A decade of Clostridioides Difficile infection – An in-depth analytical retrospective review of a single centres experience

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A decade of *Clostridioides difficile* infection – An in-depth analytical retrospective review of a single centres experience

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A thesis submitted to the School of Postgraduate Studies, Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland, in fulfilment of the degree of Masters of Science

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Declaration Form

I declare that this dissertation, which I submit to RCSI for examination in consideration of the award of a higher degree Masters of Science, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in the RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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List of abbreviations

BDU	Bed days used
CA	Community-associated
CDC	Centre for Disease Control and Prevention
CDI	*Clostridioides difficile* infection
CMT	Clinical Microbiology Team
ECDC	European Centre for Disease Control
EIA	Enzyme immunoassay
GHD	Glutamate dehydrogenase
HA	Healthcare-associated
HAI	Healthcare associated infections
HCF	Healthcare facilities
HIQA	Health Information and Quality Authority
HPSC	Health Protection Surveillance Centre
HPV	Hydrogen peroxide
HSE	Health Services Executive
ICD	International Classification of Diseases
IPCN	Infection prevention and control nurse
IPC	Infection prevention and control
IPCT	Infection Prevention and Control Team
KPI	Key performance indicators
MeSH	Medical Subject Headings
NAAT	Nucleic acid amplification testing
PAS	Patient administration system
PCR	Polymerase chain reaction
PDSA	Plan, do, study, act
PPS	Point prevalence survey
QI	Quality improvement
rCDI	Recurrent CDI
RCSI	Royal College of Surgeons Ireland

RT	Ribotype
SS	Surveillance scientist

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Summary

Background

Clostridioides difficile infection (CDI) is the leading cause of hospital-acquired infectious diarrhoea. CDI is potentially preventable and can disrupt hospital services. The Beaumont Hospital Department of Clinical Microbiology provides daily onsite *C. difficile* laboratory testing and has a comprehensive CDI prevention and control programme for over a decade. This has included a CDI surveillance programme which has not been appraised since its development.

Objectives

1. To investigate CDI trends using an observational retrospective cohort study of hospitalised patients attending Beaumont Hospital over ten years and to investigate patient factors predicting first episode of CDI and recurrence.
2. To evaluate the attributes and continued feasibility of the current CDI surveillance approach in Beaumont hospital.

Methods:

C. difficile is a standing agenda item at the weekly infection prevention and control team meeting with multi-disciplinary input and reporting to key stakeholders in real time. *C. difficile* data from 1st January 2012 to 31st December 2021 was extracted. Data included patient demographics, admission details, *C. difficile* testing and CDI case details, *C. difficile* ribotyping (RT) and CDI outbreak data. Data on antimicrobial exposure before CDI onset and specific antimicrobial CDI treatment were captured since 2016. All laboratory samples tested for *C. difficile*, irrespective of case type were analysed initially. Subsequent analysis explored the sub-groups of new onset inpatient using χ^2 analyses with unadjusted odds ratios (ORs) presented, new and recurrent CDI by Poisson regression for trends in rates and predicting factors. A Cox proportional hazards regression model for time to recurrence.

Results

Data associated with 1975 samples from 1437 patients was reviewed. This included 904 patients with 1,045 CDI episodes, 151 (8%) patients with 490 samples who initially had CDI but the subsequent episode did not meet the case definition and 382 (19%) patients with 440 samples who

never met the CDI case definition. When RT were reviewed by CDI origin and case type, no difference was observed between healthcare associated (HA) and community associated (CA) groups for the commonest RTs. CDI testing was requested by clinicians in only 22.4% cases. The majority of CDI was HA (82.2%) with more females affected than males (OR 2.3 $p<0.01$). The rate of CDI recurrence was 9.1%. Fidaxomicin as first line CDI treatment significantly reduced the hazard ratio associated with time to recurrent CDIs. Over the decade, the quarterly CDI rate did not vary significantly, however, community-associated (CA)-CDI increased. HA CDI was highest in January, March and July. There was no year without a CDI outbreak. RT 014 dominated as well as RT 078, 005 and 015 in both HA and CA CDI. The average LOS differed significantly between the HA (67.1 days) and the CA (14.6 days).

Discussion and Conclusion

Despite rigorous CDI IPC programmes HA-CDI rates have not changed, even when more sensitive testing methods were introduced, whereas CA-CDI is at its highest in a decade. These findings underpin the importance of using prospective, multidisciplinary surveillance to inform local decision making. The convergence of ribotypes between HA and CA CDI as well as the onset of CDI symptoms in the community question the traditional view of CDI as a hospital issue. Further research to trace circulating RTs between healthcare facilities and the community is needed.

