Health Protection Surveillance Centre

***Clostridium difficile* Sub-Committee 2008**

Surveillance, Diagnosis and Management of *Clostridium difficile* - associated disease in Ireland

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Health Protection Surveillance Centre 2008
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Background and Sub-Committee Membership

In July 2006, the Scientific Advisory Committee (SAC) of the Health Protection Surveillance Centre (HPSC) proposed that a sub-committee be established to produce national guidelines for the surveillance, diagnosis and management of *Clostridium difficile* - associated disease (CDAD) in Ireland. This was in response to requests from infection prevention and control teams (IPCTs) for national guidance and also to the isolation of *C. difficile* ribotype 027 for the first time in some Irish hospitals. Nominations were requested from the Royal College of Physicians in Ireland (RCPI) Faculty of Public Health Medicine, Hospital Pharmacists Association of Ireland (HPAI), Irish College of General Practitioners (ICGP), Irish Society of Clinical Microbiologists (ISCM), Infection Prevention Society (IPS) incorporating Infection Control Nurses Association (ICNA), Irish Infection Society (IIS) and the Academy of Medical Laboratory Science (AMLS). In addition, individuals with an interest in the field were invited to participate in the group.

The following are the members of the *C. difficile* sub-committee:

1. Dr Fidelma Fitzpatrick (FF), Consultant Microbiologist, HPSC (Chair)
2. Dr Susan Clarke (SC), Infectious Disease Physician, St James' Hospital (IIS)
3. Ms Annette Darcy (AD), Surveillance Scientist, Letterkenny General Hospital (AMLS)
4. Ms Breda Deasy (BD), Infection Prevention and Control Clinical Nurse Specialist, St Luke's Hospital, Kilkenny (IPS)
5. Dr Denise Drudy (DD), Centre for Food Safety, University College Dublin
6. Dr. Lynda Fenelon (LFe), Consultant Microbiologist, St. Vincent's University Hospital, Dublin
7. Ms Liz Forde (LFo), Infection Prevention and Control Clinical Nurse Specialist, Cork Community Infection Prevention and Control Services, HSE-South
8. Dr Patrick Gavin (PG), Consultant in Paediatric Infectious Diseases, The Children's University Hospital, Temple Street and Our Lady's Hospital, Crumlin
9. Dr Anne Gilleece (AG), Consultant Microbiologist, Connolly Hospital (ISCM)
10. Dr. Paul Kavanagh (PK), Specialist Registrar in Public Health Medicine, HPSC (until December 2006)
11. Dr Lorraine Kyne (LK), Consultant in Medicine for the Elderly, Mater Misercordiae Hospital, Dublin
12. Dr Ann-Marie O'Byrne (AO'B), Consultant in Public Health Medicine, HSE-Southeast (RCPI Faculty of Public Health Medicine)
13. Mr Ajay Oza (AO), Surveillance Scientist, HPSC
14. Mr Damodar Solanki (DS), Chief 2 Pharmacist, Beaumont Hospital (HPAI)

The terms of reference for the group were to review international best evidence and to make recommendations for the surveillance, diagnosis, clinical management and infection prevention and control of CDAD in Ireland.

The sub-committee first met in September 2006. Members agreed the terms of reference as listed above. Three separate sub-groups were established to review the relevant literature and produce recommendations as follows:

1. Surveillance sub-group: AO'B (Chair), AD, BD, DD, FF, LFo, LK, PK, AO
2. Diagnosis and typing sub-group: DD (Chair), AD, LFe, FF, AG, LK, AO
3. Clinical management and infection prevention and control sub-group: AG (Chair), BD, SC, FF, LFo, LFe, LK, AO'B, DS

In April 2007, on reviewing progress, it became apparent that the group required the input of an expert in paediatric clinical microbiology/infectious diseases and PG agreed to join the group.

A draft of this document was sent for consultation in October 2007 to a range of organisations (Appendix 1).

The Committee wish to acknowledge the assistance of Ms. Norma Deasy, National Communications Unit, Health Service Executive, Cork, in drafting the patient information leaflet (Appendix 10).

Foreword

- This document is aimed at healthcare professionals and outlines recommendations for the surveillance, diagnosis, clinical management and infection prevention and control of *C. difficile*-associated disease in Ireland

- This document represents the expert opinion of the *C. difficile* sub-committee following literature review and a consultative process (Appendix 1). It was not possible for the sub-committee to grade the evidence available in the literature as outlined by the Scottish Intercollegiate Guidelines Network (SIGN)[1]due to the heterogeneity of evidence available, the lack of good quality evidence available for SIGN recommendations and other work commitments of sub-committee members, which precluded a more detailed literature review

- While we accept that some aspects of the recommendations may be difficult to implement initially due to a lack of facilities or insufficient personnel, we strongly believe that these guidelines represent best practice

- Where there are difficulties, these should be highlighted locally and to the Health Services Executive (HSE) and the Department of Health and Children (DoHC) so that measures are taken by the HSE and the DoHC to ensure implementation, including the provision of appropriate resources and personnel

- The Committee recommends that these guidelines are reviewed and updated in 3-5 years

Chapter 1:
Summary of Recommendations

A: IMPLEMENTION OF THESE GUIDELINES

Recommendation 1: Responsibility for the implementation of these guidelines

- The Department of Health and Children (DoHC) and the Health Services Executive (HSE) must prioritise prevention of healthcare-associated infection (HCAI) in order to improve patient care and safety and to reduce all HCAI, including infections caused by *Clostridium difficile*. This prioritisation must include ring-fenced funding to assist healthcare facilities* and regions meet these recommendations, specifically surveillance, laboratory and infection prevention and control infrastructure and personnel

**A healthcare facility is defined as 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[2]*

B: SURVEILLANCE OF *C. DIFFICILE* – ASSOCIATED DISEASE

Recommendation 2: (Page 24 - Section 2.5)

- Healthcare facilities should perform surveillance of cases of *C. difficile* - associated disease (CDAD). This will enable baseline CDAD incidence to be calculated and a threshold incidence or prevalence of CDAD to be calculated locally that would trigger implementation of additional control interventions. This surveillance should ideally include awareness of changes in the rate and severity of complications from, or relapses of, CDAD and be performed in conjunction with surveillance of antibiotic use in that healthcare facility
- CDAD figures should be collated nationally from laboratory based sources
- This system should be mandatory through Computerised Infectious Disease Reporting (CIDR) at laboratory level, which will require that CDAD is made a notifiable disease through legislation. Additional resources and legislative change will need to be addressed at both hospital and population health level
- In the interim, pending legislative change, we have proposed a national core dataset for CDAD surveillance (Appendix 4) for use in healthcare facilities, to be used on a voluntary basis by Infection Prevention and Control Teams (Microbiologists, Infection Prevention and Control Nurses, Surveillance Scientists), Health Protection Staff (Specialists in Public Health Medicine, Medical Officers of Health, Surveillance Scientists and Communicable Disease Control Nurses) and General Practitioners. Additional resources (including IT) will need to be addressed
- In addition to the core dataset, individual healthcare facilities may wish to collect additional data for local surveillance. An enhanced CDAD surveillance dataset is proposed that could be used by healthcare facilities and also when CIDR is used for national collation of data (Appendix 5).

Recommendation 3: Case definitions for surveillance of CDAD (Page 26 - Section 2.6)

- To enable international comparisons of surveillance data, we propose that the interim case definitions proposed by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for *C. difficile* and the European Centre for Disease Prevention and Control (ECDC) should be adopted. As a minimum, in acute hospitals, data should be collated nationally on healthcare-onset, healthcare-associated cases
- These definitions are as follows:

1. *C. difficile* - associated disease (CDAD) case

This is a patient to whom *one or more* of the following criteria applies:

- Diarrhoeal* stools or toxic megacolon, with either a positive laboratory assay for *C. difficile* toxin A (TcdA) and / or toxin B (TcdB) in stools or a toxin-producing *C. difficile* organism detected in stool via culture or other means
- Pseudomembranous colitis (PMC) revealed by lower gastrointestinal endoscopy
- Colonic histopathology characteristic of *C. difficile* infection (with or without diarrhoea) on a specimen obtained during endoscopy, colectomy or autopsy

* Diarrhoea is defined as three or more loose/watery bowel movements (which are unusual or different for the patient) in a 24 hour period

This definition excludes diarrhoea* with other known aetiology (as diagnosed by the attending physician), and asymptomatic patients with a stool culture positive for toxin-producing *C. difficile* or an assay positive for *C. difficile* toxin B and/or Toxin B.

2. Severe CDAD case

This is a CDAD patient to whom any of the following criteria apply:

- Admission to an intensive care unit for treatment of CDAD or its complications (e.g., for shock requiring vasopressor therapy)
- Surgery (colectomy) for toxic megacolon, perforation or refractory colitis
- Death within 30 days after diagnosis if CDAD is either the primary or a contributive cause
- Admission to a healthcare facility for treatment of community-associated CDAD

3. Recurrent CDAD case

This is a patient with an episode of CDAD that occurs within 8 weeks following the onset of a previous episode provided that CDAD symptoms from the earlier episode resolved with or without therapy.

- CDAD cases can also be categorized with respect to their onset and origin as follows:

1. Onset of CDAD

- *Healthcare onset* Symptoms start during a stay in a healthcare facility
- *Community onset* Symptoms start in a community setting, outside healthcare facilities

2. Origin of CDAD

- *Healthcare-associated case*

  This is a CDAD case with either

  o Onset of symptoms at least 48 hours following admission to a healthcare facility (healthcare-onset, healthcare-associated)

  or

  o With onset of symptoms in the community within 4 weeks following discharge from a healthcare facility (community onset, healthcare-associated)

- *Community-associated case*

This is a CDAD case patient with either

o Onset of symptoms while outside a healthcare facility, and without discharge from a healthcare facility within the previous 12 weeks (community-onset, community-associated)

or

o With onset of symptoms within 48 hours following admission to a healthcare facility without residence in a healthcare facility within the previous 12 weeks (healthcare-onset, community-associated).

- *Unknown case*

This is a CDAD case patient who was discharged from a healthcare facility 4–12 weeks before the onset of symptoms.

Recommendation 4: Denominators for surveillance (Page 27 - Section 2.6.4)

- The Committee recommends that acute hospital healthcare-associated case rates are expressed as
  - o Cases per reporting time period (e.g., month or quarter) per 1000 patient admissions and per 10,000 patient-days (or bed-days used)
  - o Cases per number of patients tested for *C. difficile* per reporting time period
- There are no appropriate denominators at present that would enable benchmarking in settings outside acute hospitals (e.g., nursing homes). It is therefore recommended that the HSE devise appropriate internationally comparable denominators for these settings
- Community-associated case rates should be expressed as cases nationally per 100,000 population per year

C: LABORATORY DIAGNOSIS OF CDAD

Recommendation 5: Specimen selection for laboratory diagnosis (Page 30 - Section 3.3)

- All patients in whom a diagnosis of gastrointestinal infection is suspected should have a stool specimen sent promptly for microbiological analysis
- *C. difficile* toxin testing should only be performed on diarrhoeal stool specimens (from patients 2 years and over) unless ileus is present. Testing stool of children < 2 years for *C. difficile* toxin is not recommended
- Diarrhoeal stool specimens are defined as those that take up the shape of their container. In the case of ileus and suspicion of CDAD, testing of formed stool is acceptable and other diagnostic procedures (e.g., abdominal CT, colonoscopy) may be required
- All diarrhoeal specimens should be tested for *C. difficile*, however, this will have service implications for laboratories in terms of workload and staffing that will need to be addressed by the HSE in order to implement this recommendation
- Testing of asymptomatic individuals is not recommended. Similarly, because asymptomatic *C. difficile* colonisation can be present in up to 80% of healthy newborns and infants, testing diarrhoeal stools for *C. difficile* in this population is generally not recommended
- In the case where clinical suspicion of CDAD is high, yet *C. difficile* toxin is negative, patients should be retested and if negative, the specimen set up for *C. difficile* culture followed by toxin testing
- Once the diagnosis of CDAD is confirmed, patients should not be retested for *C. difficile* toxin when on treatment. If recurrence of diarrhoea after a symptom-free interval occurs, a repeat specimen should be tested for *C. difficile* toxin and other potential causes of diarrhoea excluded
- Performing a 'test of cure' or clearance on stool specimens after *C. difficile* treatment is not recommended

Recommendation 6: Laboratory diagnosis of CDAD (Page 32 - Section 3.4)

- For optimal laboratory investigation, freshly taken faecal specimens should be examined
- Specimens for transportation or specimens which cannot be examined promptly should be refrigerated at 4°C in a designated specimen refrigerator. *C. difficile* toxin is less well preserved in specimens which have been frozen at –20°C therefore, specimens for toxin detection should be stored at 4°C rather than being frozen
- All laboratories should use a method that can detect both toxin A and toxin B
- *C. difficile* can be isolated by culturing faecal samples directly onto selective agar. Media can be pre-reduced and a pre-inoculation process of heat or alcohol shock performed in order to enhance isolation
- The physician/surgeon or general practitioner involved in the patient's care is to be informed immediately of all positive *C. difficile* toxin results

Recommendation 7: *C. difficile* typing (Page 34 - Section 3.7)

- In cases of severe CDAD, or in an outbreak setting, specimens should be referred to a reference laboratory for epidemiological typing or stored at 4°C for culture at a later stage
- The Committee recommends that an Irish reference laboratory is established with appropriate funding. It also recommends that *C. difficile* culture is carried out by this reference laboratory. Pending establishment, 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

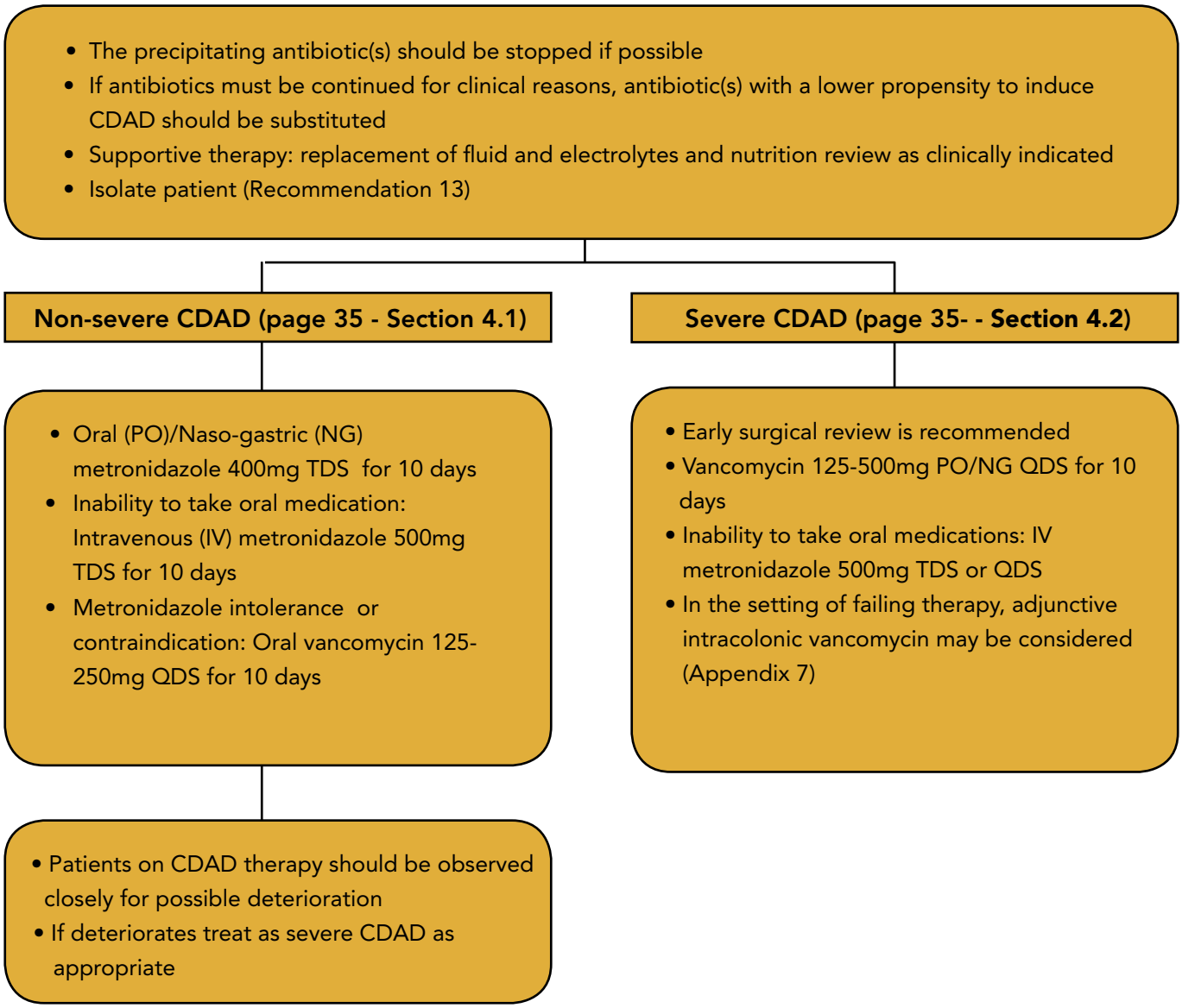
determine evolutionary trends and the emergence of virulent strains. This could be done in conjunction with laboratories abroad and as part of an international network

D: MANAGEMENT OF CDAD

Recommendation 8: Treatment of CDAD (Page 35 - Section 4.1)

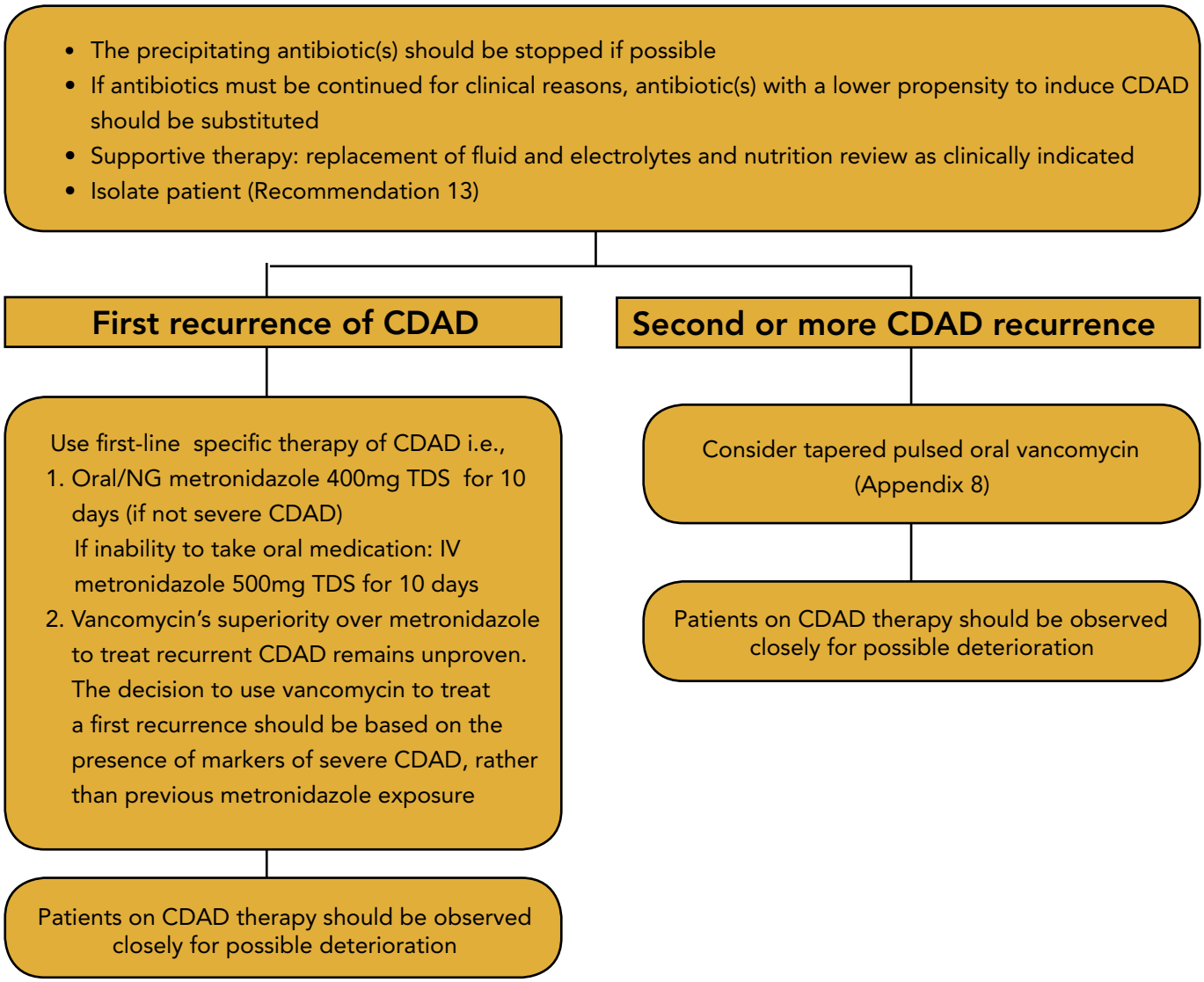
- Asymptomatic carriers of *C. difficile* should not be treated
- Antiperistaltic agents should be avoided because of lack of evidence that they improve diarrhoea in this situation and the theoretical risk of precipitating toxic mega colon by slowing clearance of *C. difficile* toxin from the intestine
- First-line specific therapy of CDAD

