *C. difficile* isolates were not typed in this study, a relationship between the HCWs and patients with CDI was not established.(118) Other studies have reported lower rate of intestinal carriage of *C. difficile* in HCWs. A Japanese study reported a carriage rate of *C. difficile* of 4.3% in HCWs.(119) Two studies reported the absence of intestinal carriage *C. difficile* in 112 and 55 asymptomatic Austrian and Israeli HCWs, respectively.(120, 121)

Although there have been published case reports of CDI in HCWs, to our knowledge there have been no studies that have investigated the rate of CDI in HCWs. It is likely that this rate, in this generally healthy population, is likely to be very low. There is very little evidence to suggest, and no international guidelines have recommended, that HCWs on antibiotics should not be caring for CDI patients/residents. We endorse the view by Kaplan *et al.* and Afron *et al.* and recommend that HCWs pay careful attention to hand hygiene during and after antibiotic therapy, after contact with any patient with diarrhoea.

2.3.6.ii HCWs can serve as transmitters. Minimising the risk of transmission to HCWs, patients/residents and the environment

To minimise the risk of transmission to HCWs, patients/residents and the environment, adherence to infection prevention and control precautions and good standards of personal hygiene is essential. For HCWs, use of personal protective equipment and hand washing with water and soap as outlined in this guideline are the most effective ways of preventing the spread of spores.(122)

2.4 Surveillance

2.4.1 What are the essentials of CDI surveillance?

The following are responsible for implementation of **recommendations 19-21**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team and Public Health Departments.

Recommendation 19

- CDI surveillance should be carried out in all acute hospitals and should not be limited to clusters/outbreaks. **Grade D**
- A threshold incidence that would trigger implementation of additional infection prevention and control interventions should be defined locally. **Grade B**

Recommendation 20

At present, children aged less than two years should continue to be excluded from CDI surveillance. **Grade D**

Recommendation 21

- Each organisation should have an identified person, who is responsible for assigning and notifying CDI cases to the Department of Public Health. **Grade D**
- For cases occurring outside of the hospital setting (community, residential care or nursing home), an agreed clear protocol with defined responsibilities for notifying the Department of Public Health is required. **Grade B**

Practical Guidance

- Case definitions for CDI surveillance (case type, severity, origin and onset of CDI) are outlined in detail on the HPSC website at <http://www.hpsc.ie/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/>. The definition of a healthcare facility for surveillance purposes is any acute care, long-term care, long-term acute care, or other facility in which skilled nursing care is provided and patients/residents are admitted at least overnight. This includes hospitals and LTCF (e.g., nursing homes).
- To ensure consistent and accurate local Computerised Infectious Disease Reporting (CIDR) notification and voluntary enhanced surveillance of CDI cases (new and recurrent), the Guideline Development Group recommend that all positive *Clostridium difficile* laboratory results are discussed with the clinician responsible for the patient/resident to ascertain that the patient/resident with the positive laboratory test result for *Clostridium difficile* meets the CDI case definition. **Grade D**
- If the case definition is met, establish whether this is a first positive *Clostridium difficile* test result or whether the patient/resident has previously had a positive *Clostridium difficile* test result. A guide to the type of notification is as follows:
 - a. if a first positive result then this is a notifiable new case of CDI
 - b. if the patient has previously had a positive result:
 - i. more than eight weeks prior and symptoms had resolved then this is a notifiable new case of CDI
 - ii. less than eight weeks prior and symptoms had resolved then this is a notifiable recurrent case of CDI
 - iii. and symptoms have not resolved then this is a repeat positive specimen from the same CDI episode and is NOT notifiable.
- If the case definition is not met, the laboratory result is not notifiable to the Department of Public Health. **Grade D**
- CDI mortality data in Ireland should be reviewed. In the first instance, this could include retrospective review of CDI as recorded on death notifications. Wherever feasible, consideration could be given to including all-cause mortality following a diagnosis of a hospital-acquired CDI. **Grade C**

The European Society for Clinical Microbiology and Infectious Diseases Study Group for *C. difficile* (ESGCD) and ECDC proposed interim case definitions for CDI surveillance.(14) The case definitions were adopted for CDI surveillance in Ireland in 2008 and are outlined above. Case definitions enable classification of CDI with respect to infection origin (healthcare-associated [HCA] or community-associated [CA]); and patient location at symptom onset (healthcare facility onset [HCO] or community onset [CO]). LTCFs and nursing homes are included in the category of a healthcare facility.

Diarrhoea is defined as three or more loose/watery bowel movements (which are unusual or different for the patient and which take the shape of the specimen container) in a 24-hour period. The above case definition excludes diarrhoea with other known aetiology (as diagnosed by the clinician) and asymptomatic patients/residents with a stool culture positive for toxin-producing *C. difficile* or an assay positive for *C. difficile* *Tcda* and/or *TcdB*.

Recurrent CDI is usually diagnosed based on characteristic clinical features, with a further positive laboratory test for *C. difficile* toxin within the eight week interval since the first positive test. On occasion, recurrent CDI may be diagnosed based on characteristic clinical features alone without a laboratory test being done. This still represents recurrent CDI. A recurrence can correspond to a relapse involving the same strain or to a re-infection with a different strain. As it is not possible clinically to differentiate between relapse and re-infection, the term recurrence is used for both scenarios.

2.4.1.i Should we include patients aged less than two years in *C. difficile* surveillance?

For surveillance purposes, a CDI case is defined as a patient aged over two years who meets the case definition as outlined above. As outlined in Section 2.5.1 the rate of *C. difficile* carriage in neonates varies widely (2.5-90%). (84, 85) In general, the isolation of *C. difficile* from children aged less than two years is regarded as colonisation as most cases are asymptomatic.

2.4.1.ii Denominator data

Recommended denominators for hospitals, long term care facilities and the community are outlined in Recommendation 23. To express *C. difficile* infection rates in settings outside of acute care facilities (e.g., residential care facilities/nursing homes) a sample sheet for use in LTCF has been developed and is available for download on the HPSC website.

- For example, at the end of the month the total number of resident days (sum of daily totals) = 600 resident days. There have been two cases of *C. difficile* infection diagnosed in the facility during the time.
- The monthly new CDI rate for the facility is calculated as: number of new CDI cases/number of resident days x 10,000 (2/600 x 10,000 = 33 CDI cases per 10,000 resident days.(68, 104)

2.4.2 What are the minimum data on *Clostridium difficile* infection that should be collected for surveillance purposes and how should it be reported?

The following are responsible for implementation of **recommendations 22-23:**

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team and Public Health Departments.

Recommendation 22

Case definitions for surveillance should not be used for deciding a clinical diagnosis of CDI.
Grade D

Recommendation 23

Healthcare facilities should collect data on CDI case type (new/recurrent), severity, origin and onset of CDI as outlined in the national enhanced surveillance protocol. **Grade D**

- **Hospitals:** For feedback and benchmarking purposes, acute hospital healthcare-associated case rates should be expressed as:
 - i. New cases acquired in that hospital-per-reporting time period (e.g. month or quarter) per 1,000 patient admissions and per 10,000 patient-days (or bed-days used),
 - ii. New cases acquired in that hospital per number of patients tested for *Clostridium difficile* per reporting time period.
- **Long-term care facilities (LTCF):** CDI infection rates in LTCF should be expressed as the number of new CDI cases acquired in that LTCF per 10,000 resident days. The rate may be calculated as follows:

$$\frac{\text{number of new CDI cases acquired in that LTCF}}{\text{number of resident days per reporting period}} \times 10,000$$
- **Community:** Community-associated case rates should be expressed as cases (new and recurrent/all cases) nationally per 100,000 population per year.
- **National:** National rates should be expressed as cases (new and recurrent/all cases) nationally per 100,000 population per year.

2.4.2.i Case definitions for CDI surveillance

It is very important to differentiate the use of case definitions for CDI notification and surveillance from clinical and laboratory criteria used in the diagnosis of CDI. Case definitions are standardised to facilitate national reporting and for international comparisons. Case definitions should not be used for deciding a clinical diagnosis of CDI.

For the purposes of CDI notification to public health and CDI enhanced surveillance, it is important that a discussion of each positive *C. difficile* laboratory result takes place between the reporting laboratory and the clinician responsible for the patient to ascertain if the case definition is met. CDI cases should be notified as new or recurrent CDI after consideration of the factors outlined in Section 2.4.1.

2.4.2.ii Acute hospitals

The *C. difficile* national enhanced surveillance form is sub-divided into six sections¹¹:

1. Patient demographics
2. CDI case type
3. Laboratory isolate details with specimen origin
4. Onset of CDI
5. Origin of CDI
6. Severity of CDI.

CDI enhanced surveillance data which is summarised in Section 1.3.1, is published on a quarterly basis by the HPSC and annually in the HPSC annual reports.^{12,13} The quarterly reports enable participating hospitals to track their CDI rates (including hospital-acquired CDI cases) over time to evaluate the effect of their improvement programmes and where relevant compare themselves

¹¹ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/CdifficileEnhancedSurveillance/>

¹² <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/CdifficileEnhancedSurveillance/Reports/>

¹³ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/CdifficileSurveillance/AnnualReports>

with the national dataset. As the *C. difficile* national enhanced surveillance form is submitted from acute hospitals and the vast majority of cases are identified based on positive microbiology laboratory results, cases with origin and onset outside of the acute hospital setting are also captured.

2.4.2.iii Long-term care facilities (LTCF)

All LTCF should have systems in place to monitor the number of new and recurrent CDI cases. The Health Information and Quality Authority (HIQA) published a set of *National Quality Standards for Residential Care Settings for Older People in Ireland in 2009*. (48)

Under Standard 26 Health and Safety (Section 25) LTCF are required to have clearly documented systems in place for detecting and responding to an outbreak of infection.(48) In Ireland, amongst healthcare-associated CDI cases, the proportion that originated in a nursing home increased from 9.5% in 2009 to 17% in 2013. One Irish study demonstrated that 10% of residents in a continuing care institution for the elderly were asymptomatic carriers of *C. difficile*.(98) This finding was replicated in a German study, in which *C. difficile* was isolated from 4.6% of nursing home residents overall, with the colonisation prevalence ranging from 0% to 10% between different nursing homes.(123) In 2010, a prevalence study involving 4,170 residents in Irish LTCF reported that 10% of residents were receiving antimicrobial therapy.(124) The prevalence of antimicrobial use and of *C. difficile* colonisation in LTCF, coupled with the frequent transfer of patients/residents both to and from acute hospitals highlights the importance of ongoing CDI surveillance in this setting. An active antimicrobial stewardship programme is also an important element for *C. difficile* control in all healthcare facilities. It is recommended that each LTCF should submit faeces specimens for microbiological investigation, to include testing for *C. difficile* from residents with unexplained diarrhoea and also to have an up-to-date documented standard operating procedure to be followed in the event of a positive *C. difficile* laboratory result from a resident and a system in place to ensure frequent review of positive *C. difficile* results to ensure prompt identification of potential clustering of CDI cases. All medical practitioners, including clinical directors of diagnostic laboratories, are required to notify the MOH of "any unusual clusters or changing patterns of any illness, and individual cases thereof, that may be of public health concern". In addition to notifying the relevant public health department, nursing home providers are also required to notify HIQA of an outbreak of infectious disease within three working days of the incident.

2.4.2.iv Primary Care

Between the introduction of the national voluntary enhanced surveillance scheme for CDI in 2009 and 2013, the proportion of CDI cases that originated in the community increased from 13% to 18% and 30% CDI cases had onset of symptoms in the community. While these cases with origin and onset outside of the acute hospital setting are being captured by statutory notification to the MOH by the clinical directors of diagnostic laboratories and by the enhanced surveillance system, it is often difficult to collect enhanced data and many of the enhanced fields are left as "Unknown". The absence of an Irish national *C. difficile* reference laboratory reduces the ability to understand and track the molecular epidemiology of true community-acquired CDI.

A review of studies performed on general practitioner (GP) patients with diarrhoea reported an incidence between 7 and 25 CDI cases per 100,000 persons per year. For studies where the number of residents in the laboratory catchment area could not be determined (thus preventing calculation of incidence rates), the proportion of patients presenting to a GP with diarrhoea who had a positive *C. difficile* test result was between 2 and 6%.(125) In a prospective, US multi-centre Emergency Department-based study of 364 adults presenting with acute gastroenteritis, *C. difficile* was detected in 5.3% of 133 faeces specimens tested.(126) A population-based study conducted in Minnesota, US between 1991 and 2005 identified 385 definite CDI cases, of which 41% were defined as community-acquired. Community-acquired CDI patients were younger,

with less severe CDI than hospital-acquired cases. The incidence of CA-CDI was 9.6 cases per 100,000 person years and a significant increase in incidence rates occurred by age and over the 14 years of the study.⁽¹²⁷⁾ Given the emergence of CDI in the community setting, GPs should submit faeces specimens for microbiological investigation, to include testing for *C. difficile* from patients with unexplained diarrhoea. This is outlined in a separate guidance document for primary care management of CDI which was produced in conjunction with the Irish College of General Practitioners (ICGP) Quality in Practice Committee and placed on the HPSC website in November 2013. (Appendix 2)

2.4.2.v. Local reporting structures – Local CDI surveillance, notification of infectious diseases and voluntary CDI enhanced surveillance scheme

The 2008 guidelines document recommended that healthcare facilities perform CDI surveillance to enable calculation of baseline incidence and a local threshold that would trigger implementation of additional control interventions. Standardised case definitions for CDI surveillance were also provided. As required by the HIQA *National Standards for the Prevention and Control of Healthcare Associated Infections, 2009*, individual healthcare facilities should have a forum for regular discussion and systematic review of patients with positive *C. difficile* laboratory results to facilitate the process of local surveillance and reporting, implementation of appropriate infection prevention and control measures and compliance with mandatory infectious diseases notification.

In 2011, a survey of 37 Irish microbiology laboratories was conducted to ascertain the approach to CIDR notification of CDI cases.¹⁴ Thirty-five laboratories (95%) provided information. The responses indicated local variation in the approach to notification with 19 laboratories (51%) routinely notifying all positive *C. difficile* laboratory results. Sixteen laboratories (43%) indicated that positive results were checked to ensure that the patient met the CDI case definition prior to notification and, for 12 of those 16 laboratories (75%), there was also local discussion of patients with positive *C. difficile* laboratory results in conjunction with the infection prevention and control team prior to notification. Twenty laboratories (54%) reported the existence of a mechanism to ensure correlation between CDI cases notified via CIDR and cases reported via the voluntary CDI enhanced surveillance scheme.

The findings of this survey are concerning for the following reasons:

1. Since new cases of CDI became notifiable in May 2008, potentially some Irish microbiology laboratories have been routinely notifying all positive *C. difficile* laboratory results, without first confirming whether or not the patient met the national recommended *C. difficile* surveillance case definition. This may result in over reporting of new CDI cases
2. Prior to January 2012, when recurrent CDI also became notifiable, a second notification of a positive *C. difficile* laboratory result from a patient who had already had a positive CDI result dated within the preceding eight weeks would be de-notified by the relevant Department of Public Health as a duplicate result. Since January 2012, recurrent CDI has also become notifiable. Thus, repeat positive results notified within eight weeks are considered to reflect recurrent CDI. However, if a repeat *C. difficile* laboratory positive result from a patient within eight weeks of the date of first positive result is notified without local discussion, patients/residents with ongoing CDI (i.e. repeat positive results in the context of infection which has not yet resolved) risk being incorrectly notified as recurrent CDI. This may result in over reporting of recurrent CDI cases
3. At the time of writing this guideline, two parallel CDI surveillance schemes exist in Ireland. If there is no mechanism in individual healthcare facilities to ensure correlation between CDI cases notified to CIDR and cases reported via CDI enhanced surveillance, this may result in a healthcare facility having incongruent *C. difficile* figures.

¹⁴ Source: HPSC 2011

2.4.3 Is there a role for collecting outcome (mortality) data and if so how is this best done?

Death within 30 days after CDI diagnosis, if CDI is either the primary or a contributory cause, is included in the case definition of severe CDI. At the time of writing of this guideline, CDI mortality data has not been collected within the national CDI enhanced surveillance scheme. The CDI severity parameters recorded in the enhanced surveillance are; ICU admission for CDI treatment or its complications and surgery for toxic mega colon, perforation or refractory colitis. A retrospective cohort study conducted in one English NHS Trust, comprising three general hospitals and seven community hospitals, reviewed CDI data between 2002 and 2008. The median patient age was 82 years. All cause mortality at 30 days was calculated as 32.5% and the authors proposed that the older age of patients in the cohort may have explained the high 30-day mortality figures. (128) A Canadian retrospective observational study concluded that hospital-acquired CDI was independently associated with an increased risk of in-hospital death. Across all baseline risk strata, for every 10 patients acquiring the infection, one patient died.(129)

Two reviews have commented on the heterogeneity in the published literature surrounding CDI mortality.(130, 131) Both concluded that CDI mortality increases with advanced age. One review of 10,975 CDI cases in 27 studies reported between 1980 and 2010 calculated the overall associated mortality to be at least 5.9% within three months of diagnosis and reported a significantly higher mortality reported from studies published after 2000. (130) A second review reported data on 24 studies published between 2005 and 2011, of which 17 documented all-cause mortality at 30 days. Of 7,774 patients, 2041 (26.3%) died within 30 days of CDI diagnosis.(131) The authors of both reviews highlighted the need for standardisation in the reporting of CDI mortality to facilitate meaningful comparison.(130, 131) Both have suggested a minimum dataset for reporting CDI mortality which should include; breakdown of mortality by age group, reporting of mortality at seven, 30 and 90 days after the first positive specimen, number of cases requiring surgery or ICU admission and use of a co-morbidity score such as the Charlson co-morbidity index.(130, 131)

2.4.4 Is community CDI a different entity to healthcare-associated CDI?

A recently published review of community CDI concluded that direct transmission of *C. difficile* from animals, food or the environment has not yet been proven, although similar polymerase chain reaction (PCR) ribotypes are found.(125) In community settings, *C. difficile* has been isolated from symptomatic and asymptomatic humans and animals, soil, food and water.(132) As outlined in Section 2.4.2, between the introduction of the national voluntary enhanced surveillance scheme for CDI in 2009 and 2013, the proportion of CDI cases that originated in the community increased from 13% to 18% and 30% CDI cases had onset of symptoms in the community. There is no formal data on PCR ribotype distribution of community CDI cases in Ireland owing to the absence of a national *C. difficile* reference laboratory. Most Irish laboratories reserve referral for ribotyping for investigation of a suspected CDI outbreak and for patients/residents with severe CDI. Therefore, it is likely that most specimens currently referred abroad from Ireland for ribotyping are taken from hospitalised patients rather than community-based patients/residents.

C. difficile ribotype 078 has emerged in Europe in recent years. A Dutch study reported an overlap between the location of pig farms and the occurrence of human CDI caused by ribotype 078 and postulated a common environmental source.(133) This ribotype has been reported in an Irish hospital and during a 2009 national one-month ribotyping project, it was the fourth commonest ribotype isolated in Ireland accounting for 10% of specimens.(20, 134) Ribotype 078 increased from 1.8% to 6.2% of specimens ribotyped by the *C. difficile* ribotyping network for England and Northern Ireland between 2007/08 and 2010/11.(19) Owing to the lack of up-to-date molecular epidemiological data regarding community-acquired CDI in Ireland, it remains unclear whether CA-CDI and HA-CDI are different entities.

2.5 Laboratory diagnosis

Early and accurate diagnosis of CDI is vital for patient management and infection prevention and control. With the exception of pseudo membranous colitis (which can only be diagnosed by direct visualisation of pseudo membranes on lower gastrointestinal endoscopy or by histopathological examination) the diagnosis of CDI is usually based on the clinical history and presentation in combination with laboratory tests.

2.5.1 Who should be tested for CDI?

The following are responsible for implementation of **recommendation 24**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Microbiology Laboratories.

Recommendation 24

- Stool testing for *Clostridium difficile* should be requested by clinicians as early as possible on all patients/residents with possible infectious diarrhoea. Waiting to initiate sampling/testing until, for example, three episodes of diarrhoea has occurred is NOT recommended. **Grade D**
- All diarrhoeal specimens (both healthcare-associated and community) should be tested for *Clostridium difficile* irrespective of the physician's request or the location of onset of diarrhoea. **Grade B**
- *Clostridium difficile* toxin testing should be restricted in children aged less than two years. Exceptions may be made at the discretion of the paediatrician/microbiologist/infectious diseases physician, based on local epidemiology data or if there is compelling evidence in an individual case. **Grade C**

All patients/residents in whom a diagnosis of infectious diarrhoea is suspected should have a stool specimen sent for microbiological analysis. In the 2008 guidelines it was recommended that all diarrhoeal specimens from patients aged over two years should be tested for CDI. This was based on the belief that if testing was restricted only to patients/residents that were admitted to a healthcare facility for more than three days or relied on accurate clinical data, e.g., prior antibiotic use being recorded on specimen submission to the laboratory, which this would lead to under diagnosis of cases. This remains the recommendation and is supported by further evidence that has emerged in the intervening period.(76, 77)

There is increasing evidence that the epidemiology of CDI has changed in recent years from primarily being a healthcare-associated disease to now being a significant issue also in the community. (Section 2.4.2) A US study demonstrated that 94% of CDI's were associated with receiving healthcare; however, 75% had their onset outside of hospitals which would lead to a significant under diagnosis of CDI if testing were confined to hospitalised patients only.(135) In addition, community-onset CDI has been diagnosed in patients without any of the traditional predisposing factors. A number of studies have found that up to 26% of patients did not have the usual recognised risk factors for CDI of healthcare contact and previous exposure to antibiotics. (76, 77) In addition, severe cases of CDI have been reported in peri-partum women without the traditional risk factors.(136)

More recently, *C. difficile* has also been recognised as a complication of IBD. The incidence of CDI among hospitalised IBD patients increased from 1% in 1998 to 3% in 2007 with an increase in disease severity.(137) CDI in IBD patients has also been associated with a significant increase in need for colectomy and even mortality with an effect that can persist up to one year after the primary infection.(138) The recent ESCMID guidelines recommend that unformed stool specimens of all patients with possible infectious diarrhoea irrespective of age, the presence/absence of the traditional risk factors or the onset of diarrhoea (community or healthcare-associated) and with

negative tests for common enteropathogens should be tested for CDI.(1) The question of when should hospitalised patients be tested for CDI is also unresolved. ESCMID guidelines recommend that all patients who have been hospitalised more than 72 hours should be tested, this is sometimes referred to as the 'three-day rule'.(1) UK guidelines, however, recommend that diarrhoeal specimens from all hospital patients should be tested and don't specify a time limit.(139)

The frequency of diarrhoea varies in definitions of CDI. Usually definitions cite the need for at least three episodes of diarrhoea, for at least two consecutive days. Such a stringent definition may be appropriate for clinical trials, but less so in a setting where transmission of infection is a concern. In the healthcare setting using a single episode of unexplained diarrhoea as a threshold to instigate testing is reasonable, therefore stools from symptomatic patients/residents should be collected as early as possible so that transmission of *C. difficile* can be minimised. In primary care, in practice patients would rarely consult their GP for diarrhoea unless it has continued for several days and therefore this problem with the definition of diarrhoea is unlikely to arise. Testing for CDI should ideally be available on a daily basis, including weekends, and results should be reported preferably within 24 hours.

2.5.1.i Should children aged less than two years be tested for *C. difficile*?

The issue of whether children under two years should be tested for CDI remains unresolved. Asymptomatic carriage of *C. difficile* is common in young children and its role in diarrhoea following antibiotic therapy is difficult to assess. Two recent reviews reported a wide variation in colonisation rates of between 2.5% and 90% in one and 37% in the second review.(85, 140) This wide variation in colonisation rates is explained by differences in laboratory testing (culture, toxin or PCR) and patient factors including prematurity, birth weight, method of feeding, duration of hospital stay, age, co- morbidities, and in some studies, prior antibiotic use. Colonisation rates decrease with age in infants. The average colonisation rate is 30% for infants aged between one and six months, 14% for those between six and twelve months, and 10% for infants over one years of age. After two years of age, the prevalence becomes similar to that of adults (0-3%).

It is unclear why the majority of neonates and infants harbouring toxigenic *C. difficile* remain asymptomatic. The reasons for low pathogenicity of *C. difficile* in this age group have been attributed to host factors such as an immature gastrointestinal tract with flora unable to compete with *C. difficile* for binding sites and absence of toxin receptors.(84, 85) High carriage rates have been associated with hospitalisation. Paediatric CDI cases have been reported to be increasing in hospitalised children and appear to have strong links to comorbidities such as malignancy, immunosuppression and bowel disorders.(85) (141)

In a US survey of 20,642 *C. difficile*-associated deaths from 1999 to 2004, only 17 occurred in children under 12 months of age. However, recent reports from the US have noted an increase incidence of CDI diagnosis in children and infants paralleling the rise in adult incidence.(80, 82) A survey of CDI in a US children's hospital from 2004 to 2006 revealed that 26% of 4895 cases were in children younger than one year.(80) Diarrhoea in infants is generally related to viral pathogens such as rotavirus and norovirus.(142, 143) In 2005, Tang *et al.* showed that infants aged less than one year with diarrhoeal symptoms harbouring *C. difficile* are clinically indistinguishable from those without the pathogen, thus suggesting no pathogenic role. In the same study, it was also found that treating this age group with antibiotics directed against *C. difficile* usually did not alter infantile diarrhoea even if *C. difficile* was present. However, as literature is limited in the area, further studies are necessary to understand the role of *C. difficile* in all infants aged less than two years and to distinguish colonisation from infection (no study specifically addressing this issue in infants between 12 and 24 months of age was found).

2.5.2 What type of specimen should be tested for CDI?

The following are responsible for implementation of **recommendation 25**:
Microbiology Laboratories.

Recommendation 25

- Only diarrhoeal (unformed) stools should be tested for *Clostridium difficile* toxin. **Grade B**
- For optimal laboratory investigation freshly taken samples should be examined. **Grade B**

The following are responsible for implementation of **recommendations 26-27**:
Clinicians.

Recommendation 26

Routine testing of stool from asymptomatic patients/residents is not clinically useful. **Grade D**

Recommendation 27

In the case of ileus and suspicion of CDI, testing of formed stool is acceptable or alternatively a rectal swab may be used. Other diagnostic procedures (e.g., abdominal CT, colonoscopy) may also be required. **Grade D**

Testing for CDI should only be performed on diarrhoeal (unformed) stool.(144) The stool specimen should take on the shape of container i.e., Bristol Stool Chart types 5-7.(145) For optimal laboratory investigation, freshly taken specimens should be examined and it is recommended that this should be done within 24-48 hours (with specimen storage at 4°C).(144) Specimens stored at ambient temperature show a decrease in toxin. Studies have shown that toxin is preserved for up to 44 days in specimens stored at 4°C.(146, 147) Toxin is less well preserved in specimens which have been frozen at -20°C; therefore, specimens which cannot be examined promptly for toxin detection should be stored at 4°C rather than being frozen.(147)

Because 10% or more of hospitalised patients may be colonised with *C. difficile* there is no value in testing formed stool for *C. difficile*. In addition, there is no evidence that screening non-diarrhoeal stools for *C. difficile* carriers contributes to the reduction of baseline CDI rates.(148-150) This also includes testing specimens for 'test-of-cure' or clearance.(151)

In the case of ileus and suspicion of CDI, testing of formed stool is acceptable or alternatively a rectal swab may be used. Other diagnostic procedures (e.g., abdominal CT, colonoscopy) may also be required.

2.5.3 When should a repeat test for CDI be performed?

The following are responsible for implementation of **recommendations 28-31**:
Clinicians.

Recommendation 28

Where a negative *Clostridium difficile* laboratory result has previously been obtained, repeat testing is NOT recommended. **Grade B**

Recommendation 29

Once the diagnosis of CDI is confirmed, patients/residents should NOT be re-tested for *Clostridium difficile* toxin when on anti-CDI treatment. **Grade B**

Recommendation 30

A test of cure after treatment is NOT recommended nor is it required prior to transfer/discharge.
Grade D

Recommendation 31

If recurrence of diarrhoea occurs after a symptom-free interval in a patient/resident with recent CDI, a repeat specimen should be tested for *Clostridium difficile* toxin and other potential causes of diarrhoea excluded. **Grade B**

Regarding the frequency of testing and policies for repeat testing, if the first specimen is negative, this appears to vary with the detection methods used by the laboratory. Several authors have suggested that it may be useful to test more than one stool specimen for *C. difficile* toxin by use of an enzyme immunoassays (EIA).(152-154) In contrast, others have shown that submission of multiple specimens for cell cytotoxicity assay (CCTA) did not increase detection of CDI.(155, 156) A more recent study assessed the value of repeat testing for *C. difficile* by PCR versus EIA and found that the diagnostic gains for repeat testing within a seven day period were 1.7% and 1.9% respectively. The authors concluded that there is little value of repeat testing for *C. difficile* by EIA or PCR.(157) As recurrence of CDI after a symptom free interval is common (up to 20-50% of cases), repeat diagnostic testing for *C. difficile* should also be performed at a new onset of diarrhoea in patients/residents whose symptoms had previously resolved. In addition, other potential causes of diarrhoea should be excluded.(158)

2.5.4 What is the best testing strategy to diagnose CDI?

The following are responsible for implementation of **recommendation 32-34:**
Microbiology Laboratories.