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1 Introduction

Healthcare associated infections (HAI) are potentially preventable infections and cause significant morbidity and mortality. The emergence of highly transmissible and multi-drug resistant HAI underpins the importance of preventing spread within healthcare facilities (HCF) to protect patients. HAI are caused by many organisms and in turn are controlled in a variety of ways. Therefore, there is no 'one size fits all' solution for infection prevention and control (IPC). Hospitals are under increasing scrutiny from the public and face pressures to meet national HAI standards and key performance indicators (KPI) which are used by the Health Services Executive (HSE) in Ireland to benchmark and assess hospitals' performance. In Ireland, many national standards and guidelines for HAI prevention and control exist. Those published by the Irish Health Protection Surveillance Centre (HPSC) and the HSE Antimicrobial Resistance and Infection Control (AMRIC) programme provide recommendations for surveillance and specific IPC and/or clinical practices. National standards published by the Health Information and Quality Authority (HIQA) promote safe and effective IPC environments within HCF. Monitoring compliance with these standards is a statutory responsibility of HIQA.

Clostridioides difficile is a Gram-positive, anaerobic, spore-forming, toxin-producing bacillus**.** *C. difficile* pathogenicity is principally mediated by two exotoxins: toxin A (TcdA) and toxin B (TcdB). *C. difficile* infection (CDI) is the leading cause of hospital-acquired infectious diarrhoea with a global incidence ranging from 1.1 to 631.8 per 100,000 population (1). CDI imposes a considerable burden on patients including debilitating and profuse diarrhoea, prolonged hospital delay, stigma and a delay in return to normal daily activities of living. It is also associated with significant economic costs (2). The reported incidence of CDI has increased in many countries, including Ireland (3, 4). The global increase in incidence and severity of CDI over the last two decades is linked to the emergence of certain lineages, including the epidemic PCR ribotype (RT) 027. CDI has been classified as an urgent public health threat by the Centre for Disease Control and Prevention (CDC) and in 2017 was associated with $1 billion attributable healthcare costs in the USA (5). In Europe, CDI is a common HAI, responsible for one in twenty HAI and 48% of gastrointestinal HAI (6). CDI risk factors include older age, comorbidities and most notably, broad-spectrum antibiotic use. CDI is potentially preventable and can disrupt hospital services with bed closures and postponed procedures (2). This becomes particularly pertinent in hospitals such as Beaumont Hospital, Dublin, with predominant multi-bedded bays and shared bathrooms for up to six patients. The spore forming nature of *C. difficile* complicates its' prevention because of resistance to many disinfectants. The consequences of CDI include an acute diarrheal illness, chronic bowl disease, life changing surgery and sometimes, death. Recurrent CDI is as an episode of infection that occurs within eight weeks of a previous

episode and in itself is a risk factor for further episodes of recurrent CDI. In comparison to the first episode of CDI, recurrent CDI is associated with significantly higher healthcare costs and prolonged hospital stay (7).

It is recommended that in the laboratory only unformed stools should be tested for *C. difficile* (8). The type of test used by any laboratory mainly depends on cost, the technical skill required and turn-around times. The use of a two-step algorithm for CDI diagnosis is recommended (9). A single stand-alone test is not recommended because of its inadequate positive predictive values at low CDI prevalence. Samples without free toxin detected by toxins A and B enzyme immunoassay (EIA) but with positive glutamate dehydrogenase EIA, nucleic acid amplification test or toxigenic culture results require clinical evaluation to distinguish CDI from asymptomatic carriage (9).

Preventing HAI, including *C. difficile,* is one of the primary goals of a hospitals' Infection Prevention and Control Team (IPCT)(10). To do this, systematic ongoing HAI data collection is needed i.e. HAI surveillance. HAI surveillance is collected by IPCTs within hospitals to monitor spread and location of infections, trend incidence of HAI over time and evaluate the efficacy of implemented prevention measures. On a broader level HAI surveillance data can be used to inform policy and facility planning at a local, regional and national level. Epidemiological surveillance has been described as "*the systematic collection, analysis and dissemination of health data for the planning, implementation and evaluation of public health programmes*" (11). The usefulness of a surveillance system should be measured by whether it leads to IPC or a better understanding of adverse health events, and systems should be modified accordingly after such a review. Attributes of quality for an epidemiological surveillance system include: 1) sensitivity; 2) specificity; 3) representativeness; 4) timeliness; 5) simplicity; 6) flexibility; and 7) acceptability (11).

C. difficile infection in Ireland

In Ireland, CDI has been notifiable since May 2008, with healthcare-associated (HA) CDI rates per 10,000 bed days used (BDU) being used as a national KPI since April 2014. A national enhanced CDI programme has been in place since 2009 with 97% of all tertiary and general hospitals taking part since quarter 1 2012(4, 12). In 2020, the CDI national crude incidence rate was 31.8 /100,000 population and the HA-CDI rate was 2.4 /10000 BDU (4). Aside from 2019, when a number of hospitals reported hospital-associated outbreaks due to a strain designated as RT 002, there has

been a trend in HA-CDI reduction with a concurrent rise in community-associated (CA) CDI. Until recently, Ireland lacked a national *C. difficile* reference laboratory, hence, limited national information on the epidemiology and clinical consequences of circulating *C. difficile* RT was available. Only 22% of CDI cases reported in 2020 had associated ribotyping data, with 078, 014, 002 and 020 being the most common (4).