(For paediatric doses refer to the British National Formulary for Children)



***Treatment of recurrent CDAD* (page 37 - Section 4.3)**

(For paediatric doses refer to the British National Formulary for Children)



Recommendation 9: Novel and emerging therapies for CDAD (Page 38 - Section 4.4)

- There is little evidence to support the use of probiotics as prophylactic agents to prevent CDAD in patients receiving antibiotics
- Routine use of *S. boulardii* or *S. cerivisiae* for the prevention or treatment of CDAD is not recommended because of the risk of fungaemia, particularly in immunocompromised and critically ill patients
- As prebiotics are not commercially available, there is no recommendation for their use
- Intravenous immunoglobulin (IVIG) is not licensed as a therapy for severe or recurrent CDAD. The optimal dose and dose frequency for this indication is not known. Despite promising results from numerous case series, the data do not provide sufficient evidence to support the use of IVIG in patients with recurrent or severe CDAD
- As further studies need to be performed on the use of nitazoxanide, rifaximin, rafalazil, par-101 and ramoplanin in CDAD, there is no recommendation for their use

E: PREVENTION AND CONTROL OF CDAD

Recommendation 10: Infection prevention and control of CDAD - Prioritisation and resources (Page 42 - Section 5.2)

- Control of HCAI must be given high priority by the DoHC, HSE and senior healthcare facility management. The provision of adequate patient isolation rooms with clinical hand washing sink, ensuite facilities and adequate

levels of healthcare worker (HCW) staffing is essential for the prevention of HCAI, including CDAD. This will have resource implications and must be given priority
- Performance targets (e.g., waiting times in the Emergency Department) should not compromise the appropriate care and isolation of patients with CDAD. This is particularly important in an outbreak setting where a ward/unit may need to suspend admissions on a temporary basis. Governance structures need to incorporate clinical risk assessment into its decision-making
- Budgetary provisions (for staffing, consumables, medication, extended hospital stay etc) need to be in place for additional expenditure necessary for hospitals that experience an outbreak/s of infection to ensure that outbreaks are managed as effectively as possible

Recommendation 11: Prudent antibiotic stewardship (Page 42 - Section 5.3)
- All healthcare facilities must have antibiotic guidelines that specifies use of narrow spectrum antibiotics for specific infections
- The duration of antibiotic therapy, drug dosage and combinations of various antibiotics should be restricted
- Interventions should consist of a mixture of educational and restrictive practice, with a multidisciplinary approach, and feedback on CDAD rates. Interventions should be monitored for unintentional clinical and microbiological outcomes

Recommendation 12: Infection prevention and control of CDAD - Physical infrastructure (Page 44 - Section 5.4)
- Healthcare facilities should have a sufficient number of patient isolation rooms with clinical hand washing sink, and ensuite toilet/bathroom to assist in the prevention and control of HCAI, including CDAD, in addition to single rooms required for other purposes
- Healthcare facilities should also provide appropriate hand hygiene and bathroom facilities to facilitate infection prevention and control and phase out large multi-bedded wards. An increase in the total number of single ensuite rooms is recommended

Recommendation 13: Infection prevention and control of CDAD - Patient placement (Page 44 - Section 5.5)
- Prompt isolation of all patients with confirmed or suspected CDAD, using Standard and Contact Precautions (Appendix 9), in a single room with clinical hand washing sink and ensuite facilities is recommended. If ensuite facilities are not available, patients with CDAD should be allocated a designated toilet or commode and not permitted to use the general toilet facilities on the ward
- Isolation with Contact Precautions may be discontinued when the patient has had at least 48 hours without diarrhoea and has had a formed or normal stool for that patient
- In an outbreak setting it may be necessary to cohort patients if sufficient single rooms are not available. Cohorted patients should be managed by designated staff to minimise the risk of cross-infection to other patients

Recommendation 14: Infection prevention and control of CDAD - Education (Page 45 - Section 5.6)
- Infection prevention and control education should be mandatory for all healthcare workers (HCWs) and should include prevention of *C. difficile* transmission. HCW education should include not only medical and nursing staff, but also allied healthcare professionals and support staff (e.g., cleaning staff, portering staff, administrative staff)
- Patients with CDAD and their visitors should be provided with a CDAD patient information leaflet outlining the infection control precautions required (Appendix 10)

Recommendation 15: Infection prevention and control of CDAD - Patient movement and transfer (Page 45 - Section 5.7)
- The movement and transport of the CDAD patient should be limited to essential purposes only
- Prior to patient transfer, transport personnel (e.g., porters, emergency medical technician) and the receiving department/healthcare facility must be informed of the need for Contact Precautions. Contaminated aprons/

gowns and gloves should be removed and disposed of and hand hygiene performed prior to transporting patients. An apron/gown and gloves should be worn prior to handling the patient at the transport destination
- Prior to accepting a patient with CDAD, it is the responsibility of the receiving facility to ensure compliance with single room, clinical hand washing sink, ensuite 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 (Recommendation 17) before use with another patient/resident

Recommendation 16: Infection prevention and control of CDAD - Hand hygiene and protective clothing (Page 46 - Section 5.8)
- Hand washing with soap (non-antimicrobial or antimicrobial) and water must be performed before and after all patient and equipment contact and after glove removal. The physical action of rubbing and rinsing is the only way to remove spores from hands
- Alcohol-based hand rubs do not have reliable sporicidal activity and are not recommended as the only hand hygiene measure when caring for confirmed or suspected CDAD patients
- In addition to Standard Precautions, gloves and aprons should be worn for contact with the patient and the patient environment (Appendix 9)

Recommendation 17: Infection prevention and control of CDAD - Environmental and equipment decontamination (Page 47 - Section 5.9)
- The environment of patients with CDAD and all patient care equipment should be thoroughly cleaned with a neutral detergent and disinfected daily with a sporicidal disinfectant (e.g., hypochlorite solution – 1000 ppm available chlorine), paying special attention to frequently touched sites e.g., bedrails, over bed table, toilets, commodes etc
- Particular attention should be given to immediately cleaning and disinfecting items likely to be faecally contaminated e.g., the under surfaces and hand contact surfaces of commodes. These items should be cleaned and disinfected after each use. All equipment used for patients should be in a state of good repair in order to facilitate effective cleaning. Cleaned commodes and bedpans should be stored under dry conditions
- Medical devices (e.g., thermometers, sphygmomanometers, stethoscopes) should be dedicated to a single patient and disposable materials used whenever possible
- 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
- Bedpan/commode utensils should be placed directly into a bedpan washer-disinfector. Bedpan washers must reach a temperature of 80°C for a minimum of 1 minute. Scheduled maintenance and validation records according to appropriate standards should be maintained to ensure appropriate cleaning and disinfection
- Environmental faecal soiling should be cleaned and disinfected immediately
- In the event of an outbreak, the frequency with which environmental cleaning and disinfection is performed should be increased on the affected ward and monitored
- Cleaning and disinfection of isolation/cohort rooms should be performed after discharge of the CDAD patient
- Further studies to evaluate effective environmentally safe agents are needed

Recommendation 18: Laundry and healthcare risk waste management (Page 49 - Section 5.10)
- 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 clearly identified with labels, colour-coding or other methods so that HCWs handle these items safely 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 then 10 minutes or preferably 71°C for not less then 3 minutes
- Disinfection of heat labile materials (according to manufacturer instructions) can be achieved at low temperatures, by introducing 150 ppm of 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 CDAD patient should be disposed of as healthcare risk waste

Recommendation 19: Outbreaks of CDAD (Page 51 - Section 5.13)

- An outbreak is defined as the occurrence of two or more epidemiologically linked CDAD cases over a defined period agreed locally, taking account of the background rate or where the observed number of CDAD cases exceeds the expected number
- Medical practitioners and clinical directors of diagnostic laboratories are required to notify to the Medical Officer of Health unusual clusters or changing patterns of illness
- The infection prevention and control team (ICPT) must always be informed when there are an increased number of suspected or confirmed CDAD cases
- An outbreak control team (OCT) that is multi-disciplinary and made up of senior professionals and decision-makers should be set up for both hospital and community CDAD outbreaks. The OCT should include infection prevention and control, clinical microbiology, infectious diseases, public health medicine, relevant physicians/surgeons, surveillance scientists, nursing and senior management as appropriate
- All healthcare facilities should ensure that there are defined and documented outbreak management processes and procedures outlining the roles and responsibilities of the OCT members
- All infection prevention and control measures (Recommendations 10-18) should be reinforced in the case of a CDAD outbreak;
  - It may be necessary to cohort patients if sufficient single rooms are not available. Cohorted patients should be managed by designated staff to minimise the risk of cross-infection to other patients (Recommendation 13)
  - The standard of environmental cleaning and disinfection should be reviewed to ensure high quality and frequency of decontamination (Recommendation 17)
  - Faecal samples from all infected patients should be stored, so they can be cultured either in the hospital or a reference laboratory and typing performed (Recommendation 7)
  - Ensure compliance with Standard and Contact Precautions (Appendix 9)
- Additional measures advised by the OCT to control the outbreak must be implemented
- The OCT will 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
- 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 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 and the number of cases has returned to the endemic level

Chapter 2: Rationale for Recommendations

1. Introduction

1.1 Background

Clostridium difficile is a spore-forming anaerobic bacterium that is widely distributed in soil and the intestinal tracts of animals. The spectrum of *C. difficile* human disease ranges from asymptomatic colonisation to potentially fatal colitis. *C. difficile* can be cultured from the stool of 3% of healthy adults and up to 80% of healthy newborns and infants. The prevalence of asymptomatic *C. difficile* colonisation ranges from less than 5% in the community to over 20% of hospitalised patients.[3] Previously, *C. difficile* was thought to affect older and/or severely ill hospital inpatients or residents of long term care facilities and was not considered pathogenic for children, however, there is some evidence that this assumption may need to be reconsidered.[4;5] Typically, *C. difficile*-associated disease (CDAD) presents as diarrhoea, abdominal cramps, fever and leucocytosis, occurring several days to up to 10 weeks after antibiotic therapy. Pseudo membranous colitis (PMC) is the most severe manifestation of disease. PMC is usually pan colitis; however, a right-sided colitis is also described, featuring fever, pain, and decreased gut motility often with only mild diarrhoea. Severely ill patients may have little or no diarrhoea due to dilation of the colon (toxic mega colon) and paralytic ileus that may result from a loss of colonic muscular tone. CDAD-associated mortality varies with the population under study and has been reported as high as 30%, although attributable mortality is thought to be lower.[6;7] The average attributable costs per CDAD case (prolonged hospital stay, additional diagnostic and treatment costs, isolation precautions, surgical procedures) has previously been estimated between $2,000 and $8,000 per case.[8-14]

The most common risk factors for CDAD are exposure to antibiotics, advanced age and hospitalisation. The most commonly reported antibiotics implicated in development of CDAD are clindamycin, the broad-spectrum cephalosporins and fluroquinolones (Section 5.3.1). However, nearly all antibiotics have been associated with CDAD, though less so with metronidazole, aminoglycosides and trimethoprim. While CDAD is a disease predominantly of older patients, other risk factors such as hospitalisation, recent gastrointestinal surgery or procedures and immunosuppressive therapy can also predispose to infection. Another proposed risk factor is exposure to proton pump inhibitors – it is thought that the increased gastric pH produced by these drugs leads to decreased destruction of spores.[15;16] However, this association has not been demonstrated in recent studies.[17;18] While CDAD is mainly healthcare - associated, there is increasing recognition of the existence of community-associated cases. A high percentage of patients with CDAD (9.3%) was found among 703 patients with diarrhoea visiting their general practitioner over a three month period, in comparison to *Salmonella enteritica* (4.8%) and Campylobacter (3%).[19]

1.2 *C. difficile* ribotype 027

C. difficile isolates can be divided into over 150 polymerase chain reaction (PCR) ribotypes and 25 toxinotypes for epidemiological purposes.[20] In Canada, a changing pattern of disease severity was observed from 1991 to 2003.[21] The number of patients with complicated CDAD (defined as having any of mega colon, perforation, colectomy, shock requiring vasopressor therapy, or death) rose significantly from around 7% in 1991-1992 to 18% in 2003. The epidemic due largely to the emergent hyper-virulent strain PCR ribotype 027 (toxinotype III), was identified in the Quebec region of Canada, where, between one and three thousand deaths may have resulted in 2003-2004.[22] PCR ribotype 027 is also referred to as North American pulsed-field type 1 (NAP1) and group BI by restriction endonuclease analysis.

The United States (US) Centers for Disease Control (CDC) reported a steady increase in the incidence of CDAD from 2.7 per 10,000 hospital admissions in 1987 to 4.2 in 2001. Since 2001, *C. difficile* ribotype 027 outbreaks have occurred in at least 16 US states.[2] In Europe, *C. difficile* ribotype 027 outbreaks have been recognised in at least 75 hospitals in England, 16 in The Netherlands, 13 in Belgium and nine in France.[2] Recently, the first case of *C. difficile* ribotype 027 in Ireland was reported from a patient transferred from a UK hospital.[23] This report also described two clusters of *C. difficile* ribotype 027 in two Irish hospitals. In England in 2006, there were 55,681 cases of CDAD reported in people aged 65 years and over, representing an 8% rise on 2005 (which had increased 17.2% in comparison to 2004).[24;25] The predominant strains referred to the Anaerobic Reference Unit prior to the random sampling scheme (Section 2.2.1) were ribotype 001. However, non-001 ribotypes now predominate

including *C. difficile* ribotype 027, which represented over 25% strains in 2005.[24] The number of deaths in the UK associated with *C. difficile* also increased from 975 in 1999 to 2247 in 2004. It is suggested that *C. difficile* ribotype 027 is associated with increased rates of community-associated CDAD.[2;15] However, this may be due to improved surveillance of diarrhoea. Another explanation is that these cases are in fact healthcare-associated but with onset in the community.[16]

1.3 Pathogenesis

CDAD is mediated by the production of two exotoxins, toxin A (TcdA) and toxin B (TcdB). Both act as enterotoxins in the human intestine.[26] Previously, toxin A was regarded as the most important factor in CDAD, but there are a number of reports describing sporadic cases and outbreaks caused by toxin A-negative strains.[27-29] While CDAD is mediated by toxin production, it is not thought that there is a correlation between toxin production and the extent of clinical disease.[30] In addition, a third toxin (binary toxin), encoded by the *cdtA* and *cdtB* genes and which is present in up to 10% of strains, is thought to play a role in virulence,[31] however, this has not been confirmed to date in animal models.[32]

C. difficile ribotype 027 is characterised by an 18-bp deletion as well as a frame shift deletion in *tcdC*, the putative negative regulator of the production of toxins A and B resulting in excess toxin production.[3] In addition, this strain also produces binary toxin. This strain produces 23 and 16 times more toxins B and A than previously described *C. difficile* strains and is associated with fluoroquinolone resistance.[3]

1.4 *C. difficile* surveillance in Ireland

Because CDAD and particularly *C. difficile* ribotype 027 has a high epidemic potential, the European Centre for Disease Prevention and Control (ECDC) has indicated that individual member states should develop early-warning mechanisms and should implement a patient-based surveillance system. While neighbouring countries such as the UK have introduced various systems of mandatory and voluntary surveillance (Section 2.2), the Republic of Ireland has no national information on the incidence of CDAD.

In the Republic of Ireland, the Health Protection Surveillance Centre (HPSC) is responsible for the collation and analysis of weekly notifications of infectious diseases from public health staff located regionally. Unlike some infectious diseases, *C. difficile* is not notifiable; therefore the national extent of CDAD in the country is unclear. The only source of national data is that from the third Hospital Infection Society (HIS) prevalence study of healthcare-associated infections (HCAI) in acute hospitals in the UK and Ireland in 2006. In this study, 36/7541 patients (0.5% prevalence) were reported as having *C. difficile* infection, the majority, 25/36 (69%) were aged over 75 years (Section 2.3.2).

While sporadic cases of *C. difficile* infection are currently not notifiable, outbreaks of infectious diseases are. Between January 2004 and December 2007, eleven outbreaks of *C. difficile* infection were reported to the HPSC, seven in acute hospital settings and four in residential institutions (Table 1.1).

In view of the paucity of information and the clear need to establish on-going national surveillance to guide future health policies and to provide a benchmark for future interventions, the Scientific Advisory Committee of the HPSC established a subcommittee to produce national guidelines on the surveillance, diagnosis and management of *C. difficile* in Ireland.

Table 1.1: *C. difficile* Outbreaks reported to HPSC January 2004 to December 2007. Data source: CIDR

HSE Region	Organism(s)	Outbreak location	Total number of patients
East	*C. difficile*	Hospital	15
East	Suspected *C. difficile*	Residential institution	11
East	*C. difficile*	Hospital	9
East	*C. difficile*	Hospital	11
North West	Norovirus and *C. difficile*	Residential institution	6
North West	Norovirus and *C. difficile*	Hospital	8
North West	Norovirus and *C. difficile*	Hospital	18
North West	Norovirus and *C. difficile*	Community hospital/Long-stay unit	20
Mid West	*C. difficile*	Hospital	46
North East	*C. difficile*	Hospital	9
North West	Norovirus and *C. difficile*	Community hospital/Long-stay unit	39

2. Surveillance of CDAD

2.1 Background

The public health importance of CDAD in Ireland is underlined by a number of factors:

- The burden of disease caused by *C. difficile*: not only is CDAD a relatively common disease, but it can be severe, associated with significant morbidity and mortality
- The potential for control and prevention: as the organism is transmissible, there is potential for spread of disease. In addition, antibiotic usage and other healthcare interventions increase the risk of the disease

Developing high quality health intelligence around CDAD in Ireland is essential for the development, implementation and evaluation of policy and practice to prevent and control the disease at local and national levels. There are a number of potential end-users for this information: for example, hospital infection prevention and control teams (IPCTs) at a local level and the National Hospitals Office (NHO) of the Health Services Executive (HSE) at a national level. This information could inform a number of actions including investigation and control of outbreaks at a local level, evaluating the effectiveness of antibiotic governance at a local or national level and developing and resourcing policy on infection prevention and control in the health care setting. The information could also have value in identifying new strains of the organisms, changes in antibiotic resistance and in organism virulence.

There is a momentum across countries to implement *C. difficile* surveillance. Soon after the *C. difficile* ribotype 027 outbreaks in Canada and the US, CDAD cases and outbreaks due to *C. difficile* ribotype 027 began to be reported in Europe.[23;33-37] Hence, the ECDC recommendation for countries to develop early-warning mechanisms and to implement surveillance systems.[4] As previously discussed (Section 1.4), the extent of CDAD in Ireland is not clear; there are no standardised laboratory testing procedures and CDAD is not a notifiable disease. This chapter describes the models of surveillance in other countries and assesses the need for and the options for surveillance in this country.

2.2 Models for *C. difficile* surveillance

The key feature of surveillance is its link to action, and for this reason it is sometimes referred to as 'information for action', since, through observation of trends in health related events by person, place and time, changes can be identified or anticipated and appropriate action, such as investigation or the implementation of control measures, taken. A summary of some *C. difficile* surveillance systems worldwide is outlined in Table 2.1.

Table 2.1: Models of *C. difficile* surveillance systems

Country	Mandatory	Voluntary	Surveys
England	+	+	
Scotland	+		
United States		+	+
Canada	+ Quebec, some other states		
Australia		+ Western Australia	
Netherlands		+	+
Belgium		+	
France	+ Hospitalised severe cases / clusters		

2.2.1 C. difficile surveillance in England, Wales and Northern Ireland

Two parallel systems of *C. difficile* surveillance have previously been in operation in England: mandatory surveillance and voluntary surveillance.

Mandatory surveillance consists of;

- Outbreak reporting
- The mandatory CDAD surveillance scheme: In operation since January 2004 in England and January 2005 in Wales and Northern Ireland. Acute NHS trusts report all CDAD cases aged 65 years and over (defined as all *C. difficile* toxin positive diarrhoeal specimens, where the patient has not been diagnosed with CDAD in the preceding four weeks).
- A random sampling scheme: In operation since January 2005. Acute NHS trusts submit isolates to the Anaerobe Reference Unit (ARU) in Cardiff.