Recommendation 32

Clostridium difficile toxin enzyme immunoassays (EIAs) are not suitable as stand-alone tests for the diagnosis of CDI. **Grade B**

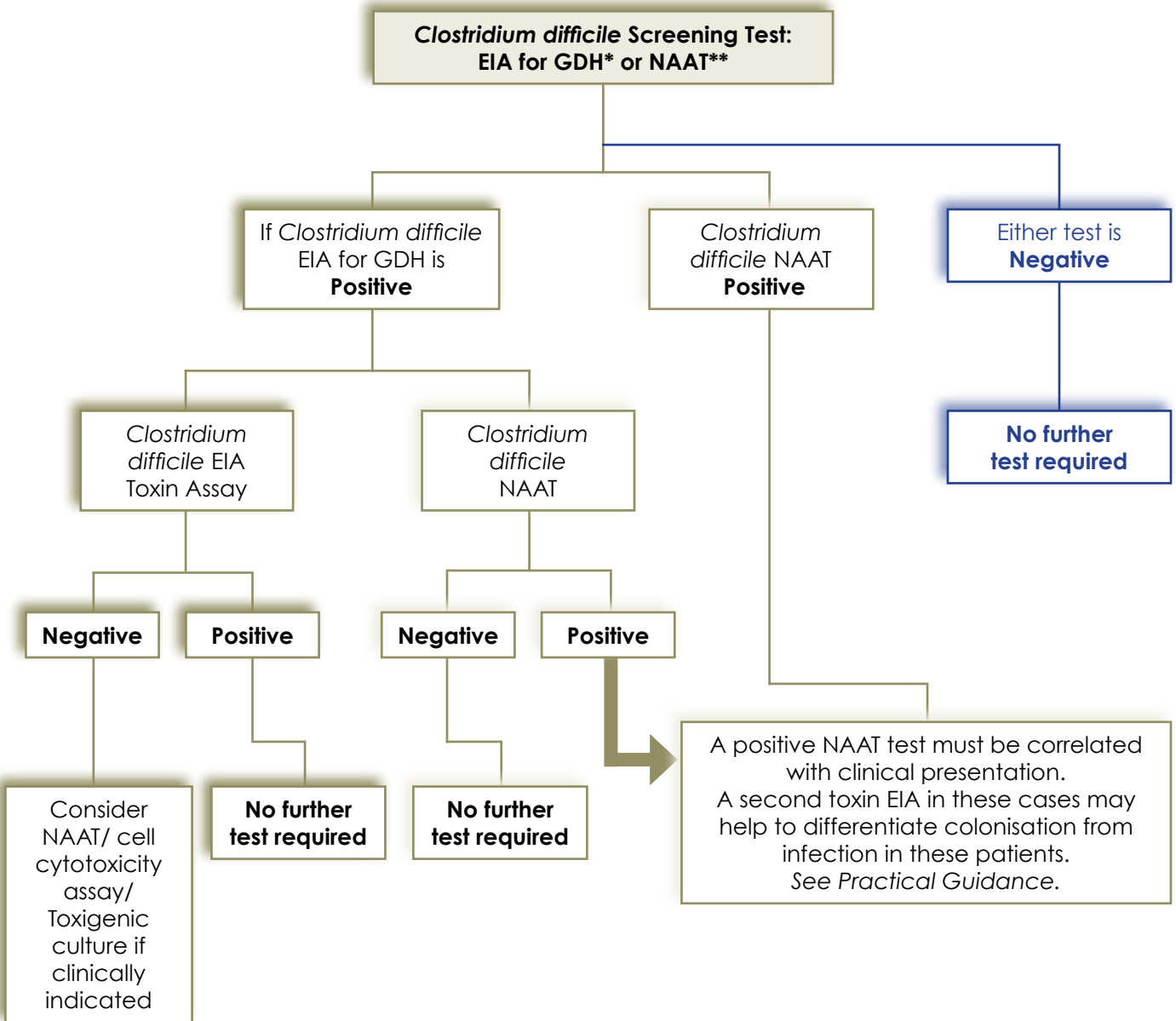
Recommendation 33

- As a screening test, EIA detection of Glutamate dehydrogenase (GDH) or Nucleic acid amplification test (NAAT) may be used. If the screening test (GDH or NAAT) is negative a second test is NOT required. **Grade B**
- If GDH screening test is positive a second test, to detect either toxin (e.g. EIA, cell cytotoxicity assay) or toxin gene assay NAAT, is required. **Grade B**
- Interpretation of positive NAAT results and consideration of the requirement for a second toxin EIA should be correlated with the clinical presentation, **Grade B**, see Figure 2.1.

Recommendation 34

If the first test is GDH and is positive, and the second test is a toxin EIA and is negative, then NAAT, cell cytotoxicity assay or toxigenic culture should be considered as an additional test. If any of these are positive, then the patient/resident should be considered to be either a carrier of a toxigenic strain of *Clostridium difficile* or a case of CDI depending on clinical assessment (i.e. the presence or absence of symptoms). **Grade B**

Figure 2.1 Summary algorithm for Clostridium difficile testing



* Enzyme Immune Assay for Glutamate Dehydrogenase
 ** Nucleic Acid Amplification Test

Practical Guidance

It is important to recognise that the detection of *Clostridium difficile* DNA by NAAT does not confirm that toxin is being produced and therefore positive tests may occur in a patient/resident who does not have CDI. In this instance the interpretation of positive NAAT test results should be correlated with the patient/resident's clinical presentation (i.e., the presence or absence of symptoms). A second toxin EIA in these cases may help to differentiate colonisation from infection in these patients/residents. See Figure 2.1.

There are a variety of test methods available to laboratories for the diagnosis of CDI. These include EIAs for toxins A and B, EIAs for GDH, CCTA, toxigenic culture and NAAT for toxin genes. The diagnosis of CDI is a rapidly evolving situation. There is no overall agreement on which test, the CCTA or toxigenic culture, is the 'gold standard' reference method for the detection of CDI which makes it more difficult to compare the different methods of detection and come to a consensus on the best diagnostic approach.

For the past two decades, EIAs for the detection of first *C. difficile* toxin A and then toxins A and B have been the most widely used diagnostic tests for the diagnosis of CDI. More recently, this diagnostic approach has been called into question by the recognition that a screening test which detects GDH was significantly more sensitive than the toxin EIAs making it an effective screening test for CDI.

2.5.4.i Cell cytotoxicity assay (CCTA)

The CCTA has traditionally been regarded as the reference ('gold standard') assay for the laboratory confirmation of CDI. This assay relies on the detection of a cytopathic effect (CPE) in cell culture that is neutralised by the presence of antibodies to *C. difficile* toxins. Cells (e.g., Vero or Hep2 cells) are cultured in the presence of faecal filtrate, with and without the presence of neutralising antibodies. These cultures are examined microscopically at 24 and 48 hours for evidence of a CPE that is prevented by the specific antitoxin. This method can detect as little as 10 picograms of toxin.(155, 159) CCTA requires the ability to perform cell culture and many diagnostic laboratories do not have this facility. In addition, the assay is slow (minimum of 24 hours), expensive, time consuming and requires a degree of expertise to recognise a CPE. Furthermore, it may lack standardisation as a variety of protocols and cell lines are used in different laboratories. (160) The sensitivity of CCTA as a single test for the diagnosis of CDI is reported to range from 67% to 100%.(161, 162)

2.5.4.ii Toxigenic Culture

Some authors consider that toxigenic culture is a more sensitive test for CDI than CCTA. (163) Toxigenic culture relies on the anaerobic culture of *C. difficile* from faeces, usually preceded by alcohol shock of the faecal specimen to remove vegetative bacteria, thus selecting the *C. difficile* spores. The faecal specimen is then cultured on specific agar plates for at least 48 hours and typical colonies identified. A number of different selective agars have been used including Cefoxitin Cycloserine Fructose Agar (CCFA) and Brazier CCEY Agar (Fastidious Anaerobe Agar with cefoxitin cycloserine and egg yolk emulsion). It is then necessary to confirm that the *C. difficile* isolates are toxigenic. This may be done using CCTA, which results in the whole process taking up to five days to confirm a toxigenic isolate. A variant approach involves testing colonies for toxin production using an EIA (although not validated for such use) which can produce a positive toxigenic culture result one-two days after the specimen is received. Similar to CCTA, toxigenic culture requires technical expertise to culture and identify *C. difficile* reliably. In addition, there are advantages associated with culture, including the ability to type isolates and perform antibiotic susceptibility testing.(164)

In summary, different reference methods produce different results for the diagnosis of CDI based on the detection of different targets. Clarity on the optimum reference 'gold' standard method requires further studies that include relevant clinical data.

2.5.4.iii Detection by tests for *C. difficile* glutamate dehydrogenase (GDH)

GDH (also known as *C. difficile* common antigen) is a constitutive enzyme produced by all strains of *C. difficile* independently of toxigenicity. Modern tests use monoclonal antibodies against the *C. difficile*-specific GDH, thus avoiding any cross-reactivity with GDH produced by other anaerobic bacteria. The initial test to detect GDH was a latex agglutination assay and had a sensitivity of only 58-68% and a specificity of 94-98%.^(161, 162) Several assays for GDH have been developed using EIA methodology. These newer assays show a sensitivity of 85- 95% and a specificity of 89-99%. Most importantly, these assays have a high negative predictive value, making them useful for rapid screening if combined with another method that detects toxin.⁽¹⁶⁵⁻¹⁶⁸⁾ Although most studies have shown a high negative predictive value for the GDH assay, it has been reported that the GDH EIA has a lower sensitivity for detecting some strains of *C. difficile*. In a recent multi-centre study, GDH-based algorithms detected *C. difficile* ribotype 027 with a sensitivity comparable to that of PCR assays, but the sensitivity was only 72.2% for non-027 strains (P=0.001).⁽¹⁶⁹⁾

A recent meta-analysis on the role of GDH for the detection of *C. difficile* in faecal specimens demonstrated a high accuracy for the presence of *C. difficile* in human diarrhoeal faeces; when compared with culture it achieved a sensitivity and specificity of over 90%. As a surrogate for toxigenic strains, the GDH yields a specificity of 80-100% with a false positivity rate of approximately 20%, as it detects both toxigenic and non-toxigenic strains. The study concluded that the GDH test has a high sensitivity and negative predictive value and would be a useful test in a dual testing algorithm when combined with a test to detect *C. difficile* toxin.⁽¹⁷⁰⁾ In a recent review, Crobach *et al.* concluded that the negative predictive value of the GDH test does not differ significantly between *C. difficile* prevalences of 5% and 20%, making it a potential candidate for inclusion in a diagnostic algorithm for CDI.⁽¹⁾ The use of algorithms is discussed further in Section 2.5.4.vii.

2.5.4.iv Enzyme immunoassays (EIAs) for toxins A and B

Many diagnostic laboratories depend on commercially available EIA tests for the detection of *C. difficile* toxin A or both toxins A and B. A UK study of nine of the most commonly used toxin EIAs found that the sensitivity ranged from 66.7% to 91.7%, and specificity ranged from 90.9% to 98.8%. The authors assessed the mean positive predictive value (PPV) under conditions of low prevalence (2%), such as might be expected among a community based population vs. a high prevalence (10%), such as a healthcare setting. The mean PPV for the low versus high groups ranged from 32.3% to 68.7%, respectively. The authors concluded that these tests should not be used as a single test for CDI.⁽¹⁷¹⁾ In a systematic review of 28 studies, assessing the six most commonly used toxin assays in the UK, it was concluded that the PPVs were unacceptably low in low-prevalence populations and should not be used as a single test for the diagnosis of CDI.⁽¹⁷²⁾ More recently, the Health Protection Agency (HPA) in the UK carried out an observational diagnostic study in four NHS laboratories using 12,441 specimens which were tested using selected commercial assays for the laboratory detection of *C. difficile* and the diagnosis of CDI. It was confirmed in this study that *C. difficile* toxin EIA's are not suitable as standalone tests for the diagnosis of CDI.⁽¹³⁹⁾

2.5.4.v Direct detection using molecular methods

Since the publication of the 2008 Irish CDI guidelines, a number of NAATs have been developed that target *C. difficile* toxin genes in an attempt to improve the accuracy of CDI diagnosis. NAAT methodology available for the diagnosis of CDI includes PCR, loop-mediated isothermal amplification and isothermal helicase-dependant amplification for the detection of *Tcda* and *tcdB* genes. NAATs for toxigenic *C. difficile* in stool specimens are now available commercially

from several manufacturers, and this may be a more sensitive and more specific approach to diagnosis of CDI than EIAs and membrane assays. The PPVs and NPVs (negative predictive values) of these tests are both higher than those of EIAs/membrane assays (NPVs usually over 95%, PPVs of over 85%). (173-175) They have been evaluated both as standalone tests and as part of algorithms; usually involving GDH tests as an initial screen. A systematic review by Crobach *et al.* recommended testing patients/residents with a two-step protocol utilizing EIA detection of GDH or toxins A and B, or a molecular test detecting *Tcdb* for the first step. (1)

Specimens with a negative test result could be reported as negative. Faeces specimens with a positive first test result should be re-tested with a method to detect faecal toxin, or with a method to detect GDH or toxin genes, depending on the assay applied as first screening test. If faecal toxins are absent but *C. difficile*, *Tcdb* or GDH is present, they suggest that CDI cannot be differentiated from asymptomatic colonisation. In an editorial on laboratory diagnosis by Wilcox, the author felt that the case for using highly sensitive NAATs without a qualifying test is not clear cut. More data on utility are necessary before this methodology can be recommended for routine testing.(176) It is important to recognise that detection of *C. difficile* DNA by NAAT does not confirm that toxin is being produced and therefore positive tests may occur in a patient/resident who does not have CDI. In this instance interpretation of positive NAAT test results should be correlated with the clinical presentation (i.e., the presence or absence of symptoms in the patient/resident). A second toxin EIA in these cases may help to differentiate colonisation from infection in these patients.

2.5.4.vi *C. difficile* culture

As outlined in Section 2.5.4.ii, *C. difficile* can be isolated by culturing faecal specimens directly onto selective agar. A pre-inoculation process of heat or alcohol shock has been shown to enhance the isolation of *C. difficile* by selecting for *C. difficile* spores. The addition of various supplements, such as cholic acid or sodium taurocholate, to selective agar has been shown to promote germination of *C. difficile* spores, also enhancing the recovery of the organism.(177) There is evidence that the medium should be pre-reduced anaerobically before specimen inoculation. Plates should be incubated anaerobically at 35°C-37°C for 48- 72 hours. Cultures may be examined after overnight incubation but should not be removed from the anaerobic cabinet (sporulation is inhibited on selective media and young cultures may die on exposure to air).(178)

C. difficile is a Gram-positive, spore-forming, strictly anaerobic rod. Routine Gram staining is not recommended. Gram staining is rarely useful directly from selective agar but from blood agar plates sub-terminal spores may be visible with most vegetative cells staining as Gram-positive with some Gram variable forms.(178) Putative *C. difficile* colonies should be sub cultured onto blood agar for anaerobic incubation. Plates should not be left on the bench any longer than is necessary as *C. difficile* will die if left exposed to oxygen for prolonged periods. Colonies of *C. difficile* can be recognised by their characteristic smell and the following characteristics:

- Lack of opacity surrounding the colonies on egg-yolk based agar
- Green-yellow fluorescence under long-wave UV light
- Agglutination with *C. difficile* latex reagent for cell wall antigen
- Positive for proline aminopeptidase.

C. difficile may also be identified using MALDI-TOF. (179)

Chromogenic culture media, such as the ID *C. difficile* prototype (IDCd) (bioMerieux, Craponne, France) are currently under evaluation. This consists of a *C. difficile* selective media which enables isolation of *C. difficile* within 24 hours and easier detection of putative colonies by virtue of an easily identifiable colour change.(180) Cultured isolates should be stored in the local laboratory in cooked meat broths (if long-term storage anticipated) or blood agar slopes (shorter term storage) for future characterisation and typing studies or sent to a reference facility.

Whilst culture is highly sensitive, it lacks specificity due to the detection of non-toxigenic strains. As non-toxigenic strains exist, cultured *C. difficile* must be also tested for toxin production.(178) Therefore, the main disadvantage of culture is the time taken to detection (usually 48 hours – but at least four days for toxigenic culture), so that culture plays little role in the day-to day diagnosis of CDI. To address this issue, a novel selective and differential agar-based assay, the CDifftox plate assay (CDPA) has been developed, which combines the isolation of *C. difficile* strains on a selective medium with the detection of active toxins (by virtue of a chromogenic change) in a single step.(181) However, this assay is not yet commercially available. Culture may also be employed in certain routine scenarios, for example, if *C. difficile* is clinically suspected, yet EIA results are negative, culture is advantageous to confirm clinical suspicion. Lozniewski *et al.* recommended that when a laboratory is using an EIA to detect toxin directly in faeces, negative results should be supported by culture findings.(182) Culture is also essential for strain typing and antimicrobial susceptibility testing. Whilst not important for laboratory diagnosis, both are of critical interest in the clinical management of individual cases and hospital outbreaks. Typing allows clonal strains to be traced and recognition of the emergence of specific virulent clones. Susceptibility testing might allow the observation of the emergence of strains with a decreased susceptibility to antimicrobials. For cases of severe CDI, or in an outbreak setting, all specimens should be sent to a reference laboratory for epidemiological typing.

2.5.4.vii What is the role of algorithms for the diagnosis of CDI?

At the present time it is not possible to be prescriptive about the optimal approach to laboratory testing for CDI. The optimal laboratory diagnosis of CDI remains an area of controversy. The availability of multiple tests with different *C. difficile* targets contributes to this uncertainty. The commonly available tests, toxin EIAs have both poor sensitivity and specificity. These deficiencies have led to the development of algorithms that combine two and sometimes three tests to improve diagnostic accuracy, however, the practicality of these will vary according to local expertise, facilities and finance. Multistep algorithms may increase laboratory costs or add delays, although interim results can be issued to minimise the latter.

Several two-step algorithms have been developed that are based on the use of GDH. (183-187) They all use GDH for screening in which a stool specimen with a negative assay is considered negative for the pathogen but a positive result requires further testing to determine whether the *C. difficile* strain is toxigenic. In addition to the advantage that a negative result can be turned around quickly, this approach may result in cost savings for laboratories. A recent study performed two-step testing of 5,887 specimens at two different hospitals.(168) The GDH test was positive for 16.2% of specimens at one hospital and 24.7% of specimens at the other. Therefore, 75-85% of the specimens did not require further testing which resulted in a cost savings of \$5,700 and \$18,100 per month.

There is still much debate over which second test to use to confirm toxigenic stains of *C. difficile*. Currently, there is no testing strategy that is optimally sensitive and specific, therefore clinical suspicion and consideration of patient risk factors are important in making clinical decisions about whom to treat, notably isolating these patients/residents as soon as is practicable while results are pending. The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) guidelines recommend the use of a 2-step method.(144) They suggest that one potential strategy is to use a 2-step method that uses EIA detection of GDH as initial screening and then use the CCTA or toxigenic culture as the confirmatory test for GDH positive stool specimens only. They do, however, advise that this approach is an interim recommendation until more data is available.

ESCMID propose that if the use of a reference method, i.e., CCTA or toxigenic culture is not practical then patients/residents should be tested with a 2-step approach.(1) In the first step, faeces specimens could be investigated with an EIA detecting GDH, an EIA detecting toxins A and B or a molecular test detecting *Tcdb*. Faeces specimens with a positive first test result should

then be retested with a method to detect free toxins in faeces, or with a method to detect GDH or toxin genes depending on the assay used in the first step.

More recently in a multicentre study of 12,420 faecal samples study in the UK, where outcomes in patients who had cytotoxin detected compared with those who were either GDH or toxin gene test positive were compared, the authors concluded that "toxin (cytotoxin assay) positivity correlated with clinical outcome, and so this reference method best defines true cases of *C. difficile* infection. A new diagnostic category of potential *C. difficile* excretor (cytotoxigenic culture positive but cytotoxin assay negative) could be used to characterise patients with diarrhoea that is probably not due to *C. difficile* infection, but who can cause cross-infection.(188) The findings resulted in a recommendation of using a 2-step algorithm comprising a GDH EIA or NAAT/PCR screening test followed by a sensitive toxin EIA test if the screening test is positive, as they found no increased mortality in the toxin negative groups.(139)

2.5.5 When should specimens be sent for susceptibility testing and molecular typing?

The following are responsible for implementation of **recommendations 35-38:**

Microbiology Laboratories.

Recommendation 35

Frozen storage of small aliquots of all toxin-positive stool specimens is recommended to ensure antimicrobial susceptibility testing can be performed and isolates can be typed retrospectively if required. **Grade D**

Recommendation 36

Specimens should be referred to a reference laboratory for epidemiological typing;

- In cases of severe CDI
- In an outbreak setting
- In a period of increased incidence of CDI: i.e. 2 or more new cases (occurring >48 hours post admission, not relapses) in a 28-day period on a ward/unit
- On a periodic basis nationally in order to monitor the molecular epidemiology of *Clostridium difficile*. It is recommended that 30% of isolates from every laboratory should be typed. **Grade D**

Recommendation 37

Antibiotic susceptibility testing of *Clostridium difficile* should be performed by a specialised (reference) centre. **Grade D**

Recommendation 38

Antibiotic susceptibility testing should be performed on a periodic basis nationally in order to monitor the molecular epidemiology of *Clostridium difficile*. **Grade D**

2.5.5.i When should susceptibility testing be performed?

An effective surveillance programme requires that susceptibility testing is performed on isolates so that resistance trends can be monitored. *C. difficile* susceptibility testing is expensive and time consuming. Susceptibility testing of *C. difficile* is not a test that is routinely performed in most microbiology laboratories particularly as many diagnostic laboratories do not perform routine culture for *C. difficile*. *In vitro*, *C. difficile* is susceptible to vancomycin; the reported minimum inhibitory concentration (MIC) required to inhibit 90% of strains (MIC 90) is 0.75-2.0 mg/L.(189, 190) A recent study found that 3% of *C. difficile* isolates had intermediate resistance to vancomycin (MIC 4-16 mg/L) but clinical correlation was not provided. (191) *In vitro*, the MIC 90 of metronidazole for *C. difficile* ranges from 0.2 mg/L to 2.0 mg/L. Resistance has been reported, including an isolate

from Hong Kong with an MIC of 64 mg/L.(192) Pelaez *et al.* found that 6.3% of Spanish isolates from patients with a first episode of CDI had an MIC of 32 mg/L or more, however, no clinical correlation was provided.(191) Other studies have shown that metronidazole susceptibility of *C. difficile* inpatients with clinical treatment failure was similar to those who had clinically responded to metronidazole therapy.(193, 194)

There is limited available data relating to the antimicrobial susceptibility of *C. difficile* isolates circulating in the Republic of Ireland. However, the 2009 national surveillance study reported that all isolates tested were susceptible to metronidazole and vancomycin, which remain the antimicrobial treatments of choice for CDI.(20, 195) The reported MIC 90s were 0.75mg/L and 0.38mg/L for vancomycin and metronidazole respectively. Although none of the Irish *C. difficile* isolates showed reduced susceptibility to either vancomycin or metronidazole, significantly higher MICs to both of these antimicrobials were detected in the most prevalent ribotypes.

Antimicrobial susceptibility testing of *C. difficile* is a task that is best done by a specialised centre. Currently, there is no such designated centre in Ireland and it is essential that such a centre be developed if a comprehensive national *C. difficile* surveillance programme is to proceed.

2.5.5.ii Which specimens should be referred for molecular typing?

Frozen storage of small aliquots of all toxin-positive stool specimens (e.g., a small Eppendorf tube full at -20°C for a rolling year) is recommended. This is so that a retrospective culture can be made should it become apparent that an outbreak of CDI or a change in incidence has taken place that might warrant culture of the organism for typing.(196) Obtaining isolates is also advisable in order to monitor antimicrobial susceptibility, especially the emergence of resistance to the current first-line treatment options of metronidazole and vancomycin.

There is currently no national reference laboratory in the Republic of Ireland for typing and antimicrobial susceptibility testing. As a result, limited research data with regard to the molecular epidemiology of Irish *C. difficile* strain types exists.(197-199) The 2009 national one-month prevalence study of 139 strains (107 were typable) from 211 patients reported Irish ribotype distribution for the first time.(20) Sixteen different ribotypes were found with 027 (19%), 106 (13%), 078 (9%), 044 (9%), 014 (8%) and 001 (7%) the most common.

There are a number of molecular typing methods that can be applied for *C. difficile* surveillance. The most common methods used include PCR ribotyping and toxinotyping, Restriction Endonuclease Analysis (REA), Pulsed Field Gel Electrophoresis (PFGE), Toxinotyping (PCR-RFLP), Multi Locus Sequence Typing (MLST), Multilocus, Multilocus Variable-Number Tandem-Repeat Analysis (MLVA), Amplified, Amplified Fragment Length Polymorphism (AFLP), and surface layer protein A gene sequence typing (slpAST). Each method has distinct advantages and disadvantages. For the early and rapid detection of outbreak situations, methods such as REA and PCR ribotyping are commonly used. For long-term epidemiology, MLST, MLVA, and AFLP are more discriminatory and may provide more epidemiological detail.

A number of PCR based methods have been developed including PCR ribotyping and toxinotyping and there is good correlation between these two methods.(200) PCR ribotyping whilst not as discriminatory as MLST, MLVA and AFLP, can identify over 400 distinct types and is the method most commonly utilised now for typing isolates. It is recommended in the outbreak situation, as it is relatively rapid to perform. One of the commercially-available real-time PCR tests for the diagnosis of CDI, the Xpert *C.difficile* test (Cepheid, Sunnydale, Ca.), reports that it can differentiate ribotype 027 from other ribotypes by detection of its *tcdC* nt 117 gene deletion. This has been evaluated by Babady *et al.* who found that the agreement between the Xpert and gene sequencing was 93%.(173) Thus, this could prove a rapid and reliable method for the detection of this virulent strain, particularly in the context of an outbreak. Toxinotyping is a PCR-based method that amplifies genes found on the pathogenicity locus. These include the genes that encode *tcdA* and *Tcdb* as well as the genes that regulate the transcription and translation

of *Tcda* and *Tcdb*. This method identifies insertions, deletions and restriction polymorphisms on the pathogenicity locus and has been important for the identification of variant *C. difficile* strains in recent years. Strains have been allocated to approximately 25 different toxinotypes. MLVA is more discriminatory than PCR ribotyping and can differentiate strains belonging to the same ribotype.(201, 202) It is considered now to be the most discriminatory method for typing, and will greatly contribute to our understanding of the epidemiology of this pathogen.(203) Recently, an automated sub typing method, repetitive extragenic palindromic PCR (rep-PCR) method (DiversiLab), has been developed. Irish isolates of ribotypes 027 and 078 from the one month national study and a previous study in 2006 were sub typed by this method, and ribotype 027 isolates were significantly more related to each other (nine different subtype profiles) when compared to ribotype 078 isolates.(204) Although critically important to identify the emergence of more virulent strain types and to identify clonal strains during an outbreak, typing is complex and time consuming and should only be carried out in specialised (reference) centres.

2.6 Management of patients with suspected/confirmed CDI

2.6.1 How should patients/residents with potentially infectious diarrhoea be managed in a healthcare facility?

The following are responsible for implementation of **recommendation 39**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 39

All patients/residents with potentially infectious diarrhoea, i.e. where there is no clear alternative cause for the diarrhoea, should be isolated immediately with Standard and Contact Precautions, i.e. placed in a single room with clinical hand wash sink and ensuite facilities until an infective cause is out-ruled. Placing the patient/resident in isolation should not be delayed while awaiting test results. **Grade D**

Practical Guidance

- The SIGHT mnemonic protocol is a useful aide memoire and should be applied by clinicians (doctors and nurses) when managing patients/residents with suspected potentially infectious diarrhoea (Table 2.3).
- Patients/residents with suspected potentially infectious diarrhoea should be monitored daily for frequency and severity of diarrhoea using the Bristol Stool Chart.¹⁵
- All medications should be reviewed by the clinical team and pharmacist (if available) – antibiotics that are no longer clinically indicated should be discontinued. Other medications that may be causing or contributing to diarrhoea should also be reviewed and stopped if safe to do so.