Infection Prevention Control and CDI testing in Beaumont Hospital

The hospitals IPCT uses evidence-based practice and national guidelines to prevent and control HAI. The mission statement of the IPCT states that "*The aim of the IPCT, with the support of all within the hospital, is to reduce the risk of infection through education, surveillance and action. This can be achieved using evidence-based practice and guidelines. The IPCT seeks to provide a management structure and service compatible with modern standards and in line with national strategies."* Adherence to these guidelines and standards are measured by conducting regular audits of practice and by reviewing surveillance data. Efforts continue despite considerable capacity, infrastructural and financial pressures and in the absence of a plan for significant refurbishment and expansion of capacity, including more single rooms. IPC practices in Beaumont Hospital are continually changing and have become more integrated with antimicrobial stewardship, patient safety and quality improvement (QI) programmes.

The Department of Microbiology in Beaumont Hospital provides daily onsite *C. difficile* laboratory testing using a two-step protocol. Beaumont Hospital has had a comprehensive multidisciplinary CDI IPC programme for over a decade including clinical antimicrobial stewardship rounds and a hospital-based QI programmes targeting CDI prevention (13). Positive *C. difficile* results are phoned daily by the clinical microbiology team (CMT) to discuss relevance, case type and recommended management plans. Patients are isolated with Contact Precautions and on discharge; hydrogen peroxide decontamination (HPV) of the room is performed prior to new patient admission.

The hospital's CDI surveillance programme has evolved over a number of years with a centralised database established in 2012 to facilitate greater multi-disciplinary input and broader data collection. This database currently stores information on over 3,000 *C. difficile* positive laboratory records dating from 2008. Data sources collated in the database include laboratory records, patient

administration system data (PAS), CMT data, infection control nurse (IPCN) data and information on CDI treatment.

New cases of CDI undergo weekly multidisciplinary review at the IPCT meeting which includes discussion regarding assignment of case definitions and management of CDI clusters and outbreaks (Appendix 1). Specimens are prospectively sent to the Leeds Regional Public Health Laboratory, UK for ribotyping. RT data is used to investigate any potential inter-hospital cross transmission. The CDI database is quality assured monthly by a consultant microbiologist and surveillance scientist. Routine data collection includes information on CDI patient demographics (age, sex) hospital length of stay and outcome on hospital discharge as well as information on the CDI disease type (origin of infection, onset of infection and severity of disease), CDI management, and RT. The CDI database is, thereafter, used for local and national reporting.

Narrative overview of CDI surveillance processes

To inform this research, an exploration of the CDI IPC surveillance literature was performed, to identify CDI surveillance methodologies in other centres, including if multidisciplinary teams such as ours were involved in the surveillance process and to investigate the impact of differing surveillance processes on CDI rates and IPC workflow and identify best practices to ensure surveillance processes in Beaumont Hospital are adequate. A literature search was conducted in PubMed, Cinahl, Embase and Cochrane databases using keywords, synonyms and subject headings. Medical Subject Headings (MeSH) headings were used in PubMed and Cochrane and Emtree headings were used in Embase. Certain qualifiers limited search parameters so as to identify studies comparable to the acute hospital setting and included:

- Studies published between January 2017 through to August 2022, to identify more recent results
- Studies published in English
- Studies reporting trends of CDI in acute hospitals as well as regional and national reports in adult populations

Key words selected were:

- *Clostridioides difficile* infection
- *Clostridium difficile* infection
- Infection prevention control

- Nosocomial
- Healthcare associated
- Rates
- Incidence
- Surveillance
- Epidemiology

Studies with time periods of less than one year and studies limited to specific patient cohorts/ specialties, e.g., surgical patients only, were excluded.

A total of 402 papers were identified with 58 duplicate records removed leaving 344 papers for inclusion. Included reports were reviewed for approaches to CDI surveillance, lessons learnt and main findings on CDI incidence trends. This narrative review below provides an overview of the key themes arising from this literature including a critical appraisal, and highlights areas requiring further research. The main themes identified were (i) Surveillance of CDI: the benefits and limitations of predefined definitions; (ii) automated CDI surveillance; (iii) Quality Improvement based CDI surveillance; (iv) Reports from hospital based CDI surveillance programmes; (v) regionally reported CDI surveillance; and (vi) nationally reported CDI surveillance.

(i) Surveillance of CDI: the benefits and limitations of predefined definitions

A set of surveillance definitions and criteria for CDI has been published by the HPSC, European Centre for Disease Control (ECDC) and CDC (5, 6, 8). These definitions recommend that patients with onset of symptoms two or more days after admission to HCFs be classified as HA CDI with the main objective of facilitating a standard approach to surveillance and to enable comparison between HCFs. In Ireland it is recommended that CDI surveillance should collate laboratory and clinical data (8). One British study using this approach found data collection and discussion time with data collection ranged from 30–90 minutes per case and further multi-disciplinary discussion added a further 15–30 minutes per case. Despite the additional workload the authors supported this approach stating it has had a positive impact on controlling case numbers (14).