The voluntary surveillance scheme was introduced in England and Wales in 1990 and extended to include Northern Ireland in 2001. Information is collected on *C. difficile* positive laboratory samples mainly through electronic reporting by laboratories. Additional information is also collected and may include patient demographics, details of detection methods used, and some antibiotic susceptibility results. In addition, isolates are voluntarily submitted to ARU for typing outside of the random sampling scheme schedule.

In April 2007, a web-based system for CDAD surveillance was introduced and NHS trusts were requested to enter all cases in individuals aged two years and over. Mandatory fields required are those to identify the case (date of birth (all cases over 2 years old to be reported); sex; specimen date; reporting laboratory and location of the patient at the time the specimen was taken). It is hoped that the inclusion of the date of birth will allow comparisons with previous years' data for the over 65s. A second voluntary page for risk factor information such as antibiotic treatment is being developed. In addition, a *C. difficile* Ribotyping Network for England (CDRNE) was established by the Health Protection Authority (HPA) in early 2007. This consists of six regional laboratories in England (Leeds, Birmingham, London, Manchester, Newcastle, and Southampton) that will provide access to *C. difficile* ribotyping according to standardised criteria. The service aims to provide timely information to help optimise the management of *C. difficile* at a local level, notably if unexplained clusters or increased severity of cases occur. Additionally, CDRNE will collect antibiotic risk and outcome data that can be used to provide more detailed information about *C. difficile* infection at a national level.

2.2.2 C. difficile surveillance in Scotland

Surveillance of CDAD in people aged 65 and over, who present with diarrhoea and a positive toxin test became mandatory on 1st September 2006. A case of CDAD is defined as someone in whom *C. difficile* toxin has been identified in stool at the same time as they have experienced diarrhoea not attributable to any other cause, or someone in whom *C. difficile* has been cultured from stool at the same time as they have been diagnosed with

PMC. The Scottish Surveillance of Healthcare Associated Infection Programme (SSHAIP) under the auspices of Health Protection Scotland (HPS) has detailed a protocol requiring laboratories to report weekly to HPS. Reporting includes mandatory variables (including patient name and age) and optional data (including recent antibiotic usage). All diarrhoeal specimens on patients aged 65 and over in a health care setting are to be tested for toxin A and toxin B using either an immunoassay or a cell cytotoxicity assay: culture is undertaken on specimens for patients with severe disease and from suspected outbreaks. In the first report, the annual rate for Scotland was 2.03 per 1000 acute occupied bed days in persons ≥ 65 years old. The annual rate per 1000 total occupied bed days (which includes acute and non-acute bed days) was 1.27. Ribotypes 106 (64%) and 001 (18.5%) were the two predominant types, with two isolates of ribotype 027 (1%) reported.[38]

2.2.3 C. difficile surveillance in United States

CDAD is not currently on the list of notifiable disease in the US. Within the Centre for Disease Control and Prevention (CDC), the Division of Healthcare Quality Promotion (DHQP) collates data from a number of sources including:

- The National Hospital Discharge Survey,[39] which is conducted annually by the National Center for Health Statistics, CDC. It consists of diagnosis and demographic data collected from a national probability sample of patient discharge records
- The National Nosocomial Infections Surveillance (NNIS) system,[40] which was developed in the early 1970s to monitor the incidence of HCAIs and their associated risk factors. NNIS is the only national system for tracking HCAIs. This voluntary reporting system has approximately 300 participating hospitals

In order to improve CDAD surveillance and prevention efforts in the US, interim surveillance definitions and recommendations were proposed by a *C. difficile* surveillance working group in early 2007.[2] Patients were categorized by the setting in which *C. difficile* was likely acquired and the group recommended minimum surveillance for healthcare settings (surveillance of healthcare facility–onset and healthcare facility–associated CDAD). In addition, denominators were proposed: these were cases per 10,000 patient-days (for healthcare facility–onset, healthcare facility–associated and community-onset, healthcare facility–associated CDAD) and cases per 100,000 person-years (for community-associated CDAD).

2.2.4 C. difficile surveillance in Canada

CDAD is not notifiable in Canada, however, Quebec has implemented mandatory reporting and other provinces are examining the same.[41] The Nosocomial and Occupational Infections Section of the Public Health Agency of Canada conducts surveillance of nosocomial and occupational infections and has undertaken a study of CDAD in Canada (http://www.phac-aspc.gc.ca/c-difficile/index.html#7).

2.2.5 C. difficile surveillance in Australia

CDAD is not notifiable in Australia. While the Virology and Serology Laboratory Reporting Scheme (LabVISE) is in operation, *C. difficile* is not included. Some states (e.g., Western Australia) operate a voluntary hospital/ laboratory based surveillance and other states are considering this (personal communication Professor Riley, Department of Microbiology and Immunology, University of Western Australia).

2.2.6 C. difficile surveillance in other European countries

2.2.6. i The Netherlands

There is no mandatory surveillance of CDAD in the Netherlands. Hospitals have their own surveillance systems for CDAD incidence and when there is a doubling of CDAD incidence, a clustering of cases, or cases with a severe course, the National Institute is informed on a voluntary basis. In addition, 15 healthcare facilities are participating in a surveillance study, coordinated by the Leiden University Medical Centre in close collaboration with National Institute of Health (personal communication Dr Ed Kuijper, Leiden University Medical Centre). In October 2005, specific CDAD ribotype 027 guidelines for infection prevention and control and treatment for hospitals and nursing homes, were published in response to outbreaks of CDAD in the Netherlands. In addition, diagnostic

facilities were increased and all laboratories were recommended to culture *C. difficile* from toxin positive faeces samples and to store the isolates. A National *C. difficile* reference laboratory was established for typing and antibiotic susceptibility testing. Microbiologists were requested to send isolates to the reference laboratory from patients with a severe course of CDAD or when an increased incidence of CDAD was noticed.[42] The first results of this surveillance have been recently published.[43]

2.2.6. ii Belgium

CDAD is not a notifiable disease in Belgium, however, outbreaks are notifiable (personal communication Dr Carl Suetens, Scientific Institute of Public Health, Brussels). In January 2006, the Scientific Institute of Public Health and the national reference laboratory established laboratory based surveillance of CDAD clusters, in addition to prospective surveillance of CDAD incidence in acute care hospitals. Laboratories send isolates when two or more CDAD cases occur in the same department within a one month period. In the incidence surveillance, hospitals report clinical and risk factor data on all CDAD cases during a six month surveillance period as well as denominator data on a web-based data entry form. Hospitals are also requested to send isolates of five consecutive CDAD patients to the reference laboratory for species confirmation, detection of *tcdC* deletion and binary toxin, typing and antibiotic susceptibility. National guidelines for prevention and control of CDAD in hospitals and nursing homes were issued in June 2006.[42]

2.2.6. iii France

The French Institute for Public Health Surveillance and the national *C. difficile* reference laboratory issued recommendations for diagnosis, early warning and surveillance of CDAD in May 2006. Severe CDAD cases (according to ECDC definitions) or hospital clusters are notifiable through an early warning and response system for nosocomial infections (this excludes community-acquired CDAD). A network of six regional laboratories has been established in order to facilitate characterisation of *C. difficile* strains. Recommendations for CDAD prevention and control were disseminated by the Health Ministry to all hospitals and nursing homes in September 2006. Prospective national surveillance of CDAD in hospitals was planned for 2007 and includes a sampling scheme in order to better assess the geographical dissemination of *C. difficile* strains.[42]

2.2.6. iv Sweden

There is no system of mandatory case-based reporting of CDAD (Anders Tegnell, Director, M.D., Ph.D M Sc, Communicable Disease Prevention and Control, SoS, National Board of Health and Welfare Stockholm Sweden).

2.3 *C. difficile* in Ireland – surveillance data

While individual healthcare facilities and some regions perform *C. difficile* surveillance, as previously discussed (Section 1.4) there is no national collation of data. Data presented below is likely to be an underestimate of the incidence and prevalence of CDAD for a number of reasons including:

- The potential underreporting of community CDAD where community samples are not routinely tested
- The lack of both international and national agreement on what specimens to test
- The lack of agreed standardised diagnostic methods
- The difficulty in defining outbreaks when background rates are not established

2.3.1 Incidence data

There is some published regional data available: For example there were 897 laboratory confirmed cases of *C. difficile* reported in HSE West (Clare, Limerick and North Tipperary) from 2003-2006. The majority were from hospitalised patients over 65 years of age. Crude comparison of population rates of CDAD suggested that the CDAD incidence was 3.4 episodes per 1000 population over 65 years in 2006 (Data courtesy Dr's Mai Mannix, Nuala O'Connell and Dominic Whyte).

In order to produce national recommendations for *C. difficile* diagnosis, the HPSC *C. difficile* sub-committee evaluated current specimen processing practices for *C. difficile* in Ireland. (Section 3.2) Part of this evaluation

asked laboratories if they were in a position to provide data on *C. difficile* for 2005. Twenty hospital laboratories provided incidence data for samples from their own hospitals, for other hospitals for which they provide the diagnostic services and for samples received from the community. Over 1,500 cases of CDAD were diagnosed in 2005 in these laboratories, however, before extrapolating from these figures it must be remembered that most of the larger laboratories provided incidence data (these laboratories would be expected to process more specimens for *C. difficile* than smaller laboratories). In all, 87% of the cases were from 29 public acute hospitals, which is equivalent to an incidence rate of 5.7 per 10,000 bed-days used. In addition, 12% of the cases reported were from community sources (GP and nursing home) and 2% were from non-acute or private hospitals. The crude incidence rate of CDAD in 2005 is therefore estimated to be 64 per 100,000 inhabitants.

2.3.2 HIS Prevalence study of HCAI in acute hospitals

In 2006, 7541 patients in 44 acute hospitals in the Republic of Ireland were surveyed in this study. The number of patients with current *C. difficile* diarrhoea (defined as a patient with diarrhoea which was positive for *C. difficile* toxin) was recorded. Thirty-six patients (0.5%) were reported as having *C. difficile* infection. 25/36 patients were aged over 75 years (Fig 2.1). 22 (61%) patients were located on general medical wards with a further 16% located on care of the elderly wards. While the overall *C. difficile* prevalence rate in the Republic of Ireland appears to compare favourably with data from the other participating countries (Table 2.2), no firm conclusion can be made until further details on patient demographics (e.g., age) in these countries is available. In addition, as the laboratory survey revealed that laboratories differ significantly in their *C. difficile* testing strategies (Section 3.2), the *C. difficile* prevalence rate in this survey may not be comparable and may be an underestimate of *C. difficile* prevalence in these hospitals.

Fig 2.1: HIS Prevalence survey 2006: Age and sex of patients with *C. difficile* in the Republic of Ireland

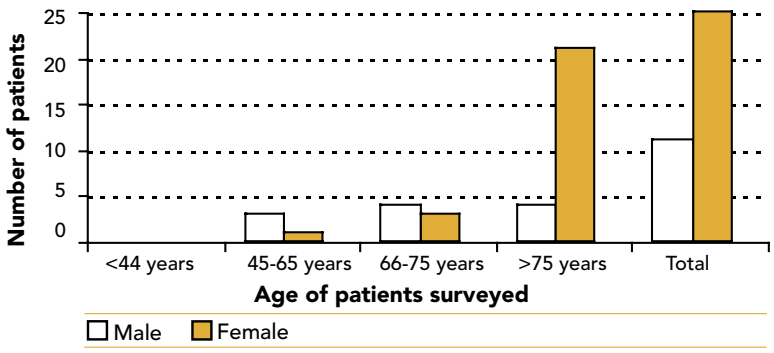


Table 2.2: HIS Prevalence survey 2006: *C. difficile* prevalence rates

Country	Patients surveyed	Patients with *C. difficile* diarrhoea	*C. difficile* prevalence rate (95% confidence interval)
Republic of Ireland	7541	36	0.48 (0.35 – 0.66)
Northern Ireland	3644	41	1.13 (0.83 – 1.52)
Wales	5734	63	1.1 (0.86 – 1.40)
England	58755	1163	1.98 (1.87 – 2.09)

2.3.3 Results from infection prevention and control nurse survey

A telephone and email survey of IPCN's was conducted by members of the HPSC *C. difficile* sub-committee in order to establish current data management practices with respect to *C. difficile* surveillance in Ireland. This survey covered 70 locations (44 acute public hospitals, five centres caring for patients with learning disabilities, nine community areas and 12 private hospitals). Thirty-four IPCNs covering 37 healthcare facilities responded (representing 33 hospitals and four community areas) While in-patient cases of *C. difficile* are managed by infection prevention and control teams (IPCTs) across the country, the range of data items collected varies. The information collected is used to guide appropriate infection prevention and control practice, to monitor CDAD

rates and alert early identification of possible outbreaks (Table 2.3).

Data are stored either as paper records or on various computer systems. Most IPCNs did not use a specific surveillance form for *C. difficile* but used a generic intestinal infectious disease data collection form. The range of data items currently collated by IPCTs includes: diagnosis method, clinical presentation (including details of complications such as mega colon, perforations or refractory colitis), prior stay in intensive care unit (ICU), previous history of CDAD, patient risk factors (e.g., age, antibiotic history, length of hospitalisation, exposure to proton pump inhibitors, laxatives and immunosuppressive drugs, co-morbidities, surgery and procedures such as tube feeding), management of CDAD (including probiotics, immunoglobulin use, antibiotic therapy, surgical procedures, ICU stay and patient isolation or cohorting) and outcome data.

Table 2.3: Current data management systems used for *C. difficile* surveillance

Data Management System	Staff performing *C. difficile* surveillance				
	IPCN & Microbiology Laboratory Scientist	IPCN	IPCN & Surveillance Scientist	Ward staff & Surveillance Scientist	Unknown
Surveillance form	-	10	-	-	-
Laboratory data	-	-	-	-	10
Laboratory data & database	-	1	2	-	1
Database	1	-	2	-	-
Surveillance form & database	-	-	4	-	-
Surveillance form & Laboratory data	-	3	-	-	-
Surveillance form, laboratory data & database	-	-	-	1	-
Scanned form & database	-	-	1	-	-
No surveillance	-	-	-	-	1

2.3.4 C. difficile typing in Ireland

There is no *C. difficile* reference laboratory in Ireland for typing or antibiotic sensitivity testing of isolates. Our laboratory survey revealed that none of the laboratories surveyed routinely type *C. difficile* strains and only 28% do so in the event of an outbreak (Section 3.2). This is likely because of the lack of a national reference laboratory, necessitating laboratories to send their strains for typing abroad. One Irish laboratory in University College Dublin performs *C. difficile* typing, however, this is a research laboratory and not a diagnostic or reference laboratory. To date, this laboratory has typed 350 Irish *C. difficile* strains, 81(23%) of which were *C. difficile* 027[42]. *C. difficile* 027 strains were sent from seven hospitals and two nursing homes.[42] However, this data is not necessarily representative of the epidemiology of *C. difficile* in Ireland as it is potentially biased, being typing data from the outbreak situation only.

2.4 The case for *C. difficile* surveillance in Ireland

In view of the paucity of information on CDAD in Ireland and the ECDC recommendation to develop early-warning mechanisms and implement national surveillance systems,[4] there is a clear need for on-going national and local surveillance, to guide future health policies and to provide a benchmark for future interventions to determine whether or not these are effective. The advantages of a CDAD surveillance system in Ireland would include:

- To ensure early detection of clusters/outbreaks so that effective control measures can be implemented
- To monitor national trends and to enable meaningful comparison to be made over time between different regions and with other countries
- To assist the evaluation of prevention and control measures
- To inform health care planning
- To support research into sources, transmission, risk factors, pathogenesis and control of *C. difficile*

The main barrier that will be encountered in establishing a surveillance system for *C. difficile* is the current lack of resources for surveillance, including staff (IPCN, surveillance scientists, laboratory scientists and microbiologists) and IT infrastructure. Feedback from participants in the HIS prevalence study (Section 2.3.2) identified these issues as potential barriers to future national HCAI surveillance initiatives. In the HIS survey, funding for external data collectors to assist local IPCTs in data collection was provided. If the data collectors were not available, many IPCTs would not have been in a position to participate due to lack of IPCT staff and inadequate hospital IT systems. A feedback questionnaire for participants indicated that if there had been no external data collectors, the additional resources that they would have required to participate in the survey included staff (IPCNs and microbiologists (93%) administrative staff (90%)), and additional IT support (54%). All participants stated that they would in principle be willing to participate in future national HCAI surveillance initiatives, however, 87% could only do so with the type of additional resources described above.

2.5 Options for *C. difficile* surveillance

Healthcare facilities should perform surveillance of CDAD cases. This will enable baseline CDAD incidence to be calculated and a threshold incidence or prevalence of CDAD to be calculated locally that would trigger implementation of additional control interventions. CDAD surveillance should ideally include awareness of changes in the rate and severity of complications from or relapses of CDAD and be performed in conjunction with surveillance of antibiotic use in that healthcare facility.

There is a case for national surveillance of CDAD in Ireland; the question arises of how best this need should be fulfilled. A number of options are presented and some strengths and limitations of each approach are appraised. The main options the group considered feasible for surveillance of *C. difficile* included statutory notification through Computerised Infectious Disease Reporting (CIDR) and Nosocomial infections surveillance system/patient safety/health care quality surveillance system (Section 2.5.1). The group considered a number of other options and discounted them for the reasons listed in Section 2.5.2.

2.5.1 Options considered feasible

2.5.1. i Statutory notification through CIDR

The 1947 Health Act entitles the Minister for Health and Children to specify by regulation the diseases that are infectious diseases and covered by legislation. The current regulations are contained in the 1981 Infectious Disease Regulations, which were revised in 1985, 1988 and 1996. On 1st July 2000, the Infectious Diseases (Amendment) Regulations, 2000 (S.I. No 151 of 2000) came into force. Under these regulations, as amended by S.I. No. 865 of 2004, the HPSC was assigned responsibility for the collation and analysis of weekly notifications of infectious diseases, taking over from the Department of Health and Children (DoHC). Important changes in the national infectious disease legislation came into operation on 1st January 2004. An amendment to the Infectious Diseases Regulations 1981 (*Infectious Diseases (Amendment) (No. 3) Regulations 2003, S.I. No. 707 of 2003*) established a revised list of notifiable diseases and introduced a requirement for laboratory directors to report infectious diseases. The list of notifiable diseases does not currently extend to include CDAD and thus would require amendment to facilitate the establishment of a mandatory system for CDAD surveillance in Ireland.

The 2004 changes to the legislation were based on recommendations of the HPSC Scientific Advisory Committee (SAC). A SAC subgroup carried out a review, which involved extensive consultation with key parties, at the request of the DoHC.[44] Changes to the list of notifiable diseases were consistent with a European Commission Decision on the communicable diseases to be progressively covered by the Community network (Commission Decision No 2119/98/EC of the European Parliament & Council).

The importance of *C. difficile* was recognised in the SAC review: as part of the review, a prioritisation exercise was undertaken by the Notifiable Diseases subcommittee. A questionnaire was sent to a number of professional groups asking them to list diseases that could be considered for notification. *C. difficile* was listed as one of the top 20 organisms that both microbiologists and IPCNs thought should be prioritised by health professionals for surveillance.[44] During the consultation, it was initially proposed that Consultant Microbiologists/Pathologists be subject to an extended list of notifiable entities under the amended Infectious Disease Regulations, which should include *C. difficile*. While this proposal was not adopted by the DoHC, the results of this review provide a useful insight into the potential acceptability of a process of mandatory notification of CDAD in Ireland. While CDAD was not specifically named in the European Commission Decision (Commission Decision No 2119/98/EC of the European Parliament & Council), nosocomial infections and antibiotic resistance were listed as Special Health Issues for consideration.

CIDR is in use in a number of Public Health departments and laboratories in Ireland and it is expected that all departments and laboratories will be operational by end 2008. The advantages of CIDR are that it is a national system where standardised information can be inputted. As CDAD is largely a hospital laboratory-based diagnosis, the Committee proposes that CDAD notifications should be mandatory and that a minimum core dataset is inputted at laboratory level (Appendix 4). Additional ring-fenced resources as highlighted in these guidelines, and legislative change will need to be addressed at both hospital and population health level in order to implement this recommendation.

In the interim, pending legislative change, we have proposed a national core dataset for CDAD surveillance (Appendix 4) for use in hospitals and other healthcare settings, to be used on a voluntary basis by IPCTs (microbiologists, IPCNs, Surveillance Scientists), Health Protection Staff (Consultants in Public Health Medicine, Senior Medical Officers, Surveillance Scientists and Communicable Disease Control Nurses) and General Practitioners. As a minimum, we propose that data should be collated nationally on healthcare-onset, healthcare-associated cases in acute hospitals (Section 2.6). In addition to the core dataset, individual healthcare facilities may wish to collect additional data for local surveillance. We have also proposed an enhanced CDAD surveillance form that could be used by healthcare facilities and also when CIDR is used for national collation of data (Appendix 5).