Table 2.3: SIGHT Mnemonic protocol

S	Suspect that a case may be infective where there is no clear alternative cause for diarrhoea.
I	Isolate the patient/resident. Consult with the infection prevention and control team where available while determining the cause of the diarrhoea.
G	Gloves and aprons must be used for all contacts with the patient/resident and their environment.
H	Hand washing with soap and water should be carried out after each contact with the patient/resident and the patient/resident's environment.
T	Test the stool for <i>Clostridium difficile</i> toxin, by sending a specimen immediately.

Adapted with permission from SIGHT Mnemonic UK protocol

¹⁵ Lewis SJ, Heaton KW (1997). "Stool form scale as a useful guide to intestinal transit time". Scand. J. Gastroenterol. **32** (9): 920–4

Patients/residents with diarrhoea should be risk assessed for the presence of potential infectious causes. All patients/residents with potentially infectious diarrhoea should be isolated immediately with Standard and Contact Precautions as described above without delay. The SIGHT mnemonic protocol is a useful tool for managing suspected potentially infectious diarrhoea.(206)

2.6.2 What infection prevention and control measures should be taken for patients/residents with diarrhoea who are GDH, EIA or NAAT positive but *Clostridium difficile* toxin negative?

The following are responsible for implementation of **recommendation 40**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 40

Patients/residents with diarrhoea and a positive GDH EIA (or NAAT) but with a negative toxin should be isolated in a single room with Contact Precautions at the earliest opportunity to reduce the risk of CDI transmission while they are symptomatic with diarrhoea. **Grade C**

This result is based on the assumption that the specimen that was tested was a diarrhoeal specimen and that this is not from an asymptomatic patient/resident with formed stool. As the sensitivity of toxin EIA's ranges from 66.7% to 91.7%, it is plausible that a negative EIA result may indicate that the patient/resident might have low levels of toxin resulting in less severe diarrhoea and thus less shedding of spores.(172) A recent study, however, found that EIA-negative patients/residents did not differ in clinical presentation from EIA-positive patients/residents, and, notably, 21% of EIA-negative patients/residents presented with severe CDI.(207) These findings would suggest that such patients/residents could be potential *C. difficile* excretors and therefore have transmission potential. It must also be remembered that there could be other potentially infectious causes for the diarrhoea, which would also require appropriate infection prevention and control measures to be in place. It is therefore recommended that patients/residents with a positive GDH EIA (or NAAT) but with a negative toxin EIA should be isolated at the earliest opportunity with other measures in place to reduce the risk of CDI transmission while they are symptomatic with diarrhoea.

2.6.3 Who should inform the patient/resident they have CDI?

The following are responsible for implementation of **recommendation 41**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 41

Patients/residents with CDI should be informed by the clinician, clinical team, general practitioner or designated senior clinical staff member primarily responsible for their care as soon as the diagnosis is made. Relevant information on preventing transmission of CDI outlining the range and need for appropriate infection prevention and control precautions should be provided (e.g. patient/resident information leaflet) and the patient/resident shown how to carry out hand hygiene. **Grade D**

National infection prevention and control standards clearly recommend that patients/residents with a HCAI are informed of this by their clinician/clinical team.(48) Relatives/carers may also need to be informed, with the appropriate authorisation, and be supplied with any relevant information and training. The provision of clear and timely information allays undue anxiety and should be given in a manner that is easily understood. In the community, this responsibility normally rests with the patient's GP or a designated senior clinical staff member if their GP is unavailable.(104)

Patients/residents with CDI and their visitors/carers should be given information on preventing transmission of CDI outlining the range and need for appropriate infection prevention and control precautions and shown how to carry out hand hygiene.(95)

Visitors should be alerted to check with ward nursing staff regarding hand washing with soap and water and other requirements before and after visiting a patient with CDI. Visitors will only need to wear gloves and aprons if assisting with personal patient care. Visitors should not use the patient/resident's bathroom and should not go into other patients/residents' rooms or bed spaces.(95)

2.6.4 How should patients/residents with confirmed CDI be managed in a healthcare facility and how should the environment/equipment be decontaminated?

The following are responsible for implementation of **recommendations 42-43:**

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 42

Any non-CDI antimicrobial therapy should be discontinued as soon as possible. **Grade C**

Recommendation 43

- Contact Precautions should be used in addition to Standard Precautions for the care of all patients/residents with CDI in all healthcare facilities.
- Hand washing should be performed with soap (antimicrobial or non-antimicrobial) and water during patient/resident care according to the World Health Organisation (WHO) 'Five Moments for Hand Hygiene':
 - Before patient contact
 - Before aseptic task
 - After body fluid exposure risk
 - After patient contact
 - After contact with patient surroundings. **Grade A**
- Chlorine-releasing agents 1,000 ppm are recommended as the disinfectant of choice for routine disinfection for CDI. In units with higher rates of endemic CDI or an outbreak setting, higher concentrations may be used and/or use of other sporicidal agents may be considered. **Grade D**

Practical Guidance

- Current international guidelines recommend environmental decontamination (after cleaning) with chlorine-releasing agents at a concentration of at least 1,000 parts per million (ppm) available chlorine (av cl). (Table 2.4)
- Contact Precautions for patient/resident with CDI include the following:

Patient/resident isolation

- The patient/resident with CDI should be isolated in a single room with ensuite facilities and a clinical hand wash sink.
- If ensuite facilities are not available, it is essential that the patient/resident with CDI has a dedicated toilet or commode and is not permitted to use the general toilet facilities on the ward/unit.

Hand washing

- Hand washing must be performed with soap (antimicrobial or non-antimicrobial) and water during patient/resident care according to the World Health Organisation (WHO) 'Five Moments for Hand Hygiene'. The physical action of rubbing and rinsing is the only way to remove spores from hands. Alcohol hand rub must not be used as an alternative to soap as *Clostridium difficile* spores are known to be highly resistant to killing by alcohol. It can be applied after washing to rid hands of remaining non-clostridial organisms.
- Patients/residents should be advised and if needed assisted, to wash their hands with soap and water and dry with paper towel after using the bathroom and before eating.

Personal protective equipment (PPE)

PPE (i.e. gloves and aprons) must be donned prior to, and subsequently removed, following each period of care activity for a patient/resident with CDI. Gloves and apron/gown should be worn when entering a room for all interactions that may involve contact with the patient/resident or potentially contaminated areas in the patients/residents' environment. (**Grade A** (gloves), **Grade D** (gowns)). PPE should be readily available to staff for this purpose.

Care equipment and the environment

Care equipment, e.g. blood pressure cuffs, thermometers, hoist slings should be dedicated to a single patient/resident with CDI.

- All care equipment must be cleaned and disinfected immediately after use on a CDI patient/resident. The use of disposable materials should be considered whenever possible.
- Thoroughly clean and disinfect the environment daily paying special attention to frequently touched sites and equipment close to the patient/resident.
- Environmental faecal soiling may be an important source of *Clostridium difficile* spores e.g. toilets and commodes/bedpans, and should be cleaned and disinfected immediately.
- After discharge of a patient/resident with CDI the room and equipment must be cleaned and disinfected thoroughly.

Laundry and Healthcare Risk Waste

- All laundry should be placed into an alginate stitched or water-soluble bag at the bedside. The sealed bag should be placed immediately into a laundry bag according to organisational and national guidelines.
- Linen should be heat-disinfected during the wash process by raising the temperature to either 65°C for not less than 10 minutes, or preferably 71°C for not less than three minutes.
- Disinfection of heat labile materials (according to manufacturer instructions) can be achieved at low temperatures, by introducing 150 ppm of available chlorine into the penultimate rinse.
- Sorting or manually rinsing soiled laundry is not recommended. A sluice cycle should be the first stage of the automated washing process.
- Within a healthcare facility waste soiled with diarrhoea (e.g. incontinence wear and wipes) from a suspected or known CDI patient/resident should be disposed of as healthcare risk waste.

2.6.4.i Patient/resident placement

C. difficile can be transmitted to patients/residents by contact with healthcare workers with transient hand colonisation, by direct contact with a patient/resident with CDI or by contact with the contaminated environment (including healthcare equipment).(23) Physical proximity to a symptomatic case has been reported as important for transmission with an attributable risk of 12% due to contaminated near patient environmental contamination and movement of contaminated equipment between patients/residents (e.g., commodes).(208, 209) The period between exposure to *C. difficile* and the occurrence of CDI has been estimated in three studies to be a median of two to three days.(144) Failure to isolate symptomatic patients/residents quickly was a major factor in two outbreaks of CDI at Stoke Mandeville Hospital.(209) Isolation/single rooms must be prioritised for isolation of symptomatic patients with suspected or confirmed CDI. The recommendation to isolate CDI patients/residents in a single room with en-suite facilities, or with an allocated commode, is based on a considerable consensus of evidence.(23, 144, 206, 210, 211) In addition, these rooms should have a clinical hand wash sink.(212-214) In community settings, if an appropriate clinical hand wash sink is not readily available, staff may use the residents hand wash basin, but must turn off the tap using a disposable paper towel. If ensuite facilities are not available, the patient/resident with CDI should have a dedicated toilet or commode and not be permitted to use the general toilet facilities on the ward/unit.

2.6.4.ii Hand hygiene

The hands of HCWs can become contaminated with *C. difficile* in both endemic and outbreak settings and hands may transmit CDI.(2, 122, 208) One of the key interventions that have been shown to be effective in the prevention of HCAI, including CDI, is good hand hygiene.(23, 215) It is recommended that hand hygiene is performed during patient care according to the WHO "Five Moments for Hand Hygiene". (Figure 2.2)

Figure 2.2: WHO 5 Moments for Hand Hygiene

WHO - World Health Organisation 5 Moments for Hand Hygiene



Based on the 'My 5 moments for Hand Hygiene', URL:
<http://www.who.int/gpsc/5may/background/5moments/en/index.html>
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Alcohol hand rub must not be used as an alternative to soap as *C. difficile* spores are known to be resistant to killing by alcohol. None of the agents used in antiseptic hand-wash or antiseptic hand-rub preparations are reliably sporicidal against Clostridia species. The physical action of rubbing and rinsing is the only way to remove spores from hands. WHO (2009) recommends hand washing with soap and water when exposure to potential spore-forming pathogens is suspected.(215) The type of soap to use (i.e., non-antimicrobial/antimicrobial) is an unresolved issue with guidelines recommending either can be used.(23)

Although direct person to person transmission has been proposed as a mode of transmission of CDI, the role of the patient/resident remains uncertain in the transmission of *C. difficile*.(23) Patients/residents should be advised to wash their hands with soap and water and dry them after using the bathroom and before eating.(217) Healthcare workers must provide assistance with hand washing for those patients/residents who are unable to perform hand washing independently. Visitors should be alerted to check with ward nursing staff regarding hand hygiene and other requirements before and after visiting a patient with CDI.

2.6.4.iii Personal Protective Equipment (PPE)

Evidence-based guidelines recommend that all healthcare workers should use disposable gloves and aprons/gowns for all contact with the patient/resident and the patient/resident's environment. (206, 211) However, gloves and aprons/gowns can become a vector in the transmission of *C. difficile* if not properly changed and disposed of between patient/resident care activities.(212) Therefore, it is essential that PPE is removed and disposed of appropriately after each patient/resident care activity.(218)

Gloves: The use of gloves followed by effective hand hygiene should decrease the concentration of *C. difficile* on the hands of healthcare workers.(144) *C. difficile* can frequently contaminate multiple skin sites of CDI patients/residents and easily be transmitted to hands.(219) A significant reduction in CDI and carriage rates was reported following the use of gloves when handling body substances.(122) Inappropriate glove use (e.g., failure to remove or change contaminated gloves) has been shown to be a contributing factor in poor hand hygiene compliance.(220) To wear gloves for an entire episode of care for a patient who requires Contact Precautions, without considering the indications for their removal (such as an indication for hand hygiene) could actually lead to cross infection.(215) In addition to wearing gloves as required for Standard Precautions, gloves should be worn when entering a room for all interactions that may involve contact with the patient/resident with CDI or potentially contaminated areas in the patient/resident's environment.

Gloves should be changed and hand washing performed:

- As soon as gloves are damaged.
- When contact with blood, another body fluid, non-intact skin and mucous membrane has occurred and has ended.
- When contact with a single patient and his/her surroundings, or a contaminated body site on a patient has ended.
- When there is an indication for hand hygiene.(215)

After glove removal and hand washing, hands should not touch potentially contaminated environmental surfaces or items in the patient's room to avoid cross-infection.

Aprons/gowns: The necessity to wear an apron/gown is based on risk assessment of the anticipated level of contact with the patient/resident and patient/resident's environment. Nurses' uniforms have been shown to be contaminated with *C. difficile* (221) and may represent direct or indirect contamination (e.g., from the environment) but not necessarily implicate transmission. (23) The need for and the type of apron/gown selected is based on the nature of patient/resident interaction, including anticipated degree of contact with infectious material and potential for

blood and body fluid penetration of the barrier.(212) In addition to wearing apron/gowns as required for Standard Precautions, wear aprons/gowns:

- When entering a room for all interactions that may involve contact with the patient/resident or potentially contaminated areas in the patient/resident's environment.

The apron/gown should be removed and hands washed:

- Immediately after contact with any infective material.
- Before leaving the patients/residents environment.

2.6.4.iv Cleaning and disinfection of equipment and the environment in a healthcare facility

The environment is an important reservoir for nosocomial CDI.(144) Environmental contamination with *C. difficile* spores is common(222, 223); spores can survive for prolonged periods in the environment(224-226) and have been found in far greater quantities in the environment of patients/residents with CDI in comparison with non-carriers.(2, 222, 224) The level of staff hand contamination is proportional to the level of environmental contamination.(222, 223) Environmental contamination is specifically common on frequently touched sites such as bed frames and in areas near the toilet and on commodes and can be persistent despite cleaning.(23, 206, 210, 227) *C. difficile* spores are resistant to many commonly used disinfectants(228, 229) and some non-chlorine based cleaning agents may lead to an increase in sporulation.(230) Current international guidelines recommend environmental decontamination (after cleaning) with chlorine - releasing agents at a concentration of at least 1,000 parts per million (ppm) available chlorine (1,000ppm av cl).(23, 144, 206, 211) (Table 2.4)

Table 2.4: Summary of international recommendations on environmental decontamination of rooms/bed spaces of patients/residents with CDI

Available chlorine* and frequency of cleaning/disinfection	Guideline
At least daily environmental cleaning using chlorine-containing cleaning agents (at least 1,000 ppm available chlorine).	Department of Health, England, 2009(206)
Regular environmental disinfection using sporicidal agents, ideally chlorine-containing agents (at least 1,000 ppm available chlorine). The choice of cleaning regime will depend on local policy.	ESCMID 2008 (23)
Use chlorine-containing cleaning agents (with at least 1,000ppm available chlorine) or other sporicidal agents to address environmental contamination in areas associated with increased rates of CDI.	SHEA/IDSA 2010(144)
In units with high rates of endemic <i>C.difficile</i> infection or in an outbreak setting, use 5,000pmm available chlorine for routine environmental disinfection e.g. daily, when spills occur and when visibly soiled.	CDC Sterilisation and disinfection guidelines 2008(231)

* Note: Contact times of chlorine containing agents not stated as their use must be in accordance with manufacturer's instructions, in use directions and health and safety precautions.

It is recommended that the rooms of patients/residents on Contact Precautions are prioritised for frequent cleaning and disinfection (e.g., at least daily) using a sporicidal disinfectant with a focus on frequently-touched surfaces (e.g., bed rails, over bed table, bedside commode, lavatory surfaces in patient bathrooms, door knobs) and equipment in the immediate vicinity of the patient.(212) Environmental faecal soiling should be cleaned and disinfected immediately.

Equipment used for patients/residents

- Should be in a state of good repair in order to facilitate effective cleaning and disinfection.
- That comes into close contact with a patient/resident with CDI should be adequately cleaned and disinfected using a sporicidal disinfectant. (Table 2.4)

- Likely to be faecally contaminated e.g., the under surfaces of commodes, should be cleaned and disinfecting thoroughly.
- Where possible should be dedicated to a single patient/resident to avoid sharing between patients/residents (e.g., thermometers, sphygmomanometers, stethoscopes, blood glucose metres, hoist slings, patient wash bowls).

Chlorine-containing agents are not without their drawbacks. In addition to being potentially corrosive at high concentrations when used over a long time period and staff and patient/resident sensitivities, chlorine-based disinfectants are sub-optimally effective in cleaning surfaces. Therefore, visibly dirty surfaces need to be cleaned with a detergent first, before using a chlorine-based disinfectant.(232) The concern is that on a busy unit, staff will not perform this extra step. The commercial availability of products that combine both detergent and chlorine-releasing agent may be useful in this regard.(233) To minimise staff and patient/resident sensitivities when using chlorine containing agents, healthcare workers must comply with health and safety precautions and the manufacturer's instructions.

A systematic review of ten studies which evaluated airborne hydrogen peroxide disinfection (in the form of vapour or dry mist) of hospital environments included three studies which evaluated its effectiveness in eradicating *C. difficile* environmental contamination.(234) In two of three included studies, fewer environmental sites were found to be culture positive for *C. difficile* after the application of hydrogen peroxide when compared with the control decontamination methods. The main disadvantage identified of this technique is that prior cleaning is required to remove soiling and the time required is proportional to the size of the area to be disinfected. In addition, airborne hydrogen peroxide requires clinical areas to be vacated, and the vapour form requires them to be sealed also. These requirements increase both the time and the costs and may be impractical to apply as a routine option.(235) These issues have also been highlighted in additional published guidelines.(206) The above systematic review concluded that further studies were needed to assess effectiveness, safety, costs and applicability of airborne hydrogen peroxide against other available cleaning methods.(234)

Cleaning by detergent alone has been shown to be insufficient to decontaminate and studies have demonstrated there is a need for a sporicidal product. In an *in vitro* study comparing five agents (three chlorine containing, one detergent and one containing hydrogen peroxide), only chlorine containing products inactivated *C. difficile* spores. Non-chlorine products were not sporicidal and actually increased sporulation.(233) Following in-situ experiments, Barbut concluded that hydrogen peroxide dry-mist disinfection might provide an appropriate alternative to sodium hypochlorite for the eradication of *C. difficile* spores in patient environments, but that further studies would be necessary to compare the impact of the disinfection processes on the incidence of CDI and to evaluate the costs and benefits of each process.(236)

A recent review concluded that while new technologies such as gaseous decontamination (gaseous hydrogen peroxide, chlorine dioxide and oxone), air decontamination and UV-based technologies may act as an alternative/supplement to manual disinfection, more extensive field trials are necessary to determine their cost effectiveness in the healthcare setting.(235) Although a number of evaluations of sporicidal activity of different chemical agents have recently been published, several authors report the lack of standardisation for testing methods. A UK task force on sporicidal disinfectants has been formed to develop a standard for laboratory testing of disinfectants which claim to have activity against *C. difficile* spores.(237-239)

Terminal cleaning and disinfection with sporicidal disinfectants of isolation rooms should be performed after discharge of the CDI patient. Prior to initiating environmental cleaning and disinfection, all privacy, shower and window curtains must be removed and sent for laundering. All disposable items including paper towels and toilet paper must be discarded.

In the event of an outbreak, the frequency with which environmental cleaning and disinfection is performed should be increased on the affected wards and monitored.

Environmental screening for *C. difficile* is not recommended after routine cleaning, however, it may be used to document environmental contamination or poor cleaning/disinfection procedures especially in an outbreak situation.(23, 144)

Use of disposable equipment has proven effective to control CDI outbreaks and the use of disposable non-critical patient care equipment e.g., blood pressure cuffs are recommended. (212, 240) If the use of common equipment or items on multiple patients/residents is unavoidable, e.g., patient hoist, these should be adequately cleaned and disinfected immediately after use and before use for another patient.

Bedpans/commode utensils should be placed directly into the washer-disinfector (which will automatically empty, clean and disinfect) and not placed temporarily on any surfaces. To achieve adequate disinfection, staff should ensure that bedpan washers heat to a minimum of 80°C and maintains that temperature for one minute.(241) Bedpan washers in poor working condition are a potential cross-infection risk.(25) Manual bedpan/commode utensil cleaning/disinfection must be avoided: staff must not empty bedpans into toilets/slucce unit and must no longer use spray wands as it poses a very high risk for environmental contamination.(242)

Covered bedpans/commode utensils should be hand held and contact with any surfaces (i.e., curtains, door handles) during the transport of the contaminated bedpan should be avoided. Cleaned commodes and bedpans should be stored under dry conditions.

No additional measures are required for cutlery and crockery. The combination of hot water and detergents used in dishwashers is sufficient to decontaminate dishware and eating utensils.

Scheduled maintenance and validation records according to appropriate standards(241) and manufacturers' instructions should be maintained for all automatic cleaning and disinfection machines, i.e., bedpan washers, laundry washing machines and dishwashers to ensure appropriate cleaning and disinfection. All equipment used for patients/residents should be in a state of good repair in order to facilitate effective cleaning.

2.6.4.v Management of laundry and healthcare risk waste

All laundry should be treated as potentially infectious and placed directly into an alginate or water-soluble bag at the bedside.(243) The sealed bag should then be placed immediately into a laundry bag according to organisational and national guidelines.(244) Staff must not manually sluce, soak or sort through soiled laundry.(245) Normal hospital laundering processes are effective for removing *C. difficile* contamination. Linen should be heat disinfected as described above. Thorough washing and rinsing at 40-50°C of fabrics requiring lower temperatures will remove most organisms. Disinfection can be achieved at low temperatures by introducing 150 ppm of chlorine into the penultimate rinse.(243) Although studies theorise that uniforms may transmit HCAI, no studies have demonstrated this in practice, therefore home laundering of uniforms for a 10-minute wash at 60°C provides effective decontamination.(246, 247)

Waste contaminated with diarrhoea from a suspected or known CDI patient should be disposed as healthcare risk waste within a healthcare facility.(248) Non-contaminated waste should be disposed as healthcare non-risk waste, e.g., paper towels, newspapers. All refuse bins should be hands free (i.e., lid cannot be opened by hand and must be pedal operated) to prevent soiling/contamination of the waste container and possible hand contamination.

2.6.5 What can you do if you have no single room available?

The following are responsible for implementation of **recommendation 44**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 44

There should be clear risk assessment protocols to prioritise patients/residents for isolation who are either suspected or confirmed with transmissible infections requiring isolation. Risk assessments should clearly document if patients/residents cannot be placed in a single room due to insufficient single rooms and reported to healthcare senior managers as an infection prevention and control risk. **Grade D**

Isolating patients/residents with CDI in a single room with ensuite and clinical hand wash sink remains the gold standard for prevention of cross infection.(213) There should be clear protocols for risk assessment of patients/residents with suspected or confirmed transmissible infections requiring isolation. Risk assessments should be clearly documented if patients/residents cannot be isolated due to insufficient single rooms. Patients/residents should only be cohorted after a risk assessment is performed by the patient's clinical and nursing team and in consultation with the bed manager and infection prevention and control team where available.

2.6.6 When can Contact Precautions be discontinued?

The following are responsible for implementation of **recommendation 45**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 45

Contact Precautions should be maintained until the patient/resident has had no diarrhoea for at least 48 hours and has had a formed or normal stool for that patient/resident. **Grade D**

There is a general consensus that patients/residents with CDI should remain in isolation with Contact Precautions until they are at least 48 hours symptom free.(23, 144, 206) However, many guidelines also include further detail that bowel movements should be back to normal for that patient/resident, i.e., as referred to in the Bristol Stool Chart.(23, 206) Retesting for *C. difficile* toxin ('test of cure') is not necessary to determine the end of isolation and Contact Precautions and should not be done.

2.6.7 When is it safe to transfer patients/residents?

The following are responsible for implementation of **recommendations 46-49**:

Healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians and Infection Prevention and Control Team.

Recommendation 46

For patient/resident transfer to another healthcare facility, if the transfer is not urgent, the receiving healthcare facility should only accept a patient/resident currently being treated for CDI if the patient/resident has had no diarrhoea for at least 48 hours and has had a formed or normal stool for that patient/resident. **Grade D**

Recommendation 47

For patient/resident transfer within a healthcare facility, movement should be limited to essential purposes only. **Grade D**

Recommendation 48

Prior to an internal patient/resident transfer (within a healthcare facility), the receiving department should be informed of the patient/resident's CDI status and the need for Contact Precautions. **Grade D**

Recommendation 49

On the patient/resident's discharge, the patient/resident's history of CDI should be included in the discharge letter and communicated clearly to the GP and to healthcare workers who may be taking care of the person. This communication will facilitate appropriate antimicrobial prescribing and reduce the risk of a possible recurrence. **Grade D**

Good communication is essential, prior to transfer/discharging patients/residents with CDI, or a history of CDI, to other healthcare facilities and the home. This facilitates appropriate precautions to be put in place to prevent cross-infection in the case of transfer to a healthcare facility and appropriate antimicrobial prescribing, if required, to prevent CDI recurrence. Prior to transfer/discharge a plan for future care should be prepared by medical and nursing staff and discussed with the patient. This care should be communicated to the relevant healthcare professionals (e.g., receiving team, GP, Public Health Nurse).(95)

The transfer of patients/residents between wards or between healthcare facilities has been implicated in the spread of CDI. Movement of patients/residents between wards was identified as a contributory factor in two outbreaks of CDI.(24, 209)

- The movement and transport of the isolated patient with CDI should be limited to essential purposes only.
- If transport or movement is necessary, staff should ensure that Contact Precautions are maintained to minimise the risk of transmission to other patients/residents and the contamination of environmental surfaces or equipment.
- Performing a 'test of cure' after CDI treatment is not recommended and not required prior to transfer/discharge.
- Prior to internal patient/resident transfer, the receiving department should be informed of the patients/residents CDI status and the need for Contact Precautions.

2.6.7.i Transfers to other healthcare facilities

For transfers to another healthcare facility, if the transfer is not urgent, the receiving healthcare facility should only accept a patient/resident currently being treated for CDI if

- the patient/resident has had no diarrhoea for at least 48 hours
and
- has had a formed or normal stool for that patient/resident.

If transfer to another healthcare facility is medically necessary for a patient/resident with symptomatic CDI, the receiving healthcare facility should be informed of the patients/residents CDI status/history.(95) Transport personnel (e.g., porters, emergency medical technician) and the receiving healthcare facility should be informed of the need for Contact Precautions. Contaminated aprons/gowns and gloves should be removed and disposed and hand hygiene performed prior to transporting patients/residents. Apron/gown and gloves should be donned to handle the patient/resident at the transport destination.(212)

Prior to accepting a patient/resident with CDI, it is the responsibility of the receiving facility to ensure compliance with single room, clinical hand washing sink, en-suite facilities and Contact Precautions. The receiving ward/department, bed manager must be notified.

Transport equipment (stretcher, bed, wheelchair) used for the transfer should be cleaned and disinfected immediately after use, i.e., before use with another patient/resident.

2.6.8 How should patients/residents with confirmed CDI be managed at home?

The following are responsible for implementation of **recommendation 50**:

Healthcare facility Senior Management team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Clinicians, Infection Prevention and Control Team and Public Health Nurses.

Recommendation 50

Patients/residents and their families should receive an information leaflet¹⁶ outlining appropriate precautions that should be taken by the person with CDI and their family. The risk of household contacts acquiring *Clostridium difficile* once a patient/resident has been discharged is considered very low but this risk may be higher for those household contacts receiving antimicrobial therapy.

Grade C

Practical Guidance

In the home, the following precautions are advised (all **Grade D**):

Hand washing

Hand hygiene is the single most important infection prevention and control measure.

- Carers, including family and healthcare workers if assisting with personal care, should wash their hands thoroughly with soap and water and dry.
- The person with CDI should wash their hands thoroughly with soap and warm water and dry them after using the bathroom, before preparing food and before eating.

Personal protective equipment (PPE)

Disposable gloves and aprons should be worn by healthcare workers when attending to a patient/resident who has diarrhoea. These should be removed and disposed of immediately after the episode of care. Hand hygiene should then be carried out as described above.