Two studies investigated the appropriateness of the time cut-offs used in CDI case definitions for assignment of HA and recurrent CDI status. In a 2018 study, the authors conducted a sensitivity

analysis by varying the times used to assign HA CDI. The authors concluded that the two-day cut off overestimates HA CDI and suggested using either a five or six day cut off for the HA CDI category (15). Likewise, a second study also recommended a day five cut off for determination HA CDI *versus* CA CDI (16). One study, investigating the appropriateness of using an eight-week window to assign a recurrent episode of CDI, suggested that a 20-week window may be a more appropriate timeframe (17).

In the absence of a definition-based approach, rates of CDI can be based solely on *C. difficile* laboratory results. In these situations, the CDI rate is precedented by the testing algorithms and platforms employed. One US study observed that reported HA CDI rates would double if the more sensitive method of PCR testing alone was used (18). A second study concluded that such an approach led to an over reporting of HA CDI by 38% (19). Other studies reported successful reduction in HA CDI by either by refining clinical criteria for testing for CDI and / or by changing to a less sensitive diagnostic platform (19-24).

(ii) Automated CDI surveillance

Surveillance of CDI using laboratory data in tandem with clinical data, which considered the gold standard of CDI surveillance, is time consuming, labour intensive, and challenging to implement consistently across HCF. A number of studies have proposed using automated approaches for CDI surveillance where laboratory data is linked to International Classification of Diseases (ICD) patient data. One six-month US study reported that using this approach of combining laboratory results to ICD codes to automatically assign CDI case type matched 80% of case findings when the corresponding clinical data-based surveillance system was used and was an adequate proxy measure of CDI for public reporting purposes (25). The Canadian experience reported by Almond *et al.,* where laboratory data matched to ICD code data found this approach identified nearly 97% of those identified using the traditional gold standard surveillance method. This population-based study was conducted from 2015 and 2017 and included all patients > 1 year old admitted to the health services in Alberta (16). One Spanish hospital reported their experience over five years of a multimodal training program for improving CDI surveillance and prevention. They reported that using a diagnostic algorithm found a higher incidence of CDI and those with active CDI case finding noted higher rates of HA CDI (26).

Another US study explored the possibility of using an automated surveillance approach linking laboratory data to hospital administrative data. In their findings the authors reported that they "*assessed the validity of using a laboratory-identified method for capturing HA-CDI cases in a large population cohort of over 4 million people over a 2-year period. The laboratory surveillance method is highly sensitive, and not overly specific. If jurisdictions were to rely exclusively on the laboratory method, they would need to consider that higher hospital-acquired rates may be observed*" (27). Gase *et al.,* also surmised that "*because of the substantial morbidity, mortality, and cost burdens of CDI, the use of standardized definitions and data collection methods is needed to monitor the incidence of disease and effectiveness of control measures. Public reporting will likely impact infection control practices within facilities and allow evaluation of clusters, rate trends, and costs associated with the disease*". Bearing this in mind, the use of such automated approaches is questionable given that it is recommend that policy makers should "*ensure that the evidence is objective, in order to ensure that such evidence is not misused to justify decisions that should be made (or rejected) on the basis of other considerations*" and" *recognise that good evidence is likely to result in better policy decisions, but good policy cannot be deduced from evidence alone.*" (25).

(iii) Quality Improvement based CDI surveillance

HAI surveillance strategies can be integrated with QI principles, techniques, and management tools to considerably strengthen surveillance programmes and IPC approaches. These approaches would use a cyclical approach to lean process improvement. Improta *et al.,* used this approach (Figure 1) over two years to successful reduce the number of patients colonised with sentinel bacterial (28). However reports of similar approaches specific to CDI are limited and did not emerge as a theme.