Another interim option pending legislative change, is the use of the 'Acute Infectious Gastroenteritis (AIG)' section in CIDR to record CDAD cases. CDAD cases could be initially recorded under the heading of AIG and then subsequently analysed. While this option will not permit the collection of enhanced data such as that proposed in Appendix 5, it would enable commencement of CDAD surveillance in those departments and laboratories where CIDR is currently in use.

2.5.1. ii Nosocomial infections surveillance system/patient safety/health care quality surveillance system

Ireland does not currently operate a dedicated system for the surveillance of nosocomial infection. Similar systems operate internationally (and are sometimes linked to systems for monitoring patient safety and health care quality) and are used to provide surveillance information on *C difficile*. An advantage of this system is that it separates the surveillance of nosocomial infections from other infectious diseases; this is valuable, since these systems often have different requirements and different target audiences. If such a system were to be developed in Ireland, then inclusion of *C. difficile* should be a priority.

2.5.2 Other options considered

2.5.2.i Periodic special surveys, e.g., HIS prevalence study

In the Republic of Ireland, 44 acute hospitals participated in the 2006 HIS prevalence survey of HCAI. This survey gave useful information on the burden of *C. difficile* (and other HCAI) in Ireland and demographic and risk factor data. The limitations to repeating this survey includes a lack of personnel to collect surveillance data and the lack of an appropriate integrated national IT infrastructure. Because of a shortage of IPCN WTEs, completing this survey required recruitment of trained data collectors in addition to IPCNs for the time period of the study. Also, as it is a prevalence study indicating levels of infection at a particular point in time, there is a lack of real time information to identify outbreaks and monitoring of trends could be problematic.

2.5.2.ii Use of routine health information

While this is a useful approach to highlight the burden of the disease, timeliness means that it will lack real-time information to identify outbreaks. Monitoring secular trends in the Hospital In-Patient Enquiry (HIPE), a discharge based national database, will be a challenge as the system underwent significant development in 2005 which reduces comparability with pre-2005 hospitalisation data. Moreover, the completeness and accuracy of coding of *C. difficile* would require careful examination if HIPE were to be used as a leading source for surveillance of the disease.

2.6 Case definitions

For international comparisons of CDAD data, it is essential that standardised case definitions for CDAD are used for national surveillance. In addition, there needs to be standardisation of diagnostic testing nationally for accurate comparisons; however, this will have resource implications (Section 3). The ESCMID Study Group for *C. difficile* and the ECDC have proposed interim case definitions for CDAD.[4] For international comparison of data, this committee recommends that these definitions are adopted (Section 2.6.1). As a minimum, data should be collated nationally on healthcare-onset, healthcare-associated cases in acute hospitals. ESCMID also provide definitions that enable classification of cases with respect to the origin of CDAD (healthcare-associated or community-associated) and the onset of symptoms (within the context of healthcare or within the community), however, many healthcare facilities will be unable to collect this level of detail unless extra resources (both personnel and IT) are allocated.

2.6.1 Case definitions

2.6.1. i CDAD Case

This is a patient to whom one or more of the following criteria applies:

- Diarrhoeal stools or toxic megacolon, with either a positive laboratory assay for *C. difficile* TcdA and /or TcdB in stools or a toxin-producing *C. difficile* organism detected in stool via culture or other means
- Pseudomembranous colitis revealed by lower gastrointestinal endoscopy
- Colonic histopathology characteristic of *C. difficile* infection (with or without diarrhoea) on a specimen obtained during endoscopy, colectomy or autopsy

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

The ESCMID/ECDC group recommends that this definition may be focused on the first criterion in laboratory-based surveillance systems performing tests for *C. difficile* only on unformed stools (i.e., stools that take the shape of their container). All three criteria can be used in patient-based surveillance systems targeting diarrhoeal symptoms.

2.6.1. ii Severe CDAD case

This is a CDAD patient to whom any of the following criteria apply:

- Admission to an intensive care unit for treatment of CDAD or its complications (e.g., for shock requiring vasopressor therapy)
- Surgery (colectomy) for toxic megacolon, perforation or refractory colitis
- Death within 30 days after diagnosis if CDAD is either the primary or a contributive cause
- Admission to a healthcare facility for treatment of community-associated CDAD

2.6.1. iii Recurrent CDAD case

This is a patient with an episode of CDAD that occurs within 8 weeks following the onset of a previous episode provided that CDAD symptoms from the earlier episode resolved with or without therapy.

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 as a designation for both.

A similar definition of a recurrent CDAD case for surveillance has also been proposed in the US.[2] This group advises that the recurrent CDAD case definition may be implemented for laboratory-based reporting systems on the basis of when the last positive laboratory test was as follows:

- An additional positive result of a laboratory test performed on a specimen collected 2 weeks or less after the last specimen that tested positive represents continuation of the same CDAD case
- An additional positive result of a laboratory test performed on a specimen collected 2-8 weeks after the last specimen that tested positive represents a recurrent CDAD case
- An additional positive result of a laboratory test performed on a specimen collected more than 8 weeks after the last specimen that tested positive represents a new CDAD case

2.6.2 Origin of CDAD

2.6.2. i Healthcare-associated case

This is a CDAD case with either

- Onset of symptoms at least 48 hours (>48 hours) following admission to a healthcare facility (healthcare-onset, healthcare-associated)

or

- With onset of symptoms within 4 weeks following discharge from a healthcare facility (community onset, healthcare-associated).

2.6.2. ii Community-associated case

This is a CDAD case patient with either

- Onset of symptoms in the community, without discharge from a healthcare facility within the previous 12 weeks (community-onset, community-associated)

or

- With onset of symptoms within 48 hours following admission to a healthcare facility without residence in a healthcare facility within the previous 12 weeks (healthcare-onset, community-associated).

2.6.2. iii Unknown case

This is a CDAD case patient who was discharged from a healthcare facility 4–12 weeks before the onset of symptoms.

2.6.3 Onset of CDAD

2.6.3. i Healthcare onset

Symptoms start during a stay in a healthcare facility.

2.6.3. ii Community onset

Symptoms start in a community setting, outside healthcare facilities.

2.6.4 Denominator data

2.6.4.i Acute hospitals

For feedback and benchmarking purposes, The Committee recommends that acute hospital healthcare-associated case rates are expressed as

- Cases per reporting time period (e.g., month or quarter) per 1000 patient admissions and per 10,000 patient-days (or bed-days used).
- Cases per number of patients tested for *C. difficile* per reporting time period

2.6.4.ii Other settings

In contrast to the acute hospital setting, there are no appropriate denominators at present that would enable benchmarking in settings outside acute hospitals (e.g., nursing homes). It is therefore recommended that the HSE devise appropriate internationally comparable denominators for these settings. However, community–associated case rates can be expressed on a national level annually as cases per 100 000 population over the reporting period.

2.6.4.iii Other considerations

Recurrence rates should be separated from other cases when calculating healthcare- or community-associated case rates. Rates of severe CDAD should be expressed as a percentage of the CDAD cases that occurred during the reporting period along with the absolute number of severe cases.

2.7 National standardised data collection form

A national standardised data collection form would be of benefit in determining the size and extent of the problem of CDAD in Ireland. To determine if *C. difficile* forms were widely used across the country and to determine how data were used, a survey was conducted of IPCNs (Section 2.3.3 and Table 2.3). Nine forms specific to *C. difficile* were received, five from public hospitals, two from private hospitals and two from community services. These data collection forms were assimilated and then modified after discussion and consultation to produce a proposed national core dataset (Appendix 4) and enhanced surveillance forms (Appendix 5).

3. Laboratory Diagnosis of *Clostridium difficile*

3.1 Background

There are several laboratory methods available for CDAD diagnosis. These can be broadly divided into three groups:

- Detection of *C. difficile* products (toxin, glutamate dehydrogenase)
- Detection of *C. difficile* genes (16S rRNA, toxin genes)
- Isolation of toxin-producing *C. difficile* in culture

With the exception of PMC (which can be confirmed by endoscopy or histopathology), the diagnosis of CDAD requires the detection of *C. difficile* toxin in diarrhoeal stool specimens. Toxins of *C. difficile* can be detected either by virtue of their biological properties (e.g., cell cytotoxicity assay) or by immunological methods (e.g., enzyme immunoassays - EIAs). More recently, a number of molecular methods to directly detect toxin by real-time PCR have been developed. In addition, molecular typing methods can be applied to cultured strains to determine strain clonality and antibiotic susceptibility testing can determine patterns of antibiotics resistance. Whilst direct detection by EIA can be carried out in most routine microbiology laboratories, molecular detection, typing and antibiotic susceptibility testing are usually carried out in specialised centres. Recent guidelines from the UK suggest that a method that demonstrates toxin A & B in faecal specimens by either immunoassay or cell cytotoxic assay should be used.[45] Although the United States and many European Union countries recommend only using EIA kits as the sole test for *C. difficile* toxin detection,[45] research has shown that increased yields of positive results can be obtained by using culture in combination with these kits.[46;47] This strategy has recently been demonstrated to produce high sensitivity (>90%) and specificity (>98%) when used to detect for CDAD.[48] This strategy is currently recommended in Denmark and Belgium.

3.2 Laboratory survey of *C. difficile* diagnosis in Ireland

In order to produce national recommendations for *C. difficile* diagnosis, the group designed a questionnaire to evaluate all aspects of current specimen processing practices for *C. difficile* in Ireland (Appendix 6). As not all hospitals have a microbiology laboratory on-site, questionnaires were only sent to those hospitals with laboratories. In November 2006, questionnaires were sent to 44 acute hospitals laboratories. Questionnaires were returned from 29 laboratories (66% response) providing *C. difficile* diagnostic services to 34 hospitals. 25/29 (86%) laboratories processed specimens for *C. difficile* and four (13.8%) laboratories did not perform *C. difficile* diagnosis on-site but rather forwarded specimens to an outside laboratory for processing. 16 (64%) laboratories processed specimens for other hospitals. Specimen selection strategies and repeat testing policies are outlined in Table 3.1. Of the 25 laboratories that tested specimens for *C. difficile*, four (16%) did not had a standard operating policy for *C. difficile* testing, however, all tested for *C. difficile* toxin (Table 3.1) Seven (28%) laboratories typed strains in the case of an outbreak. These isolates were typed either in the UK (two laboratories) or at University College Dublin (three laboratories). The location of typing was unknown for one laboratory. 25 facilities were happy to provide incidence data for 2005 (Section 2.3.1).

Table 3.1: Survey of 25 Irish Laboratories that process specimens for *C. difficile*

		Number
Specimen selection	Examined for *C. difficile* only when requested to do so	7 (28%)
	Screening procedures used: • Stool consistency (all liquid stools) • Patient age (all specimens from patients > 1year) • Patient location (e.g., oncology & high-dependency care units) • History of antibiotic therapy • Clinical criteria • Nosocomial diarrhoea suspected	18 (72%) 7 1 2 4 5 8
Repeat testing policy	No policy All repeat specimens tested Weekly After ten days After two weeks Four weeks after the last positive specimen Individual case-by-case basis After discussion with the consultant microbiologist	5 5 2 1 3 4 3 2
Routine *C. difficile* diagnostic methods	Toxin detection by EIA • No details • Meridian Premier Toxin A + B • Meridian Premier Immunocard A+ B • Techlab *Clostridium difficile* Tox A/B II ™ • Combination of Meridian PremierToxinA + B & Meridian Immunocard A+ B • Remel Xpect® *Clostridium difficile* Toxin A/B Test Kit • VIDAS[R] *C. difficile* Toxin A II (CDA 2) assay (bioMerieux, Inc.)	25 2 12 4 3 2 1 1
	Cytotoxicity assay	3
	PCR	0
	Culture-Routine Culture only in specific circumstances	0 6
Culture methods	Selective agar Blood agar following faecal alcohol shock	3 3

3.3 Specimen selection and storage

All patients in whom a diagnosis of gastrointestinal infection is suspected should have a stool specimen sent for microbiological analysis. While the issue of specimen selection is of importance in the day-to-day management of patients, there is surprisingly little in the literature on this topic. UK recommendations are based on the assumption that the presence of *C. difficile* toxin is only of clinical relevance in patients with diarrhoea and that CDAD occurs rarely in children under two years. Hence, the recommendation to restrict testing to diarrhoeal stools only; a diarrhoeal stool being defined as one that takes up the shape of its container. In addition, testing of children under two years is not advised.[45] A recent study evaluated this approach and supported the recommendation that testing should only be performed on stools that take up the shape of their container. In this study, restricting testing to liquid stools only (as opposed to 'soft' samples – 'soft' being defined as diarrhoeal according to the definition above, but not liquid) would have missed at least 55% of clinically significant results. However, refusing to test samples that did not take up the shape of their container did not seem to cause the diagnosis of CDAD to be delayed or missed.[49] Other authors also recommend that tests for *C. difficile* or its toxins be done only on diarrhoeal (unformed) stool specimens unless an ileus is present.[50;51] While screening cultures have been performed on asymptomatic patients during hospital outbreaks,[52-55] there is no evidence that screening non-diarrhoeal *C. difficile* carriers contributes to the reduction of baseline CDAD rates.

We agree with the above approach that non-diarrhoeal specimens are not tested for *C. difficile* toxin. There is

no value in testing stools of asymptomatic patients, including follow-up for 'test-of-cure' or clearance unless an outbreak is being investigated. One recent study in long-term care residents found that asymptomatic carriers have the potential to contribute to disease transmission in an outbreak setting because of relatively high rates of skin and environmental contamination,[56] however, further studies in the endemic setting are warranted to evaluate this. Similarly, because asymptomatic *C. difficile* colonisation can be present in up to 80% of healthy newborns and infants, testing diarrhoeal stools for *C. difficile* in this population is generally not recommended. We therefore recommend that *C. difficile* toxin testing should only be performed on diarrhoeal stool specimens (from patients >2 years) unless ileus is present. Testing stool of children <2 years for *C. difficile* toxin is not recommended. In the case of ileus and suspicion of CDAD, testing of formed stool is acceptable and other diagnostic procedures (e.g., abdominal CT, colonoscopy) may be required.

With regard to which patients to test, a few groups have looked at this issue. In one study prior antibiotic therapy, significant diarrhoea (defined as new onset of greater than three partially formed or watery stools per 24 hour period), and abdominal pain were independent predictors of a positive *C. difficile* cytotoxin assay result. A decision rule (defined as positive if prior antibiotic use and either significant diarrhoea or abdominal pain are present) that was applied to specimens before testing demonstrated sensitivity and specificity of 86 and 45%, leading the authors to conclude that patients without prior antibiotic use and either significant diarrhoea or abdominal pain may not routinely require cytotoxin testing.[57] One of the main disadvantages of this approach is the reliance on accurate clinical data being recorded on sample submission to the laboratory, which in practice may be an unattainable goal. The UK recommend testing all patients (both out-patient and in-patient specimens). Their belief was that the increased costs would be offset against the anticipated benefits of improved patient diagnosis and population epidemiology. This issue prompted much discussion within our group – we agree that if the decision to test specimens relies on accurate clinical data being recorded on sample submission to the laboratory that this will lead to under diagnosis of cases, as in practice clinical details are infrequently recorded. In addition, if testing was restricted to patients that were admitted to a healthcare facility for more than three days, this would also lead to under diagnosis of cases, unless accurate clinical data (e.g., recent hospital admission or antibiotics) that would direct the laboratory to test for *C. difficile* was recorded. We therefore recommend that all diarrhoeal specimens are tested for *C. difficile*, however, this will have service implications for laboratories in terms of workload and staffing that will need to be addressed by the HSE in order to implement this recommendation.

Regarding the frequency of testing and policies for repeat testing if the first sample is negative, this appears to vary with the detection methods used by the laboratory. Previously guidelines recommended submission of additional specimens for *C. difficile* toxin if a single sample is negative and clinical suspicion is high.[58] One study demonstrated increased sensitivity of *C. difficile* detection with submission of a second sample at a time when the laboratory was using an EIA method.[59] In contrast, others have shown that submission of multiple samples for cell culture cytotoxicity assay (CCCA) did not increase detection of *C. difficile* infection.[60;61] The Committee recommends that in the case where clinical suspicion of CDAD is high, yet *C. difficile* toxin is negative, patients should be retested and if negative and the patient has not been treated with specific antibiotic therapy, the specimen set up for *C. difficile* culture and toxin testing (Section 3.5). Once the diagnosis of CDAD is confirmed, patients should not be retested for *C. difficile* toxin when on treatment. If recurrence of diarrhoea after a symptom-free interval occurs, a repeat specimen should be tested for *C. difficile* toxin and other potential causes of diarrhoea excluded. As previously discussed, we do not recommend performing a 'test of cure' or clearance on stool specimens after *C. difficile* treatment.

For optimal laboratory investigation, freshly taken faecal specimens should be examined. Samples stored at ambient temperature show a decrease in toxin. Brazier reported complete inactivation of toxin in 20% of stool specimens sent through the post.[62] Specimens which cannot be examined promptly should be refrigerated at 4°C in designated specimen fridges and not stored in food or drug fridges. Studies have shown that toxin is preserved for up to 44 days in specimens stored at 4°C.[62;63] Toxin is less well preserved in specimens which have been frozen at –20°C, therefore, specimens for toxin detection should be stored at 4°C rather than being frozen.[63]

3.4 Direct detection methods

Laboratories that perform *C. difficile* testing should participate in an external Quality Assurance scheme (e.g., NEQAS (http://www.ukneqasmicro.org.uk) or Lab Quality (www.labquality.fi)).

3.4.1 Cell culture cytotoxicity assay

CCCA which detects the presence of toxin B is considered to be the gold standard and can detect as little as 10 picograms of toxin.[60;64] Toxin B induces cell rounding and a cytopathic effect (CPE) when administered to cell lines.[65] Furthermore, toxin A negative toxin B positive strains have a modified toxin B and induce a differential cytopathic effect and can there be identified using this method. The observation of CPE and its neutralisation with *C. difficile* antitoxin is used to positively detect the presence of *C. difficile* toxins. However, not all laboratories have tissue culture facilities and the assay is slow (42-72 hours for a result), laborious and time consuming. Furthermore, it may lack standardisation as a variety of protocols and cell lines are used in different laboratories. A study in 2003 demonstrated that only 16% of European laboratories surveyed were using the CCCA.[64]

3.4.2 Enzyme immunoassays

All laboratories should use a method that can detect both toxin A and toxin B. A wide variety of commercial EIAs in many formats exist for detection of *C. difficile* toxins. Many of the newer assays which detect both toxin A & B, are suitable for the rapid and automated analysis of large numbers of specimens. Several studies have evaluated the performance of these EIAs by comparison with the gold standard.[66-69] These assays generally perform well with regard to specificity. However, there is a wide range of published performances for sensitivity of these assays (94.5%,[67] 75-96%,[62] 80%[68]). In reality, the sensitivity rate of these assays is even lower when compared with *C. difficile* culture. Recent studies demonstrate that EIA assays in general have significantly reduced sensitivity (65-85%).[48;70] Two recent Irish studies demonstrated sensitivity rates of 59 and 64% respectively using toxin A and B EIAs.[71;72] This low sensitivity can lead to increased reporting of false negative results, subsequently presenting problems with clinical diagnosis and infection control. In 2001, 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.[47] Despite poor sensitivity there are advantages to using EIAs including ease of use, rapid-same day results and suitability for automation. The advantage of rapid results is of particular significance in that it influences initiation of prompt therapy and infection prevention and control interventions.

A new rapid immunochromatography test, the Immunocard Toxins A&B (ICTAB; Meridian), has recently been introduced. The ICTAB is a single-test enzyme immunoassay for the detection of TcdA and TcdB in faecal samples within 20 minutes. No sample pre-treatment is required, and an internal procedure control is integrated in each card. Studies have determined that this assay compares well with other methods (sensitivities 79% and 88% for the IPTAB and the real-time PCR, respectively).[73] The main disadvantages of this assay is that it is more expensive than other EIAs and is not suitable for automation.