Waste and environmental decontamination

- Waste soiled with diarrhoea (e.g. incontinence wear) should be disposed of in a safe manner (i.e. the waste bag should be sealed to ensure that the bag will not leak or that the outside of the bag could become contaminated).
- The person with CDI should be facilitated and encouraged to maintain good personal hygiene standards:
 - o Personal items such as towels and face cloths should not be shared.
 - o Persons with CDI should avoid using the same toilet as other family members if possible. If this is not possible, after an episode of diarrhoea, the bathroom should be first cleaned with detergent and water and then disinfected with a mixture of bleach and water as instructed on the container. Special attention should be paid to frequently touched sites (e.g. sink taps, flush handle, toilet seats) and the toilet bowl.
- The immediate environment of the person with CDI should be cleaned with detergent and water, paying particular attention to hand contact surfaces (e.g. bedside table, hand rails). If soiled, following cleaning, the area should then be disinfected as above.

Laundry

- Used laundry should be machine-washed separately from other washing on the hottest wash cycle suitable for linen and clothing.
- Laundry soiled with diarrhoea should first be machine washed using a cold pre-wash cycle and then washed using detergent powder/liquid at the hottest wash cycle tolerated for the clothing.

Community healthcare workers may find “*Infection Prevention and Control - An Information booklet for Home Helps and Personal Assistants*” useful.¹⁷

¹⁶ <http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/Factsheets/File.2946.en.pdf>

¹⁷ <http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Factsheet/>

On the patient/resident's discharge, the patient/resident's history of CDI should be included in the discharge letter and communicated clearly to the GP and to healthcare workers who may be taking care of the person. This communication will facilitate appropriate antimicrobial prescribing and reduce the risk of a possible recurrence.

Communication regarding the patient/residents history of CDI at the receiving healthcare facility/GP is an essential part of safe care as describe above. This communication will facilitate appropriate antimicrobial prescribing if required to reduce the risk of a possible recurrence. The principles of caring for the patient with CDI are similar irrespective of whether the patient is located in a healthcare facility or at home. Detailed guidelines dealing with specific issues that may arise for persons with CDI in the home and the community have been published elsewhere.(249)

In the home, recommendation 50 and practical guidance above summarise the precautions required when caring for persons with CDI. These include good hand hygiene by all (including the person with CDI), environmental hygiene, waste and laundry management.

The absolute risk for secondary CDI among household contacts of index patients is thought to be low. A recent retrospective study reported that five of 1,061 spouses and three of 501 children (under 25 years) living in the same household as the index patient developed CDI.(250) All but one of the secondary cases occurred within two months of the index case. The attack rate was 4.71/1,000 (spouses) and 5.99/1,000 (children), and the relative risk was 7.61 (95% confidence interval [CI], 5.77-9.78) and 90.6 (95% CI, 33.89-487.64) for the three months after the diagnosis in the index case. The authors proposed that one reason for the low transmission rate of *C. difficile* is that the majority of household contacts do not receive antimicrobial therapy during the time when they might be colonised with a *C difficile* strain from the index patient. The paper concludes that, although the relative risk of CDI among household contacts is somewhat increased for a few months, the absolute risk is too low to justify interventions, apart from avoiding unnecessary courses of antimicrobial agents.

2.7 Treatment of patients/residents with CDI

2.7.1 How is the first episode of CDI best treated?

The following are responsible for implementation of **recommendations 51-53:**

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 51

Patients/residents with CDI should be reviewed on a daily basis by the medical and nursing team for deterioration, monitoring the frequency and severity of diarrhoea using the Bristol Stool Chart.¹⁸

Grade D

Recommendation 52

Patient/resident classification by disease severity as outlined in Figure 2.3 is recommended for appropriate management. Common elements of severity scores that may be used in patient/resident assessment include leucocytosis, elevated serum creatinine and age over 60 years.

Grade C

Recommendation 53

Patients/residents with CDI and marked or increasing leucocytosis or other signs of fulminant colitis should undergo prompt CDI management review, to include a surgical assessment. **Grade C**

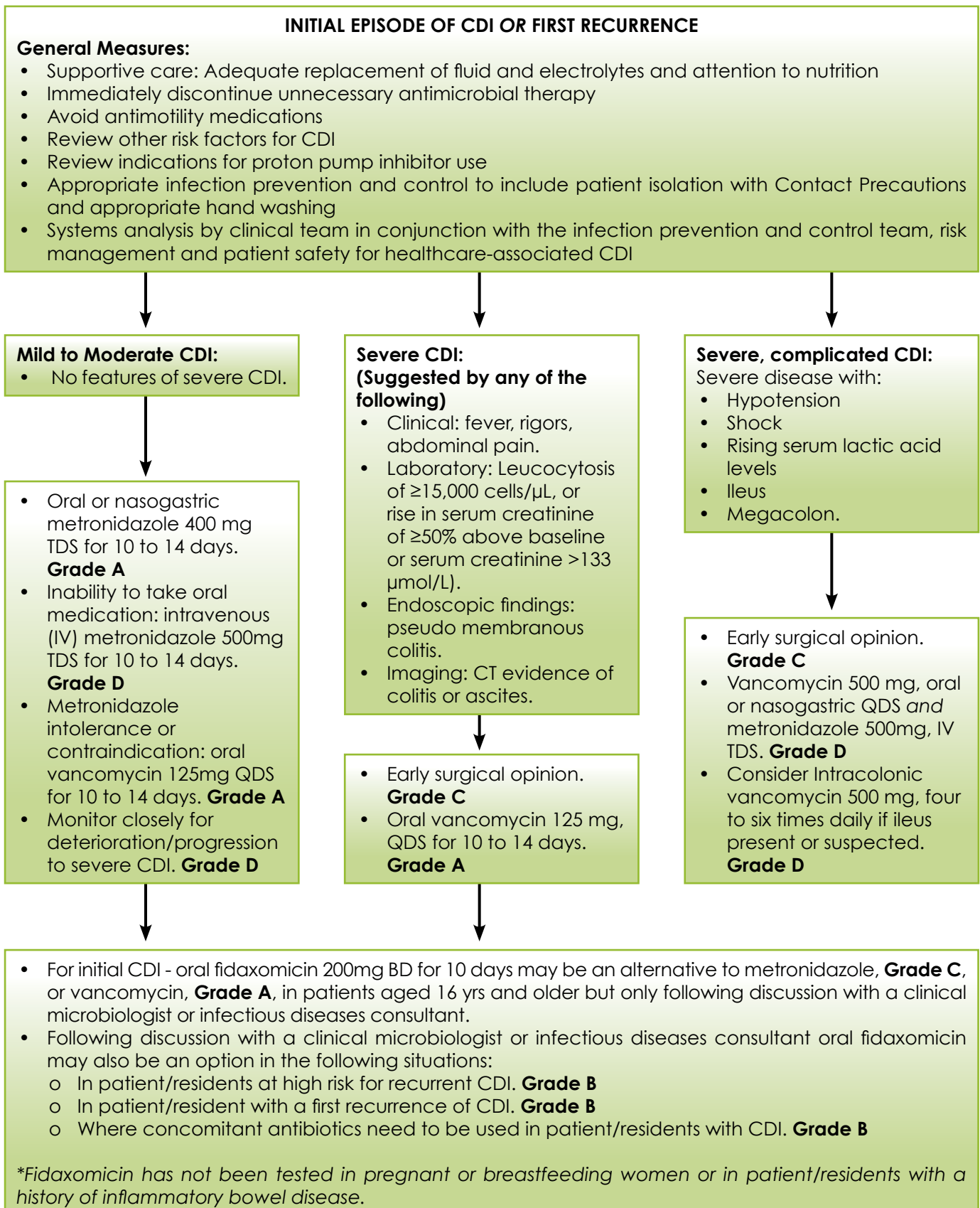
Practical Guidance

- Treatment of CDI is stratified by disease severity and summarised in Figure 2.3.
- To date, there are no published validated clinical prediction scores for CDI or a single specific test for severe CDI.
- **Prescribers Notice**
 - Healthcare staff should use clinical judgement, medical and nursing knowledge in applying the guidance in Figure 2.3 and give due regard to individual circumstances presented by each patient/resident and available resources.
 - Refer to BNF for children or local paediatric formulary for doses of metronidazole and vancomycin for paediatric patients.

¹⁸ <http://www.sthk.nhs.uk/library/documents/stoolchart.pdf>

Practical Guidance

Figure 2.3: CDI disease severity stratification - general and specific treatment measures for initial episode of CDI and first recurrence⁽²⁵¹⁾



The first approach in the treatment of CDI should be, if possible, to stop the precipitating antimicrobial(s). If antimicrobials must be continued for clinical reasons, antimicrobial(s) with a lower propensity to induce CDI should be substituted. Supportive therapy with replacement of fluids and electrolytes is also crucial at the early stage for these patients.

2.7.1.i Classification of CDI by severity

Classification of CDI by severity of disease is important to ensure appropriate clinical decisions are made for patient/resident management. Severe CDI can be difficult to diagnose as there is no single specific test; rather the diagnosis is reached using a combination of clinical, laboratory, radiological and endoscopic findings. Patients/residents with severe ileus or colon wall oedema may not have diarrhoea and the clinical spectrum of severe infection varies considerably. Without diarrhoea, frequently patients/residents are initially misdiagnosed.⁽⁸⁾ Laboratory investigations may not be necessarily sent, therefore, maintaining a high clinical suspicion of CDI is essential. Indeed some authors advocate that CT findings of pan colitis with an appropriate clinical history may be an indication for surgery.⁽⁸⁾ A number of factors have been associated with progression to severe and fulminant colitis including recent surgery (previous 30 days), advanced age, recurrent CDI, increased comorbidity burden (e.g., using Charlson co morbidity index), IBD, immunosuppression and leucocytosis $>16,000/\mu\text{l}$ at initiation of therapy.⁽²⁵²⁾

There are a number of severity scores for CDI, ^(253, 254) however, to date none have been prospectively validated. Two of these scores have been used to predict the outcome of anti-CDI therapy in prospective clinical trials.^(254, 255) A review of eleven such systems that used various combinations of 17 clinical variables to stratify patients into two or three categories outlined the wide range of severity definitions used, and the lack of evidence for inclusion of some variables.⁽²⁵⁶⁾ Common elements of the above severity scoring systems include leucocytosis, elevated serum creatinine, high diarrhoea frequency, abdominal pain, ileus and abnormal CT scan findings. Belmares *et al.* constructed a scoring system based on variables previously suggested that correlate with a higher disease severity: temperature $>38^{\circ}\text{C}$; ileus; hypotension; leucocytosis; and specific CT abnormalities.⁽²⁵³⁾ Likewise, Zar *et al.* developed a similar scoring system in which one point was awarded for each of the following: age over 60 years; temperature $>38.3^{\circ}\text{C}$; albumin $<2.5\text{mg/dL}$ or peripheral WBC count $>15,000\text{cells/mm}^3$; and two points if there was endoscopic evidence of PMC or the patient was admitted to ICU.⁽²⁵⁴⁾ Patients with <2 points were considered to have mild CDI and those with ≥ 2 points were considered to have severe CDI. A more recent scoring system which subdivided CDI into three categories (mild-moderate, severe and fulminant colitis), used eight variables which included number of loose stools daily, fever, leucocyte count, severe abdominal pain, rising creatinine levels, multi-organ dysfunction, complete ileus or toxic mega colon and radiological signs of colitis, ileus or toxic mega colon.⁽²⁰⁶⁾

Recently, a clinical prediction rule (age ≥ 60 years, peak serum creatinine $\geq 1.5\text{ mg/dL}$ and peak leukocyte count of $\geq 20,000\text{ cells}/\mu\text{L}$) was prospectively validated in a multicentre study¹⁹. Patients in the validation group with a low CDI severity score (0 or 1) had an 11.2% risk of severe outcomes as compared to 38.1% in those with a high severity score (2-3). This score may be useful to identify high risk patients who will be likely to benefit from more aggressive therapy including the early administration of oral vancomycin.

2.7.1.ii Choice of anti-CDI therapy

Table 2.5 summarises what agents are available in Ireland for the treatment and management of CDI. Guidelines for general and specific treatment of the initial episode of CDI stratified by disease severity are outlined in Figure 2.3 and practical guidance.

¹⁹ (Personal communication: Dr. Lorraine Kyne).

One review summarised the evidence base for management of CDI in adults.(257) This review outlined the results of eleven randomised trials (1,463 patients), three of which compared metronidazole and vancomycin and eight that compared either vancomycin or metronidazole with another agent. The trials had small sample size and varied significantly with respect to methodology and definitions used. In addition, the effect of ribotype was analysed in one trial only. The review concluded that no agent is clearly superior for the initial cure of CDI though recurrence is less frequent with fidaxomicin when compared with vancomycin. There was no significant difference in initial cure, recurrence, duration of diarrhoea or clearance of toxin/organism between vancomycin and metronidazole. In the past, it was thought that metronidazole was a better choice for treatment of mild to moderate CDI on the basis that vancomycin could predispose to VRE; however, both agents have now been linked with the emergence of VRE.(258) Cost may therefore influence the decision to use one drug over the other with metronidazole the significantly cheaper drug at present (Table 2.5). The evidence supporting the superiority of vancomycin over metronidazole for treatment of severe CDI is not strong and comes from one study only. In this study the per protocol subgroup and modified intention to treat analysis demonstrated a significant difference; however, a strict intention-to-treat analysis did not.(257) The authors of the review concluded that, as severe CDI is associated with significant morbidity and mortality, that the use of vancomycin in this context was reasonable.

Table 2.5: Drugs available for treatment of CDI in Ireland – See Figures 2.3 and 2.4 for treatment guidelines.

Drug (generic; trade)	Formulation	Dose, frequency & duration ^a	Cost of therapy € ^b
Metronidazole (Flagyl®)	400mg tablets	400mg po tds for 10 days	3.55
	200mg/5ml suspension	400mg po tds for 10 days	22.20
	500mg/100ml infusion	500mg iv tds for 10 days	77.90
Vancomycin (Vancocin®; several manufacturers of injection)	125mg capsules	125mg po qds for 10 days	194.57
	Injection compounded as 125mg/5ml oral solution ^c	125mg po/ng qds for 10 days	306.30 ^c
		500mg ng qds for 10 days	1225.20 ^c
		Oral vancomycin taper/pulse ^g	262.67 (capsules) 459.45 (solution) ^c
Fidaxomicin (Dificlir®)	200mg capsules	200mg po bd for 10 days	1500
Rifaximin (Normix®)	200mg capsules ^d	400mg po tds for 20 days	174.99 ^d
S. boulardii (Perenterol®)	250mg capsules ^e	500mg po bd for 28 days	151.20 ^e
IVIG (Flebogamma®; Kiovig®)	Flebogamma DIF® IV solution	400mg/kg iv single dose ^f	1758.40 ^f
	Kiovig® IV solution	400mg/kg iv single dose ^f	2184 ^f

Notes.

- Dose, frequency, and duration as per recommendation from guidelines or trials and do not imply therapeutic equivalence.
- Drug costs obtained from pharmacy drug dispensing and ordering software (CliniSCRIPT.NET© 1987-2012), except where indicated. Accessed March 2014
- Price from specialist manufacturer (ref. The cost is 50 to 80% lower if Vancomycin solution is made for hospital in-patients/residents by the pharmacy department.
- 200mg capsules not licensed in Ireland supplied on named-patient/named-doctor basis by drug importing company. Licensed preparation Targaxan® 550mg tablets available however no information for treatment of CDI.
- Drug not licensed in Ireland, supplied on named-patient/named-doctor basis by drug importing company.
- Cost based on dose for 70kg adult patient.
- Oral Vancomycin 125mg qds for 7 days, then 125mg bd for 7 days, then 125mg daily for 7 days, then 125mg every other day for 7 days, then 125mg every 3 days for 7 days. (259)

2.7.2 Can anti-motility agents be used in the treatment of CDI?

The following are responsible for implementation of **recommendations 54-55**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 54

Anti-motility agents should be avoided as adjunctive treatment for initial episodes of CDI. **Grade D**

Recommendation 55

Anti-motility agents may play a role in the management of persistent diarrhoea in patients/residents who are stable and not unwell (normal white cell count and absence of abdominal pain or distention) despite more than 20 days treatment for CDI. The potential benefits in these patients/residents include more rapid resolution of diarrhoea and symptom relief for the patient/resident and also a theoretical reduction of environmental contamination with infected stool. **Grade D**

Practical Guidance

- The decision to use anti-motility agents requires a careful risk/benefit assessment taking into account the duration and severity of CDI.
- The potential risks of using anti-motility agents in CDI include obscuring symptoms of CDI and precipitating complications such as ileus or toxic megacolon.

At present, there is a lack of definitive data to support or refute the use of antimotility agents as adjunctive therapy for CDI. The recommendation to avoid antimotility agents in CDI has been based on theoretical rationale, anecdotal evidence, case reports and studies.(144, 260) The pathological effects of *C. difficile* are mediated by the secreted toxins A and B, which cause colonic mucosal injury and inflammation.(261, 262) The proposed hypothesis is that decreased intestinal peristalsis may allow for increased contact time between *C. difficile* organisms, the toxins produced, and the mucosal epithelium leading to worsening outcomes.(189, 263, 264) There have been several case reports describing adverse events, such as toxic megacolon, exacerbation of colitis, and systemic infection, associated with the use of antiperistaltic agents for CDI.(265-269) The above hypothesis has been challenged in a recent systematic review.(270). Data was gathered from case reports or case series and one retrospective review. The authors found little evidence to support the hypothesis that worsened outcomes are associated with antimotility therapy of CDI. They also proposed that antimotility agents when combined with active antibacterial CDI treatment may provide symptomatic relief to patients/residents with CDI diarrhoea, but evidence base is weak and more rigorously controlled studies are needed. A randomised, double-blinded, placebo-controlled pilot study to test this hypothesis was conducted in 2009(271) but, to date, no results have been published. In an editorial commentary of the above systematic review, Gerding provides a cautionary note to the recommendations of Koo *et al.* and highlights certain discrepancies.(272) Evidence for lack of adverse effects when antimotility agents were used in CDI therapy was from single retrospective study with small numbers (23 patients).(273) They also extrapolated evidence from the use of antimotility agents in treatment of travellers 'diarrhoea.

Current treatment guidelines for CDI from USA(144), UK(206), and Europe(260) recommend that antimotility agents should be avoided especially in the acute setting. However, the UK/DOH 2008 guidelines do make a recommendation for the use of antimotility agents in patients/residents with persistent diarrhoea despite prolonged antibacterial CDI treatment. It is also recommended as a treatment option in multiple recurrent CDI, especially if there is evidence of malnutrition or wasting. However, in both recommendations, the antimotility agents are used alone, the patient must meet specific criteria, and close supervision is required.

2.7.3 When do you refer a patient/resident with CDI for surgical review?

The following are responsible for implementation of **recommendations 56-57**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 56

Patients/residents with severe CDI should be managed by a multidisciplinary team to include a clinical microbiologist and/or infectious diseases physician and a surgeon. Surgical review should be requested at an early stage once severe or severe complicated CDI is clinically suspected as outlined in Figure 2.3. **Grade C**

Recommendation 57

If the multidisciplinary team agrees that surgery is indicated, at present, subtotal colectomy with an end-ileostomy is the recommended procedure. Segmental resection that risks leaving diseased colon behind is NOT recommended. **Grade C**

Practical Guidance

- The decision that surgical management is required for CDI should be taken by the multidisciplinary team. Surgery should be considered if there is systemic inflammation and the patient's condition has deteriorated and is not responding to anti-CDI therapy (including toxic megacolon, an acute abdomen and severe ileus).
- Serum lactate may serve as a marker for severity and evidence would suggest that surgery should be performed before lactate exceeds 5.0mmol/L.
- Recently, loop ileostomy and colonic lavage combined with antimicrobial treatment (intra-colonic ante-grade vancomycin and IV metronidazole) has been proposed as an alternative to colectomy in the treatment of severe, complicated CDI, however further studies are required to evaluate this approach.

There are many unanswered questions with respect to the surgical management of CDI. Evidence from large-scale studies to assist in guiding surgical management is lacking. There are no published randomised, controlled trials evaluating the role of surgery in managing PMC, therefore, recommendations are based mainly on non-randomised observational cohort or case control studies. There are no clear guidelines on how and when to refer patients for surgical assessment or clear protocols to guide the timing of surgical intervention. CDI-related colectomy rates between 2.7 and 32 colectomies per 1,000 CDI cases have been reported, though many of these studies are single centre and/or reported in a CDI outbreak setting.(274-282) A recent multicentre study in a non-outbreak setting reported an overall colectomy rate of 8.7 per 1,000 CDI cases (0 to 23 across hospitals).(283) Onset of disease outside hospital was an independent risk factor for colectomy with colectomy rates for community-onset CDI significantly higher than healthcare-onset CDI (16.5 and 4.3 per 1,000 CDI cases respectively). A variety of factors associated with improved survival after CDI-related colectomy has been identified. In general, colectomy performed early in the course of fulminant colitis, before the patient becomes critically ill, is associated with improved survival. (275, 277, 279, 284, 285) The reported post-emergency colectomy mortality of CDI patients is high (48%-57%) with a variety of reported indications for surgery including acute abdomen, radiological signs of acute disease, toxic mega colon, perforation, peritonitis and failure of medical therapy.(8, 286) Why post-operative mortality in these patients is so high is unclear though delays in surgical intervention, inappropriate patient selection because of a lack of clearly defined guidelines and difficulty in predicting the clinical course of CDI are thought to contribute.(287)

2.7.3.i Which patients should be considered for surgery?

It is generally agreed that severely ill patients with CDI should have an early surgical assessment for possible colectomy.(281, 288, 289) While there is evidence to suggest that abdominal CT offers a high degree of sensitivity in diagnosing PMC, it does not aid the surgeon in predicting the need for surgical intervention.(286)

The progression to fulminant CDI requiring surgery is highly variable. It is not clear what initiates the transition from mild to severe disease, nor why some patients develop severe CDI and others don't though host (age, underlying co morbidities, immune status) and organism (virulence, antimicrobial resistance) factors clearly play a role. Several studies have attempted to establish what clinical clues could be used to predict which patients may have a poor post-operative outcome (i.e., attempting to offer guidance on surgical timing and patient selection). Overall, the evidence suggests that patients with CDI and marked or increasing leucocytosis should undergo a prompt CDI management review, to include a surgical assessment, however, which criteria to use to select patients that may benefit from surgery is not clear.

Shock, vasopressor therapy, and high leucocytosis correlates with increased mortality after colectomy.(284) In an ICU setting during a 027 outbreak, colectomy was lifesaving in patients aged ≥ 65 years and with a leucocytosis of $\geq 20 \times 10^9/L$ or serum lactate between 2.2 and 4.9 mmol/L.(285) It was suggested that colectomy should be considered before lactate levels increase to ≥ 5 mmol/L. The main indications for colectomy included shock despite vasopressors, mega colon, failed medical management and perforation. An eight year retrospective review of 36 adult patients with severe CDI who underwent colectomy revealed that preoperative vasopressor requirement and preoperative intubation were risk factors for post-operative mortality and should lead to rapid surgical intervention.(277) In this series, a minority of patients with CDI had surgical management (36/3237); with no standard indication for surgery (common indications were haemodynamic instability, peritonitis and failure to respond to medical management). Interestingly, age, APACHE II score²⁰, lactate, immunosuppression or prior metronidazole therapy had no impact on postoperative mortality in this group. Likewise, a 12-year retrospective review of 73 patients undergoing colectomy for CDI found that vasopressor requirement, mental state changes and duration of medical management of CDI pre-operatively were significant predictors of mortality.(280) While mental state changes and vasopressor requirements are general indicators of severe infection, the longer duration of pre-operative medical therapy in the mortality group supports their conclusion that post-operative mortality can be reduced by prompt surgical intervention once medical management has failed. Again, a minority of patients with CDI required surgical management (73/5718) and age, ASA score, underlying immunosuppression, pre-existing conditions (diabetes, IBD, respiratory, renal or coronary artery disease) or antimicrobial treatment for *C. difficile* had no impact on mortality. In addition to a longer trial of medical management, patients that survived had significantly lower lactate levels than the mortality group; however, this association was not borne out on multivariate analysis. Likewise, a more recent paper on 130 patients with severe CDI that required emergency colectomy reported that predictors of mortality included a pre-operative lactate of > 5 mmol/L (75% mortality rate), leucocytosis of $> 50 \times 10^6/L$ (73% mortality) and albumin < 15 g/L (52% mortality).(290)

2.7.3.ii When to operate?

There are no clear guidelines to establish when medical management has failed, no time frame that defines how long medical management should be attempted or no clearly identified risk factors that should trigger surgical intervention before shock and end organ damage ensue.

²⁰ APACHE II - Acute Physiology and Chronic Health Evaluation II. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985). "APACHE II: a severity of disease classification system". *Critical Care Medicine* **13** (10): 818-29.)

A retrospective review of 13 post colectomy patients found that elevated white blood cell count (34,600/ μ L or greater), hypoalbuminemia (1.5 g/dL or less), septic shock with requirements of vasopressors, and respiratory failure were independent predictors of mortality. Patients who underwent colectomy earlier (mean time from presentation to surgery 2.4 ± 1.5 days) had decreased mortality. Interestingly, age, presenting symptoms, co morbidities, creatinine levels, and CT scan findings did not influence outcome.(291) A recent review proposed the following criteria that may assist in the decision making process and outlined a management algorithm. (292) The authors recommended that patients with confirmed or suspected CDI who failed to respond to maximum medical therapy and develop three of the following should be referral for surgical assessment: abdominal pain, abdominal distension, localised tenderness, pyrexia $>38^{\circ}\text{C}$ and tachycardia >100 beats per minute. In addition, if the patient is over 65 years old and develops four of the following, they should be considered for an emergency colectomy: WBC $>16 \times 10^9$ /l, lactate >2.2 mmol/l, albumin <30 g/l, blood pressure <90 mm Hg and CT/endoscopy evidence of severe colitis in spite of maximum anti-CDI therapy.

2.7.3.iii Surgical technique

Although selected patients are sometimes considered for segmental colectomy or even defunctioning colostomy combined with intensive medical therapy, most authors advocate total or subtotal colectomy and ileostomy as the operation of choice.(277, 279, 280, 284, 285, 293-295) In the past, partial colectomy with removal of the grossly affected area of the colon was performed in an attempt to decrease morbidity, however as affected colons could potentially be left behind leading to relapses/disease progression this is no longer advocated.(287) However, most studies are small with the largest reported series consisting of 73 patients.(278, 293, 296) It is worth noting that the external appearance of the colon may be deceptively normal despite severe mucosal disease, and this should not influence the decision to resect the entire colon.(278) Recently loop ileostomy and colonic lavage has been proposed as an alternative to colectomy in the treatment of severe, complicated CDI.(297) In this study, a loop ileostomy was created in 42 patients with severe, complicated CDI and intraoperative colonic lavage performed with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy. This was followed by postoperative antegrade instillation of vancomycin flushes via the ileostomy. Forty-two patients were treated during this time period. The operation was accomplished laparoscopically in 35 patients (83%). This strategy resulted in significant reduced mortality compared to their historical population (19% vs. 50%; odds ratio, 0.24; P = 0.006) with preservation of the colon in 39 of 42 patients (93%).

2.7.4 What is the role of fidaxomicin?

The following are responsible for implementation of **recommendation 58**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 58

Following discussion with a clinical microbiologist or consultant in infectious diseases, fidaxomicin may be used in these situations:

- As an alternative to vancomycin for adult patients/residents with mild-moderate or severe CDI. **Grade A**
- In patients/residents at high risk for recurrent CDI. **Grade B**
- With a first recurrence of CDI. **Grade B**
- Where concomitant antibiotics need to be used in patients/residents with CDI. **Grade B**

Practical Guidance

- In the case of CDI due to PCR ribotype 027, fidaxomicin was not associated with fewer CDI recurrences (in contrast to reduced recurrent CDI due to non 027 ribotypes). **Grade B**
- No clinical trials or studies have directly compared the efficacy or safety of fidaxomicin with metronidazole, however expert opinion would consider fidaxomicin to have similar advantages to vancomycin. **Grade C**

Fidaxomicin, is a poorly absorbed macrocyclic antimicrobial with potent in-vitro activity against *C. difficile* and limited activity against normal faecal flora.(298) Fidaxomicin was given market authorisation in Ireland on December 2011. The evidence supporting the licensed indication is from two recent double blind, randomised controlled phase III trials. One trial was conducted in North America (study 003) and the other in Europe and North America (study 004), both trials studied the safety and efficacy of fidaxomicin (200mg po bd) vs. vancomycin (125mg p qds) for 10 days in patients aged 16 years and older with mild to severe CDI.(299) In both studies fidaxomicin was found to be non-inferior to vancomycin with regard to clinical cure; in the modified ITT group (mITT) for study 003 (fidaxomicin 88.2% versus vancomycin 85.8%) and for study 004 (fidaxomicin 87.7% versus vancomycin 86.8%). A secondary outcome measure of the trials was the rate of recurrence for CDI. The recurrence rate was significantly reduced in patients given fidaxomicin compared with vancomycin (mITT group): 15.4% versus 25.3% (p=0.005) in study 003 and 12.7% versus 26.9% (p=0.0002) in study 004. These studies also showed that in patients infected with the aggressive NAP1/B1/207 strain of CDI, there was no significant difference in recurrence rates between fidaxomicin and vancomycin (mITT): 27% vs. 21% in study 003 and 22% vs. 38% in study 004. What implication this particular finding has for clinical practice will depend on the current prevalence rate of this strain in Ireland.