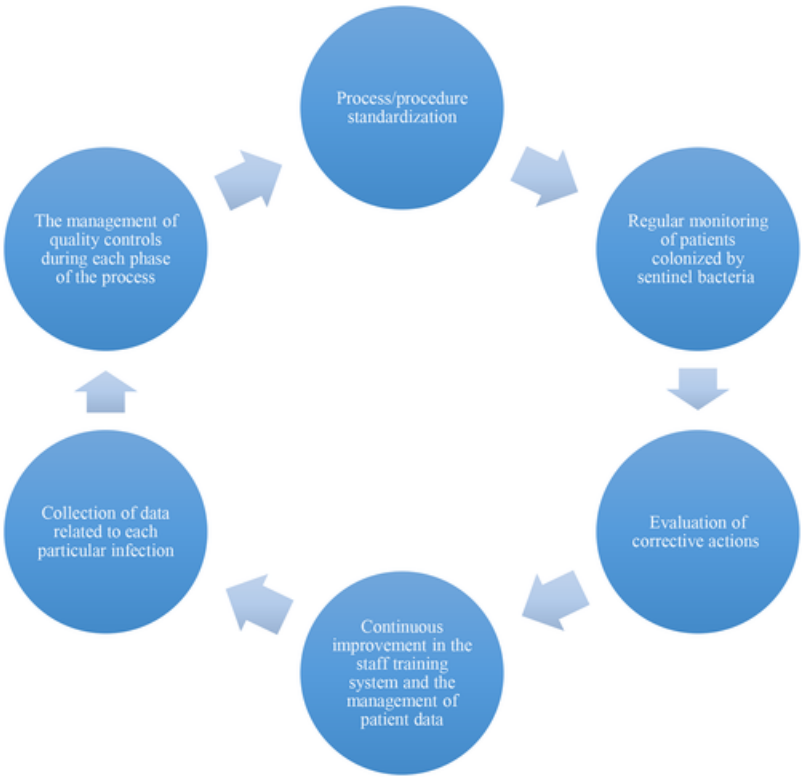


Figure 1: Quality control plan cycle

A summary of CDI epidemiological studies meeting the inclusion criteria where QI was mentioned are as follows. One US based study assembled a clinical nurse specialist lead multidisciplinary performance improvement team to facilitate early recognition of patients with suspected or diagnosed CDI and thus prevent onward spread. The team included administration, clinical nurses, IPC, nurses from the quality department, dietary services, environmental services, antimicrobial support network, and pharmacy. This study detailed their plan, i.e., do, study, act (PDSA), a QI approach and then reported a reduction in CDI rates by 2.4% over a two-year period. While successful outcomes were reported, the rates were expressed as percentage positivity of the facilities occupancy (29). A second US study also described their experience of how a multidisciplinary team implemented a CDI performance improvement project. While success in decreasing HA CDI were reported, rates were again presented as percentage incidence rates and the authors focused on testing algorithms (30).

A large multi-centre study over four years in the US used a multifaceted approach from a public health perspective where hospitals were invited to participate in a QI initiative to identify and address gaps in IPC approaches to CDI. Intervention hospitals had a 45% greater *C. difficile* reduction compared with control hospitals (31).

(iv) Reports from hospital based CDI surveillance programmes

A number of studies focusing on CDI prevention in the hospital setting were identified. One study in an Italian hospital over a two-year period found that multi-pronged strategies have proven effective in reducing CDI from 6.27 per 10,000 bed days used (BDU) in 2016 to 2.76 during 2018. The strategies adopted focused mainly on patient isolation, reinforcement of proper hand hygiene techniques, antimicrobial stewardship and environmental disinfection (32).

A US study investigating the implementation of electronic hand hygiene monitoring and performance improvement interventions in a 555-bed urban safety-net level I trauma centre in Denver over three years found an improvement in hand hygiene was associated with a reduction in HA-CDI cases. This study had before and after intervention periods of 18 months and reported that the impact of the intervention was limited only to CDI with no observed impact on other HAI rates (33).

A study at a hospital in Pennsylvania showed how the successful introduction of a hydrogen peroxide vapour (HPV) decontamination system successful reduced HA CDI from 4.6 to 2.7 per 10,000 patient days. However, there were a number of shortcomings that may make coming to firm conclusions more difficult, namely that a CDI case was defined as a *C. difficile* positive stool diagnostic test on unformed stool specimens, during the study period the HCF moved from a GDH assay plus enzyme-linked immunosorbent assay to a two-step algorithm of PCR followed by toxin EIA, and finally, HA CDI was assigned where there was no history of recent *C. difficile* in the prior eight weeks and the laboratory test was positive after three days of hospitalization (34).

Another US-based study over a two-year period (2017-19) used a chart review to verify CDI case type, however, samples collected before day four of hospitalisation were excluded. Their testing algorithm advised not to test stool samples for CDI where patients had received laxatives. They author also substituted from PCR testing to a cell cytotoxicity assay for stool specimens that were EIA negative and GDH positive, a less sensitive testing method. Unsurprisingly this combined laboratory and clinical approach resulted in a decrease in CDI and was felt to identify fewer false positive CDI cases (35).

A study evaluating the efficacy of electronic hand hygiene monitoring systems in reducing HA CDI used ICD codes to measure and assess changes in CDI over time. This five-year study used a mixed analysis qualitative approach (to identify potential barriers to hand hygiene) as well as a quantitative approach to track and assess changes in CDI rates. The study had a low participation rate (33%). One hospital reported hand hygiene compliance increased by 20%-30% and HA-CDI decreased by 70%, however, these results were difficult to maintain in the long-term (36). A similar mixed methods approach over a 36-month period in three hospitals assessed CDI rates from a national database before and after a targeted assessment strategy to reduce CDI. The authors reported that the CDI incidence rate fell by 12% and suggested that such an approach "*can serve as a model of coordinated and targeted prevention efforts*" (37).

A six-year US study used an interrupted time series approach to investigate the efficacy of IPC measures to combat CDI. Their findings showed that "*Multiple aggressively implemented infection control interventions targeting CDI demonstrated a disappointing impact on endemic CDI rates over 6 years"*. The authors also acknowledged that "*Diagnostic stewardship successes appear to be driven by a decrease in testing volume rather than prevention of actual disease"'* (38).

A Swedish study investigated the impact of reducing cephalosporin use as a strategy to decrease HA CDI in two hospitals, one with an antibiotic stewardship programme limiting cephalosporin use, between 2007 and 2015. Their main conclusion was that "*Decreased use of cephalosporins is an effective strategy to decrease HCF-CDI incidence over time in a setting with high incidence and low antibiotic use"*. However, this study used all laboratory positive *C. difficile* results with the added caveat that three different laboratory tests were used during the study period which varied in sensitivity and specificity (39).