3.4.3 Direct detection using molecular methods

Developments in molecular techniques for the direct detection of *C. difficile* toxin have been hampered by the difficulty of DNA extraction from faecal specimens and the presence of multiple inhibitory factors in faecal specimens that inhibit PCR. Recent advances with commercial DNA extraction kits has led to new developments in direct molecular detection methods.[73] Belanger *et al* devised a molecular method that detected toxin B by real time PCR.[74] Although this study incorporated only 29 toxin positive stools, the method demonstrated very high sensitivity (97%) and specificity (100%) when compared to the cytotoxicity assay. Other more recent studies using real time PCR to detect the toxin B gene (*tcdB*) have shown similar results.[73] Whilst less sensitive than culture, these techniques are more sensitive than EIAs and provide rapid accurate results. They reported a sensitivity, specificity, positive predictive value and negative predictive value of 100%, 94%, 55% and 100% respectively compared to the CCCA. Most recently, a Real Time PCR protocol has been developed with a turnaround time of 4 hours and improved sensitivity when compared to EIA methodology.[75]

3.5 C. difficile culture

C. difficile can be isolated by culturing faecal samples directly on to selective agar. A number of different selective agars have been used including Cefoxitin Cycloserine Fructose Agar (CCFA) and Brazier CCEY Agar (Fastidious Anaerobe Agar (FAA) with cefoxitin cycloserine and egg yolk emulsion). 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. It has also been suggested 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).[76]

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.[76] Putative *C. difficile* colonies should be sub cultured onto blood agar for anaerobic incubation. Plates should not be left out 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

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.[76] Therefore, the main disadvantage of culture is the time taken to detection (usually 48 hours – but at least 4 days for toxigenic culture), so that culture plays little role in the day-to day diagnosis of CDAD. One exception may be if *C. difficile* is clinically suspected, yet EIA results are negative: in these cases 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.[47] Culture is also essential for strain typing and antibiotic 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.[77] Susceptibility testing might allow the observation of the emergence of strains with a decreased susceptibility to antibiotics. For cases of severe CDAD, or in an outbreak setting, all specimens should be sent to a reference laboratory for epidemiological typing.

3.6 *C. difficile* susceptibility testing

An effective surveillance programme requires that susceptibility testing is performed on isolates so that resistance rates and trends can be monitored to track the emergence of drug resistance. *C. difficile* susceptibility testing is usually determined by either E-test or agar/broth dilution. Both methods are 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* (Table 3.1). Data is therefore not currently available on the susceptibilities of Irish *C. difficile* strains. *In vitro*, *C. difficile* is susceptible to vancomycin; the reported minimum inhibitory concentration (MIC) required to inhibit 90% of strains (MIC90) is 0.75-2.0 mg/L.[78] 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.[79] *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,[80;81] including an isolate from Hong Kong with an MIC of 64 mg/L.[82] Pelaez *et al* found that 6.3% of Spanish isolates from patients with a first episode of CDAD had an MIC of 32 mg/L or more, however, no clinical correlation was provided.[79] 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.[6; 83] Antibiotic 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 national surveillance programme of *C. difficile* infection is to proceed.

3.7 Molecular typing

In cases of severe CDAD, or in an outbreak setting, specimens should be referred to a reference laboratory for epidemiological typing or stored at 4°C for culture at a later stage. There is currently no national reference laboratory in the Republic of Ireland for typing and antibiotic susceptibility testing. As a result, we have limited research data with regard to the molecular epidemiology of Irish *C. difficile* strain types.[23; 29; 84] The Committee recommends that an Irish reference laboratory is established with appropriate funding. It also recommends that *C. difficile* culture is carried out by this reference laboratory. Pending establishment, 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 could be done in conjunction with laboratories abroad and as part of an international network.

There are a number of molecular typing methods that can be applied for *C. difficile* surveillance. The most common methods used include PCR ribotyping, Restriction Endonuclease Analysis (REA), Pulsed Field Gel Electrophoresis (PFGE), Toxinotyping (PCR-RFLP), Multi Locus Sequence Typing (MLST) and more recently Multilocus Variable-Number Tandem-Repeat Analysis (MLVA). Each method has distinct advantages and disadvantages. PFGE has been considered the gold standard for bacterial typing as it based on restriction of the complete bacterial genome. However, it requires specialised equipment, technical skill and takes 3-4 days for a result. In addition, several *C. difficile* strains produce endonucleases which can degrade DNA preventing these strains from being accurately typed using this method. A number of PCR based methods have been developed including PCR Ribotyping and toxinotyping and there is good correlation between these two methods.[85] PCR ribotyping whilst not as discriminatory as PFGE or REA, can identify >135 distinct types. 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. In the last year, two publications have applied MLVA to *C. difficile* and found that this method is more discriminatory than PCR ribotyping and can differentiate strains belonging to the same ribotype.[86; 87] Although critically important to identify the emergence of more virulent strain types and to identify clonal strains during an outbreak, typing should only be carried out in specialised centres.

4. Management of CDAD

4.1 Treatment of *C. difficile* infection

The first approach in the treatment of CDAD should, if possible, be to stop the precipitating antibiotic(s). Studies have shown that CDAD will resolve in 15-23% of patients if antibiotics are discontinued.[88; 89] It is difficult, however, to predict which patients will clear the infection spontaneously and it is often not feasible to discontinue antibiotics for clinical reasons. In addition, the time between the onset of symptoms and the confirmation of CDAD may be a few days and further delay in initiating treatment may lead to clinical deterioration. Thus, in theory, discontinuing antibiotics and observing the response may be effective for some patients but it is difficult to apply this approach in practice to all patients. If antibiotics must be continued for clinical reasons, antibiotic(s) with a lower propensity to induce CDAD should be substituted. Supportive therapy with replacement of fluids and electrolytes is also crucial at the early stage for these patients. Antiperistaltic agents should be avoided because of the theoretical risk of precipitating toxic mega colon by slowing clearance of *C. difficile* toxin from the intestine.[78; 90]

Specific treatment for CDAD is indicated where

- It is not possible to discontinue antibiotics because of the underlying condition
- If symptoms don't resolve following cessation of the precipitating antibiotic
- Where the patient has systemic symptoms (particularly if there is evidence of severe colonic inflammation or pseudo membrane formation)

Asymptomatic carriers of *C. difficile* should not be treated.[91] Initial treatment of non-severe CDAD should be with oral metronidazole. Metronidazole, vancomycin, teicoplanin, and less often, bacitracin have all been used to treat CDAD because these antibiotics inhibit growth and toxin production by *C. difficile*. A Cochrane database review of antibiotic treatment for CDAD concluded that metronidazole, teicoplanin, fusidic acid, rifamixin and bacitracin were as effective as vancomycin for initial symptomatic resolution.[92] The review was unable to make a specific antibiotic recommendation for the treatment of CDAD as the results suggested that a number of antibiotics are equivalent at achieving early symptomatic cure. Most clinical experience, however, has been with metronidazole and vancomycin.

A number of studies comparing oral metronidazole to oral vancomycin indicate that with the exception of severe CDAD, metronidazole is as effective as vancomycin and less expensive.[78;93] As a result of concerns that the widespread use of vancomycin could lead to the spread of vancomycin-resistant pathogens, metronidazole is presently considered the initial choice antibiotic for CDAD, with the exception of severe CDAD where vancomycin is recommended as first-line therapy.[20;94;95] There have been concerns recently that metronidazole may not be as effective for treating CDAD as has been demonstrated in previous prospective randomized trials.[6; 96] However, both studies were observational and lacked a clinical definition of diarrhoea. These studies do, however, have implications for the first-line treatment of CDAD, especially in view of recent reports of increasing CDAD frequency, mortality and morbidity rates. However, it has been suggested that despite these studies metronidazole should remain as the first-line agent for most cases of CDAD but that careful monitoring of the response to therapy is required.[97]

The mean time for diarrhoea resolution has been shown to be 3-4 days in prospective trials, but most patients will show some improvement of symptoms within 1-2 days of starting therapy.[97] It should not be concluded that treatment has failed before 6-7 days of therapy.[97] Antibiotic therapy for 10 days is indicated for mild CDAD. Most *C. difficile* infections respond to either metronidazole or vancomycin. Therapeutic failure requires confirmation of the diagnosis and the exclusion of ileus or toxic mega colon, as both conditions may prevent the drugs from reaching sufficiently high levels in the colon lumen. Patients with ileus may benefit from higher doses of oral vancomycin (500mg every 6 hours).[90]

4.2 Assessment of severity: severe and refractory CDAD

Expert opinion favours the use of vancomycin over metronidazole for the treatment of patients with severe CDAD on the basis of higher intracolonic drug concentrations, lower risk of bacterial resistance and possibly

faster clinical responses.[20; 94;95] However, it can be difficult to predict which patients are going to have a more complicated course. In addition, there is currently no widely accepted definition of CDAD severity. Clinical symptoms and signs of more severe CDAD may include fever, profuse diarrhoea, abdominal pain and leucocytosis.[98] The presence of complications of colitis, such as sepsis, volume depletion, hypotension, electrolyte imbalance, peritonitis, paralytic ileus and toxic mega colon are usually taken to indicate severe disease.[98] A white blood cell count of greater than 20 x10^9/L and elevated serum creatinine are also markers of severe disease.[96; 97] Recently, several investigators have developed scoring systems for CDAD severity. Belmares *et al* constructed a scoring system based on variables previously suggested in the literature to correlate with a higher disease severity: fever, ileus, hypotension, leucocytosis, and specific CT abnormalities (Table 4.1).[99] In a retrospective survey of 102 patients, they found that 70% of patients responded to metronidazole within 6 days and 91% by 24 days. The *C. difficile* disease score was higher amongst true failures (2.89 ± 1.4) than amongst all metronidazole responders (0.77 ± 1.0). A score of >2 was associated with metronidazole failure. Validation of this score is required in a prospective study.

Table 4.1: CDAD disease score – Belmares *et al* [99]

Variable	Points
Fever (38°C)	1
Ileus[a]	1
Systolic blood pressure < 100mmHg[b]	1
Leucocytosis WBC < 15,000/mm^3 WBC ≥ 15,000/mm^3, < 30,000/mm^3 WBC > 30,000/mm^3	 0 1 2
CT scan findings (thickened colonic wall, colonic dilatation, ascites) No findings 1 finding ≥ 2 findings	 0 1 2

[a] ileus diagnosed by clinical or radiographic findings

[b] any single reading within 3 days of CDAD diagnosis

A similar CDAD severity score was developed by Zar *et al* for use in a randomised double blind, controlled trial of vancomycin versus metronidazole for CDAD in patients stratified by disease severity (Table 4.2).[94] Patients with <2 points were considered to have mild CDAD and those with ≥2 points were considered to have severe CDAD. Among the patients with mild CDAD, treatment with metronidazole (250mg four times per day) or vancomycin (125mg four times per day) resulted in clinical cure in 90% and 98% of the patients, respectively. Among the patients with severe CDAD, treatment with metronidazole and vancomycin resulted in clinical cure in 76% and 98% of the patients, respectively. These results suggest that metronidazole and vancomycin are equally effective for the treatment of mild CDAD but that vancomycin may be more effective for the treatment of severe CDAD.[94; 100]

Table 4.2: CDAD severity score – Zar *et al* [94]

Variable	Points
Age >60years	1
Temperature>38.3°C	1
Albumin level <2.5mg/dL or peripheral WBC count >15,000cells/mm3*	1
Endoscopic evidence of PMC	2
Treatment in the ICU	2

* Within 48 hours of study enrolment

In some circumstances, oral therapy cannot be given especially in severely ill or post-operative patients. Intravenous metronidazole 500mg every 6-8 hours may be given in this situation.[101] However, some data report therapeutic failure of this regimen in the setting of a dynamic ileus.[102] Adjunctive intracolonic vancomycin (ICV) may be an effective adjunctive therapy in the setting of severe CDAD.[103;104] In a small study, clinical resolution of severe colitis was achieved in 8 out of 9 patients treated with adjunctive ICV.[103] In this case series, ICV was found to be a safe, practical and effective adjunctive therapy for severe CDAD. The same authors reviewed the literature and identified successful outcomes in 20 (83.3%) of 24 episodes of *C. difficile* colitis treated with adjunctive ICV. As ICV has not been evaluated in randomised controlled clinical trials, questions regarding efficacy, optimal dosing and duration of therapy are unanswered. At the University of Washington if a patient fails to respond to metronidazole therapy within 3 days, it is recommended that they are switched to oral vancomycin 500mg four times a day and ICV (500mg of IV vancomycin in 100ml of normal saline per rectal Foley, clamping for 60 minutes, repeating every 6 hours).[105] Reported methods of administration of ICV are listed in Appendix 7.

Severely ill patients should, in addition to their antibiotic therapy, have an early surgical assessment for possible colectomy.[97;98] In the setting of an outbreak of CDAD associated with ribotype 027, investigators found that colectomy could be lifesaving in patients aged ≥65 years with fulminant colitis and with a leucocytosis of ≥20x10^9/L or serum lactate between 2.2 and 4.9mmol/L (adjusted odds ratio for death, 0.22; 95% confidence interval, 0.07 to 0.67, P=0.008).[106]

4.3 Treatment of recurrences

CDAD recurs after treatment in 8-50% of cases.[13;50] A recurrent CDAD case is defined as a patient with an episode of CDAD that occurs within 8 weeks following the onset of a previous episode.[4] Recurrences can correspond to either a relapse of the original strain or a re-infection with a different strain,[107-109] however, there is no universal agreement on how to clinically distinguish whether a second episode of CDAD is a re-infection or a relapse. If a patient has two or more episodes of CDAD, the risk of additional recurrences increases to 50-65%.[110] Risk factors for recurrence include new exposure to antibiotics, age greater than 65 years, severe underlying disease, low serum albumin level (<2.5g/dL), ICU stay, prolonged hospitalisation and low levels of antibodies to *C. difficile* toxin A.[111-113]

4.3.1 Treatment of first recurrence of CDAD

The first step in managing suspected recurrence is to discontinue, if possible, the precipitating antibiotic(s) and to confirm the diagnosis. If antibiotics must be continued for clinical reasons, antibiotic(s) with a lower propensity to induce CDAD should be substituted (Section 5.3). Patients with recurrences of CDAD pose a therapeutic dilemma: should metronidazole or vancomycin be prescribed? Recent findings suggest that, when used to treat a first recurrence, metronidazole and vancomycin are associated with the same frequency of a second recurrence, regardless of which of the two agents had been used to treat the initial episode. It is therefore recommended that metronidazole should be used for most patients with a first recurrence of CDAD. The decision to use vancomycin as a treatment for a first recurrence should be based on the presence of markers of severe disease at the time of the first recurrence, rather than on previous drug exposure, however, vancomycin's superiority over metronidazole remains unproven.

4.3.2 Treatment of multiple recurrences

At present, there are few choices or strategies for the treatment of patients with multiple (≥ third episode) recurrences of CDAD. A number of different dosing strategies for oral vancomycin including tapered-pulsed treatments have been studied. These regimens are 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).[114] 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.[115] A regimen for tapered vancomycin therapy is outlined in Appendix 8.

Other treatment modalities for recurrent CDAD include:

- Some success in small numbers of patients with the use of combined vancomycin and rifampicin for 7-10 days,[116] however, there have been no randomised controlled trials published. Therefore, there is no recommendation for the use of adjunctive rifampicin
- Anion exchange resins, such as cholestyramine (4g three or four times daily for 1–2 weeks) bind *C. difficile* toxins and may be used in conjunction with antibiotics to treat frequent relapses, especially at the end of therapy.[117] Because cholestyramine may bind vancomycin and toxins, it should be taken at least 2 to 3 hours apart from vancomycin[118]
- Probiotics have also been investigated as alternative therapies for preventing the recurrence of CDAD (Section 4.4.1). Probiotics may aid in restoring the normal flora and neutralizing *C. difficile* toxins
- Intravenous immunoglobulin therapy (Section 4.4.3)
- Faecal transplant (Section 4.4.9)

4.4 Novel and emerging treatments

4.4.1 Probiotics

Probiotics are non-pathogenic microbes administered to improve intestinal balance and restore normal micro flora. In a recent meta-analysis, three types of probiotics (*Saccharomyces boulardii, Lactobacillus rhamnosus* GG, and probiotic mixtures) significantly reduced the relative risk of antibiotic associated diarrhoea but not CDAD (relative risk (RR)=0.43, 95% confidence interval (CI) 0.31, 0.58, p< 0.001).[119] Probiotics combined with one of the two standard antibiotics to treat CDAD significantly reduced the risk of recurrence (RR =0.59, 59% 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 CDAD.[119] In a randomized placebo-controlled trial of 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). *S. boulardii* had no effect on recurrence rates in 64 patient who were treated for a first episode of CDAD (19 versus 24% with placebo).[120] 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 CDAD (35 versus 65%). A follow-up study performed to standardise the dose and duration of antibiotic 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).[121]

A recent trial randomised 135 elderly hospitalised patients receiving a new course of antibiotics to either a probiotic yoghurt drink (containing *Lactobacillus casei* DN 114001, *L. bulgaricus,* and *Streptococcus thermophilus*) or placebo for the duration of antibiotic therapy plus one week reported that significantly fewer patients given the probiotic drink developed diarrhoea (Odds ratio 0.25, 95% CI 0.07 – 0.85).[122] The probiotic drink also appeared to prevent CDAD (0% versus 17% with placebo) and no adverse side effects were reported. 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.[123; 124] 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.[125]

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.[120] In a meta-

analysis, no cases of bacteraemia of fungaemia or other serious adverse event were reported.[119] However, there have been case reports of fungaemia and bacteraemia in immunocompromised patients receiving probiotics.[126-128] *S. boulardii* is available without prescription in the United States as Florastor (250mg capsules). In continental Europe, probiotics are considered medicines and *S. boulardii* is marketed as Ultra-Levure (Biocodex), Ultralevura (Bristol-Myers Squibb), Codex (Zambon Farmaceutici) and Perenterol (Biomed).[128] This product is unlicensed in Ireland and must be given to a patient on a named-doctor, named-patient basis. While it is not readily available, it can be imported into Ireland through a specialist drug procurement supplier. Until recently, it was believed that *S. boulardii* was distinctly different from *S. cerevisiae* 'Bakers yeast',[129] however, despite certain phenotypic differences, genotypic and proteomic analysis have definitely recognized *S. boulardii* as a member of the species *S. cerevisiae*.[128] 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 CDAD.[127; 128] Thus, routine use cannot be recommended.

4.4.2 Prebiotics

Prebiotics are non-digestible food components (starch or fibre) that stimulate the growth of bifidobacteria. A randomized trial of 142 CDAD cases treated with standard antibiotics with or without an adjunctive prebiotic (oligofructose) demonstrated that significantly fewer patients in the prebiotic group (8.3%) had recurrent CDAD within 60 days compared to those in the placebo group (34.3%, $p<0.001$).[130] However, as prebiotics are not commercially available, there is no recommendation for their use.

4.4.3 Immunoglobulin treatment

Asymptomatic carriers of *C. difficile* have higher serum concentration of IgG anti-toxin A antibodies compared to patients with CDAD.[111] 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.[112] Several cases reports regarding the use of intravenous immunoglobulin (IVIG) to treat refractory or severe CDAD have been published but no randomized controlled clinical trials have been performed.[131-138] Therefore, there is no published data from which to create evidence-based recommendations. The largest case series of IVIG treatment for severe CDAD was published recently.[138] Eighteen patients who received IVIG treatment were pair-matched by propensity scoring with 18 patients with similar disease severity who had not received IVIG treatment. There were no statistical differences in clinical outcomes between the two groups as measured by all cause mortality, colectomies and length of stay.[138] Different doses of IVIG (150-400mg/kg, 1-3 doses) administered at varying frequencies, with or without adjunctive treatment with oral anti-*C. difficile* antibiotics have produced varying results (Table 4.3). IVIG is expensive (52.4 Euro / gram – January 2008 pricing) and may be associated with acute renal failure, vascular thrombosis, anaphylaxis and infusion-associated reactions.

However, IVIG is not licensed as a therapy for severe or recurrent CDAD. The optimal dose and dose frequency for this indication is not known. Despite promising results from numerous case series, the data do not provide sufficient evidence to support the use of IVIG in patients with recurrent or severe CDAD outside of a controlled trial.