In a post-hoc analysis of the two studies, Mullane *et al.* (300) noted that concomitant antimicrobials were prescribed for 275 patients (27.5% of total). In the absence of concomitant antimicrobials use during the 10 days treatment phase, clinical cure rates for fidaxomicin and vancomycin were similar (92.3% versus 92.8%; p=0.80). However, when patients received one or more antimicrobials concurrently, clinical cure rates was 90% versus 79.4% (p=0.04), respectively. Recurrence rates were lower with fidaxomicin compared to vancomycin (16.9% versus 29.2%; p=0.048) when patients received other antimicrobials. Post-hoc analysis of the combined positive RCTs reported that in patients with a first recurrence of CDI, fidaxomicin was superior to vancomycin in preventing a second recurrence of CDI within 28 days (19.7% versus 35.5%; P<0.05).

Both trials had specific exclusion trial in particular, patients <16yrs old, pregnant or breastfeeding women, and >1 prior CDI episode in the past 3 months. Also, its role in severe complicated CDI has not been fully investigated (see trial exclusion criteria), and there is limited experience in patients with co-morbidities such as renal impairment, hepatic impairment or IBD.

Caution is required when transferring the results of these studies to routine clinical practice as current guidelines would recommend different treatments according to disease severity. Many patients included in the studies had mild to moderate CDI (approximately 60%), for these patients recommended treatment is with metronidazole and not vancomycin. As there are no direct trials comparing metronidazole to fidaxomicin in the treatment of patients with CDI, an indirect comparison has been conducted utilising methodology proposed by Bucher *et al.*.(301) The comparison utilised data from the two pivotal fidaxomicin versus vancomycin studies and the study by Zar *et al.* comparing vancomycin versus metronidazole.(254) The main outcome of this comparison was that there was no difference in clinical cure and recurrence rates between fidaxomicin and metronidazole; however, the odds ratio for clinical cure or recurrence favoured fidaxomicin in non-severe CDI patients but was not statistically significant. The indirect comparison has a number of limitations in terms patient population, methodology and use of a metronidazole dose different to that recommended in current guidelines. With these differences in mind the findings of the indirect comparison should be interpreted with caution.

The evidence available therefore suggests some advantages of fidaxomicin over vancomycin in the treatment of CDI, and subject to a satisfactory pharmacoeconomic analysis and following discussion with a clinical microbiologist or specialist infectious diseases consultant expert in the field, may be used in the following situations:

- As an alternative to vancomycin for adult patients with mild-moderate or severe CDI.
- In patients at high risk for recurrent CDI or with a first recurrence of CDI.
- Where concomitant antimicrobials need to be used in patients with CDI.

A recently published evidence summary from NHS-NICE has suggested similar advice regarding the latter two points.

There have been two analyses conducted in the UK which give some indication regarding cost-effectiveness for fidaxomicin. These are summarised in Appendix 11.

- All Wales Medicine Strategy Group.(302)
- The Scottish Medicines Consortium and Scottish Medical Council.(303)

The cost-effectiveness evaluation performed by the National Centre for Pharmacoeconomics (NCPE) is summarised in Appendix 11. A copy of the report is available at: www.ncpe.ie.

2.7.5 Can you predict patients/residents that are more likely to get recurrence?

Practical Guidance

- A clinical prediction rule based on the presence of two or more of the following has been shown in one study to predict recurrence with a diagnostic accuracy of over 71%: age over 65 years, presence of severe or life-threatening underlying disease (Modified Horns Index of 3 or 4) and use of additional (non-CDI) antimicrobials after discontinuation of CDI therapy. **Grade B**
- Of patients/residents treated for CDI, 20% or more of them will have at least one additional episode.
- Risk factors for recurrence are similar to risk factors for initial episodes and include history of previous CDI (more than one recurrence), increased age, co-morbidity (more severe underlying disease and/or renal failure), functional dependency, and continued use of (non-CDI treatment) antimicrobials after CDI diagnosis and/or after CDI treatment.

Recurrent CDI itself is a significant risk factor with the risk of recurrence increasing significantly with each episode of recurrent CDI.(260, 304, 305) Other risk factors include continued use of antimicrobials other than those used to treat CDI, use of acid anti-secretory drugs, age over 65 years, duration of hospitalisation, underlying disease and immunosuppression.(144, 306-308) The development of a protective antibody-mediated immune response to *C. difficile* toxins also influences a patients risk for recurrent CDI.(309)

Predicting which patients will develop recurrent CDI would be clinically useful. This would enable healthcare facilities to minimise recurrence risk (e.g., avoid concomitant antimicrobials, avoid unnecessary PPIs, etc.) and also by heightening awareness, facilitates prompt diagnosis and treatment of recurrences. The modified Horn's index categorises the severity of a patients underlying illness on the basis of clinical judgment:

1. Mild (single mild illness).
2. Moderate (more severe illness but uncomplicated recovery expected).
3. Severe (major complications or multiple conditions requiring treatment).
4. Fulminant (catastrophic life-threatening illness).

Hu *et al.* (308) developed and validated a prediction tool for recurrent CDI based on three clinical parameters:

- a. Age > 65 years.
- b. Severe or extremely severe underlying disease (modified Horn's Index 3 or 4).
- c. Continued antimicrobial use (other than metronidazole or vancomycin) after CDI treatment.

Patient with a score ≥ 2 were at high risk for recurrent CDI (diagnostic accuracy >72%).

Kyne *et al.* (2001) have also shown that serum IgG antibodies to toxins A and B were higher in subjects with single episode of CDI than in those with recurrent CDI. Adding serum IgG anti-toxin A measurement to Hu *et al.*'s prediction tool did not increase diagnostic accuracy.

2.7.6 How do you manage a patient/resident with first recurrence of CDI?

The following are responsible for implementation of **recommendation 59**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 59

Treatment of the first recurrence is as for the first episode of CDI, stratified by disease severity as outlined in Figure 2.3. **Grade D**

Practical Guidance

The first step in managing possible recurrent CDI is to discontinue the precipitating antimicrobial(s) if possible and to confirm CDI by stool testing as outlined in this guideline. If antimicrobials must be continued for clinical reasons, antimicrobials with a lower propensity to induce CDI should be selected.

All antimicrobial and other drug therapy should be reviewed and consideration given to stopping medicines that can cause diarrhoea, discontinue precipitating antimicrobials if possible, provide supportive therapy and isolate patient with Contact Precautions as outlined in these guidelines. The patient should be observed closely for possible deterioration. The patients/residents nutritional status should also be reviewed and adequate fluid and electrolytes maintained.

If recommendations used to reduce CDI outbreaks are followed, these would help reduce recurrence:

- Restriction of antimicrobial use and good antimicrobial stewardship.
- Reducing exposure to *C. difficile*.
- Interrupting *C. difficile* transmission by using contact isolation and good hand hygiene.
- Early identification of recurrence and appropriate treatment.

2.7.7 How do you manage second and subsequent recurrences and what do you do if a patient/resident keeps getting recurrences?

The following are responsible for implementation of **recommendation 60**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 60

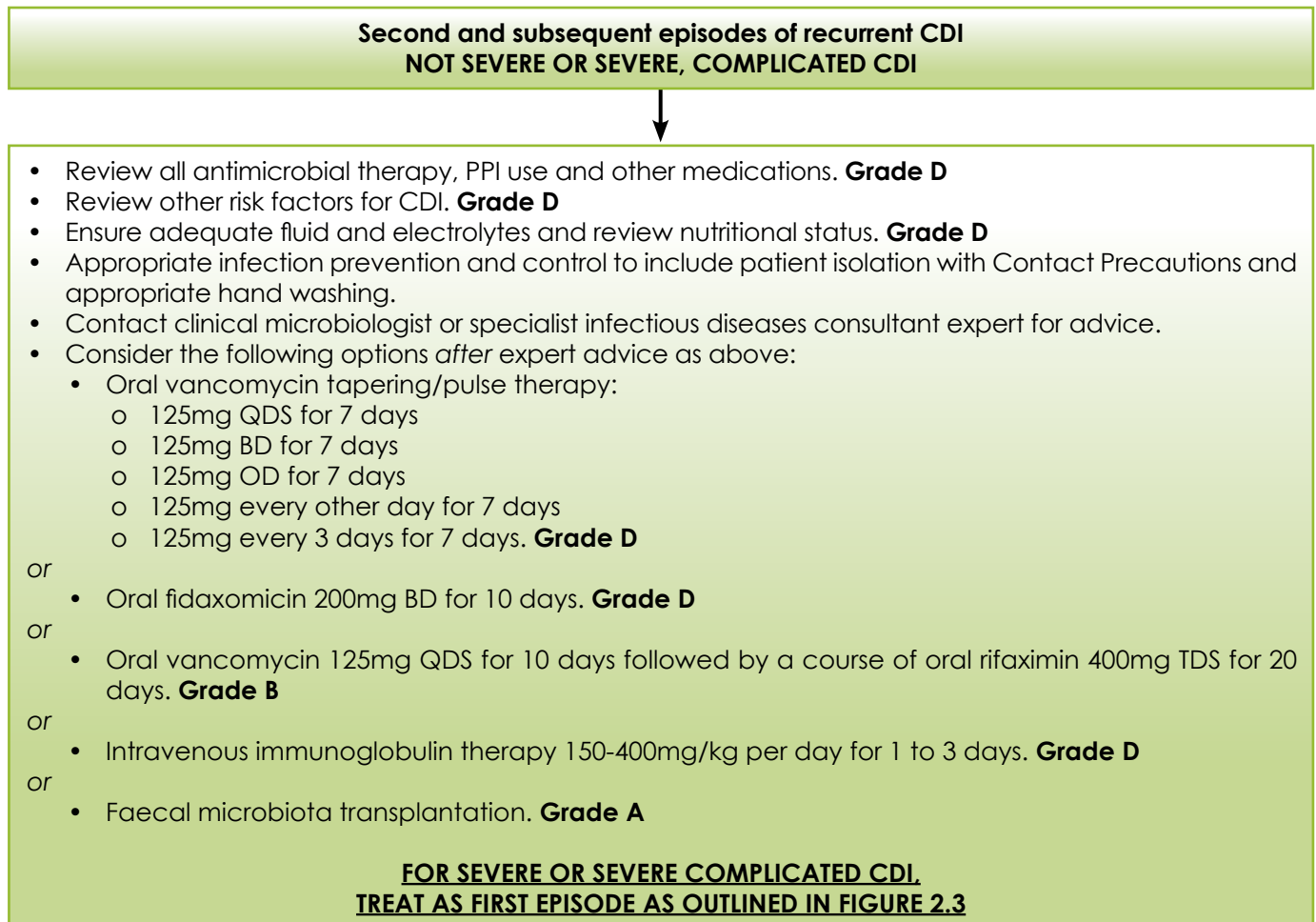
The management of patients/residents with second and subsequent recurrences of CDI is outlined in Figure 2.4.

Practical Guidance

- Consider supervised trial of anti-motility agents alone if post-infective irritable bowel syndrome is suspected after more than 20 days of anti-*Clostridium difficile* treatment (only if patient/resident has a normal white cell count and no abdominal symptoms or signs of severe CDI)
- **Prescribers Notice**
 - Healthcare staff should use clinical judgement, medical and nursing knowledge in applying the guidance in Figures 2.3 and 2.4 and give due regard to individual circumstances presented by each patient/resident and available resources.
 - Refer to BNF for children or local paediatric formulary for doses of metronidazole and vancomycin for paediatric patients.

All drug therapy should be reviewed and consideration given to stopping medicines that can cause diarrhoea, discontinue precipitating antimicrobials if possible, provide supportive therapy and isolate the patient/resident with Contact Precautions as outlined in this guideline. The patient/resident should be observed closely for possible deterioration and their nutritional status reviewed with adequate fluid and electrolytes maintained.

One option is vancomycin, using a tapered and/or pulsed regimen. This regimen is thought to work because administering vancomycin over an extended time period at decreasing doses or intermittent delivery gradually clears *C. difficile* by eradicating cells as spores germinate and may aid in the restoration of normal flora. McFarland *et al.* found that a tapering course of vancomycin (over a mean of 21 days) resulted in significantly fewer recurrences (31%, $p=0.01$), as did pulsed dosing of vancomycin with 125-500mg every 3 days over a mean of 27 days (14.3%, $p=0.02$). (276, 304) In a case series of 22 patients who were treated with a tapered regimen of vancomycin (125 mg every 6 hours for 1 week, 125 mg every 12 hours for 1 week and 125 mg daily for 1 week) followed by a pulsed dosing regimen (125 mg every second day for 1 week and then 125 mg every 3 days for 2 weeks), there were no recurrences after a mean follow-up of 6 months. (310)

Figure 2.4: Management of multiple (second and subsequent) recurrences of CDI

Rifaximin is a non-absorbable semi synthetic analogue of the rifamycin antimicrobial rifampicin. It is approved for the treatment of travellers' diarrhoea caused by non-invasive strains of bacteria in patients aged 12 years or older in the US and patients aged 18 years or older in UK. It is also has been recently approved by the FDA in US for the treatment of hepatic encephalopathy. Published clinical evidence from three case series, one prospective pilot study and one RCT shows positive findings.(311) Due to the potential development of rifamycin-resistant C.difficile, the use of rifaximin may be limited to "chaser" regimens.(312) Recent RCT using rifaximin 400mg orally TDS for 20 days post CDI antibacterial treatment showed a decreased incidence of recurrent CDI in the active arm when compared to placebo, however, the study did not have significant power as only 69 patients were included.(313) Of note, rifaximin is not licensed in Ireland and would have to be imported in on named-doctor-patient basis via a specialist company.

Numerous case series/studies highlight the efficacy of faecal microbiota transplantation in restoring the colonic microflora of patients with recurrent CDI. Faecal microbiota transplantation involves the administration of 30-50g stool in normal saline from healthy donors by enema, via nasogastric tube, or colonoscopy.(314, 315) A systematic review of intestinal microbiota transplant (IMT) for recurrent CDI reported that it was highly effective with 92% of patients experienced resolution and 89% after one infusion.(316) The effectiveness varied by route of instillation, donor, volume of faecal microbiota transplantation, and treatment prior to transplant. Up to January 2013, evidence was based on case series and reports and so was weak. Several clinical trials are ongoing in US, Canada, and the Netherlands addressing the above issues.(317) In January 2013, an RCT which compared the duodenal infusion of donor faeces after vancomycin therapy and

bowel lavage with vancomycin therapy either alone or with bowel lavage was reported.(318) The study population of mainly elderly patients reflects the population in whom CDI develops in daily practice. Three groups of patients at risk for recurrent CDI were excluded; patients with prolonged immunodeficiency, critically ill patients who were admitted to an ICU and patients requiring additional antimicrobials to treat infections other than *C. difficile*. Nevertheless, the outcome favoured faecal microbiota transplantation (81% response) above vancomycin therapy either alone (31%, $P < 0.001$) or with bowel lavage (23%, $P < 0.001$) in patients with relapsed CDI in whom standard therapy with vancomycin has failed. Infusion of donor faeces resulted in improvement in the microbial diversity similar to that of healthy donors, which persisted over time, with an increase in Bacteroidetes species and clostridium clusters (Firmicutes), whereas Proteobacteria species decreased. After 43 of the planned 120 patients had undergone randomisation, the trial was closed to new enrolment by its data and safety monitoring board because almost all patients in the two control groups had a recurrence. The optimal protocol for donor-faeces infusion is still unknown. In the above study patients were pre-treated with vancomycin and bowel lavage, following a previously published protocol. However the contribution of bowel lavage in this process is unclear, the amount of faeces required is unknown and the importance of varying potential routes of infusion (nasoduodenal tube, enema, or colonoscopy) has yet to be elucidated. An example procedure for faecal microbiota transplantation is shown in Appendix 8.(319)

There are no RCTs of the use of fidaxomicin for the treatment of multiple CDI recurrences. The recommendation for its use in this setting is based on extrapolation from a post-hoc analysis of the two large phase III RCT's of fidaxomicin versus vancomycin, a small case series and from review of microbiological data of the effect of fidaxomicin on the faecal microbiome and *C. difficile* spore production.

- Post-hoc analysis of the RCT's comparing fidaxomicin to vancomycin shows an advantage of the former for the management of a first recurrence of CDI.(299, 320) Of the 1164 patients enrolled in these trials, 128 patients with a first recurrence of CDI were enrolled. In this sub-group, further CDI recurrence within 28 days occurred in 35.5% of patients treated with vancomycin and 19.7% of patients treated with fidaxomicin (-15.8% difference; 95% confidence interval, -30.45 to -0.3%; $p = 0.045$). (321)
- A recent case series of three patients with multiple recurrences of CDI reported successful interruption of recurrences using fidaxomicin.(322) These patients had been maintained on low-dose vancomycin for up to 30 months and were then switched to a 10 day course of oral fidaxomicin 200mg bd. Two patients had no further recurrences at 9 and 10 month follow-up. The third patient had no recurrence for three months but subsequently had a recurrent episode in the setting of treatment for a urinary tract infection.
- Data from microbiological studies suggest that fidaxomicin may be associated with lower recurrence rates because it has less effect on the intestinal microbiome during and after treatment of CDI(323) and has also been associated with lower post-treatment *C. difficile* spore counts compared to vancomycin.(298)

Other options to consider for the management of patients/residents with multiple recurrences are outlined in Figure 2.4. The potential role of intravenous immunoglobulin is summarised in Section 2.7.11.iv

2.7.8 Do probiotics play a role in prevention or management of CDI?

The following are responsible for implementation of **recommendation 61**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 61

From current evidence probiotics cannot be recommended for the treatment or prevention of CDI. **Grade C**

Ten studies have looked at the use of probiotics in the treatment and prevention of CDI (Appendix 6).

2.7.8.i Probiotics for the treatment of CDI

In the treatment of primary CDI, rates of resolution of CDI for probiotics (81%) compared to placebo (75%) is not statistically different.(305) Three studies focussed on the treatment of recurrent CDI. There was no significant difference in the resolution of CDI between the interventions compared in two of the studies.(324, 325)

2.7.8.ii Probiotics for the prevention of CDI

Seven studies investigated the use of probiotics in the prevention of primary CDI.(305, 326-331) Only one study showed a significantly lower incidence of CDI diarrhoea compared to placebo.(331) However, this study has a number of limitations including highly selective inclusion and exclusion criteria (135 patients were recruited from 1760 screened individuals, with only 113 followed up for evidence of diarrhoea) leading others to question how data pertaining to less than 7% of a potential target population could be extrapolated to routine use. In addition, the authors did not correctly identify which probiotic strain was investigated and only one of the three probiotic strains were correctly identified (*L. casei* DN 114 001). As closely related strains have been shown to have differing probiotic activities, this is essential in order to extrapolate findings to other settings. In the six other studies there was no significant difference in the incidence of CDI diarrhoea.

Three studies involved probiotics in the prevention of recurrent CDI. Wult showed no benefit in the use of probiotic (*Lactobacillus planetarium*) with metronidazole compared to metronidazole with placebo.(324) In a trial involving 124 patients, *S. boulardii* (1g/day for 4 weeks) was given in combination with either metronidazole or vancomycin versus placebo (for the first 10 days of treatment).(305) *S. boulardii* had no effect on recurrence rates in 64 patients who were treated for a first episode of CDI (19 versus 24% with placebo). In contrast, *S. boulardii* was associated with a significant reduction in the recurrence rate in the 60 patients who had a history of at least one prior episode of CDI (35 versus 65%). A follow-up study performed to standardise the dose and duration of antimicrobial therapy showed that the combination of *S. boulardii* and high-dose vancomycin (2 g/day) reduced the frequency of recurrences, but *S. boulardii* had no effect when combined with low dose vancomycin (500mg/day) or metronidazole (1g/day).(325)

2.7.8.iii Systematic reviews and meta-analysis of the use of probiotics in CDI

There have been three systematic reviews and one meta-analysis about the effectiveness of probiotics for treating CDI and one systematic review which looked at both treatment and prevention of CDI using probiotics. Authors of the systematic reviews noted that there was variability in study methodology such as type of probiotic used, outcome measures, and type of subjects. This heterogeneity does not support the pooling of results as is normally done in meta-analyses.

A Cochrane review concluded that there was insufficient evidence to support the use of probiotic in CDI, and that the studies were small and lacked power.(332) Eddins noted that there was sparse evidence that probiotics may reduce the risk of CDI or recurrence,(333) as did Segarra-Newnham though they highlighted that risks may outweigh benefits for debilitated and immunosuppressed patients.(334) Likewise, a systematic review by Dendukuri found no evidence for probiotics in the treatment of CDI and sparse evidence for probiotics in the prevention of recurrent CDI.(335) In the one meta-analysis, three types of probiotics (*Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and probiotic mixtures) significantly reduced the relative risk of antimicrobial associated diarrhoea but not CDI (relative risk (RR) =0.43, 95% confidence interval (CI) 0.31, 0.58, $p < 0.001$). (336) Probiotics combined with one of the two standard antimicrobials to treat CDI significantly reduced the risk of recurrence (RR =0.59, 95% CI 0.41, 0.85, $p = 0.005$). The types of probiotics included in the trials were *S. boulardii*, *L. rhamnosus* GG, *L. plantarum* 299v and a mixture of *L. acidophilus* and *Bifidobacterium bifidum*. However, only *S. boulardii* showed significant reductions in recurrences of CDI. It must be noted that the above meta-analysis has been met with some criticism.(55) Points noted were the combination of findings from studies of treatment and prevention of adults and children, conducting a pooled analysis on results from heterogeneous outcome measures, analysis of results of studies with low quality due to flawed designs or methods, and lack of independent review as the investigator reviewed their own studies. In a very recent systematic review and meta-analysis by Johnston *et al.*, the investigators suggest moderate evidence that prophylactic probiotics prevent CDI. However, as with the other studies above, results were pooled from heterogeneous sources which would lead to criticisms as before. In addition, in 13 of the 20 trials reviewed, data on CDI were missing for 5% to 45% of patients and the investigators assumed plausible outcomes.(337)

2.7.8.iv Safety of probiotics in CDI

In a clinical trial setting there appears to be very few side effects associated with probiotic use. Mc Farland *et al.* reported more thirst and constipation in patients taking *S. boulardii* compared to control patients.(305) In a meta-analysis, no cases of bacteraemia or fungaemia or other serious adverse event were reported.(294, 336) Recently, there have been several reports of *S. cerevisiae* fungaemia and deaths particularly in immunocompromised and critically ill patients who received a commercial preparation of *S. boulardii* for either prevention or treatment of CDI.(338, 339) Thus, routine use cannot be recommended.

2.7.9 How should patients/residents with inflammatory bowel disease (IBD) and confirmed/suspected CDI be managed?

The following are responsible for implementation of **recommendation 62**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 62

A high clinical suspicion should be maintained for CDI in IBD patients/residents. CDI should be considered in any IBD patient/resident presenting with diarrhoea and abdominal pain, even with a prior colectomy. **Grade D**

Practical Guidance

- CDI in patients/residents with IBD should be managed as outlined in Figures 2.3 and 2.4.
- Early advice from an infection specialist (clinical microbiologist/infectious diseases physician) should be sought.

Patients with IBD, both Crohn's disease and ulcerative colitis, have an increased incidence of developing CDI.(138, 340, 341) CDI risk factors in IBD patients are similar to that of the general

population. In addition, colonic disease and, in particular, the use of steroids and immune modulators may increase risk of CDI.(138, 342, 343). However, the IBD cohort seems to have worse outcomes than the general population when infected with *C. difficile*. Community acquisition appears to be a factor in CDI in IBD with up to 79% cases reported as community-acquired.(344) In one Irish study, detection of toxigenic *C. difficile* was more common in IBD patients (8.2%) when compared with healthy volunteers (1.0%). The authors noted that the ribotypes isolated were community strains and concluded that strain diversity was consistent with community acquisition from a multitude of sources.(345) Interestingly, pathogenic *C. difficile* was found to be present in 8% of asymptomatic IBD patients.(345) The clinical relevance of this is not yet known.

Presentation of CDI in IBD patients can often be difficult to distinguish from a flare of disease. IBD patients with CDI may be younger and without previous exposure to antimicrobials. These patients may also present with atypical symptoms such as bloody diarrhoea. Furthermore, there are reports of CDI occurring in the small bowel and in the residual colon post operatively. Clinical suspicion is, thus, essential. Imaging is rarely helpful. Endoscopy can help out rule other causes although findings are often inconclusive.(346) Laboratory diagnosis is important and a positive test result should be used within the clinical context.

There are few specific guidelines on management of CDI in IBD patients.(347) There are currently no recommendations for a specific antimicrobial therapy. Of note, vancomycin has been shown to decrease colectomy rates in IBD patients with CDI, when used as a first line agent. (348) Metronidazole is still an option.(349) It has the benefit of achieving therapeutic levels in the large bowel, via the intravenous route if oral intake is poorly tolerated. Oral metronidazole and vancomycin enemas can be used concordantly as treatment if disease activity is severe.(254)

There may also be the dilemma of needing to treat the CDI, while also treating the Crohn's disease with immune modulators. This is often a difficult decision, particularly in severe IBD. Studies currently differ on whether maintenance immunosuppressive therapy alters the course of CDI. However, starting an immunosuppressive medication or indeed escalating a treatment regime, while being treated for CDI is not recommended. An expert gastroenterology opinion should be sought at the earliest possible time in difficult cases. The timing of reintroduction or escalation of immunosuppressive therapy is also an issue. The patient should remain symptom free for at least 48-72 hours before considering this and it should only be started in consultation with a gastroenterologist.

The optimal timing of surgery also remains controversial. It is generally accepted that those who have not responded to medical therapy within 48 hours, as well as those who develop severe ileus, multiorgan failure, bowel perforation or toxic megacolon benefit from surgery.(350) Additional predictors for poor outcome in IBD include a low albumin level (<30 g/l), a raised creatinine (>150 micromol/L) and a low haemoglobin (<9g/dl). (403) Early referral to a specialist surgical team should be sought if patient is not improving.

There are numerous novel forms of therapy for CDI, including rifaximin and immunoglobulins. There is no current evidence to support these therapies and, if they are being considered, an expert gastroenterologist should again, be consulted.(351)

In summary, a high clinical suspicion should be maintained for CDI in IBD patients. It should be considered in any IBD patient presenting with diarrhoea and abdominal pain, even with a prior colectomy. Vancomycin may be used as first line antimicrobial therapy in severe disease. Given the fact that there are no consensus recommendations, early advice from a specialist service should be sought.

2.7.10 Is there a role for combination antimicrobial therapy/adjuvant therapy in CDI?

The following are responsible for implementation of **recommendations 63-66**:

Healthcare Facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship team and Clinicians.

Recommendation 63

There is insufficient evidence to support the use of combination antimicrobial therapy in non-severe CDI. **Grade D**

Recommendation 64

Combination therapy with oral or nasogastric vancomycin and intravenous metronidazole is recommended as initial therapy in severe complicated disease. **Grade D**

Recommendation 65

In severe CDI with ileus, use a combination of intracolonic vancomycin and intravenous metronidazole and/or nasogastric vancomycin. **Grade D**

Recommendation 66

There is limited evidence for use of intravenous immunoglobulin as adjuvant therapy in severe or recurrent CDI. **Grade D**

2.7.10.i Combination therapy for the first episode of CDI

Optimal treatment of CDI involves oral antimicrobial administration. In severe and/or complicated CDI, the presence of ileus may impair the delivery of orally administered vancomycin or metronidazole to the colon. When oral therapy cannot be given, especially in severely ill or post-operative patients, intravenous metronidazole can be used. Intravenous administration of metronidazole diffuses from the serum of inflamed colon into the lumen and also undergoes hepatic recirculation, providing comparable concentrations to oral administration.(349) Evidence from case series supports use in the treatment of CDI.(352) However, some data report therapeutic failure of this regimen in the setting of dynamic ileus.(353) Intracolonic vancomycin may be an effective adjunctive therapy as this strategy attempts to achieve higher concentrations of drug within the colon than may be achieved by oral administration of vancomycin or metronidazole alone.(144, 354)

In severe forms of CDI, antimicrobials used to treat may fail resulting in progressive colitis with high morbidity and mortality. One factor that may play a role is the time lag for antimicrobials to reach adequate intracolonic levels.(349) In this context, the use of combination therapy in severe complicated CDI is based on expert opinion and clinical experience.(144, 206, 260)

There is insufficient evidence to support the use of combination therapy in mild to moderate disease.(144) One RCT study looked at metronidazole plus rifampicin versus metronidazole alone for first episodes of CDI.(355) Although it had low statistical power, the trial did not show a trend toward better result when rifampicin was added to metronidazole. In contrast, the combination therapy resulted in significantly higher mortality when compared to that with metronidazole only. UK guidelines recommend that in severe CDI the addition of oral rifampicin (300mg twice daily) or IV immunoglobulin (400mg/kg) to standard therapy may also be considered. The rationale for this is that even though there are no robust data to support this recommendation, the very poor prognosis may justify aggressive therapy.(206) One case report showed success in a 74 year old man with CDI refractory to metronidazole and vancomycin when rifampicin 600mg twice daily was added to therapy.