(v) Regionally reported CDI surveillance

A 2019 Californian study reviewed findings of a national healthcare safety network between 2014 and 2017 for Orange County and found that "…..*following implementation of a regional, coordinated CDI prevention collaborative in Orange County, California, we observed a statistically significant 4% monthly decrease in HO-CDI rates*", however, this was a voluntary study and not reflective of all facilities in the region (40).

One Canadian study reported that between 2008 and 2015 CA CDI in the Quebec province increased significantly despite an overall decrease in HA-CDI incidence and suggested that such a divergence suggests a need to devote more attention to CA-CDI (41). This finding was further supported by Xia *et al* where they reported that in *"Canada overall, the rate of HA-CDI has been decreasing and the rate of CA-CDI has been increasing, although this calculation was impeded by discrepancies in CDI-related definitions among provincial surveillance programs. Nationally-adopted common definitions for CDI would enable better comparisons of CDI rates between provinces and a calculation of the pan-Canadian burden of illness to support vaccine decision-making"* (42).

A 15-year (1997 to 2012) study from a Scottish health board serving 11% of the Scottish population used microbiology and electronic laboratory records to obtain numerator data on CDI. This study utilised large data repositories and successfully showed a decline in CDI which coincided with a rapid decline in multidrug-resistant hospital epidemic ribotypes which was preceded by an antibiotic stewardship programme. However, algorithms were used to assign onset as linkage to hospital episode data was not feasible (43). A similar approach was taken in a study performed in Oxford and Leeds with similar findings (44).

In Italy a regional study conducted between 2010 and 2015 showed a high variability in CDI rates between hospitals. The hospitals included large urban hospitals and smaller outlying hospitals. Interestingly in this study the "*incidence of CDI in the smaller hospitals varied considerably over the years due to the occurrence of clusters which, on account of the lower denominators (patients-days), had a marked influence on the annual rates. On the other hand in the larger hospital the CDI rates were stable over time"* (45).

(vi) Reports from National CDI surveillance programmes

The implementation of a robust national surveillance system has been successful in Ireland with laboratory based surveillance using standardised CDI case definitions in place since 2008 and enhanced surveillance with additional details of CDI origin and onset since 2009. However, this experience has not been replicated elsewhere (4).

Until 2018, there was no systematic, annual surveillance for CDI in France. Instead point prevalence surveys (PPS) were repeated at regular intervals, as well as data from the *C. difficile* national reference laboratory, which focuses mainly on severe cases and outbreak investigation. In 2016 a simple surveillance tool, 'DIFTEC™', was developed to evaluate diagnostic and management of CDI in France. The main findings of a review of two years of 'DIFTEC' data (2016-17) showed most CDI cases were HA (78%) with rates of recurrence and mortality similar to those reported in the literature (46). However, changes in incidence were not explored. A second study analysed numerous CDI data sources including: a CDI incidence survey conducted annually from 2016-18, PPS data (conducted every five years), data from the national hospital coding system, data from the national CDI reference laboratory (whose primary function is follow the epidemic clone 027 and the potential emergence of more epidemic-prone or more virulent clones), and notifications to the national HA infections early warning and response system, all utilising different case definitions. The main finding of this study found "*that despite an increase of CDI incidence between 2010 and 2016, the incidence of CDI cases in France in 2016 remains below the European average"* (47).

In conclusion, there are a number of studies reporting trends of CDI over prolonged periods of time, however, these tend to be population-based studies using national databases. The appropriateness of using a 48-hour window to discern HA and CA has been questioned but conclusions were based on statistical findings. Reports of automated based surveillance, combining laboratory, PAS and ICD systems, as a possible alternative to a manual multi-disciplinary approach, are not without fault. Hospital-based reports of CDI provide useful information but tend to focus over shorter time periods and on reporting impacts of implemented quality improvement approaches. This literature search indicated that extensive research has been published on the incidence of CDI both at local, national and international level, however, little has been published on a standardised multi-disciplinary manual approach over longer time periods as is the approach in Beaumont Hospital.

2 Rationale for this study

The CDI surveillance database in Beaumont Hospital has evolved since it was first introduced to meet the changing data collection needs of the IPCT. Data submission for the national enhanced CDI surveillance programme co-ordinated by the HPSC is also extracted from the database. However the systems attributes have not been appraised in terms of the seven characteristics recommended by Thacker *et al* (11). To date, reported CDI epidemiology tends to focus on short to medium time periods (3, 48-50). The CDI surveillance systems have been *in situ* in Beaumont Hospital for over a decade.

The main aim of this research was to retrospectively investigate multi-disciplinary IPCT data collected prospectively on CDI trends in hospitalised patients attending Beaumont Hospital over ten years (2012 -2021) and to investigate patient, hospital and other factors predicting a first episode of CDI and predicting time to recurrence. In addition, the attributes and continued feasibility of the current CDI surveillance approach was evaluated.