Table 4.3: Case reports of IVIG use in patients with CDAD

Reference	Patients	IVIG regimen	Response
Leung (1991)[131]	5 children	400mg/kg every 3 weeks for up to 6 months	No recurrence (4); one recurrence (1)
Warny (1995)[132]	1	400mg/kg, 2 doses 28 days apart plus vancomycin	No recurrence at 16 months
Salcedo(1997)[133]	2	200-300mg/kg	1 recurrence 1 month later
Beales (2002)[134]	4	400mg/kg, 2 doses 21 days apart plus vancomycin taper	No recurrences at 10, 8, 7, and 5 months
Wilcox (2004)[135]	5	300-500mg/kg; 1 doses (2 patients), 2 doses (2 patients), 6 doses (1patient)	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)[136]	1	400mg/kg on 3 consecutive days	No recurrence 4 months later
McPherson[137] (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) [138]	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

4.4.4 Nitazoxanide

Nitazoxanide may be a useful alternative for patients who cannot tolerate or fail treatment with metronidazole. Nitazoxanide 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*.[139] It also achieves high colonic levels after oral administration.[140] Musher *et al* in a randomized double-blind trial found that nitazoxanide was 'not inferior' to metronidazole in terms of primary response rate or recurrence rate.[140] Currently in the US, there is a Phase III study of compassionate use of nitazoxanide in patients who have failed conventional therapy and a Phase III study comparing outcomes with nitazoxanide versus vancomycin in patients who have failed previous treatment with metronidazole.[141]

4.4.5 Ramoplanin

Ramoplanin is an oral, non-absorbable lipoglycodepsipeptide antibiotic that blocks peptidoglycan synthesis. This agent has *in vitro* activity against *C. difficile*, including isolates with reduced susceptibility to metronidazole or vancomycin. Studies investigating its activity and efficacy in patients with CDAD are underway.[141]

4.4.6 Rifaximin

Rifaximin is a non-absorbable semi synthetic analogue of the rifamycin antibiotic rifampicin. In the US it is FDA-approved for the treatment of travellers' diarrhoea caused by non-invasive strains of *E. coli* in patients aged 12 years or older. The use of rifaximin for the treatment of CDAD has been evaluated in one open-label randomized study comparing rifaximin with vancomycin. The investigators found that rifaximin orally 200mg three times daily was as efficacious as vancomycin 500mg twice daily.[142] There is an ongoing study in the US to elucidate the role of rifaximin in CDAD.[141]

4.4.7 Tolevamer

Tolevamer is a soluble, high molecular weight non-antibiotic polymer that binds *C. difficile* toxins. In a randomized trial involving 222 patients with mild-moderately severe CDAD, Tolevamer at a dose of 6g/day was non inferior to vancomycin for the resolution of diarrhoea. There was a non-significant trend toward a lower recurrence rate with high dose tolevamer compared to vancomycin (10 versus 19%).[143] However, results from the Phase III multicenter study comparing tolevamer with vancomycin and metronidazole revealed that tolevamer had a lower success rate than either vancomycin or metronidazole; clinical success rates (resolution of diarrhoea and absence of severe abdominal discomfort due to CDAD on Day 10) were 47% for tolevamer, 81% for vancomycin and 72 % for metronidazole.[144]

4.4.8 Other drugs

Par 101 (Optimer Pharmaceuticals, San Diego, California, USA) is a macrocycle with poor oral absorption, that has moderate activity against some Gram-positive cocci and excellent activity against *C. difficile*. It is currently under investigation in a multinational, multicentre, double blind, randomized study to compare its safety and efficacy when taken with vancomycin.[20]

Another drug in the pipeline is rafalazil (ActivBiotics, Lexington, Massachusetts, USA) which is currently undergoing phase II studies.[20]

4.4.9 Faecal transplant

Faecal transplant involves the administration of 30-50g stool in normal saline from healthy donors by enema, via nasogastric tube, or colonoscopy. Case reports have described its use in refractory CDAD,[145-147] however, there are no comparative studies on its effectiveness or safety.

4.4.10 Vaccination

Currently no vaccine exists to protect individuals against CDAD. Acambis plc, Cambridge UK and Cambridge Massachusetts, have developed a vaccine comprised of a partially purified preparation of inactivated toxins A and B. A phase 1 trial of 50 healthy adults evaluated the safety, tolerability and immunogenicity of this investigational vaccine at different dose levels. Four intra-muscular doses of this toxoid vaccine were found to be well tolerated and highly immunogenic. During 2007, formulation work to improve the stability profile identified a number of vaccine formulations that showed improved stability profiles compared with material used in previous Phase 1 trials. One of these formulations will be selected for the manufacture of clinical trial material to be conducted during 2008. Acambis plans to initiate a proof-of-concept trial of its vaccine towards the end of 2008.[148]

5. Prevention and Control of CDAD

Control of HCAI must be given high priority by senior management, the DoHC and the HSE. The provision of adequate isolation facilities with clinical hand washing sink, ensuite facilities and adequate levels of healthcare worker (HCW) staffing is essential for the prevention of HCAI, including *C. difficile*. This will have resource implications, but must be given priority. Healthcare providers (both hospitals and other healthcare settings) should promote practices known to reduce the incidence of CDAD. Interventions for the prevention and control of CDAD include antibiotic manipulations (Section 5.3) and compliance with infection prevention and control measures (Section 5.4 onwards). Both interventions need to be applied together.[45]

5.1 Background

C. difficile can be transmitted from patient-to-patient, via contaminated HCW hands, or via environmental (including healthcare equipment) contamination. Compliance with infection prevention and control practices is crucial in reducing the incidence of CDAD.[45] Linking surveillance of sporadic cases of CDAD with infection prevention and control measures can reduce the incidence of nosocomial infection by up to 70% and allows early treatment of symptomatic patients, thereby reducing the burden of disease.[149] 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 (e.g., commodes).[45]

The prevention and control of *C. difficile* may be best achieved by the use of Standard and Transmission-based (Contact) Precautions (Appendix 9). Standard Precautions should be used when exposure to blood, body fluids, non-intact skin or mucous membranes is anticipated. Contact Precautions are designed to reduce the risk of transmitting *C. difficile* by direct or indirect contact. Direct contact transmission occurs when micro organisms are transferred from one infected person to another person, e.g., direct patient-to-patient contact. Indirect contact transmission involves the transfer of an infectious agent to a contaminated intermediate object or person, e.g., hands of healthcare personnel or patient care equipment, such as commodes or patient call bells.[150] The principles of caring for the patient with CDAD are similar irrespective of whether the patient is located in a healthcare facility or at home. Guidelines dealing with specific issues that may arise for patients in the home and the community have been published elsewhere.[151]

5.2 Performance targets and staffing levels

Sufficient numbers of staff must 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.[152]

A higher bed-occupancy rate means that there is less time for thorough cleaning between patients and a higher probability of transmission of infection between patients. This was cited as a contributory factor in the Maidstone outbreak.[153] 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.[152] Performance targets (e.g., waiting times in the Emergency Department) should not compromise the appropriate care and isolation of patients with CDAD. This is particularly important in an outbreak setting where a ward/unit may need to suspend admissions on a temporary basis.

5.3 Prudent antibiotic stewardship

Prior antibiotic use is associated with CDAD in the vast majority of patients. Although most antibiotics have been associated with a predisposition to CDAD the most commonly implicated are clindamycin, cephalosporins (particularly cefotaxime), penicillins and fluroquinolones whether used alone or in combinations. There are numerous examples of restrictive antibiotic policies associated with a reduction in the rates of CDAD.[54;154;155]

In 2003, the UK National *Clostridium difficile* Standards Group (NCdSG) looked at various interventions for the control of CDAD including antibiotic manipulations.[45] It was emphasised that prior antibiotic use, especially cephalosporins, was a major risk factor for the development of CDAD. Evidence from the use of restrictive antibiotic policies shows this type of intervention is effective in reducing the incidence of CDAD. In a Cochrane Collaboration Review conducted by a British Society of Antimicrobial Chemotherapy (BSAC)/HIS Working Party which examined interventions designed to improve antibiotic prescribing practices,[156] five of the 66 studies reviewed looked at CDAD incidence as an outcome. The findings from these studies and other papers are summarised below.

5.3.1 Antibiotic associations

- Cephalosporins:

There is good evidence to implicate cephalosporins in the development of CDAD and studies restricting the use of cephalosporins have been successful in reducing CDAD. [54; 154; 157; 158]

- Clindamycin:

This antibiotic has been associated with CDAD since the 1970s, and restriction during outbreaks has been linked with a reduction in cases of CDAD. [155; 159; 160]

- Fluoroquinolone:

Fluoroquinolone use as a risk factor for CDAD was highlighted during an outbreak of *C. difficile* ribotype 027 in Quebec in 2002, when there was a strong association with CDAD.[17] In addition, there was also an association with the duration of use for quinolones and cephalosporins. Initially, quinolones were thought to confer a low risk for CDAD, when this antibiotic class was used in preference to cephalosporins, to reduce the incidence of CDAD. [154;161;162] However, current reports now identify cephalosporins and fluroquinolones as major risk factors in case-controlled studies.[163;164] The explanation for this may be due to the emergence of a fluoroquinolone resistant strain of *C. difficile*[165] and the high usage of this antibiotic class.[4; 166] It has been postulated that there may be two processes at work. Older agents like levofloxacin do not have enhanced anaerobic activity and therefore are unable to exhibit an inhibitory effect on *C. difficile* isolates. Increased use and concomitant use of other antibiotics may lead to increased CDAD rates. Newer fluoroquinolones (gatifloxacin and moxifloxacin) have enhanced anaerobic activity and disrupt gut flora even more leading to an increase in CDAD rates.[167] Although some studies suggest that newer fluoroquinolones are more likely to cause CDAD than levofloxacin or ciprofloxacin,[168;169] others have not found this.[170] Biller *et al* failed to control an outbreak associated to a change from levofloxacin to moxifloxacin by switching back to levofloxacin.[171] This was in contrast to study by Gaynes *et al* and may have been due to increase in levofloxacin use after the switch back.[169] Although reports now implicate fluoroquinolones in outbreaks of CDAD,[167] it should be noted that clindamycin and cephalosporins still play a prominent role.

- Other antibiotics:

Nearly all other antibiotics have been associated with CDAD, however, the disease is particularly linked with the use of broad-spectrum antibiotics.[172] A retrospective case-controlled study examining antibiotic use and subsequent CDAD concluded that patients are more likely to acquire CDAD if they take imipenem (Odds ration (OR) 3.31), ceftazidime (OR 2.45), clindamycin (OR 2.02), or moxifloxacin (1.67).[163] Therefore, less broad-spectrum agents should be used if clinically appropriate (e.g., benzyl penicillin, gentamicin, trimethoprim). Bignardi produced antibiotic ranking tables after a meta-analysis of studies investigating the association between antibiotic use and CDAD.[173] However, the validity of the studies examined in this meta-analysis was subsequently questioned by Thomas,[174] who found only two studies of reasonable quality, and these suggested an association between clindamycin, cephalosporins, penicillin and CDAD.[175;176] The authors recommended more well-designed studies to examine these associations.

5.3.2 Formularies, prescribing behaviour, and antibiotic restrictions

Antibiotic formularies and prescribing guidelines have been advocated for the management of many clinical

conditions. The implementation of these may have adverse microbiological outcomes. Studies have shown that the use of cephalosporins for community-acquired pneumonia recommended by the British Thoracic Society has resulted in an increased incidence of CDAD.[158; 161; 162] Quite a few studies introduced the concept of 'narrow spectrum' antibiotic policies which were successful in reducing CDAD rates; the agents used were benzyl penicillin, amoxicillin, trimethoprim and gentamicin.

Piperacillin-tazobactam is a 'broad spectrum' antibiotic with a low incidence of CDAD rates. Shortages of this antibiotic occurred in 2002 and several studies looked at the consequence of this. Mendez *et al* evaluated the impact of this shortage on antibiotic prescribing and the incidence of VRE and CDAD.[177] In this study, the rate of CDAD was reduced while VRE remained the same. Subsequent multivariate analyses suggested reduced use of ceftriaxone and increased use of levofloxacin correlated with the decreased rate of CDAD. Other studies reported increased use of cephalosporins, in particular third generation cephalosporins, and the subsequent increase in CDAD.[178; 179]

Even if broad spectrum antibiotic use is reduced by restrictive formularies and policies, this may not result in reduced CDAD. Berild *et al* compared the incidence of CDAD in two university hospitals.[180] A higher incidence of CDAD was recorded in one, even though it had reduced usage of broad-spectrum antibiotics and clindamycin. The investigators noted that lack of facilities for infection prevention and control and higher bed occupancy could have contributed to the higher incidence in this hospital and recommend a combination of rational antibiotic use and infection prevention and control for successful outcomes.

In the Cochrane review described above, interventions were classed as either educational (persuasive) or restrictive or a combination of both.[156] The authors found that restrictive interventions had a greater immediate impact than educational interventions, but there is scope for both and more studies are needed. Similar findings were noted in the NCdSG-UK report.[45] Several studies have highlighted the successful use of a multidisciplinary approach to implementing antibiotic policies and the use of feedback with respect to infection rates.[181-183] It should be noted that all of the CDAD studies described above had microbiological outcomes as their primary end-point. Rao *et al* [184] suggested that consideration should also be given to the consequences of restricting the use of antibiotics and any unintentional adverse clinical or microbiological outcomes.[45; 156]

5.4 Physical infrastructure

Environmental contamination is an important factor in the spread of *C. difficile* and is especially pronounced if a patient has explosive diarrhoea.[185] Physical proximity to a symptomatic case has been reported as important for transmission with an attributable risk of 12% due to contaminated near-patient environment and movement between patients of contaminated fomites such as commodes.[45] Failure to isolate symptomatic patients quickly was a major factor in two outbreaks of CDAD at Stoke Mandeville Hospital.[186] The provision of adequate isolation facilities is essential for the prevention of HCAI, including *C. difficile*. Healthcare facilities should have a sufficient number of patient isolation rooms with clinical hand washing sinks and ensuite toilet/bathroom to assist in the prevention and control of HCAI, including CDAD, in addition to single rooms required for other purposes. Healthcare facilities should also provide appropriate hand hygiene and bathroom facilities to facilitate infection prevention and control and phase out large multi-bedded wards. An increase in the total number of single ensuite rooms is recommended.

5.5 Patient placement

Prompt isolation in a single room with clinical hand washing sink and ensuite facilities using Standard and Contract Precautions is recommended for all patients with known or suspected CDAD.[150] If ensuite facilities are not available it is essential that patients with CDAD have a dedicated toilet or commode and are not permitted to use the general toilet facilities on the ward. While The Committee recommends that all patients require isolation, we recognise that many healthcare facilities have limited isolation facilities.

In an outbreak setting (Section 5.13), the number of CDAD cases may exceed the availability of single rooms and alternative placement options include:

- Cohort ward or bay with a dedicated nursing staff for the area
- Isolation / dedicated ward in the event of a large outbreak[150]

In addition to isolation procedures, it is essential that patients with CDAD have a dedicated toilet or commode and are not permitted to use the general toilet facilities on the ward. Patients with asymptomatic colonisation are not thought to represent a significant risk for cross-infection or to need treatment and therefore single room placement for these patients is not advised.[45] Isolation with Contact Precautions may be discontinued when the patient has had at least 48 hours without diarrhoea and has had a formed or normal stool for that patient.[150; 187]

5.6 Education for healthcare workers and visitors/carers

5.6.1 Education for healthcare workers

All HCWs caring for patients with CDAD should be aware of appropriate infection prevention and control precautions and the healthcare facilities policy on caring for patients with CDAD. Staff education and training on infection prevention and control issues with an emphasis on transmission routes should be mandatory for all HCW. 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).

As the majority of HCW have few risk factors for CDAD, and cases in HCW are rare despite the large potential for exposure to *C. difficile*, the risk of HCW acquiring CDAD is thought to be low. While a small number of cases in HCW on antibiotics have been reported,[188] adherence to infection prevention and control precautions as outlined in these guidelines and good standards of personal hygiene will minimise the risk to HCW.

5.6.2 Education of visitors and carers

Patients with CDAD and their visitors/carers should be given information on preventing transmission of CDAD outlining the range and need for appropriate infection prevention and control precautions and shown how to carry out hand hygiene (e.g., patient information leaflet – Appendix 10). Visitors should be alerted to check with ward nursing staff regarding hand hygiene and other requirements before and after visiting a patient with CDAD. Visitors should not use the patient's bathroom and should not go into other patients' rooms or bed spaces.

5.7 Patient movement and transfer

The transfer of patients between wards or between healthcare facilities has been implicated in the spread of CDAD. Movement of patients between wards was identified as a contributory factor in two outbreaks of CDAD at Stoke Mandeville Hospital.[152; 186]

- The movement and transport of the isolated patient with CDAD should be limited to essential purposes only
- Performing a 'test of cure' after CDAD treatment is not recommended and not required prior to transfer if the patient does not have diarrhoea (Recommendation 5)
- If transport or movement is necessary, staff should ensure that precautions are maintained to minimise the risk of transmission to other patients and the contamination of environmental surfaces or equipment
- Prior to internal patient transfer, the receiving department should be informed of the patients CDAD status and the need for contact precautions
- For transfers to another healthcare facility, if the transfer is not urgent, the receiving healthcare facility should only accept a patient currently being treated for CDAD if
    - o The patient has had no diarrhoea for at least 48 hours
    - and
    - o Has had a formed or normal stool for that patient
- Prior to patient transfer to another healthcare facility, the receiving healthcare facility should be informed of the patients CDAD status/history. 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. Apron/gown and gloves should be donned to handle the patient at the transport destination[150]
- Prior to accepting a patient with CDAD, it is the responsibility of the receiving facility to ensure compliance

with single room, clinical hand washing sink, ensuite 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 (Section 5.9)

5.8 Hand hygiene and protective clothing (Appendix 9)

5.8.1 Hand hygiene

The hands of HCWs can become contaminated with *C. difficile* in both endemic and outbreak settings,[189;190] and hands may transmit CDAD.[45] Levels of HCW hand contamination have been shown to be proportional to the level of environmental contamination[45] though demonstrating cause and effect is difficult. One of the key interventions that have been shown to be effective in the prevention of HCAI, including CDAD, is good hand hygiene. None of the agents (including alcohols, chlorhexidine, iodophors or triclosan) used in antiseptic hand-wash or antiseptic hand-rub preparations are reliably sporicidal against *Clostridium* species. The current National Guidelines for Hand Hygiene in the Healthcare Settings recommend that after caring for a patient with CDAD the healthcare worker should wash hands with soap (antimicrobial or non-antimicrobial) and water.[191] If a non-antimicrobial soap is used, after drying, an alcohol hand rub should be applied to the hands.[191]

5.8.2 Gloves

A recent study has demonstrated the importance of wearing gloves when contacting the skin of CDAD patients: *C. difficile* was found to frequently contaminate multiple skin sites of CDAD patients and could easily be transmitted to the investigators hands.[192] Another study demonstrated a significant reduction in *C. difficile* infection and carriage rates on two high-risk hospital wards following the use of gloves when handling body substances.[190] 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.[193]

In addition to wearing gloves as required for Standard Precautions, gloves should also be worn when entering a room for all interactions that may involve contact with the patient or potentially contaminated areas in the patients' environment.

Gloves should be removed
- Immediately after contact with any infective material
- Before touching non-contaminated items and environmental surfaces
- Before leaving the patients environment

Hands should be washed immediately after glove removal as outlined above. 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.

5.8.3 Aprons and gowns

The necessity to wear an apron/gown is based on risk assessment of the anticipated level of contact with the patient and patient environment. Nurses uniforms have been shown to be contaminated with *C. difficile*.[194] The need for and the type of apron/gown selected is based on the nature of patient interaction, including anticipated degree of contact with infectious material and potential for blood and body fluid penetration of the barrier.[150]

In addition to wearing apron/gowns as required for Standard Precautions aprons/gowns should also be worn
- When entering a room for all interactions that may involve contact with the patient or potentially contaminated areas in the patients environment.

Apron/Gown should be removed
- Immediately after contact with any infective material
- Before leaving the patients environment

Hands should be washed immediately after apron/gown removal as outlined above.

5.9 Cleaning of the environment and patient care equipment

5.9.1 The role of the environment as a reservoir for C. difficile

The environment is thought to be an important reservoir for *C. difficile* spores. Transmission to patients during CDAD outbreaks may occur via contaminated environmental surfaces or via the hands of HCWs.[108;189;195] Combinations of infection prevention and control and environmental control programmes are thought to reduce the environmental reservoir and therefore reduce cross-infection.[149;196] However, the true significance of the environment as a potential reservoir for *C. difficile* and its role in subsequent patient infection remains unclear – it is difficult to determine whether environmental contamination is a cause, or a consequence, of diarrhoea.

Environmental contamination with *C. difficile* spores is common and persistent despite cleaning. Spores have been demonstrated in 34–58% of sites in hospital wards,[108;197] and can survive up to five months in the environment.[198-200] Predictably, spores have been found in far greater quantities in the environment of patients with CDAD in comparison with non-carriers.[108; 189; 198] In one study, one quarter of environmental sites in side rooms of patients with CDAD sampled over a four-week period were contaminated with *C. difficile* despite routine detergent cleaning. The need to clean frequently touched sites and the immediate bed space area was emphasized as the bed frame was the most frequently positive site, although the floor was the most contaminated site in terms of the total numbers of colonies recovered.[201] Other sources of environmental contamination can include carpets,[202] thermometers,[203] staff uniforms,[194] and blood pressure cuffs.[204] In another study, while *C. difficile* was not recovered from the environment of two new wards before opening, the environment became rapidly contaminated after ward opening, with CDAD incidence data correlating significantly with the prevalence of environmental *C. difficile* on one ward but not the other. As over 90% of *C. difficile* environmental isolates represented a single endemic clone, it was difficult to determine whether the principle source of cross-infection was infected patients or contaminated environment.[197]

Contamination of HCWs hands can lead to, and result from, contamination of the environment. It has been demonstrated that the level of HCW hand contamination is proportional to the level of environmental contamination.[108;197] High-touch housekeeping surfaces in patient-care areas (e.g., doorknobs, bedrails, light switches, wall areas around the toilet in the patient's room, and curtains) should be cleaned and/or disinfected more frequently than surfaces with minimal hand contact.[205] Where an environmental reservoir is suspected and the degree of contamination is high, routine cleaning procedures should be reviewed and the need for additional trained cleaning staff should be assessed.[150]

5.9.2 Cleaning – detergents or disinfectants?

C. difficile spores are resistant to many commonly used disinfectants.[206;207] Nosocomial outbreaks of CDAD have been linked to the spread of *C. difficile* spores via floors and other surfaces in the rooms of symptomatic and asymptomatic patients.[189;208;209]

The choice of cleaning agent may also result in persistence of *C. difficile* spores in the hospital environment. Wilcox and Fawley reported that some non-chlorine based cleaning agents may lead to an increase in sporulation, whereas the chlorine-releasing agents tested did not. Hence, the incorrect use of environmental cleaning agents may in fact increase the persistence of organisms and lead to increased risk of infection.[210]

In another study, the incidence of CDAD was reduced after the environmental disinfectant (a quaternary ammonium solution) was changed to a 10% hypochlorite solution in the rooms of patients with CDAD in a bone marrow transplantation (BMT) unit.[196] When the quaternary ammonium solution was restarted in the BMT unit, rates of CDAD rose suggesting that hypochlorite solution is effective in reducing risk of infection in high-risk clinical areas. However, these results were not reproducible on two other units (an ITU and a general medical ward), environmental *C. difficile* prevalence was not measured, and antibiotic use altered during the study period.