2.7.10.ii Combination therapy for recurrent CDI

For recurrent CDI, there has been some success in small numbers of patients with the combination of vancomycin and rifampicin for seven to ten days.(356) However, the evidence for this is from case series and is of limited value. (Note UK guidelines recommend oral vancomycin 125mg qds plus oral rifampicin 300mg bd for two weeks as treatment option in recurrent CDI).(206)

Non-standard interventions such as probiotics, prebiotics, vaccines, and immunotherapy are frequently used as adjuncts to standard CDI antimicrobial treatment. Their effectiveness is variable and will be discussed in later sections.

2.7.11 What is in the future for CDI and where is this likely to fit in?

2.7.11.i Nitazoxanide

Nitazoxanide may be a useful alternative for patients who cannot tolerate or fail treatment with metronidazole. It is a new thiazolide antiperistaltic agent that has excellent activity in treating protozoal and helminthes infections. It is FDA approved for the treatment of diarrhoea caused by *Cryptosporidium spp.* and *Giardia* infections. *In vitro*, nitazoxanide has excellent activity against *C. difficile*.(357) It also achieves high colonic levels after oral administration.(358) A randomized double-blind trial reported that nitazoxanide was 'not inferior' to metronidazole in terms of primary response or recurrence rate.(358) The latest RCT showed that nitazoxanide had a similar end of therapy response as vancomycin, and could be a safe and effective option for recurrent or refractory CDI.(359) However, nitazoxanide is not licensed in Ireland and would have to be imported in on named-doctor-patient basis via a specialist company.

2.7.11.ii Ramoplanin

Ramoplanin is an oral, non-absorbable lipoglycopeptide antimicrobial that blocks peptidoglycan synthesis. It has *in vitro* activity against *C. difficile*, including isolates with reduced susceptibility to metronidazole or vancomycin. Phase II trial shows equivalence to vancomycin for CDI treatment, doses of 200mg or 400mg orally BD for 10 days.(360) In December 2009, the drug was entering phase III trial with special protocol assessment from FDA, no new update as yet.(361)

2.7.11.iii Tigecycline

There is some evidence from case series reports in which tigecycline was used as salvage therapy for treatment of CDI refractory to vancomycin and metronidazole.(362) Intravenous tigecycline was also successful in treatment of severe or severe complicated CDI when prior therapy has failed.(363) Again, evidence is based on six case reports only. Currently, an open label study is being conducted looking at intravenous tigecycline plus standard treatment in mild to severe CDI.(367)

2.7.11.iv Intravenous immunoglobulin

Asymptomatic carriers of *C. difficile* have higher serum concentration of IgG anti-toxin A antibodies compared to patients with CDI.(364) In addition, failure to mount an adequate IgM and IgG immune response to toxin A during the course of an illness is associated with *C. difficile* recurrence.(309) Several cases reports regarding the use of intravenous immunoglobulin (IVIG) to treat refractory or severe CDI have been published but no randomized controlled clinical trials have been performed. (Table 2.6) Therefore, there is no published data from which to create evidence-based recommendations. Different doses of IVIG (150-400mg/kg, 1-3 doses) administered at varying frequencies, with or without adjunctive treatment with oral anti-*C. difficile* antimicrobials

have produced varying results (Table 2.6). IVIG is expensive and may be associated with acute renal failure, vascular thrombosis, anaphylaxis and infusion-associated reactions.

Several reviews indicate a possible benefit with IVIG in severe CDI and its use may be considered in refractory and recurrent CDI.(365-367) However, the evidence is based on case series/reports with small numbers that were not randomised or controlled. Overall, IVIG may be useful as adjunct therapy in those patients who have failed initial therapy or in seriously ill patients when surgery is being considered. Although caution is warranted in the latter case with a higher mortality rate (57%) reported in 21 patients treated with IVIG for severe CDI.(367) It was observed that these patients had a higher APACHE II score on the day of IVIG infusion. The possible reason for this is that IVIG may have a role to play in severe CDI as long as it confined to the colon. However, once extra-colonic organ dysfunction and systemic inflammatory response syndrome develop, IVIG may be less beneficial, probably advocating earlier use of IVIG in select patients.

2.7.11.v Monoclonal antibodies against *C. difficile* toxin A+B

A phase II RCT, double-blind trial for serum antibodies against *C. difficile* toxin A found no difference in recurrence between groups, although time to recurrence was longer in the antibody group. (380) Also, recurrence of CDI was associated with lower concentrations of anti-toxin A and B, as well as *C. difficile* strain. In a randomized, double blind, placebo-controlled study in 200 patients (10mg/kg of two monoclonal antibodies against *C. difficile* toxin A+B plus standard treatment vs. standard treatment plus placebo), antibody treatment reduced CDI recurrence compared to the standard regimen (7% versus 25%).(381) Merck have taken licence to further develop this drug. (382) Two large phase 3 randomised, double blind, controlled trials are currently being conducted (MODIFY-I and MODIFY-II), with a completion date of May and July 2014.

2.7.11.vi Vaccines

C. difficile toxoid vaccine has the potential to help control CDI as serum anti-toxin A and B immunoglobulin G antibody levels are associated with protection against recurrent CDI.(383, 384) Initial work with a *C. difficile* toxoid vaccine (formalin-inactivated, containing toxins A and B partially purified from cultures of *C. difficile*) showed safety, tolerability and immunogenicity in healthy adults (385) and was associated with resolution of recurrent *C. difficile* associated diarrhoea.(384) Formulation work to improve stability was carried out and two phase 1 RCT, double blind, placebo trials were completed .(386) Fifty healthy adults (18-55 years) and 48 elderly (≥ 65 years) volunteers were randomised to receive the vaccine (2mcg, 10mcg, and 50mcg) or placebo on Days 0, 28, and 56. There was no seroconversion for placebo volunteers. Vaccine safety and tolerability was comparable to placebo, and there was robust seroconversion for toxin A and B. The highest response was in the 50mcg dose group, antibody titres decreased by Day 236 and immunity declined more rapidly in the elderly. Sanofi-Aventis are currently conducting two Phase 2 studies with this vaccine looking at recurrence of CDI in patients with first episode of CDI, completion dates are June 2012 and January 2013. Also, work is being undertaken by another company, Intercell AG, on another candidate vaccine. (Appendix 7)

Table 2.6: Case reports of IVIG use in patients with CDI

Reference	Patients	IVIG regimen	Response
Leung (1991)(368)	5 children	400mg/kg every 3 weeks for up to 6 months	No recurrence (4); one recurrence (1)
Warny (1995)(369)	1	400mg/kg, 2 doses 28 days apart plus vancomycin	No recurrence at 16 months
Hassett (1995)(370)	1	30g every 2 weeks	1 recurrence
Salcedo(1997)(371)	2	200-300mg/kg	1 recurrence 1 month later
Beales (2002)(372)	4	400mg/kg, 2 doses 21 days apart plus vancomycin taper	No recurrences at 10, 8, 7, and 5 months
Wilcox (2004)(373)	5	300-500mg/kg; 1 doses (2 patients), 2 doses (2 patients), 6 doses (1 patient)	No recurrence at 6 weeks (1), 3 months (1), 9 months (1); died after 6th dose (1); died 1 week after cessation of symptoms (1)
Murphy (2006)(374)	1	400mg/kg on 3 consecutive days	No recurrence 4 months later
Conc (2006)(375)	20	30g twice	No recurrence (18); one recurrence (2)
McPherson(376) (2006)	14	150-400 mg/kg plus oral vancomycin or metronidazole	4 patients with no recurrence at 7, 10, 14 and 21 days; 6 patients with no recurrence at 4, 6, 11,12 and 13 (2pts) months; 4 patients died 7, 11, 17, and 18 days after IVIG, all of whom still had diarrhoea
Juang (2007) (377)	18	200-300 mg/kg plus IV metronidazole and oral vancomycin	3 patients required colectomy and 3 died. However, similar outcomes in severity matched non-IVIG control group
Hassoun (2007)(378)	1	40mg/kg once	Severe colitis patient survived
Chandrasekar (2008)(379)	1 1	400mg/kg 3 times 400mg/kg for 5 doses	No recurrence Severe colitis patient survived.
Abougergi (2010) (367)abo	21	300mg/kg – 250mg/kg for 5 doses	Only 9 of 21 patients with severe CDI survived

2.8 Management of outbreaks and clusters

2.8.1 How can you recognise a cluster/potential cluster and what should you do next?

The following are responsible for implementation of **recommendations 67-69**:

Specialists in Public Health, healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship Team and Clinicians.

Recommendation 67

Medical practitioners and clinical directors of diagnostic laboratories are required to notify unusual clusters or changing patterns of illness to the Medical Officer of Health (MOH) (who is the local Director of Public Health, or the designated Specialist in Public Health Medicine (SPHM)).

Legal requirement.

Recommendation 68

When an outbreak of CDI is suspected, an outbreak control team (OCT) should be established. The decision to convene an OCT will be made by the hospital chief executive or general manager/network manager or the relevant local community services senior manager, on the advice of: the consultant medical microbiologist and/or the MOH (Local Department of Public Health). **Grade D** (Suggested members of the OCT are outlined in Recommendation 70).

Recommendation 69

Nursing homes are required to inform the Health Information and Quality Authority (HIQA) of an outbreak within three working days. **Legal requirement**

Practical Guidance

- A cluster/outbreak is defined as the occurrence of two or more epidemiologically linked CDI cases over a defined period, taking account of the background rate or where the observed number of CDI cases exceeds the expected number.
- Each healthcare facility should have a surveillance system in place that enables timely alerts of a change in *Clostridium difficile* incidence that may indicate a possible CDI cluster/outbreak.
- Recognition of a cluster/outbreak needs an alert/trigger mechanism in place with rapid and reliable diagnosis to facilitate early intervention. Use of statistical tools such as statistical process control charts may assist to distinguish between natural and unexpected variation and identify when numbers of CDI cases are exceeding normal expectations for that ward. **Grade D**

Under the Infectious Diseases (Amendment) Regulations 2011 (SI452 of 2011) medical practitioners, including clinical directors of diagnostic laboratories, are required to notify new and recurrent cases of CDI to the Medical Officer of Health (MOH) (who is the local Director of Public Health or the designated Specialist in Public Health Medicine (SPHM)).(28) A cluster/outbreak is defined as outlined above in practical guidance. Medical practitioners and clinical directors of diagnostic laboratories are required to notify unusual clusters or changing patterns of illness.

Initial identification will involve:

- Prompt identification of unexplained diarrhoea.
- Sending a stool specimen to exclude an infectious cause (faecal specimens from all infected patients/residents should be stored so that typing can be performed).(Section 2.5)
- Notification of the infection prevention and control team to gain advice and support in managing the situation.
- When a cluster/outbreak of CDI is suspected, an OCT should be considered. The decision to convene an OCT will be made by the Hospital Chief Executive or general manager/area

manager or the relevant local community services senior manager, on the advice of the Consultant Medical Microbiologist and/or the MOH (Local Department of Public Health).

2.8.2 Who should be on the Outbreak Control Team (OCT) and what is its function?

The following are responsible for implementation of **recommendation 70**:

Specialists in Public Health, healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship Team and Clinicians.

Recommendation 70

All healthcare facilities should ensure that there are documented outbreak management processes and procedures that are reviewed and updated on a regular basis outlining the roles and responsibilities of the OCT members. The OCT should be multi-disciplinary and made up of senior professionals and decision-makers (Table 2.7). Where an outbreak involves healthcare facilities in more than one area, the composition of the OCT should reflect this and include a Specialist in Public Health Medicine from the HPSC. A decision should be taken at the initial stage as to which area takes the lead role. **Grade D**

Practical Guidance

The role of the OCT is that of an advisory body working with relevant staff members to advise on and co-ordinate the following:

- Epidemiological investigation of the cluster/outbreak and confirmation that a cluster/outbreak has occurred.
- Development of an outbreak control strategy including implementation of control measures and monitoring of their effectiveness.
- Development of an appropriate communications strategy; provision of support, advice and guidance to individuals and the various organisations directly involved in dealing with the outbreak.
- To declare when the outbreak is over and prepare a report to include recommendations for prevention of a further outbreak and dissemination of lessons learnt.

Table 2.7: Recommended membership of a CDI Outbreak Control Team

	Acute Hospital	Community
Chair	Hospital CEO/manager	Local community services senior manager or Department of Public Health specialist/Medical Officer of Health ¹
Team	Department of Public Health Specialist/Medical Officer of Health ¹ (MOH) Consultant physician/surgeon Occupational health physician Consultant medical microbiologist Infection prevention and control nurse(s) Infectious disease physician Antimicrobial pharmacist Surveillance scientist Director of nursing Clinical director(s) Ward/Department nurse manager of affected area(s) Chief/Senior laboratory scientist Bed manager Patient services manager/ household services manager Patient representatives office Others as appropriate ²	Local community services senior manager (if not the chair should be a member of the OCT) or Department of Public Health specialist/Medical Officer of Health ¹ (if not the chair should be a member of the OCT) Attending medical officer or general practitioner Occupational health physician (if available) Consultant medical microbiologist (if available) Infection prevention and control nurse(s) (if available) Healthcare facility manager or representative Local pharmacist (as appropriate) Surveillance scientist Director of nursing/nurse in charge Ward/department nurse manager of affected area(s) Others as appropriate ²

¹ The MOH will notify the HPSC.

² Others that should be included in the process and kept informed include risk management/communications officer(s)

The role of the OCT is that of an advisory body who will work with relevant staff members to advise on and co-ordinate the following:

- a) Investigation of the outbreak by careful assessment of all the epidemiological information available, i.e., confirmed and probable cases, typing, dates of onset, links between cases, size of population containing the cases, homogeneity of population containing the cases.
- b) Review of the evidence in (a) above and confirm that there is a CDI outbreak. Initial information should be provided to the HPSC via CIDR.
- c) Development of a strategy to deal with the outbreak and to allocate individual responsibilities with timelines for implementing action.
- d) Implementation of control measures and to monitor their effectiveness in dealing with the outbreak and in preventing further spread.
- e) Provision of advice to management on the necessary action to control the outbreak

- f) Agreement of a communications strategy to provide clear, consistent and accurate information and keep relevant persons within the hospital/nursing home, health area, outside agencies, the general public and the media appropriately informed.
- g) Provision of support, advice and guidance to individuals and the various organisations directly involved in dealing with the outbreak.
- h) Declaration that the outbreak is over and preparation of a report to include:
 - Review of the experiences of all participants involved in the management of the outbreak.
 - Identification of shortfalls and particular difficulties encountered
 - Review of the outbreak/policy in accordance with the above and update if appropriate.
 - Recommendations, if necessary, regarding structural or procedural improvements which would reduce the chance of a reoccurrence of the outbreak.
 - Outcome and lessons learned which should be disseminated so that the incident becomes a positive learning experience for those involved in the implementation of the control measures.(387)

This report should be submitted to the head of the relevant healthcare facility (e.g., Hospital Chief Executive/General Manager). Where there are difficulties, these should be highlighted locally and to the appropriate regional/national management structures so that measures are taken to ensure implementation of recommendations, including the provision of appropriate resources and personnel. HIQA should also be included in this process in the case of Nursing Homes.

Effective communication with relevant authorities, other professional groups, the media and the general public during an outbreak is an important aspect of outbreak management. All relevant information should be shared as appropriate with these groups. The OCT should endeavour to keep the public and media as fully informed as possible without prejudicing the investigation and without compromising any statutory responsibilities, legal requirements or patient confidentiality. At the first meeting of the OCT, arrangements for dealing with the media should be discussed and agreed. A decision should be made as to whether a member from the Communications Department should be in attendance at OCT meetings. Timely press statements should be agreed by the OCT, or by a small sub-group, with the agreement of the OCT. No other member of the OCT should release information to the press without the agreement of the Team. The contents of press statements should be given to the healthcare facilities medical and nursing staff and field workers to ensure that consistent advice is being provided to patients/residents, visitors and the public.

2.8.3 What are the most important measures to implement during an outbreak of CDI?

The following are responsible for implementation of **recommendations 71-73**:

Specialists in Public Health, healthcare facility Senior Management Team (e.g. CEO, Director of Nursing/Midwifery, Clinical Director and Director of Finance), Infection Prevention and Control Team, Antimicrobial Stewardship Team and Clinicians.

Recommendation 71

Control of CDI in outbreaks requires implementation of antimicrobial stewardship and measures to prevent cross infection to other patients/residents. This usually involves infection prevention and control and antimicrobial stewardship measures including early isolation of patients/residents with Contact Precautions, education of staff and patients/residents/visitors, re-enforcement of local antimicrobial prescribing guidelines with avoidance of inappropriate broad-spectrum antimicrobial therapy, increased environmental and equipment cleaning and disinfection and optimising hand hygiene by all. **Grade D**

Recommendation 72

All efforts should be made to prioritise patients/residents with CDI for isolation. Patients/residents with suspected infectious diarrhoea in whom the cause of diarrhoea has not been determined should be isolated in a single room pending diagnosis. If the number of CDI cases exceeds the availability of single rooms for isolation, and risk assessment has confirmed that there is no other option for isolation of patients/residents with CDI, then alternative placement options include:

- a. Cohort ward or bay with dedicated nursing staff for the area
- b. Isolation/dedicated ward in the event of a large outbreak.

Cohorted patients/residents should be managed by designated staff to minimise the risk of cross infection to other patients/residents. **Grade D**

Recommendation 73

If a large outbreak of diarrhoea occurs such that there are insufficient single rooms for every affected patient/resident, then the ward should be immediately closed to admissions. **Grade D**

The effectiveness of each individual measure that has been outlined above has not been determined in an outbreak setting as most studies and reports use a combination of different measures.(23)

Additional measures during an outbreak of CDI should include:

- Early and rapid diagnosis of CDI cases – there should be a low threshold for the rapid evaluation of patients/residents with diarrhoea on wards/units with active cases of CDI.
- Review of antimicrobial prescribing (types of agents and duration) with the emphasis on reducing inappropriate use of broad-spectrum antimicrobials as outlined in this guideline.
- Staff cohorting may be necessary to manage an outbreak. Sufficient numbers of staff should be rostered to provide patient care commensurate with infection prevention and control practices. The Stoke Mandeville inquiry found that levels of staffing made it particularly difficult for nurses to find the time to practice control of infection effectively.
- Education of all staff on the mode of transmission of CDI and reinforcement of all infection prevention and control precautions is key.
- Timely and clear communication of the outbreak control measures to other departments and to patients/resident and visitors within the healthcare facility to inform them of the infection prevention and control precautions that have been implemented is essential. Patient/resident confidentiality should be maintained at all times in this process.
- The standard of hand, environmental and equipment cleaning should be audited and reviewed (e.g., hand hygiene audit results, cleaning audit, bed pan washer audit, etc.).
- Where an environmental reservoir is suspected and the degree of contamination is high, routine cleaning/disinfection procedures should be reviewed.
 - The need for higher concentration disinfection (228)/alternative validated sporicidal agent must be considered. (234)
 - The requirement for additional trained cleaning staff or additional training of current cleaning staff should be assessed.(212)
 - The cleaning team should be educated regarding the importance of good standards of cleaning and decontamination in the context of a CDI outbreak/cluster.(23)
- Patient movement and transfer should be restricted as outlined in this guideline.
- Interim policies for patient admission, placement and staffing should be implemented as required to prevent further cross infection.
- Sensible management (restriction) of visiting to all healthcare facilities may assist in controlling a CDI outbreak.

When transmission continues despite the assignment of the above measures and dedicated staff, the unit or facility should be closed to new admissions. Performance targets (e.g., waiting times in the Emergency Department) should not compromise management of the outbreak and should, with discussion with healthcare facility management, be suspended for the course of the outbreak. When transmission continues despite all of the above measures, the unit should be vacated for intensive environmental cleaning and disinfection to eliminate all potential environmental reservoirs of *C. difficile*. An outbreak may be declared over by the OCT when there are no new cases or the number of cases has returned to the endemic level.(388)

2.8.3.i What are the most important antimicrobial stewardship measures to implement during an outbreak of CDI?

As with the infection prevention and control literature, several papers have reported the introduction of a combination of different strategies at the time of an outbreak in an effort to control increasing numbers of CDI. As a result, it is difficult to identify the specific effects of an antimicrobial prescribing intervention. Some studies introduced between two to nine different interventions at the time of an outbreak, six of which involved strategies to improve antimicrobial prescribing.(150, 198, 389, 390) The introduction of a *C. difficile* infection prevention and control care bundle during an outbreak of a hyper virulent strain of *C. difficile* at a teaching hospital in Pittsburgh resulted in a significant decrease in CDI. This bundle consisted of education, increased and early case finding, expanded infection-control measures, development of a *C. difficile* infection management team and an antimicrobial management programme.(391) An antimicrobial restriction policy was enforced by infectious diseases physicians and pharmacists. Restricted antimicrobials included clindamycin, ceftriaxone and levofloxacin specifically and other broad spectrum antimicrobials. Monthly antimicrobial use trends were monitored closely. CDI decreased significantly but this cannot be attributed to the antimicrobial management programme alone.

A similar bundle approach was implemented at a teaching hospital in Boston, reducing the incidence rate of healthcare-associated CDI by 40% from 1.1 cases per 1,000 patient days before the intervention to 0.66 cases per 1,000 patient days afterwards.(392) This bundle consisted of three strands:

- An educational campaign which encouraged personnel to promptly initiate diagnostic testing, isolation and treatment.
- A prevention bundle which allocated specific responsibilities to the various categories of staff and included specific infection-control practices, e.g., e-mail alerts for positive toxin assays and environmental services to decrease transmission of the disease.
- A treatment bundle that standardised the treatment of patients/residents with severe CDI and provided guidelines for when to consider surgical consultation.

A reduction in the incidence of CDI of the order of 40% resulted, which was sustained for the study duration of 21 months. A multi-hospital outbreak of *C. difficile* ribotype 027 occurred in Northern Ireland between 2007 and 2008.(393) Sub-optimal compliance with antimicrobial guidelines and infection prevention and control policies were identified as causes of the outbreak. The authors found a significant association between the restriction of fluoroquinolones and the reduction in the incidence of CDI and concluded that antimicrobial stewardship is an essential element of multiple interventions to control CDI outbreaks.

In summary, the following measures should be considered by the OCT for implementation during a CDI cluster/outbreak as outlined elsewhere in this guideline;

- Activation of CDI trigger tool in affected ward/area/unit.
- Re-enforcement and audit of local antimicrobial prescribing guidelines, with emphasis on duration and choice of agent.
- Cessation of broad spectrum antimicrobial therapy where possible or switch to narrow spectrum agent if necessary.
- Specific review of the use of fluoroquinolones, cephalosporins and clindamycin.
- Ensure the duration of surgical prophylaxis is kept to a minimum – single dose at induction unless otherwise indicated.
- Ensure anti-CDI therapy is suitable for the patient/resident and that dose and frequency are correct.
- Review of PPI use and stop where there is no indication for its use.
- Ensure prokinetic therapy such as erythromycin, domperidone etc. are discontinued in the CDI affected patient.

3 Appendices and References

Appendix 1

Guideline Development Group; Terms of reference, membership, conflicts of interest and contribution of members to the guideline.

Terms of Reference

To update the 2008 national guidelines - Surveillance, Diagnosis and Management of *Clostridium difficile* (HPSC 2008).

Membership and Conflicts of Interest

Chair: Dr Fidelma Fitzpatrick (FF), Consultant Microbiologist, of the HPSC and Beaumont Hospital, Dublin.

Members:

- Dr. Karen Burns (KB), Consultant Microbiologist, HPSC and Beaumont Hospital
- Dr. Susan Clarke (SC), Infectious Disease Physician, St James' Hospital (IDSI)
- Ms. Annette Darcy (ADa), Surveillance Scientist, Letterkenny General Hospital, Donegal (Surveillance Scientists Association)
- Ms. Breda Deasy (BD), Infection Prevention and Control Clinical Nurse Specialist, St Luke's General Hospital, Kilkenny (IPS)
- Dr. Anne Dee (AD), Specialist in Public Health Medicine, HSE Midwest, Limerick (RCPI Faculty of Public Health Medicine)
- Dr. Lynda Fenelon (LFe), Consultant Microbiologist, St. Vincent's University Hospital, Dublin
- Ms. Sarah Foley (SF), Antimicrobial Pharmacist, Beaumont Hospital, (IAPG)
- Ms. Liz Forde (LFo), Infection Prevention and Control Clinical Nurse Specialist, Cork Community Infection Prevention and Control Services, HSE-South
- Dr. Patrick Gavin (PG), Consultant in Paediatric Infectious Diseases, The Children's University Hospital, Temple Street and Our Lady's Hospital, Crumlin
- Dr. Anne Gilleece (AG), Consultant Microbiologist, Connolly Hospital (ISCM)
- Dr. Lorraine Kyne (LK), Consultant in Medicine for the Elderly, Mater Misericordiae Hospital, Dublin
- Mr. Stephen Murchan (SM), Surveillance Scientist, HPSC
- Dr. Sinéad Mc Dermott (SD), Specialist Registrar, Clinical Microbiology
- Mr. Stephen Mc Mahon (SMcM), Irish Patients Association
- Prof. Deirdre Mc Namara (DM), Associate Professor and Consultant Gastroenterologist, Adelaide and Meath Hospital, Trinity College Dublin
- Ms. Sinéad Morrissey (SM), Practice Development Facilitator, Nursing Homes Ireland
- Dr. Coilín ÓhAiseadha (CO), Specialist Registrar in Public Health Medicine, Dept. of Public Health, HSE Limerick
- Ms. Grainne O'Reilly (GR), Medical Scientist, Mater Misericordiae University Hospital (AMLS)
- Dr. Jennifer O'Hanlon (JH), Specialist Registrar in Public Health Medicine
- Dr. Fiona Roche (FR), Surveillance Scientist, HPSC (joined December 2012)
- Mr. Damodar Solanki (DS), Chief 2 Pharmacist, Beaumont Hospital (HPAI)

Conflicts of Interest

- FF: FF has not received funds for speaking, consultancy or advisory board membership, owns no stocks, shares nor patents. FF was supported to attend CDI Europe meetings (travel and accommodation) by Astellas Pharma Europe Ltd.
- KB: KB has received sponsorship from Astellas, Novartis and Pfizer to attend and present at European educational meetings.
- LF: LF is a member of the Advisory Board for Astellas Pharma Co. Ltd for Fidaxomicin.
- SF: SF has received travel grants from MSD, Novartis and Astellas to attend and present at European clinical microbiology conferences.
- AG: AG has received sponsorship from Novartis and Pfizer to attend international educational meetings. AG is a member of the Advisory Board for Astellas Pharma Co. Ltd for Fidaxomicin.
- LK: Funded by a Clinician Scientist award from the HRB. LK has received a once off honorarium for attendance at an Astellas advisory board meeting.
- SM: SM received an honorarium from Novartis for workshop facilitation.
- DS: DS has availed of sponsorship to attend professional meetings and seminars in clinical pharmacy, microbiology, and critical care from the following pharmaceutical companies; Astellas, MSD, Eli Lilly, Pfizer, GlaxoSmithKline and Baxter.

None to declare: SC, ADa, BD, AD, LFo, PG, SD, SM, SmcM, DM, CO, GR, JH, FR.