3 Objectives

Specific objectives

1. To investigate and understand time trends in the incidence and recurrence of CDI in patients attending Beaumont Hospital between 2012 and 2021
2. To investigate patient, hospital and other factors predicting time to recurrence and predicting severe cases of CDI. Factors of interest include:

   Patient related factors

   a. Age by CDI type
   b. Sex by CDI type
   c. Length of hospital stay before onset by CDI type
   d. Antimicrobial exposure at time of onset by CDI type
   e. Previous negative stool samples tested for CDI in the 12 weeks before the first positive sample

   CDI related factors

   f. Origin of infection
   g. Ribotypes (phenotypic profile of samples) by CDI type
   h. CDI treatment prescribed by CDI type
   i. Increased sensitivity of testing platforms

Secondary objectives

i. To investigate the seasonality of CDI in Beaumont hospital over the ten years
ii. To use a reflexivity approach to review the motivation, benefits, limitations and context of the current multi-disciplinary approach to CDI surveillance in place in the hospital.

4 Methods

4.1 Study details

Trends in CDI were investigated using an observational cohort study. CDI data collected prospectively was retrospectively extracted from the centralised CDI database from 1st January 2012 to 31st December 2021.

Monthly numbers of bed days used (BDU) and admissions over the ten years were used as denominators and were provided by the hospitals' information management department. They also provided information on the patients' average age by specialty, average length of stay (LOS) by speciality, and hospital activity levels over the 10 years. The onset and origin of cases were assigned as per case definitions in line with Irish and European CDI guidelines (13, 51) (Appendix 1). The reporting of this observational study followed STROBE guidelines (52).

4.2 Study setting

Beaumont Hospital is an 800 bed, tertiary referral teaching hospital based in North Dublin, Ireland with specialties in neurosurgery and kidney transplantation. It is the second-largest hospital in the Republic of Ireland. The hospital has over 800 beds; 136 single rooms, 77% with *en suite* facilities and 12 airborne isolation rooms. Most accommodation is multi-occupancy with one shared bathroom amongst up to six patients. Over the study period there was a mean of 24,494 inpatient admissions annually, 76% acute (emergency) admissions. In 2021, the proportion of emergency admissions increased to 80%. The annual average inpatient LOS over the study period ranged from 9.1 to 9.9 days (mean 9.47 days). Renal patients had on average the shortest LOS (mean 6.5 days, range 5.9 to 6.9 days) and Medicine for the Elderly the longest (mean 23.4 days, range 16.1 to 30.3 days) (Appendix 2). The average age of Beaumont Hospital inpatients annually ranged from 55.2 to 60.6 years (mean 57.8 years) (Appendix 3).

Beaumont Hospital is a member of the Royal College of Surgeons in Ireland (RCSI) Hospital group. The hospital's Department of Microbiology provides a comprehensive range of diagnostic and clinical services to Beaumont Hospital, other institutions and the surrounding community. The

clinical microbiology team (CMT) provides advice concerning the clinical significance and IPC implications of isolates, antimicrobial therapy and management of sepsis.

4.3 CDI testing and infection prevention and control (IPC)

All stool samples which take the shape of the container, that are received in the microbiology laboratory, are tested daily onsite for *C. difficile* toxin irrespective of clinician request. From Q1 2015, this has consisted of a two-step protocol (*C. difficile tcdB* PCR and if positive, enzyme immunoassay (EIA) for *C. difficile* toxin). Prior to Q1 2015, the two-step protocol consisted of glutamate dehydrogenase / *C. difficile tcdB* PCR testing. The laboratory does not culture stool specimens. As a result *C. difficile* antimicrobial susceptibility data is not available or reported. This had been in place since 2008. Positive results are phoned daily by the clinical microbiologist to discuss relevance and recommend management plans. The records of any *C. difficile* positive samples in the previous week are discussed at the weekly IPCT with information from IPC, CMT as well as previous CDI history and recent hospital admissions are jointly reviewed. A decision as to CDI case type, in accordance with national case definitions is agreed. This information includes details of other possible causes of a patients symptoms. The surveillance scientist ensures the database is reflective of agreed changes. Any discrepancies between data sources are reviewed by the consultant on call and a final decision as to a patient's case type made by them.

The first positive sample per patient, irrespective of case type, are prospectively sent to the Leeds Regional Public Health Laboratory, UK for ribotyping which is used to investigate potential inter-hospital cross transmission.

CDI surveillance:

The Hospitals CDI surveillance programme has evolved over a number of years with standardised CDI surveillance first established in 2008, in line with national protocols and definitions, and centralised in 2012. One of the primary roles of the Hospitals surveillance scientist is to develop and implement surveillance processes for infectious disease surveillance. The HPSC provides a recommended data capture form and a protocol for completion of this form ("Protocol for Completion of Enhanced Surveillance) (13). The recommended data collection form as well as algorithms on how to assign CDI case type and CDI origin are provided by the HPSC (Appendices 4 to 6). How data collection

processes are implemented are left to hospitals to be decided locally. The protocol provided by the HPSC says that the form (shown in Appendix 4) can be used to collect data which can then be transcribed into an excel file, or the data can be entered directly into an excel file. Once completed this excel file is submitted to the HPSC. Hospitals are provided with feedback reports in the form of excel files quarterly. These files can be used locally by hospitals to compare their data over time (trend) as well as to other hospitals of similar types to national data overall (benchmarking)