A prospective crossover study on two elderly medical wards found that hypochlorite cleaning resulted in a significant decrease in the incidence of *C. difficile* in one ward in comparison with neutral detergent. The incidence of *C. difficile* was significantly associated with the proportion of culture-positive environmental sites on this ward. However, these results could not be reproduced on the other ward.[211] During an outbreak of CDAD, surface contamination of *C. difficile* was decreased to 21% of the initial levels with the use of unbuffered hypochlorite, and the outbreak subsequently ended. The use of phosphate-buffered hypochlorite was shown to be even more effective, as its use resulted in a 98% reduction in surface contamination.[209]

Once an area becomes contaminated with *C. difficile*, it is difficult to render it *C. difficile* free. Daily detergent-based cleaning of side rooms of patients with CDAD over a four-week period still lead to a quarter of environmental samples positive for *C. difficile*. While cleaning did result in a reduction in the overall side room prevalence from 35% initially, to 16% in week 4, *C. difficile* could still be isolated from the environment.[201] However, contamination may also persist after environmental cleaning with hypochlorite.[209; 211]

Overall, it appears that hypochlorite-based cleaning may be more effective at reducing levels of environmental *C. difficile* spores and not induce sporulation. The Committee therefore recommend that the environment of patients with CDAD and all patient care equipment should be thoroughly cleaned with a neutral detergent and disinfected daily with a sporicidal disinfectant (e.g., hypochlorite solution – at least 1000 ppm available chlorine). However, hypochlorites are not without their drawbacks: in addition to being potentially corrosive at high concentrations over a long-time period and staff and patient sensitivities, hypochlorite-based disinfectants have a reduced effectiveness in cleaning surfaces. Therefore, visibly dirty surfaces need to be cleaned with a detergent first, before using a hypochlorite disinfectant. 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 hypochlorite components may be useful in this regard. To minimise staff and patient sensitivities when using chlorine-releasing disinfectants, staff must comply with health and safety precautions and manufacturers instructions.

There is therefore a need to evaluate other environmentally friendly effective products. Perasafe (1.6% peracetyl ions equivalent to 0.26% peracetic acid) and acidified nitrate were shown to have cidal activity against *C. difficile* spores, independent of the organic load.[212] Both of these chemicals are considered to be environmentally safe and showed a satisfactory cleaning effect. Another agent that has demonstrated activity is a disinfectant based on accelerated hydrogen peroxide technology (Virox STF-contains 7% hydrogen peroxide) and is a safer and environmentally benign disinfectant in comparison with chlorine-based products.[213] Hydrogen peroxide vapour has been shown to be effective in eradicating *C. difficile* environmental contamination. The main disadvantage of this technique is that it involves having to vacate and seal clinical areas. This is unlikely to be feasible for Irish hospitals which have few single rooms, high bed occupancy and large multiple-bedded ward bays. As a result it may not be possible to vacate or seal off clinical areas to allow decontamination.

5.9.3 Recommendations for cleaning of the environment and patient care equipment

The Committee recommends that the environment of patients with CDAD should be cleaned and disinfected daily with sporicidal disinfectants (e.g., hypochlorite solution 1000 ppm available chlorine), paying special attention to frequently touched sites including bed side rails, telephone, call bells, light switches, door handles, etc. Particular attention should be given to cleaning and disinfecting items likely to be faecally contaminated, e.g., the under surfaces of commodes. These items should be cleaned and disinfected after each use. All equipment used for patients should be in a state of good repair in order to facilitate effective cleaning. Cleaned commodes and bedpans should be stored under dry conditions. Environmental faecal soiling should be cleaned and disinfected immediately. Terminal cleaning and disinfection with sporicidal disinfectants of isolation rooms should be performed after discharge of the CDAD patient. In the event of an outbreak, the frequency with which environmental cleaning is performed should be increased on the affected wards and monitored.

Patient care equipment may become contaminated by *C. difficile*. The degree of contamination may vary depending on the numbers of patients affected and whether the patients are incontinent. Blood pressure cuffs and thermometers have been identified as environmental sources of contamination.[45] Tube feeding, particularly

post pyloric feeding, has been identified as an independent risk factor for *C. difficile* acquisition.[45] Possible explanations include handling of equipment by contaminated HCWs, contaminated formula, or change in intestinal environment following tube feeding. All equipment that comes into close contact with the CDAD patient should be adequately cleaned and disinfected using a sporicidal agent (e.g., hypochlorite solution 1000 ppm), immediately after use. Non-critical patient-care equipment (e.g., thermometers, sphygmomanometers, stethoscopes, blood glucose metres) should be dedicated to a single patient to avoid sharing between patients and cleaned carefully after use. Use of disposable equipment has proven effective to control CDAD outbreaks,[214] and the use of disposable non-critical patient care equipment e.g., blood pressure cuffs has recently been recommended by the CDC.[150] If use of common equipment or items is unavoidable, these should be adequately cleaned and disinfected immediately after use, i.e., before use for another patient.

Bedpan washers in poor working condition resulting in visibly soiled bedpans following the wash–disinfection cycle were identified as a potential risk of cross-infection in the Maidstone and Tunbridge Wells NHS Trust *C. difficile* outbreak report.[153] 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. Bedpans/commode utensils should be placed directly into the washer-disinfector 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.[215]

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[215] 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.

Environmental screening is not recommended for routine post-cleaning screening, however, it can be used to document environmental contamination or poor cleaning/disinfection procedures.

5.10 Laundry and healthcare risk waste management

5.10.1 Laundry

All laundry should be treated as potentially infectious and placed directly into an alginate or water-soluble bag at the bedside.[216] The sealed bag should then be placed immediately into a laundry bag according to organisational and national guidelines.[217] Sorting or manual rinsing of contaminated laundry is not recommended – a sluice cycle should be the first stage of the automated washing process. Bags containing contaminated laundry must be clearly identified with labels, color-coding, or other methods so that HCWs handle these items safely, regardless of whether the laundry is transported within the facility or destined for transport to an off-site laundry service.[205]

Normal hospital laundering processes are effective for removing *C. difficile* contamination. Linen should be heat disinfected during the wash process by raising the temperature to either 65°C for not less then 10 minutes or preferably 71°C for not less then three minutes. 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.[216]

As previously mentioned, nurses uniforms have been shown to be contaminated with *C. difficile*.[194] However, although studies theorise that uniforms may transmit HCAI, no studies have demonstrated this in practice.[218] Home laundering of uniforms for a 10-minute wash at 60°C provides effective decontamination.[219]

5.10.2 Healthcare risk waste disposal

Waste contaminated with diarrhoea from a suspected or known CDAD patient should be disposed as healthcare risk waste within a healthcare facility.[220] 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.

5.11 Discontinuation of CDAD Precautions[187]

Isolation with Contact Precautions (Appendix 9) may be discontinued when the patient has had at least 48 hours without diarrhoea and has had a formed or normal stool for that patient. Retesting for *C. difficile* toxin is not necessary to determine the end of isolation and should not be done. On resolution of CDAD symptoms or patient discharges/transfer, cleaning and disinfection of the environment must occur as described in Section 5.9. 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.

5.12 Prevention and control of CDAD outside healthcare facilities

C. difficile has been identified as the most common infectious cause of diarrhoeal illness in nursing homes in the USA. Outbreaks of CDAD have been reported in geriatric hospital units, rehabilitation hospitals and skilled nursing facilities.[221] In Ireland, four of eleven *C. difficile* outbreaks occurred in residential/long stay units (Section 1.4) and 12% of 1500 cases reported from 20 laboratories were from community sources (Section 2.3.1).

5.12.1 Communication

Good communication is essential, prior to discharging patients with CDAD or a history of CDAD from acute hospitals to other healthcare facilities and the home (Section 5.7).
This facilitates

- Appropriate precautions to be put in place to prevent cross-infection
- Appropriate antibiotic prescribing, if required, to prevent CDAD recurrence

Being informed of a patients CDAD history will assist the GP/medical officer to

- Prescribe an antibiotic with a lower propensity to CDAD recurrence if repeated antibiotic treatment is required (Section 5.3)
- Be alert to suspect a recurrence of CDAD, if a patient develops diarrhoea following discharge

5.12.2 Care of patients with CDAD in the home

In the home, the following precautions are advised:

- Hand hygiene is the single most important infection control measure.
    - o Carers, including family and healthcare workers, should wash their hands thoroughly with soap and water and dry, if assisting with personal care
    - o Patients should wash their hands thoroughly with soap and warm water and dry them after using the bathroom, before preparing food and before eating
- Disposable gloves and aprons should be worn by healthcare workers when attending to a patient 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 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 should become contaminated)
- The patient 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 Patients should avoid using the same toilet as other family members if possible
    - o 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

  - o The patients immediate environment 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
- Soiled laundry should be machine-washed separately from other washing on the hottest wash cycle suitable for linen and clothing.
- Patients and their families should receive the patient information leaflet (Appendix 10)

5.13 CDAD outbreaks

5.13.1 Definition

An outbreak is defined as the occurrence of two or more epidemiologically linked CDAD cases over a defined period agreed locally, taking account of the background rate or where the observed number of CDAD cases exceeds the expected number. Detection of new CDAD outbreaks can be difficult where there are high or continuously rising numbers of cases and the background rate is not clear. The NCdSG – UK took account of this in defining outbreaks as the occurrence of two or more related cases over a defined period taking account of the background rate. Recognition of an outbreak needs an alert mechanism in place with rapid and reliable diagnosis to facilitate early intervention. Use of statistical tools such as statistical process control (SPC) charts may assist IPCTs to distinguish between natural and unexpected variation and identify when numbers of CDAD cases are exceeding normal expectations for that ward.

Medical practitioners and clinical directors of diagnostic laboratories are required to notify to the Medical Officer of Health unusual clusters or changing patterns of illness.[222] The IPCT should always be informed when there are an increased number of suspected or confirmed CDAD cases.

5.13.2 Establishment of the outbreak control team

When an outbreak of CDAD is suspected, an outbreak control team (OCT) should be established. The decision to convene an OCT will be made by the Hospital CEO or general manager / network manager or the PCCC local health office manager on the advice of the

- Consultant Medical Microbiologist
- Medical Officer of Health (MOH)

The OCT should be multi-disciplinary made up of senior professionals and decision-makers (Table 5.1). Where an outbreak involves more than one HSE Health 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. All healthcare facilities shall ensure that there are defined and documented outbreak management process and procedures outlining the roles and responsibilities of the OCT members.

Table 5.1: Recommended Membership of a CDAD Outbreak Control Team

	Acute Hospital	HSE PCCC
Chair	Hospital CEO, Network Manager or General Manager	Local Health Office Manager
Team	Department of Public Health Specialist/ Medical Officer of Health*	Department of Public Health Specialist /Medical Officer of Health*
	Consultant Physician/Surgeon	Attending Medical Officer or General Practitioner
	Occupational Health Physician	Occupational Health Physician
	Consultant Medical Microbiologist	Consultant Medical Microbiologist
	Infection Prevention and Control Nurse	Infection Prevention and Control Nurse
	Infectious Disease Physician	Healthcare Facility Manager or representative
	Surveillance Scientist	Surveillance Scientist
	Director of Nursing	Matron/Charge Nurse
	Ward/Department nurse manager of affected area (s)	Ward/Department nurse manager of affected area (s)
	Bed Manager	
	Patient Services Manager/ Household Services Manager	
	Patient representatives office	
Other relevant staff as considered necessary which may include a communications/press officer, a laboratory representative, an antibiotic pharmacist (if present in the facility), and a public health nurse (in a Nursing Home outbreak).		

*The MOH will notify the National Director for Population Health and the HPSC.

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

- To investigate 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
- To review the above evidence and confirm that there is a CDAD outbreak. Initial information should be provided to the HPSC (by fax or email) by a public health specialist using a preliminary outbreak notification form
- To develop a strategy to deal with the outbreak and to allocate individual responsibilities for implementing action
- To implement control measures and to monitor their effectiveness in dealing with the outbreak and in preventing further spread
- To advise management on the necessary action to control the outbreak
- To agree a communications strategy to provide clear, consistent and accurate information and to keep relevant persons within the hospital/nursing home, HSE Health Area, outside agencies, the general public and the media appropriately informed
- To provide 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:
  - o A review of the experiences of all participants involved in the management of the outbreak
  - o Identifying shortfalls and particular difficulties encountered
  - o A review of the outbreak plan in accordance with the above
  - o Make recommendations, if necessary, regarding structural or procedural improvements which would reduce the chance of a reoccurrence of the outbreak
  - o The outcome and lessons learned should be disseminated so that the incident becomes a positive learning experience for those involved in the implementation of the control measures[223]
- This report should be submitted to the head of the relevant healthcare facility (e.g., Hospital CEO/manager). Where there are difficulties, these should be highlighted locally and to the HSE and the DoHC so that measures are taken by the HSE and the DoHC to ensure implementation of recommendations made by the OCT including the provision of appropriate resources and personnel

Effective communication with relevant authorities, other professional groups, the media and the general public during an outbreak is an important aspect of outbreak management (Appendix 11). All relevant information should be shared as appropriate with these groups. The OCT will 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.

5.13.3 Outbreak control

Infection prevention and control is especially important in the control of *C. difficile* transmission in outbreaks.[45] Each healthcare facility should have a surveillance system in place that enables timely alerts of a change in *C. difficile* incidence that may indicate a possible CDAD outbreak. Initial identification of an outbreak will involve

- Prompt identification of unexplained diarrhoea
- Sending a stool specimen to exclude an infectious cause (faecal samples from all infected patients should be stored so that typing can be performed (Section 3.7)
- Notification of IPCN/IPCT to gain advice and support in managing the situation

Control of CDAD in outbreaks requires the following:

- Isolation of symptomatic patients in single rooms with clinical hand washing sink and ensuite facilities. Where adequate numbers of isolation facilities are not available, patients should be cohorted or an isolation ward opened (Section 5.4). During outbreaks there is strong evidence of exogenous acquisition of CDAD
- Restriction of patient movement (Section 5.7)
- If patients require transfer, notify the receiving facility or department that the transfer is from an outbreak area and advise the receiving facility/department of the precautions to be followed (Appendix 9)
- Communication of the outbreak control measures in place to other departments within the healthcare facility
- Education of all staff on the mode of transmission and reinforcement of all infection prevention and control precautions to be used (Appendix 9)
- Communication with patients and visitors to inform them of the infection control precautions that have been implemented while maintaining patient confidentiality
- Sensible management of visiting to all healthcare facilities may assist in controlling a CDAD outbreak
  - o During an outbreak, visiting should be restricted
  - o Children should, where possible, not visit during an outbreak
- Where an environmental reservoir is suspected and the degree of contamination is high, routine cleaning procedures should be reviewed and the need for additional trained cleaning staff should be assessed[150]
- Environmental cleaning and disinfection with sporicidal disinfectants (Section 5.9)
- Disposable non-critical patient-care equipment should be used if possible
- Review antibiotic prescribing (types of agents and duration) with the emphasis on reducing inappropriate use of broad-spectrum antibiotics
- Staff cohorting may be necessary to manage an outbreak. Sufficient numbers of staff must 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.[152]

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 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 and the number of cases has returned to the endemic level.[187]

Chapter 3:
Appendices and Reference List

Appendix 1:

A draft of this document was sent to the following groups for consultation:

Academy of Medical Laboratory Science
Emergency Medicine Association
CIDR Management Team – HPSC
Dr. Ed Kuijper, Chair, ESCMID study group for *C. difficile*
Irish College of General Practitioners
Irish Society of Clinical Microbiologists
Irish Society of Gastroenterologists
Irish Society of Physicians in Geriatric Medicine
Irish Patients Association
Intensive Care Society of Ireland
Infection Prevention Society (formerly Infection Control Nurses Association)
Irish Infection Society
Nursing Home Association South East
Public Health Medicine Communicable Disease Group
Royal College of Physicians of Ireland (RCPI)
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
The Federation of Irish Nursing Homes

Appendix 2:

Definitions used in this document

- **Healthcare facility (HCF)**

An HCF is defined as 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

- **Diarrhoea**

Diarrhoea is defined as three or more loose/watery bowel movements (which are unusual or different for the patient) in a 24 hour period and there is no other recognized aetiology for the diarrhoea (e.g., laxative use)

- **Diarrhoeal specimen**

Diarrhoeal stool specimens are defined as those that take up the shape of their container

Appendix 3:
Abbreviations

AMLS	Academy of Medical Laboratory Science, Ireland
ARU	Anaerobe Reference Unit, Cardiff, Wales
BSAC	British Society for Antimicrobial Chemotherapy
CCCA	Cell culture cytotoxicity assay
CDAD	*C. difficile*-associated disease
CDC	Centres for Disease Control & Prevention, US
CIDR	Computerised Infectious Disease Reporting
CPE	Cytopathic effect
DoHC	Department of Health and Children, Ireland
DHQP	Division of Healthcare Quality Promotion, US
ESCMID	European Society for Clinical Microbiology & Infectious Diseases
ECDC	European Centre for Disease Prevention and Control
EIA	Enzyme immunoassay
HCAI	Healthcare-associated infection
HCW	Healthcare worker
HIPE	Hospital in-patient enquiry
HIS	Hospital Infection Society
HSE	Health Services Executive, Ireland
HPA	Health Protection Agency, UK
HPAI	Hospital Pharmacists Association of Ireland
HPS	Health Protection Scotland
HPSC	Health Protection Surveillance Centre
IPCT	Infection prevention and control team
ICU	Intensive care unit
ICGP	Irish College of General Practitioners
ICNA	Infection Control Nurses Association
IPS	Infection Prevention Society incorporating IPCNA
IPCN	Infection prevention and control nurse
IIS	Irish Infection Society
ISCM	Irish Society of Clinical Microbiologists
IVIG	Intravenous immunoglobulin
MIC	Minimum Inhibitory Concentration
MLST	Multilocus sequence typing
MLVA	Multilocus Variable-Number Tandem-Repeat Analysis
MOH	Medical Officer of Health
NCdSG	National *Clostridium difficile* Standards Group, UK
NNIS	National Nosocomial Infections Surveillance, US
NHO	National Hospitals Office, HSE
NHS	National Health Service, UK
OCT	Outbreak control team
PCCC	Primary, Community and Continuing Care, HSE
PCR	Polymerase chain reaction
PFGE	Pulsed field gel electrophoresis
PMC	Pseudo membranous colitis
RCPI	Royal College of Physicians in Ireland
REA	Restriction Endonuclease Analysis
SAC	Scientific Advisory Committee
SSHAIP	Scottish Surveillance of Healthcare-associated Infection Programme, HPS-Scotland
TcdA	*C. difficile* toxin A
TcdB	*C. difficile* toxin B
WTE	Whole time equivalent

Appendix 4:

Proposed national core dataset for CDAD cases

Section	Field	Options / Comments
Patient details	Patient identifier	
	Gender	Female/Male/Unknown
	Date of birth	
	Patient location	Hospital/nursing home/at home/ other
	Part of outbreak	Yes/No If yes–CIDR number
Administration	Date of notification/report	
	Notified/Reported by	

Appendix 5:

Proposed dataset for enhanced surveillance on CDAD cases

Section	Field	Options / Comments
Patient details	Patient identifier	
	Date of admission to hospital	Not in hospital / admission date
	Admission from	Home/other hospital/ other healthcare facility/ other
Clinical details of CDAD	Case type	Case/recurrent/severe
	Origin	Healthcare-associated/community-associated / unknown case
	Onset	Healthcare-onset / community-onset
	Symptoms	Diarrhoea/vomiting/abdominal pain / temperature>38°C/abnormal white cell count
	Severity	ICU admission/surgery/ other complications
	Outcome	Remains in hospital/discharged/transfer to another healthcare facility/ death
	Date of outcome	
Risk factors	Intrinsic	Over 65/underlying disease/immunosupression
	Extrinsic	Surgery/antacids-laxatives/food
	Other intervention	Catheter/respiratory care/nasogastric feeding
	Environmental	Contact with other case in ward/hosp/nursing home/home plus ICU dates before and after CDAD
	Antibiotic history in previous 8 weeks	Yes/no/unknown
	Antibiotics	Unknown/list of antibiotics
Isolate details	Specimen identifier	
	Date of 1st specimen	
	Specimen type	Faeces/rectal swab/other
	Test method-EIA	Yes/no
	Test method – Cytotoxicity	Yes/no
	Test method – Culture	Yes/no
	Test method -PCR	Yes/no
	Antibiogram	List of drugs
	Typing results	Not done/result
	Isolate saved in lab	Yes/no

Appendix 6:

Questionnaire on diagnosis of *C. difficile* in Irish Laboratories

1. Diagnostic method routinely used for *C. difficile* in your laboratory:

Does your laboratory

a. Process faecal specimens for *C. difficile*?
Yes / No / Yes but done elsewhere
If tested elsewhere, please state where:

b. Process faecal specimens for *C. difficile* for other hospitals? Yes / No
If yes, please list the hospitals:

c. Have an SOP for processing faecal specimens for *C. difficile*? Yes / No

d. Test for toxin directly from stools? Yes / No
Cytotoxicity assay Yes / No
ELISA Yes / No
Toxin A only Yes / No
Toxin A and B Yes / No
Please specify
PCR Yes / No
Other Yes / No
Please provide details:

2. Culture of *C. difficile* strains

Does your laboratory culture *C. difficile*? Yes / No / Yes but done elsewhere

- Selective agar Yes / No
- Please specify the selective medium used:
- Alcohol shock Yes / No
- Alcohol shock and selective agar Yes / No

Does your laboratory confirm toxin detection on *C. difficile* isolates? Yes / No

- Toxin detection from strains Yes / No
- Cytotoxicity assay Yes / No
- EIA Yes / No

Please specify EIA:

- PCR Yes / No

3. Typing of *C. difficile* strains

Does your laboratory type *C. difficile* isolates? Yes / No / Yes but done elsewhere
Please specify method and laboratory:

4. Strategy for *C. difficile* testing (SPECIMEN SELECTION)

[ ] Only when specifically requested

[ ] Systematically based on the following criteria:

[ ] On all stool cultures sent to the laboratory

[ ] On stools from certain departments (if so please specify below)

[ ] On all liquid stools

[ ] If antibiotic treatment is stated

[ ] In cases of suspected nosocomial diarrhoea

[ ] Only on patients over a certain age (age cut-off……)

[ ] On outpatient community specimens

[ ] Other criteria please specify:

5. Strategy for REPEAT *C. difficile* testing

Does your laboratory have a policy on repeat testing for patients previously positive for *C. difficile* toxin? Yes / No

[ ] Once a week

[ ] All repeat specimens tested

[ ] Positive specimens are not retested for 4 weeks

Appendix 7:

Intracolonic vancomycin regimens

Two methods for administration of vancomycin intracolonically are described in the literature:

- An IV solution of vancomycin 0.5-1.0g is dissolved in 1L normal saline. An 18G Foley catheter is inserted per rectum and the balloon is inflated. The vancomycin solution is instilled into the rectum in 30ml aliquots every 4-12 hours and retained for 60 minutes by clamping catheter. Once retention time complete, the catheter is unclamped, the balloon deflated and the catheter removed. This process can be repeated every 4-12 hours pending a clinical response.[103]

- An enema containing vancomycin 500mg in 500ml of normal saline is administered twice daily with a 5-10 minute retention time. Treatment is for 10 days.[224]

Appendix 8:

Regimen for tapered pulsed oral vancomycin therapy[225]

Vancomycin

- 125mg 6 hourly for 7 days
- 125 mg 12 hourly for 7 days
- 125 mg daily for 7 days
- 125 mg every other day for 7 days
- 125 mg every 3 days for 7 days

Appendix 9:

Precautions for caring for patients with CDAD

(Contact precautions adapted from Siegel, et al[150], Standard Precautions adapted by kind permission from HPSC (2005) Report of the HPSC Sub-Committee on Verotoxigenic E. coli)

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
	Apply to all patients, residents and clients irrespective of their perceived infection risk	***When the patient has had at least 48 hours without diarrhoea and has had a formed/normal stool for that patient, Contact Precautions can be discontinued,*** **HOWEVER STANDARD PRECAUTIONS MUST BE CONTINUED**
PATIENT PLACEMENT	Include the potential for transmission of infectious agents in patient placement decisions. Where possible, place patients who contaminate the environment or cannot maintain appropriate hygiene in single rooms,	Place all patients with suspected or known CDAD in a single room with clinical hand washing sink and ensuite facilities. If ensuite facilities are not available, dedicate toilet or commode for patients' sole use. Place a notice on the isolation room door advising those entering to report to staff-in-charge before entering. In an outbreak situation, if the number of patients with CDAD exceeds the availability of single rooms, alternative placement options include: • Cohort ward or bay with a dedicated nursing staff for the area. • Isolation / dedicated ward in the event of a large outbreak.
PATIENT MOVEMENT AND TRANSFER		**Limit the movement and transport of the patient to essential purposes only.** Prior to patient transfer • Inform transport personnel (e.g. porters, emergency medical technician) and the receiving department/healthcare facility of the need for Contact Precautions. • Remove contaminated aprons/gowns and gloves and dispose and perform hand hygiene prior to transporting patients. Don apron/gown and gloves prior to handling the patient at the transport destination. Prior to accepting a patient with CDAD, it is the responsibility of the receiving facility to ensure compliance with single room, clinical hand washing sink, ensuite facilities and Contact Precautions. The receiving ward/ department, bed manager must be notified. Transport equipment (stretcher, bed, wheelchair) used for the transfer must be cleaned and disinfected before use with another patient/resident.

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
HAND HYGIENE *Patients should wash their hands after toileting and before meals. HCW should provide assistance with hand washing for those patients who are unable to perform hand washing independently*	Hand Hygiene is recommended: • Before and after each episode of patient contact • Between individual patient contacts. • After contact with blood, body fluids, secretions or excretions, whether or not gloves are worn. • After handling soiled/contaminated equipment, materials or the environment. • Immediately after removing gloves or other protective clothing Hand may be decontaminated using both plain soap and warm water or if hands are physically clean, an alcohol based hand rub.	**In addition to carrying out hand hygiene as required in Standard Precautions** Hands should be washed before and after each contact with patient equipment Hands should be washed with soap (antimicrobial or non-antimicrobial) and water.[191] **None of the agents (including alcohols, chlorhexidine, iodophors or triclosan) used in antiseptic hand-wash or antiseptic hand-rub preparations are reliably sporicidal against *C. difficile*. The physical action of rubbing and rinsing is the only way to remove spores from hands.**
GLOVES Should be worn as single use items Should conform to European Community Standards.	Gloves are recommended: • For all activities that carry a risk of exposure to blood, body fluids, secretions or excretions, sharps or contaminated instruments • When touching mucous membranes and non-intact skin. • When handling contaminated equipment, e.g. commodes or bedpans. Gloves should be: • Put on immediately before an episode of patient contact, and removed as soon as the activity is completed • Changed between caring for different patients and between different care activities on the same patient. • Disposed of as health care risk waste if contaminated with blood, body fluids	**In addition to wearing gloves as required for Standard Precautions**, wear gloves when entering a room for all interactions that may involve contact with the patient or potentially contaminated areas in the patients environment. Remove gloves • Immediately after contact with any infective material • Before touching non-contaminated items and environmental surfaces • Before leaving the patients environment Wash hands as above immediately after glove removal.
EYE, NASAL AND MOUTH PROTECTION (e.g., goggles, visors and face masks)	Facemasks and eye protection are recommended where there is a risk of blood, body fluids, secretions or excretions splashing into the face or eyes. Masks should be single use and fluid resistant.	

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
APRONS	Disposable plastic aprons should be worn where there is a risk that clothing or skin may become exposed to blood, body fluids, excretions or secretions. Fluid repellent gowns may be required if there is a risk of extensive exposure to the above.	**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 or potentially contaminated areas in the patients' environment. Remove apron/gown • Immediately after contact with any infective material • Before leaving the patients environment Wash hands as above immediately after apron/gown removal.
PATIENT CARE EQUIPMENT	Handle equipment soiled with blood, body fluids, secretions and excretions in a manner that prevents skin and mucous membranes, contamination of clothing, and transfer of micro-organisms to other patients and environments. Ensure that reusable equipment is not used by another patient until it has been cleaned and reprocessed appropriately.	• Dedicate medical devices (e.g., thermometers, sphygmomanometers, stethoscopes, glucose metres) to single patient use and disposable materials used whenever possible. • Only take essential equipment and supplies into the room. Do not stockpile as unused stock will have to be discarded on cessation of Isolation Contact Precautions. • Patient charts/records should not be taken into the room.

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
ENVIRONMENTAL AND EQUIPMENT DECONTAMINATION	• Routine environmental cleaning is required to minimise the number of micro-organisms in the environment. • Particular attention should be given to frequently touched surfaces and those most likely to be contaminated with blood or body fluids e.g. bedrails, mattresses, bedside tables, commodes, doorknobs, sinks, surfaces and equipment close to the patient. • Chemical disinfectants are not recommended for routine environmental cleaning. • All equipment should be in a state of good repair in order to facilitate effective cleaning. • Place bedpan / commode utensils directly into bedpan washer-disinfector. Bedpan washers must reach a temperature of 80°C for a minimum of 1 minute. Monitor and record correct temperatures reached and the cleaning efficacy of bedpan-washers. • All equipment should be stored dry. • Non-critical items such as commodes, intravenous pumps must be thoroughly cleaned prior to use on another patient/resident. If soiled with blood or body fluids, disinfect using a chlorine-releasing solution of 1000ppm, or equivalent according to manufacturers' instructions, rinse and dry. The area should be well ventilated to avoid toxic fumes. • When using disinfectants, staff should follow the manufacturer's instructions for dilution and contact times.	**In addition to environmental and equipment decontamination as required for Standard Precautions:** • Thoroughly clean the environment and all patient care equipment **daily** with a neutral detergent and disinfect with a sporicidal disinfectant (e.g., hypochlorite solution –1000 ppm), paying special attention to frequently touched sites and equipment close to the patient. • Particular attention should be given to cleaning and disinfecting immediately items likely to be faecally contaminated e.g., the under surfaces and hand contact surfaces of commodes. • Environmental faecal soiling should be cleaned and disinfected immediately. • Cutlery and crockery - No additional measures are required for cutlery and crockery washed in a dishwasher. On patient discharge/transfer cleaning and disinfection of the environment must occur upon resolution of CDAD symptoms or when a CDAD patient has their accommodation changed or is discharged from a room. • 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 • All sterile and non-sterile supplies in the patient environment to be discarded on patient transfer/discharge.

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
LAUNDRY CARE:	• Laundry should be handled and transported in a manner that prevents transmission of micro-organisms to other patients, HCWs or the environment. • Laundry should be categorised and segregated according to recommended guidelines • Staff handling soiled linen should wear gloves and a disposable plastic apron. • Soiled and infectious linen should be carefully placed in an alginate stitched or water soluble bag with a tie. Then place bag into a colour-coded laundry bag which should be securely closed prior to transport to an approved laundry capable of dealing with potentially contaminated linen • Staff should not manually sluice or soak soiled or infected linen /clothing because of the risk of cross infection[226] • Soiled linen should be transported and stored safely. • Linen should be heat disinfected during the wash process by raising the temperature to either 65°C for not less then 10 minutes or preferably 71°C for not less then 3 minutes. • Disinfection of heat labile materials (according to manufacturer instructions) can be achieved at low temperatures by introducing 150 ppm of chlorine into the penultimate rinse.	**In addition to handling and transportation of laundry as required for Standard Precautions:** All laundry should be carefully placed in an alginate stitched or water soluble bag and then placed into a laundry bag clearly identified with labels, colour-coding or other methods prior to transport to an approved laundry capable of dealing with contaminated linen.
DECONTAMINATION OF MEDICAL DEVICES	• Medical devices designated as "Single Use Only" must not be reprocessed or reused under any circumstances (MDA DB 2000), (MDD) 93/42/EEC  This symbol means "Single Use Only" (BS EN 980:1997). • Reusable medical devices should be cleaned and reprocessed according to the manufacturer's instructions and local policy.	

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
MANAGEMENT OF HEALTH CARE RISK WASTE:	Dispose of healthcare risk waste in accordance with the Department of Health & Children's National Guidelines for Waste Disposal,[227] which outlines the categorisation and segregation of health care waste. DISPOSAL OF SHARPS: • Syringes and needles should be disposed of as a single unit. • Used sharps should be carefully discarded into designated sharps containers at, the point of use. • Needles should not be re-capped, bent, broken or disassembled. • Sharps should not be passed from person to person by hand. • Guidelines should be available at local level on the management of needle stick and sharps injuries.	Waste contaminated with diarrhoea from a suspected or known CDAD patient should be disposed as healthcare risk waste within a healthcare facility No additional precautions are needed for non-healthcare waste that is being removed from rooms of patients on Contact Precautions

	STANDARD PRECAUTIONS	CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)
SPILLAGES	• Spillages of blood, urine, faeces or vomit should be dealt with immediately wearing protective clothing (i.e. disposable gloves and apron). **For spillages of body fluid (e.g., urine, faeces or vomit),** • Soak up as much of the visible material as possible with disposable paper towels. • Dispose of the soiled paper towels according to national guidelines. • Clean the area using warm water and general purpose neutral detergent. • Disinfect using a chlorine-releasing solution of 1000ppm, or equivalent according to manufacturers' instructions, rinse and dry. • Discard gloves and apron according to national guidelines. • Wash and dry hands thoroughly. • Do not apply chlorine-based disinfectants directly onto spillages of urine as it may result in the release of chlorine vapour. **For blood spillages:** • Decontaminate all blood spills with a chlorine based disinfectant (e.g., powder, granules or liquid containing 10,000ppm available chlorine) or suitable alternative, in line with the manufacturer's instructions and local policy. • Wipe up the spillage with disposable paper towels and discard into a yellow plastic bag. Wash the area with a general purpose neutral detergent and water. • Discard gloves and apron according to national guidelines. • Wash and dry hands thoroughly For all surfaces/items contaminated with blood or body fluids, following cleaning disinfect using a chlorine-releasing solution of 1000ppm, or equivalent according to manufacturers instructions, rinse and dry.	

Appendix 10:
Patient information leaflet

are fit to go home. Your doctor will let you know if you need to continue treatment at home.

Can *Clostridium difficile* diarrhoea come back?

Yes, some patients may suffer a relapse of diarrhoea. Please contact your GP/family doctor if you develop diarrhoea after you are discharged from hospital and let him/her know that you had *Clostridium difficile* recently. If you need antibiotics for another illness please tell your GP/family doctor that you recently had *Clostridium difficile*.

If I have *Clostridium difficile* diarrhoea at home how do I stop my family from catching it?

To reduce the risk of spreading *Clostridium difficile* to others, take the following steps:

- Wash your hands thoroughly with soap and warm water and dry them after using the bathroom and before eating.
- Be strict with your personal hygiene – do not share personal items such as towels and face cloths.
- Machine wash soiled laundry separately from other washing on the hottest wash cycle suitable for linen and clothing.
- Tell your family or carers to wash their hands thoroughly with soap and water and dry them after caring for you.
- Try to avoid using the same toilet that your family members use. If this is not possible, ensure that the toilet is cleaned and disinfected after your use.
- Clean surfaces in bathrooms on a regular basis with household detergents. If you have had diarrhoea, then disinfect with a mixture of bleach and water as instructed on the container. Pay special attention to sink taps, flush handle, toilet seats and lastly the toilet bowl

How to wash your hand properly

1. Wet your hands under running water
2. Lather with soap
3. Cover all parts of you hands
4. Rinse well under running water
5. Dry thoroughly

It should take around 30 seconds to wash your hands properly.

Further information:

You can also get more information from the Health Protection Surveillance Centre (HPSC) website www.hpsc.ie.

Go into the Topics A-Z section of the site and then click *Clostridium difficile*.

Published on behalf of the *Clostridium difficile* Sub-committee of the Scientific Advisory Group, Health Protection Surveillance Centre.

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Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

hpsc

Health Protection Surveillance Centre

Clostridium difficile

Patient information leaflet

This leaflet is intended for patients in hospital, their families and carers to give them a greater understanding of *Clostridium difficile*.

What is *Clostridium difficile*?

- *Clostridium difficile*, also know as '*C. difficile*' and '*C. diff*' is a bacteria (germ) that normally lives in your large intestine (gut/bowel).
- *Clostridium difficile* is usually found in the large intestine (bowel). A small proportion (less than 1 in 20) of the healthy adult population carry a small amount of *Clostridium difficile* and don't experience any problem with it. It is kept in check by the normal, 'good' bacteria of the intestine.
- However, when you take an antibiotic, some of the 'good' bacteria die causing the *Clostridium difficile* bacteria to multiply and you may get an infection in your large intestine.

What are the symptoms of *Clostridium difficile*?

- If you become infected with *Clostridium difficile* you may get diarrhoea, which has a very unpleasant smell.
- You may also suffer from stomach cramps, fever, nausea and loss of appetite.
- Most people only get mildly ill and recover fully from it.
- However, in certain circumstances you may get seriously ill and develop colitis (inflammation of the bowel). If the colitis is severe it can be life threatening.

How is *Clostridium difficile* diagnosed?

- A sample of diarrhoea is sent to the laboratory for testing. Staff in the laboratory test for *Clostridium difficile* bacteria in the diarrhoea.

Is *Clostridium difficile* contagious?

- Yes, it is. If you have *Clostridium difficile* diarrhoea, the *Clostridium difficile* bacteria can survive on your hands and surfaces for a long time unless they are washed. It can then pass from your hands and surfaces to others through unwashed hands and soiled equipment.
- To prevent *Clostridium difficile* from spreading, you, your family members and hospital staff need to regularly wash your hands and clean and disinfect equipment.

If you don't have diarrhoea, *Clostridium difficile* cannot be spread to other people.

Who is most likely to get *Clostridium difficile* diarrhoea?

You are most at risk of developing infection if you:

- Are taking or have recently finished taking antibiotics,
- Have spent a long time in hospital or other healthcare settings (e.g., nursing homes),
- Are older,
- Have a serious illness,
- Have a weakened immunity (e.g., receiving cancer treatment),
- Have had bowel surgery,

What treatment will I get if I have *Clostridium difficile* diarrhoea?

- In some cases, certain antibiotics may have caused the diarrhoea so you may have to stop taking them.
- You may be given other antibiotics which are effective against the *Clostridium difficile* bacteria.
- It is important to drink enough fluids so that you don't become dehydrated because of the diarrhoea.

What happens if I have *Clostridium difficile* diarrhoea while I'm in hospital?

- You will be moved to a single room or special ward and given a toilet or commode for your own use.
- You must make sure to wash your hands with soap and water after using the toilet and before meals.
- Staff looking after you will wear aprons and gloves and wash their hands after caring for you.

Can I have visitors if I am infected with *Clostridium difficile*?

- Yes, you can have visitors as healthy people are at very little risk of getting *Clostridium difficile* unless they are taking antibiotics. If you have any concerns about someone visiting, please seek advice from nursing staff first.
- Your visitors will be asked to report to the nurse in charge before visiting you.
- Ask your visitors to wash their hands with soap and water after visiting you.
- Your visitors will need to wear gloves and aprons if they are helping with your personal care.
- Your visitors should sit on the chairs provided, not on your bed and only use the public toilets.

Will any of my treatment be delayed because I have *Clostridium difficile* diarrhoea?

- Your tests or treatment should continue as planned, with staff taking the correct precautions to prevent *Clostridium difficile* spreading.
- Some non-urgent tests may be delayed if you have severe diarrhoea.

How will I know when the *Clostridium difficile* is no longer infectious?

- Once the diarrhoea has stopped for at least 48 hours and your bowel motion is back to normal you are on the mend.
- However, *Clostridium difficile* bacteria may remain in your bowel for sometime afterwards and the diarrhoea may return requiring further treatment.

Can I go home with *Clostridium difficile* diarrhoea?

You should normally wait until the diarrhoea has settled and your doctor is satisfied that you

Appendix 11:

Communications with the media by the Outbreak Control Team (OCT)

- The OCT will 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 will release information to the press without the agreement of the Team.

- Contents of press statements should be given to hospital medical and nursing staff and field workers to ensure that consistent advice is being provided to the public

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