Contributions

These guidelines have been published in two formats – a summary document outlining the key recommendations and practical guidance and this full version document which contains more detail including the rationale for the recommendations. The main guideline document is divided into eight sections. All Guideline Development Group members reviewed each version of the draft document by email and contributed where appropriate at meetings, however, some members took the lead on sections of this document as follows:

- Preparation of Main Document and Summary Document: FF
- Main Document
 - Background: FF, JH, KB
 - Section 2.1: National recommendations: FF
 - Section 2.2: Essential elements of a CDI prevention and control programme: FF, GR, SMcM, KB, LFo, BD
 - Section 2.3: Prevention of CDI: SF, FF, LK, LFo, BD
 - Section 2.4: Surveillance: KB, SM, FR
 - Section 2.5: Laboratory Diagnosis: AG, LFe, SD, GR
 - Section 2.6: Management of patients/residents with suspected/ confirmed CDI: AD, AG, CO, FF, LFo, BD, GR
 - Section 2.7: Treatment of CDI: DS, LK, SC, DM, FF, PG, GR
 - Section 2.8: Management of outbreaks and clusters: AD, BD, SF, LFo, CO

Additional Contributions and Review

- Management of CDI in Primary Care: FF, Dr. Nuala O Connor, Dr. Maria O Mahony, ICGP
- Figure 2.4: Dr Katie McFaul, SpR in Infectious Diseases, St. James Hospital
- Section 2.3.6: Dr Blanaid Hayes, Consultant in Occupational Health Medicine, Beaumont Hospital
- Section 2.7.3: Mr. Eadhbhard Mulligan, Consultant Surgeon, Connolly Hospital
- Section 2.7.9: Dr. Barry Hall, Inflammatory Bowel Disease Fellow, Department of Clinical Medicine, AMNCH
- Appendix 9: Dr. Suzanne Corcoran, Consultant Microbiologist, Bons Secours Hospital, Dublin

Appendix 2

Summary of tools to assist implementation of the National Clinical Guideline.

Relevant links available at:

<http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Clostridiumdifficile/Publications/>

Management of patients/residents with suspected/confirmed CDI (healthcare facilities and primary care)

- Patient/resident information leaflet
- CDI management and treatment algorithms;
 - Management of CDI in Primary Care
 - First episode and first recurrence of CDI
 - Second and subsequent recurrences.

Management of patients/residents with suspected/confirmed CDI (healthcare facilities)

- Infection prevention and control precautions (Contact Precautions)
- Guidance (risk assessment) for decision makers on isolation. Appendix 6, page 55 of the MDRO guidelines
- Sample care plan for patients/residents with CDI
- Sample daily check list for sluice room and equipment
- Sample systems analysis tool for healthcare facility-associated CDI

Prevention of CDI, clusters and outbreaks in healthcare facilities

- Sample patient information leaflet for patients/residents prescribed an antimicrobial course
- Infection prevention and control precautions - Standard and Contact Precautions:
- Bristol Stool Chart
- CDI surveillance protocol
- CDI case definitions
- Algorithms to define case type and origin of infection
- Calculation of resident days for CDI surveillance in long-term care facilities
- Hand hygiene audit tool
- National antimicrobial stewardship guidelines
- Sample CDI trigger tool

Key performance indicators for the prevention and control of CDI

- 1. Number of new cases of CDI acquired in the healthcare facility per reporting time period (e.g., month or quarter)**
 - Hospitals: per 1,000 patient admissions and per 10,000 patient days (or bed days used)
 - Long-term care facilities: per 10,000 resident days
- 2. Hospital antibiotic consumption (Defined daily doses/100 bed days used)**
- 3. Hand hygiene compliance score (%)**
 - Overall and per each of the WHO 5 moments
 - By staff group
 - By ward or unit

Appendix 3

Details of data of cases of CDI in acute hospitals in the Republic of Ireland from 2008-2013 inclusive extracted from HIPE, ESRI.

The HIPE (Hospital In-Patient Enquiry) data set, records data on discharges from all publicly funded acute hospitals. There are 56 HIPE hospitals, 38 of which are in Money Follows the Patient. These allow comparison of discharge rates between populations of different age composition, and also of discharge rates over time. HIPE is the only source of morbidity data available nationally for acute hospital services in Ireland. All acute public hospitals participate in HIPE reporting on over 1.5 million records annually.

Data Collected

Data for 1995 to 2004 were classified using ICD-9-CM. All HIPE discharges from 2005 are now coded using ICD-10-AM (The Australian Modification of ICD-10 incorporating the Australian Classification of Health Interventions).

HIPE data are used by the Department of Health and the Health Service Executive in the planning, provision and measurement of acute hospital services.

The HIPE scheme was established in 1971 by the Health Research Board (HRB). Between 1990 and 2013 the Economic and Social Research Institute (ESRI) oversaw the administration and management of this scheme on behalf of the Health Service Executive (HSE) and the Department of Health (DoH).

From January 1, 2014 the National Casemix Programme and the Health Research and Information Division at the ESRI became the Healthcare Pricing Office (HPO). This Office has responsibility for the HIPE scheme. While the HPO will initially be established on an administrative basis, in the HSE, it is planned that this Office will ultimately be established on a statutory basis. This development is in line with the proposals in the 'Money Follows the Patient' policy paper published by the Department of Health in February 2013. Each HIPE discharge record represents one episode of care and patients may have been admitted to more than one hospital with the same or different diagnoses. In the absence of a Unique Patient Identifier the records therefore facilitate analyses of hospital activity rather than incidence of disease.

In the analysis presented in this guideline, parameters selected were patients with CDI 'All diagnoses' can include patients who are admitted with other illnesses as their primary complaint. Using the 'A047' Enterocolitis due to *Clostridium difficile* code for CDI. Only those aged 2 or over were included as this is consistent with the case definition for notifiable diseases for the HPSC.

1. Table 1 Discharges with *C. difficile* infection 2008 – 2013, 2+ years

Year	Number of discharges with CDI 'All' diagnosis
2008	1,414
2009	1,298
2010	1,226
2011	1,184
2012	1,073
2013	1,045

Source: HIPE, ESRI 2014

Appendix 4

Literature review

For the updated guidelines, Guideline Development Group members completed the review and analysis of data published since publication of the 2008 guidelines. PubMed was searched in all cases, with the addition of Cochrane and Scopus in some cases. Searches were restricted to Human studies published in English. The searches for the individual section are outlined below.

Background

Computerised literature searches of Pub Med, Cochrane and Scopus were performed. A search of www.ClinicalTrials.gov was also conducted using the term "*Clostridium difficile*" and all current and proposed studies were reviewed. Human studies in the English language were searched from 1st January 2007 to 30th September 2012.

Search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD AND guidelines, standards, clinical impact, cost, financial impact, cost savings, epidemiology, Ireland, typing, hospitals, nosocomial, community, healthcare-associated, home, surveillance, mortality, implementation, barriers, facilitators

31 articles and reports were included in this section of the review.

Essential elements CDI prevention and control programme

Search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD in combination with the following in Pub Med, Cochrane and Scopus: Assurance, patient safety, patient engagement, audit, care bundle, trigger, root cause, systems analysis, targets, management, indicators.

17 references were included in this section of the literature review.

Prevention of CDI

Search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD in combination with the following in Pub Med, Cochrane and Scopus: Prevention, antimicrobial stewardship in the community, antimicrobial stewardship measures to reduce *Clostridium difficile*, education, proton pump inhibitors, acid suppressants, asymptomatic, carrier, colonisation, Isolation, Single room, Contact Precautions, guidelines, Communication, Outbreak, Hospital, healthcare facility, community or home, Reduced infection rates.

56 references were included in this section of the review.

Surveillance

Search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD in combination with the following in Pub Med, Cochrane and Scopus: hospitals, nosocomial, community, healthcare-associated, home, epidemiology, surveillance, mortality, paediatric, outbreak, children.

24 references were included in this section.

Laboratory Diagnosis

Search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD were combined with the terms in a search of PubMed : diagnosis, PCR, EIA, typing , glutamate dehydrogenase, algorithm, molecular diagnosis, molecular typing.

82 references were included in this part of the review.

Management of patients/residents with suspected/confirmed CDI

Search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD in combination with the following: Guidelines, suspected, GDH positive and toxin negative, asymptomatic, carrier, colonisation, treatment, infection control, infection prevention and control, visitors, isolation, duration of isolation, single room, contact precautions, communication, decontamination, disinfection, cleaning, housekeeping, chlorine, chlorine-releasing agents, chlorine based disinfectant, hypochlorite, contact times for disinfectant, concentration or parts per million available chlorine, sporicidal activity and effectiveness, adverse effects of sporicidal agents, cost of sporicidal agents, sodium hypochlorite, hydrogen peroxide, peracetic acid, equipment contamination, staff. For the section on *C. difficile* in IBD a search of PubMed was undertaken, and the search terms used were: meta-analysis, *Clostridium difficile*, inflammatory bowel disease, ulcerative colitis, Crohn's disease.

A separate PubMed search was carried out using the terms: *C. difficile*, *Clostridium difficile*, CDI, asymptomatic, carrier, colonisation, infection prevention control, isolation, transmission, treatment, management.

66 references were included in this part of the review.

Treatment of CDI

For this section, three searches were carried out. Initially, Computerised literature searches of PubMed from 1997 to July 2012 were performed. The search of the English-language literature used the terms "*Clostridium difficile*", "epidemiology", "treatment", and "infection control" and focused on human studies only. A secondary search was also conducted using the terms "*Clostridium difficile* treatment" and "probiotics", "intravenous immunoglobulins", "nitazoxanide", "rifaximin", "ramoplanin", "tolevamer", "rifalazil", "fidaxomicin" or "vaccination".

A search of www.ClinicalTrials.gov was also conducted using the term "*Clostridium difficile*" and all current and proposed studies were reviewed.

Finally for this section, the search terms: *C. difficile*, *Clostridium difficile*, CDI, CDAD were used in combination with the following in searches of Pub Med, Cochrane and Scopus: Guidelines and management, first episode, second episode, recurrence, recurrence prediction, severe, severe complicated, surgery, metronidazole, vancomycin, indications for surgery, Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, paediatric, children, combination therapy, clinical trials, monoclonal antibody, faecal transplantation, faecal microbiota transplantation, probiotics, intravenous immunoglobulins, nitazoxanide, rifaximin, tigecycline, ramoplanin, tolevamer, rifalazil, fidaxomicin, vaccination

163 references were included in this section of the literature review.

Management of outbreaks/clusters

A PubMed search of the MESH terms *Clostridium difficile* AND Outbreak OR cluster OR prevention was performed.

15 references which were included in this section.

Appendix 5

Details of consultation process: 18th October 2012-22nd November 2012

Patients and members of the public	<ul style="list-style-type: none"> • Publication on HPSC website • HSE patient advocacy • Irish Patients Association
External review	<ul style="list-style-type: none"> • Professor Ed Kuijper, Chair, ESCMID study group for <i>C. difficile</i> Executive Committee and Department of Medical Microbiology, Leids Universitair Medisch Centrum, Leiden, The Netherlands. • Professor Ciarán P. Kelly, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA (recommendations 51-66)
Clinical leaders and healthcare managers	<ul style="list-style-type: none"> • HSE Clinical directors • HSE Clinical leads and programme managers • HSE regional quality and risk managers • HSE regional HCAI committees
National committees	<ul style="list-style-type: none"> • RCPI clinical advisory group on HCAI and AMR • HSE National Incident Management Team • HPSC CIDR User Group • HPSC Scientific Advisory Committee
Professional groups	<ul style="list-style-type: none"> • Academy of Medical Laboratory Science • Emergency Medicine Association • Hospital Pharmacists Association of Ireland (HPAI) • Irish Antimicrobial Pharmacists Group • Irish College of General Practitioners • Irish Society of Clinical Microbiologists • Irish Society of Gastroenterologists • Irish Society of Physicians in Geriatric Medicine • Irish Pharmacy Union • Intensive Care Society of Ireland • Infection Prevention Society • Irish Infection Society • Nursing Homes Ireland • Public Health Medicine Communicable Disease Group • RCPI Faculty of Pathology • RCPI Faculty of Public Health Medicine • RCPI Faculty of Paediatrics • RCPI Faculty of Occupational Health Medicine • Royal College of Surgeons in Ireland (RCSI) • RCSI Faculty of Radiologists • Surveillance Scientists Association

Consultation submissions were received from the following individuals and groups and discussed in December 2013.

- Professor Ed Kuijper, Chair, ESCMID Study Group for *Clostridium difficile*
- Dr. Peter Finnegan, Specialist in Public Health Medicine, HSE-NE Department of Public Health
- Professor Martin Cormican, Consultant Microbiologist, Galway University Hospital
- Dr. Karina O'Connell, SpR Clinical Microbiology, Beaumont Hospital
- Mr. James Powell, Surveillance Scientist, Mid-Western Regional Hospital
- Mr. John Green, GS Medical Ltd
- Dr. Rory Goodbody, Medical Scientific Liaison (APCL), Dr. Andreas Karas, Senior Director Medical Affairs (APEL) and Dr. Elizabeth O'Brien Bergin, Head Medical Dept (APCL), Astellas Pharma Co. Ltd. (APCL), Astellas Pharma Europe Ltd. (APEL)
- Dr. Jennifer Martin, Specialist in Public Health Medicine, Department of Public Health, HSE East
- Dr. Phil Jennings, Director of Public Health, Department of Public Health, HSE - Midland Area
- Dr. Sarah Doyle and Dr. Catherine Lynch, Specialists in Public Health Medicine on behalf of Department of Public Health, HSE-SE
- Dr. Breida Boyle, Consultant Microbiologist, St. James' Hospital
- Ms. Helen Murphy and Ms. Aileen O'Brien, Infection Control/Communicable Disease Nurse Managers Department of Public Health HSE Dublin, Wicklow and Kildare
- Ms. Ann Higgins, Infection Prevention Society
- Ms. Eileen Hickey, infection prevention and control nurse specialist, in Kerry General Hospital
- Infection Prevention and Control Team, Beaumont Hospital, Dublin
- Infection Prevention and Control Team in Mayo General Hospital
- Ms. Marena Burd, infection prevention and control nurse specialist
- Ms. Sheila Donlon, Infection Control Manager, HPSC
- Irish Antimicrobial Pharmacists' Group (IAPG) and Hospital Pharmacists Association (HPAI)
- Prof. Timothy J. McDonnell, RCPI/HSE Clinical lead, COPD Programme and Consultant Respiratory Physician, St. Vincent's University Hospital
- Dr. Maria O'Mahony, ICGP

Professor Ciarán P. Kelly, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA, reviewed recommendations 51-66 in December 2012 after redrafting following the consultation process.

Appendix 6

Summary of probiotic trials in prevention and treatment of CDI

Study	Specimen	Intervention/ Comparison	C. difficile Diarrhoea (Diarrhoea and CD Toxin +)	Later Recurrence of C. difficile Diarrhoea
Surawicz, 1989(394) United States (RCT)	318 hospitalized patients given new antimicrobials 180 completed study, 138 had <i>C. difficile</i> tested	Probiotic: Sacchromyces boulardii (250 mg capsule with 1 g <i>S. boulardii</i> bid) (n=116) Placebo bid (n=64)	Overall incidence of CDI: Probiotic: 3/116 (2.6%) Placebo: 5/64 (7.8%) Incidence of diarrhoea in 48 patients had stools that were CD toxin+: Probiotic: 3/32 (9.4%) Placebo: 5/16 (31%)	
McFarland, 1995(395) United States (RCT)	193 hospitalized adults on new betalactam antimicrobial ±another antimicrobial and no diarrhoea 129 (67%) completed study	Probiotic: Lyophilized <i>S. boulardii</i> 3x10 ¹⁰ cfu (1 g) PO in two 250 mg capsules/d within 72 hrs of antimicrobial and until max of 28 days (n=97) Placebo 1 g (undefined) (n=96)	Overall incidence of AAD: Probiotic: 3/97 (3.1%) Placebo: 4/96 (4.2%) Development of ADD in 24 patients with positive CD assays: Probiotic: 3/10 (30%) Placebo: 4/14 (29%)	
Lewis, 1998(327) United Kingdom (RCT)	72 Hospitalized elderly (≥65 years) patients started on antimicrobials Mean age (range): 74 (70-85) years	Probiotic: <i>S. boulardii</i> (113mg) (Ultra- Levure, Biocodex, Montrouge, FR) 2x/ day(n=33) Placebo (undefined) 2x/day (n=36)	Overall incidence of CDI: 4 patients had diarrhoea stools that were CD toxin+ (not reported by treatment arm) Not statistically significant	
Can, 2006 (330) Turkey (RCT)	151 adult inpatients 25–50 yrs who had chemotherapy and antimicrobials	Probiotic: <i>S. boulardii</i> + antimicrobials (β-lactam) (n=73) Placebo + antimicrobials(n=78)	Overall incidence of CDI: 8 patients had diarrhoea, only two CD toxin + (both in the placebo group Probiotic: 0/73 (0%); Placebo: 2/78 (2.6%)	
Thomas, 2001(328) United States (RCT)	302 hospitalized patients on antimicrobials 267 (88%) completed study	Probiotic: Lactobacillus GG(20 x 10 ⁹ cfu + inulin filler) (CAG Functional Foods, Nebraska) 1 capsule 2x/d x14 d (n=133) Placebo (inulin filler) (n=134)	Overall incidence of CDI: Only 5 patients (1.9%) with positive CD toxin: Probiotic: 2/133 (1.5%) Placebo: 3/134 (2.2%), p >0.99	

Study	Specimen	Intervention/ Comparison	C. difficile Diarrhoea (Diarrhoea and CD Toxin +)	Later Recurrence of C. difficile Diarrhoea
Plummer, 2004(329) United Kingdom (RCT)	150 elderly hospitalized patients started on antimicrobials 138 (92%) completed study	Probiotic: Lactobacillus acidophilus and Bifidobacterium bifidum, 2 x10 ¹⁰ cfu in 1 capsule/d (Cultech, Saanse) for at least 20 of antimicrobial therapy (n=69) Placebo (n=69)	CD diarrhoea, 1st testing, during diarrhoea and antimicrobial tx in hospital: Probiotic: 2/69 (3%); Placebo: 5/69 (7%) CD diarrhoea, 2nd testing of same patients after antimicrobials completed or at discharge: Probiotic: 2/69 (3%); Placebo: 6/69 (9%)	
Hickson, 2007(331) UK (RCT)	135 hospital patients on antimicrobials given tx until tx was finished + 1 week; If discharged from hospital and stayed on antimicrobials, continued tx; C. difficile testing and follow up occurred for 4 weeks after tx ended	Probiotic: L. casei DN-114001 (L casei imunitass, 1 x 10 ⁸ cfu/ ml) + S.thermophilus (1 x 10 ⁸ cfu/ml) + L. bulgaris(1 x 10 ⁷ cfu/ ml) in yogurt drink (Actimel, Danone, FR) (n=69) Placebo:sterile milkshake (Yazoo, Campina NE) (n=66)	Overall incidence of CDI: Probiotic: 0/57: Placebo: 9/53 (17%), p=0.001 Absolute risk reduction = 17% (95% CI 7% to 27%)	
McFarland, 1994(305) United States	124 in patients active CDI on vancomycin or metronidazole 104 (84%) completed the study Mean age 58.1 Gender: Male 23% 64 patients had initial CDI and 60 had recurrent CDI	Probiotic-Lyophilized S.boulardii 3x10 ¹⁰ cfu (1 g) PO in two 250 mg capsules/days x 4 weeks and standard anti-CDI therapy, (n=57). Probiotic given within 4 days of treatment Placebo and standard anti- CDI therapy (n=67).	N/A	Probiotic: 26.3% (15/57) subjects with recurrence Placebo: 24.3% (8/33) with initial CDI had CDI recurrence and 64.7% (22/34) with recurrent CDI had another Recurrence
Surawicz 2000(325) United States (RCT)	32 randomized adult inpatients and outpatients, 32 with recurrent CDI	CDI subjects: Probiotic: S. boulardii (1 g/d) + high dose oral vancomycin (2g/d) (n=18) Placebo (1 g/d) + high-dose oral vancomycin (2g/d) (n=14)	N/A	Recurrence: Probiotic: 3/18 (17%) Placebo: 7/14 (50%), p=0.05

Study	Specimen	Intervention/ Comparison	<i>C. difficile</i> Diarrhoea (Diarrhoea and CD Toxin +)	Later Recurrence of <i>C. difficile</i> Diarrhoea
Wullt, 2003(324) Sweden (RCT)	29 adult patients- 9 centres: + CD toxin assay within 6 days of enrolment at least 1 prior episode CDI in past 2 months and ongoing diarrhoea 8 patients (28%) lost to follow up were not included in analysis, 21 completed trial	Probiotic: L. plantarum in fruit drink with oats fermented by L. plantarum 299v (5 x 10 ¹⁰ cfu) x 38 days and Metronidazole (400 mg tds po) x 10 days Metronidazole + placebo fruit drink with chemically acidified oats	Clinical cure: no diarrhoea (≥ 3 loose stools x 2 days) on days 5-10 of tx Probiotic: 11/12 (92%) Placebo: 9/9 (100%)	Total recurrences: Probiotic: 4/11 (36%) Placebo: 6/9

Appendix 7

Summary of clinical trials for CDI management (396)

Study Drug	Sponsor	Study Characteristics	Dates: Start/Completion	Outcome Measure	NCT Number
Vaccines					
<i>Clostridium difficile</i> Toxoid Vaccine (ACAM-CDIFF™) (Injection)	SANOFI-AVENTIS	RCT; Double Blind; Intervention Phase 2 N=650; 18-85 yr; 1st Episode of CDI. Placebo/ <i>Clostridium difficile</i> Toxoid Vaccine± adjuvant	Feb 2009/ Feb 2012	Recurrence of CDI. Safety and Immunogenicity.	NCT00772343
<i>Clostridium difficile</i> Toxoid Vaccine (ACAM-CDIFF™) (Injection)	SANOFI-AVENTIS	RCT; Double Blind; Intervention Phase 2 N=650; 40-75 yr; At risk of CDI. Placebo/ <i>Clostridium difficile</i> Toxoid Vaccine± adjuvant – High/Low dose.	Oct 2010/ Jan 2013	Safety and Immunogenicity.	NCT01230957
IC84 vaccine (injection)	INTERCELL AG	RCT; Open label; Intervention Phase 1; N=80; 18yr+ Vaccine for <i>C. difficile</i> toxin A+B ± adjuvant (dose finding study)	Dec 2010/ Dec 2012	Safety and Immunogenicity. Dose response.	NCT01296386
Monoclonal Antibodies					
Colostrum derived Antibodies against <i>Clostridium difficile</i> (Oral)	HADASSAH MEDICAL ORGANISATION	RCT; Double Blind; Intervention Phase 2 / 3 N=300; 18yr + Placebo/Colostrum	Sep 2011/ Nov 2013	Recurrence of CDI in index cases. New cases of CDI in close contacts.	NCT00747071
Human Monoclonal Antibodies to <i>Clostridium difficile</i> Toxin A and B. (MK-3415;MK-6072;MK-3415A) (Injection)	MERCK	RCT; Double Blind; Intervention Phase 3: N=1600; 18yr+ Placebo/MK-3415(toxin A)/MK-6072(toxin B)/MK-3415-A (toxin A+B) plus standard of care antimicrobial therapy. (MODIFY I)	Oct 2011/ May 2014	Recurrence of CDI. Global cure and recurrence after initial cure.	NCT01241552
Human Monoclonal Antibodies to <i>Clostridium difficile</i> Toxin A and B. (MK-6072;MK-3415A) (Injection)	MERCK	RCT; Double Blind; Intervention Phase 3: N=1200; 18yr+ Placebo/MK-6072(toxin B)/MK-3415-A (toxin A+B) plus standard of care antimicrobial therapy. (MODIFY II)	Feb 2012/ July 2014	Recurrence of CDI. Global cure and recurrence after initial cure.	NCT01513239

Study Drug	Sponsor	Study Characteristics	Dates: Start/Completion	Outcome Measure	NCT Number
Oral Anti-C. difficile Agents					
Oral Fidaxomicin (feasibility study in neonates)	ASTELLAS	Observational; Prospective N=60; <28 days	March 2012/ Feb 2013	Feasibility of potential intervention study.	NCT01533844
Oral LFF571	NOVARTIS	RCT; Single Blind; Intervention Phase 2; N=160; 18-90 yr 1st episode or 1st relapse of moderate CDI. Vancomycin vs. LFF571 (4 dose ranges)	Oct 2010/ May 2013	Difference in clinical response rate for LFF571 vs. vancomycin. Relapse rate. Safety and efficacy of LFF571.	NCT01232595
Oral Fidaxomicin	WASHINGTON SCHOOL OF MEDICINE /CDC	RCT; Double Blind; Intervention Phase 4; N=418; 18yr + Placebo/Fidaxomicin (patients on broad spectrum antibacterials)	April 2012/ March 2016	<i>Clostridium difficile</i> isolated from stool.	NCT05112668
Oral CB-183,315	CUBIST PHARMACEUTICALS	RCT; Double Blind; Intervention Phase 2; N=210; 18yr+ Oral vancomycin vs. CB-183,315 (dose ranging study)	April 2010/ May 2011	Safety and Relative Efficacy Relative CDI recurrence rate.	NCT01085591
Oral CB-183,315	CUBIST PHARMACEUTICALS	RCT; Double Blind; Intervention Phase 2; N=608; 18 – 90yr Oral vancomycin vs. CB-183,315 (dose 250mg)	May 2012/ Dec 2014	Number of participants with clinical cure.	NCT01597505 (Colorado) NCT0159831 (Georgia)
Oral ACT-179811	ACTELION	RCT; Double Blind; Intervention Phase 2; N=92; 18yr+ ACT-179811 (3 doses) vs. active comparator. 1st episode CDI or 1st recurrence.	Dec 2010/ June 2012	Efficacy, safety and tolerability. Clinical cure and disease recurrence.	NCT01222702
Oral Fidaxomicin	OPTIMER	Safety study; Open label Phase 2A; N=32; 6months – 18yr Oral fidaxomicin in paediatric patients with CDI	May 2012/ March 2013	Safety, tolerability, and clinical response.	NCT01591863
Oral VP20621	VIROPHARMA	RCT; Double Blind; Intervention Phase 2; N= 240; 18yr+ Placebo vs. VP20621 (2 doses)in recurrent CDI	May 2011/ Feb 2013	Safety and tolerability.	NCT01259726
Probiotics					
Oral VSL #3	NHS UK	RCT; Double Blind; Intervention Phase 2/3; N=450; 18yr+ Placebo/VSL#3 in patients on systematic antimicrobials	April 2010/ Dec 2012	Development of AAD. Development of CDI. LOS in hospital.	NCT00973908
Oral Probiotics Go Live™	SOUTH SHORE HOSPITAL	RCT; Double Blind; Intervention N=600; 18yr+ Enhanced probiotic vs. placebo in patients taking antimicrobials	July 2012/ Oct 2014	Incidence of CDI in patients taking Go Live™	NCT01596153
Perenterol® Forte	BERNHARD NOCHT INSTITUTE FOR TROPICAL MEDICINE	RCT; Double Blind; Intervention Phase 3; N=1520; 18yr+ <i>S. boulardii</i> vs. placebo in patients on systemic antimicrobial therapy	June 2010/ July 2012	Incidence of AAD. Incidence of CDI.	NCT01143272

Study Drug	Sponsor	Study Characteristics	Dates: Start/Completion	Outcome Measure	NCT Number
Danone™	UNIVERSITY OF SUSSEX	RCT; Double Blind; Intervention N= 1200; 55yr+ Live probiotic vs. placebo in patients taking antimicrobials	Oct 2009/ Oct 2012	Incidence of diarrhoea. Incidence and duration of <i>C. difficile</i> toxin and rate of recurrence of <i>C. difficile</i> toxin positive diarrhoea.	NCT01087892
Faecal Microbiota Transplantation					
Faecal Transplant "synthetic stool"	QUEENS UNIVERSITY	Non-randomised; Open label N=30; 18yr+ Synthetic stool vs. pure culture from healthy donor in patients with recurrent/refractory CDI	Jan 2010/ Jan 2013	Number of participants cured of CDI.	NCT01372943
Faecal Transplant	UNIVERSITY HEALTH NETWORK TORONTO	RCT; Open; Intervention Phase 2/3; 18yr+: N=146 Oral vancomycin followed by faecal transplant or tapering vancomycin for recurrent CDI	Oct 2010/ Dec 2013	Number of patients with recurrent CDI. Safety of faecal transplant.	NCT01226992
Faecal Transplant	MCMASTER UNIVERSITY	RCT; Double Blind; Intervention Phase 2; N=120; 18yr+ Faecal transplant vs. oral vancomycin for refractory/ recurrent CDI.	Sep 2011/ June 2013	Compare cure, treatment failure, and relapse rate. Safety of faecal transplant.	NCT03198969
Fresh vs. Frozen and thawed Faecal Transplant	MCMASTER UNIVERSITY	Rct; Double Blind; Intervention Phase 2; N=136, 18yr + Fresh Human Biotherapy vs. Frozen-and-thawed Human Biotherapy for recurrent CDI	July 2012/ July 2014	Safety of therapy. Assess cure and recurrence of CDI.	NCT01398969
Miscellaneous					
Tigecycline (injection)	GARY E STEIN	Prospective observational study Open label; Intervention;N=20;18yr+ Tigecycline plus standard treatment in mild to severe CDI.	July 2011/ July 2013	Safety and Efficacy of tigecycline. Recurrence rate of CDI.	NCT010401023
Surgery for Fulminant <i>Clostridium difficile</i> Colitis.	MASSACHUSETTS GENERAL HOSPITAL	RCT; Open; Intervention N=100; 18yr+ Ileal diversion and lavage vs. total abdominal colectomy	Jan 2012/ Feb 2014	ICU length of stay. Mortality.	NCT01441271
Intracolonic Vancomycin	WILLIAM BEAUMONT HOSPITAL	RCT; Double Blind; Intervention Prospective; N=20; 18yr+ Intracolonic vancomycin vs. saline in Severe <i>C. difficile</i> colitis.	April 2011/ Feb 2012	Resolution of diarrhoea/WCC. Mortality and colectomy.	NCT01846059

Appendix 8

Example of faecal microbiota transplantation protocol for recurrent CDI. (319)

Screening of donors

- Potential donors have to fill in an extensive questionnaire. Donors with abnormal bowel motions, abdominal complaints, symptoms indicative of irritable bowel syndrome, an extensive travel history or predisposing factors for potentially transmittable diseases are excluded.
- If they are considered eligible after completing the questionnaire, their faeces and blood are further screened as below.

Donor	Faeces	Blood
Parasitology	Stool ova and parasites test "Triple faeces test" <i>Cryptosporidium</i> <i>Microsporidium</i>	<i>Strongyloides</i> <i>Entamoeba</i>
Microbiology	Faecal culture for common enteropathogens and <i>Clostridium difficile</i>	<i>Treponema palladium</i>
Virology		Cytomegalovirus, Epstein-Barr virus, hepatitis A/B/C viruses Human immunodeficiency virus, human T-lymphocyte virus

Pre-treatment of patient

- Vancomycin 500mg orally four times daily for four days.
- Whole bowel lavage with macrogol solution (4 litres) taken after day 4 of Vancomycin.
- Nasoduodenal (nasojejunal) tube is placed radiologically or endoscopically, abdominal x-ray performed to check position.

Preparation of donor faeces

- Faeces are collected and weighed from donor (approximately 60-120g)
- 300-400mL normal saline (0.9% NaCl) is added and mixed until a smooth suspension is created.
- Faeces solution is poured through a double gauze and put in glass bottle.
- Within six hours after production by the donor, the faeces are instilled through a nasojejunal tube.

Appendix 9

Intracolonic vancomycin regimens

Several methods for administration of vancomycin intracolonic are described in the literature: Although the optimal dosing and volume has not been established by clinical trials and case descriptions vary widely, rectal vancomycin is often given as a retention enema containing 500 mg in 100 mL of normal saline every 6 hours. (144, 354, 397-400)

Method

- An IV solution of vancomycin 500mg is dissolved in 100 ml normal saline.
- An 18G Foley catheter is inserted per rectum and the balloon is inflated.
- The vancomycin solution is instilled into the rectum and retained for 60 minutes by clamping the catheter.
- Once retention time is complete, the catheter is unclamped, the balloon deflated and the catheter removed.
- This process can be repeated every 6 hours depending on the clinical response. (144, 354) (1, 2)

One report suggests that patients with megacolon may benefit from colonoscopic decompression and placement of a tube in the right colon which can be perfused with a 1 mg/mL solution of vancomycin in normal saline to deliver a total dose of 1 to 2 g per day (354); however, this requires further study.

Dose adjustments may be required depending on individual circumstances including extent of colonic disease and patient weight. It is important to note that vancomycin can be absorbed through inflamed colonic mucosa and cause toxicity if it accumulates in patients with renal failure.

Appendix 10

Glossary of terms and abbreviations

Definitions within the context of this document

Healthcare facility	Any acute care, long-term care, long-term acute care, or other facility in which skilled nursing care is provided and patients are admitted at least overnight.
Healthcare staff	Includes medical doctors, nurses, healthcare assistants, biomedical scientists, pharmacists, allied health and social care professionals and healthcare management.
Clinician	A healthcare professional such as a doctor or nurse involved in clinical practice.
Infection prevention and control team	<p>A group of people from within and outside the service, with complementary knowledge and skills relating to infection prevention and control. The structure of the team should be based on current accepted best practice. Below is an example of an Infection Prevention and Control team and is for guidance purposes only:</p> <ul style="list-style-type: none">• Consultant clinical microbiologist• Infectious disease consultant• Infection prevention and control nurse specialist• Surveillance scientist/medical scientist• Antimicrobial pharmacist• Occupational health physician.

Abbreviations

AFPL:	Amplified Fragment Length Polymorphism
AIG:	Acute Infectious Gastroenteritis
AMR:	Antimicrobial resistance
BD:	Bis In Die/twice daily
BNF:	British National Formulary
CCFA:	Cefoxitin Cycloserine Fructose Agar
CCTA:	cell cytotoxicity assay
CDAD:	<i>Clostridium difficile</i> associated disease
CDI:	<i>Clostridium difficile</i> infection
CDRN:	<i>Clostridium difficile</i> ribotyping network
CIDR:	Computerised Infectious Disease Reporting
CIR:	Crude incidence rate
CME:	Continuing medical education
CPE:	Cytopathic effect
DoH:	Department of Health
DRG:	Diagnosis related group
EIA:	Enzyme immunoassay
ESCMID:	European Society for Clinical Microbiology and Infectious Diseases
ESRI:	The Economic and Social Research Institute
ECDC:	European Centre for Disease Prevention and Control
ESGCD:	European Society for Clinical Microbiology and Infectious Diseases Study Group for <i>Clostridium difficile</i>
GDH:	Glutamate dehydrogenase
GP:	General practitioner
HCW:	Healthcare worker/healthcare staff
HCAI:	Healthcare associated infection
HPA:	Health Protection Agency
HPSC:	Health Protection Surveillance Centre
HIQA:	Health Information and Quality Authority
HIPE:	Hospital In-Patient Enquiry
HSE:	Health Services Executive
IBD:	Inflammatory bowel disease
IDSA:	Infectious Disease Society of America
ICU:	Intensive care unit
IPC(T):	Infection prevention and control (team)
LOS:	Length of stay
LTCF:	Long-term care facility
MIC:	Minimum inhibitory concentration
MLST:	Multi Locus Sequence Typing
MLVA:	Multilocus Variable-Number Tandem-Repeat Analysis
MOH:	Medical Officer of Health
MRSA:	Meticillin resistant <i>Staphylococcus aureus</i>
NAAT:	Nucleic acid amplification tests
NCPE:	National Centre for Pharmacoeconomics
NICE:	National Institute for Health and Clinical Excellence
NHS:	National Health Service
OD:	Once daily
OCT:	Outbreak control team

PCR:	Polymerase chain reaction
PPM:	Parts per million
PFGE:	Pulsed Field Gel Electrophoresis
PPE:	Personal Protective Equipment
PPIs:	Proton pump inhibitors
PPV:	Positive predictive value
QDS:	Quater Die Sumendus/four times daily
RCT:	Randomised controlled trial
REA:	Restriction Endonuclease Analysis
SAC:	Scientific advisory committee
SAPG:	Scottish Antimicrobial Prescribing Group
SD:	Standard deviation
SHEA:	Society for Healthcare Epidemiology of America
slpAST:	Surface layer protein A gene sequence typing
SPHM:	Specialist in Public Health Medicine
SPC:	Statistical Process Control
TDS:	Ter Die Sumendum/three times daily
UCL:	Upper control limit
US:	United States
UK:	United Kingdom
WHO:	World Health Organisation

Appendix 11

Budget impact assessment

Economic Impact Report

Key message

This review of the literature on the economic evaluation of the prevention, detection and treatment of *Clostridium difficile* and the budget impact analysis support the clinical guideline recommendations.

The report was completed by Dr. Jennifer O'Hanlon Specialist Registrar in Public Health Medicine, Mr. Damadar Solanki, Chief Pharmacist, Beaumont Hospital, and Michelle O'Neill, Senior Health Economist, Health Technology Assessment Directorate, Health Information and Quality Authority in collaboration with Dr. Fidelma Fitzpatrick, Chair, *C. difficile* subcommittee, Dr. Mary O'Riordan, Specialist in Public Health Medicine and Mr. Gethin White, Health Service Executive library services.

Economic literature review results

A systematic review of the economic evaluation literature of *Clostridium difficile* was conducted, the detailed search terms are provided in Table 4. Of the thirty-four studies identified, nine were excluded (three were available as abstracts only (1, 2) and six did not report any relevant economic data (3-7). The remaining 25 studies covered a broad range of topics: antimicrobial stewardship programmes; screening; disinfectant; detection; treatment as well as fifteen studies focusing on the economic burden of *Clostridium difficile* infection (CDI) (1, 8-17). The cost-effectiveness literature is presented first, grouped under three broad headings, prevention, detection and treatment, followed by a consideration of the potential budget impact. All costs presented have been inflated and converted into 2013 values for Ireland using the relevant national Consumer Price Index (CPI) and Purchasing Power Parity (PPP) unless otherwise stated.

Prevention

a) Antibiotic Stewardship Programmes (ASP)

Two US studies were retrieved which compared the costs and clinical outcomes before and after the implementation of an ASP. These showed a reduction in CDI rates, antimicrobial use and pharmacy costs. (18, 19) Both studies reported similar percentage reductions (9.75% and 13.3%, respectively) in the cost of antimicrobials per patient day following the implementation of the ASP. In the study by Malani *et al.*, implementation of an ASP in a community hospital reduced the odds of developing CDI by approximately 50%. (19) However, it must be noted that there is no consensus on what constitutes an optimal ASP, therefore programmes may differ in their costs and efficacy.

b) Screening

One retrieved US study showed that screening hospital admissions for CDI and implementing contact isolation precautions for all those who screened positive was cost-effective (20), (incremental cost-effectiveness ratio \leq €219/QALY for all scenarios tested). The cost per case averted ranged from a cost saving of €233 to a cost of €3,486. The cost-effectiveness was influenced by compliance with isolation precautions and prevalence: screening appeared to be cost saving when all the following were met: \geq 10.3% colonisation rate, \geq 6% infection probability and when compliance with contact isolation was \geq 25%.

c) Disinfectant

Comparison of the clinical effectiveness and the cost of eight CDI environmental disinfectants (hydrogen peroxide vapour, dry ozone, chlorine releasing agent, microfibre cloths used in combination with and without a chlorine releasing agent, high temperature over heated dry

atomised steam cleaning in combination with a sanitising solution, steam cleaning and peracetic acid wipes) was examined in a small randomised prospective study. (21) The study investigated the reduction in *C. difficile* colony count pre and post disinfection with the agent. (21) It showed that the three most clinically effective products were hydrogen peroxide (350-700 ppm), 1000ppm chlorine-releasing agent and peracetic acid wipes. It found the traditional cheapest method (chlorine-releasing agent, €190 per month) was as effective as the more modern methods, some of which were up to 8 times more expensive.

In summary, although there is limited cost-effectiveness literature, it does suggest that ASP are both clinically effective and cost-effective. Screening hospital admissions for *C. difficile* is reported as highly cost-effective, and under certain conditions it may even be cost saving. The cheaper method of chlorine disinfectant for reducing colony count of *C. difficile* was shown to be as effective as more expensive modern methods.

Detection

CDI testing strategies include various options such as enzyme immune assays (e.g. GDH), on demand PCR tests (odPCR e.g. NAAT) and cell cytotoxicity assays.

A cost-effectiveness study by Schroeder *et al.* (22) compared multiple CDI testing algorithms including lateral-flow GDH/odPCR, lateral flow GDH-Tox/odPCR, EIA toxin, stand alone on demand PCR, batch PCR and direct tissue culture cytotoxicity. For every 10,000 symptomatic adults, on demand PCR preceded by lateral flow GDH testing generated 831 true-positive results costing €1,321 per case treated. (22) Stand-alone odPCR was more effective and more expensive identifying an additional 174 true-positive cases costing €5,698 per additional case treated compared to on demand PCR preceded by lateral flow GDH testing. This cost-effectiveness analysis showed that odPCR was favoured over other testing choices, but should be preceded by GDH testing if a missed CDI case resulted in less than €4,129 of extended hospital costs and GDH testing had a sensitivity of more than 93% or if the symptomatic carrier percentage among the toxin culture positive cases was more than 80%. (22)

Several two-step algorithms have been developed that are based on the use of GDH. (3-7) They all use GDH for screening in which a stool specimen with a negative assay is considered negative for the pathogen but a positive result requires further testing to determine whether the *C. difficile* strain is toxigenic. In addition to the advantage that a negative result can be turned around quickly, this approach may result in cost savings for laboratories. A recent study compared the clinical and cost outcomes when performing a two-step testing (GDH followed by CCNA test) of 5,887 specimens at two different hospitals.(23) The GDH test was positive for 16% of specimens at one hospital and 24% of specimens at the other. Therefore, 75-85% of the specimens did not require further testing which resulted in a cost savings of 61% (€151,609) over the first 6 months after implementation, compared with full CCNA testing for all specimens.

In summary, there is no international consensus on the most cost-effective and efficient testing algorithm for *C. difficile*. Rapid testing was shown to be more cost-effective over non-rapid tests, two step testing using GDH as a screening tool has been shown to be cost saving and odPCR testing, is shown to be cost-effective, but more expensive and should be preceded by GDH testing if the cost of a missed CDI case is less than €4,129 and the GDH test has a high sensitivity.

Treatment

Fidaxomicin is a new treatment for CDI. The National Centre for Pharmacoeconomics (NCPE) appraised a company submission on the cost-effectiveness of fidaxomicin for the treatment of CDI compared with metronidazole (used to treat initial non-severe CDI and first non-severe recurrence) and oral vancomycin (used to treat severe CDI and first non-severe recurrence) in Ireland. A target population of all CDI patients was chosen for the base case analysis and three additional patient subgroups were also considered: patients with non-severe CDI, patients with severe CDI and patients with a first recurrence. Fidaxomicin is significantly more expensive than

metronidazole and vancomycin, however it was found to be dominant (more effective and less costly) for all patients with CDI and for all patient subgroups. The estimates of cost-effectiveness were driven mainly by the relative reductions in recurrence of CDI which were subject to significant uncertainty. However, evaluation of the combined uncertainty in probabilistic sensitivity analysis demonstrated that there was an 82% probability that fidaxomicin is cost-effective at a willingness to pay of €45,000/QALY. (24)

All Wales Medicine Strategy Group (AWMSG) also reported fidaxomicin to be dominant (less costly and more effective) than vancomycin for the treatment of patients with severe or recurrent CDI. They have recommended it should be prescribed on the advice of consultant microbiologist and restricted to use in patients with severe CDI or recurrent CDI.(25) In Scotland, the Scottish Medicines Consortium has restricted the use of fidaxomicin to treatment of adults with a first CDI recurrence on the advice of a microbiologist or infectious disease consultant, where again it was found to be dominant in this group compared with vancomycin or metronidazole. The SMC rejected the company's submission for first line use in adults with severe CDI on the basis that the economic analysis was not sufficiently robust. (26)

A study by Bartsch *et al.* examined CDI treatment using fidaxomicin as a first line treatment in three scenarios: a)no fidaxomicin, b)only fidaxomicin and c) fidaxomicin based on strain type. They concluded that as a first-line treatment, fidaxomicin would have to cost less than €124 per treatment episode to be cost-effective in all CDI and between €132 and €330 to become cost-effective for certain strains of CDI (20), this is considerably lower than the current cost of €1,500 per treatment episode of fidaxomicin in Ireland.

In summary, fidaxomicin is significantly more expensive than both metronidazole and vancomycin. While there is conflicting international evidence regarding its cost-effectiveness as a first line agent, the NCPE has advised that it is cost-effective in Ireland in all CDI patients (at a willingness to pay threshold of €45,000/QALY), and should be prescribed in line with this National Clinical Guidelines.

Budget impact of the proposed guidelines for *C. difficile* prevention and control

Scope of the budget-impact analysis

Rather than cost each recommendation statement, the cost-impact analysis focuses on two main areas as determined by discussions with the *C. difficile* guideline development group (GDG):

1. Overall cost implications of *C. difficile* prevention and control
2. Additional cost implications that may arise from changes in the updated guidelines.

Overall cost implications

CDI costs money. Patients with CDI spend significantly longer in hospital, on average, an additional one to three weeks which contributes significantly to additional hospital costs. (17) CDI is also associated with an increased risk of hospital readmission. (27) Other costs include additional infection prevention and control measures required for CDI patient management, and when outbreaks occur, cohort isolation and ward closure (28) which impacts significantly on a hospital's day to day business (e.g., patient throughput via the Emergency Department).

Fifteen of the retrieved studies considered the economic impact of CDI, ten from the US (1, 8, 11-13, 15-17) and one each from Germany(29), Europe (14), Australia (10) and Spain(9).

A systematic review of European studies estimated the incremental cost of CDI per case ranged from €5,798 to €11,202. (14) A German matched case control study(29) found that most of the additional cost was due to the significantly longer hospital stay (median of seven days) for patients with CDI. The overall cost to Europe is likely to rise in line with an ageing population: by 2050 more than 134 million Europeans will be aged 65 years or older. (28)

For the US studies, the direct attributable cost of CDI per case was estimated to range from €6,255-€11,210 (8, 15), which is consistent with those found in European studies. Costs were significantly

higher in patients with co-morbidity, (e.g., patients with IBD) and recurrent CDI cases also had significantly higher costs due to extended re-hospitalisation, laboratory tests to confirm a recurrent infection and the cost of additional and often extended anti-CDI therapy. The total costs for recurrent CDI has been shown to be approximately three-fold higher than for a primary episode of CDI. (30) The overall impact on the US was estimated to range from €408 million – €4.5 billion per year (1, 15).

Recently, in the UK, NICE estimated the impact of a 5%, 10% and 15% reduction in the number of *C. difficile* cases (using the September 2010 to August 2011 *Clostridium difficile* surveillance reports). A 5% reduction in *C. difficile* cases would reduce national NHS costs by an estimated £4.65 million annually based on 2010/11 data (Table 1).

Table 1 Anticipated reduction in national costs (pounds sterling) due to reduction in the number of *C. difficile* cases (31)

Percentage reduction	<i>C. difficile</i> anticipated cost reduction £
5%	4,650,000
10%	9,290,000
15%	13,940,000

The report also outlines the types of benefits (e.g., improved efficiencies) and cost savings that could be expected with further reductions in *C. difficile* and other healthcare-associated infection (HCAI) (Table 2)

Table 2 Costs avoided by reducing CDI

<ul style="list-style-type: none"> • Drug therapy • Hospital readmissions and potentially, repeat procedures • Decontamination • Laboratory and imaging investigations • Litigation • Ward closures • Medical, nursing and management time • Increased community nursing/rehabilitation as a result of morbidity following HCAI

Over 60 Irish hospitals participate in the Hospital In-Patient Enquiry (HIPE) Scheme. HIPE is a computer-based health information system designed to collect medical and administrative data regarding discharges from and deaths in acute hospitals. Each HIPE discharge record represents one episode of care and patients may have been admitted to more than one hospital with the same or different diagnoses. In the absence of a unique patient identifier in HIPE, the unit of measurement is discharges and not patients. The records therefore facilitate analyses of hospital activity rather than incidence or prevalence of disease. HIPE does not collect data on visits to the Emergency Department or outpatient clinics. In order to estimate the number of inpatients with a diagnosis of CDI in Ireland, the HIPE database was examined from 2008 to 2013 (Appendix 3). In the analysis presented in this guideline, all discharges which had 'A047' Enterocolitis due to *Clostridium difficile* code recorded in any diagnosis field were included. Only those patients aged two or over at the time of discharge were included as this is consistent with the case definition for notifiable diseases for the HPSC.

These data indicate that the number of cases per annum declined 1,414 in 2008 but has remained steady over the last 3 years (see Table 3). As there are no published Irish data on the additional cost of hospital care attributable to CDI, values from a systematic review of European literature, where

the additional cost per case was estimated to range from €5,798 to €11,202, were combined with the HIPE data to calculate the potential attributable cost of CDI in Ireland. Based on these data, the estimated additional cost of treating hospital inpatients with CDI in 2013 ranged from €6.1-€11.7 million. However, it must be noted that this may be an underestimate of the true cost, as this figure does not include the cost of care of CDI in the community setting.

Table 3 Hospital inpatient discharges with a diagnosis of C. difficile infection 2008 – 2013

Year	Number of patients with CDI 'All' diagnosis	Estimated cost range attributable to C difficile
2008	1,414	€8.2-€15.8 million
2009	1,298	€7.5-€14.5 million
2010	1,226	€7.1-€13.7 million
2011	1,184	€6.8-€13.2 million
2012	1,073	€6.2-€12.0 million
2013	1,045	€6.1-€11.7 million

Note: Data include all discharge episodes in patients aged ≥2 years at time of discharge and the code A047' Enterocolitis due to Clostridium difficile recorded in any diagnosis field, all costs have been inflated to reflect Irish 2013 values.

Source: HIPE, Economic and Social Research Institute (ESRI).

Possible additional cost implications of 2013 guidelines update

The 2014 guidelines are an update of previous national guidelines published in 2008. While there is a dearth of national information on the compliance with implementation of the 2008 national CDI guidelines, as part of the national clinical programme for the prevention and control of healthcare-associated infections and antimicrobial resistance, there have been improvements in hand hygiene and antimicrobial stewardship, education and monitoring.

The available international evidence suggest that the full implementation of the National Clinical Guideline should have a positive impact on the control and prevention of health care associated infections in general, including a reduction in the number of patients acquiring CDI in healthcare facilities. This would include reduced healthcare facility stay, avoid the need for additional investigations and treatments and potentially have a wider benefit to society with respect to patients being able to return to work.

The overall consensus of the Guideline Development Group was that costs incurred with the implementation of these 2014 guidelines would likely be offset by savings and result in more efficient use of existing healthcare resources and facilities. However, points a-e below show some changes or new recommendations that might result in an increase in resource consumption.

- a) *Fidaxomicin*: Fidaxomicin is significantly more expensive than other treatment alternatives, however it has been shown to be cost-effective in Ireland at a willingness to pay threshold of €45,000/QALY. The potential budget impact was reported in the company submission to the NCPE over a five year time horizon assuming that 25% of fidaxomicin prescribing would be on the High Tech drug scheme and the remainder in the hospital setting. The gross drug budget impact was estimated to range from approximately €88,000 in year one to approximately €1.55million by year five. The net budget impact was estimated to increase from €20,000 in year one to €0.3million by year five. This includes the cost offsets from replacing prescriptions for vancomycin and metronidazole and reduced length of stay from recurrences avoided. However, the NCPE noted that this analysis may have overestimated the reduction in recurrence rates, and potential savings, as many of these patients will have co-morbidities which may prolong hospital stay, thus underestimating the potential budget impact. (24)

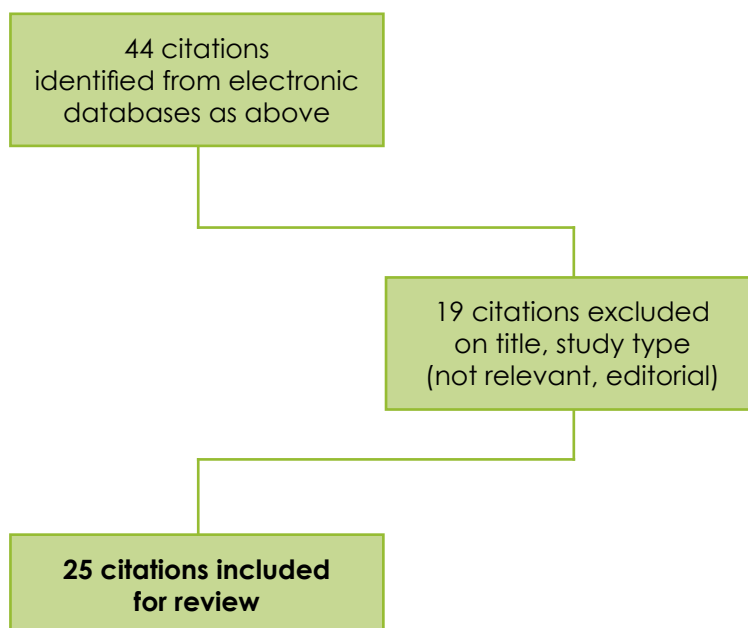
- b) *Laboratory testing*: At present, most laboratories have transitioned to a two-step testing process, however, there is no international consensus on which combination of tests are the most cost-effective and efficient. Until there is more evidence to identify a superior testing algorithm, maintaining the status quo of current laboratory tests for *C. difficile* is the most practical procedure and will not incur additional costs.
- c) *Single Irish Reference laboratory*: There is no single Irish *C. difficile* reference laboratory, UK laboratories are used to perform this testing instead. Introducing a single Irish reference laboratory would potentially produce savings derived from the reduction of UK laboratory costs and the improved capacity to capture important intelligence around *C. difficile* types prevalent in the Irish setting. However, significant costs would be incurred by the setting up and resourcing of a national centre. A full detailed business case would need to be performed to determine the potential costs and benefits of this recommendation.
- d) *Access to expert advice regarding infection control in the non-acute sector*: A further gap identified by the Guideline Development Group was the lack of access to expert advice for infection control in the community. Reduction of infection and prevention of *C. difficile* in community healthcare settings is anticipated to improve acute healthcare setting HCAs and ultimately reduce the burden and cost of such illness on the patient and healthcare setting. There is no consensus on the best delivery model, and consideration will need to be given to the local resources and facilities available. To determine the most efficient approach to facilitate this measure, a formal needs assessment guided by public health expertise and subsequent business case would need to be developed.
- e) *Information Technology Systems merger*: Ensuring appropriate linkage and compatibility of IT systems that are used for the collection, collation and dissemination of *C. difficile* data will ensure the free flow of information between relevant stakeholders, enabling timely and appropriate action to respond to any change in the profile of *C. difficile* across the country. However, a more detailed business case examining the requirements for such a process is beyond the scope of this budget impact assessment.

Methods

The search strategy is based on the one used in the clinical literature review with the addition of an economic filter (32) for the Medline and EMBASE search including the Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

Table 4: Economic Filter

ID	Search	Hits
6	*Economics/	21479
7	*Economics, Medical/	21559
8	*Economics, Pharmaceutical/	5872
9	exp "Costs and Cost Analysis"/	400064
10	exp Health Care Costs/	224939
11	exp decision support techniques/	64779
12	exp models, economic/	102782
13	markov chains.sh.	8346
14	montecarlo method.sh.	35519
15	uncertainty.sh.	10158
16	quality of life.sh.	308452
17	quality-adjusted life years.sh.	5950
18	exp health economics/	564180
19	exp economic evaluation/	190553
20	exppharmacoeconomics/	160770
21	exp economic aspect/	1047120
22	quality adjusted life year/	15615
23	quality of life/	308452
24	exp "costs and cost analyses"/	168352
25	(economic impact or economic value or pharmaco-economics or health care cost or economic factors or cost analysis or economic analysis or cost or cost-effectiveness or cost effectiveness or costs or health care cost or cost savings or cost-benefit analysis or hospital costs or medical costs or quality-of-life).sh.	592852
26	(econom\$ or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget\$ or afford\$ or pharmacoeconomic or pharmaco-economic\$).ti,ab.	1046158
27	(cost\$ adj1 (util\$ or effective\$ or efficac\$ or benefit\$ or consequence\$ or analy\$ or minimi\$ or saving\$ or breakdown or lowering or estimate\$ or variable\$ or allocation or control or illness or sharing or life or lives or affordabl\$ or instrument\$ or technolog\$ or day\$ or fee or fees or charge or charges).ti,ab.	212069
28	(decision adj1 (tree\$ or analy\$ or model\$)).ti,ab.	20279
29	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).ti,ab.	8947
30	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.	63557
31	(sensitivity analys\$s or quality-adjusted life year\$ or quality adjusted life year\$ or quality-adjusted life expectanc\$ or quality adjusted life expectanc\$).ti,ab.	11826
32	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).ti,ab.	45098
33	(decision adj1 (tree\$ or analy\$ or model\$)).ti,ab.	20279
34	or/6-33	2377303

Figure 2 Flow chart of excluded studies

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