When CDI surveillance was first required, CDI data was captured in standalone excel files with data transcribed manually. IPC and surveillance scientists kept and maintained records locally with IPCNs capturing onset and isolation information in their files. Surveillance transcribed laboratory results and CMT case type. The complexity and requirements of CDI surveillance became particularly evident in 2008 when the hospital managed a significant outbreak of the hypervirulent strains RT 027 and RT 078 (53). Concerted efforts by the IPCT were undertaken to streamline and centralise surveillance. Constrained funding meant that members of the team were limited in the software options available for surveillance. In 2012 a centralised database was developed to identify new laboratory records of CDI automatically and accurately. Access software™ (Microsoft, Redmond, WA), widely available software, was used to house laboratory results. The database was further developed and tailored to enable user-specific access so that requirements of the IPCT members were met. The database has continued to be developed and is now a repository of clinical, IPC, RT and patient outcome data.

The CDI database is used to generate lists of all PCR positive CDI results in the previous week, irrespective of the EIA result. This list is circulated before the weekly IPCT meeting, with multi-disciplinary input from clinical microbiology, IPC and epidemiology in advance of the meeting and is then followed by final MDT discussion at the weekly meeting. The list circulated provides EIA result details. Agreed data is then finalised in the database by the surveillance scientist and cases notified to public health as appropriate. Data is quality assured monthly with all *C. difficile* cases in the previous month discussed by a consultant microbiologist and the surveillance scientist with review of clinical microbiology consultation notes.

The following data on all *C. difficile* positive stool samples is prospectively entered into the centralised CDI database: patient demographics (age, sex,), admission details (length of hospitalisation, emergency/elective, admitting speciality), details of *C. difficile* testing results,

assignment of CDI case or does not meet the case definition 'DNMCD' and CDI case details (new/recurrent, origin and onset, severity, and patient outcome at discharge) (Appendix 1). Since 1st January 2016, data on antimicrobial exposure before CDI onset and details of anti-microbial CDI treatment has been captured. Patient outcome at time of discharge is captured from the PAS. Information regarding recurrent CDI is dependent upon the patient being an inpatient or within the catchment area of the Hospital at time of symptoms onset.

Increased incidence, i.e., two or more positive CDI patients in clinical areas, are discussed at weekly IPCT meetings and as appropriate with senior management. Trigger tools are activated in these areas (54). Outbreaks are declared on identification of a third patient and an outbreak control team is convened. Retrospective outbreaks can be identified on review of ribotyping results. Outbreak summary data are stored by the IPCT and associated line list of cases are stored in the centralised database.

Over the study period the following occurred:

1. Q1 2013: Introduction of hydrogen peroxide vapour decontamination of single rooms following CDI patient discharge
2. Q1 2015:
    - Ward review of all CDI patients by clinical microbiologist
    - Introduction of PCR/EIA testing algorithm
    - Fidaxomicin as first line anti-microbial CDI treatment (after review by clinical microbiologist)
    - Rolling ward programmes of commode, mattress and bedpan replacement.
3. Q1 2019: Hospital-wide outbreak of *C. difficile* RT002
4. Q2 2020 - 2021**:** COVID-19 pandemic

4.4 Ethics approval

Included data are collected routinely as part of clinical management and no patient identifiable data were included. The study was conducted by researcher who is a healthcare professional employed by the hospital and has access to records as part of their duties. The study was approved by the Beaumont Hospital (Medical Research) Ethics Committee in June 2019 (REC reference 19/33) and was also registered as a clinical audit by the Hospitals' Clinical Audit and Governance Department in April 2022 (Audit number 22170A01).

4.5 Data analysis

4.5.1 Part 1: Sample and RT overview

All samples, irrespective of CDI case or DNMCD status, were included in the first analysis. The following data was removed from the database and not analysed:

- Repeat samples, i.e., where a patients' case classification remained unchanged from that assigned to their preceding positive sample
- Samples for external HCFs. In such cases communication of results is completed by the hospitals CMT, however, no clinical advice or IPC follow up is required by the hospital's IPCT as these are addressed by other agencies

Each patient had their samples group and categorised into either:

- Case only – all *C. difficile* samples taken from the patient were CDI cases
- DNMCD only – none of the *C. difficile* samples taken from the patient were CDI cases
- Case changing to DNMCD – first *C. difficile* sample (s) taken from the patient were CDI. Subsequent sample (s) were DNMCD
- DNMCD changing to a case– first *C. difficile* sample (s) taken from the patient were DNMCD. Subsequent sample (s) were CDI case(s)

Each patient's first sample with a recorded RT, irrespective of CDI case, was included in the ribotype review.

4.5.2 Part 2: Analysis by case type

The second analysis focused on data from CDI patients who had been admitted to the hospital and were known to meet the healthcare associated (HA) or community associated (CA) definition. The following data were removed from the dataset for this analysis.

- Patients assigned DNMCD
- Patients without an admission to the hospital
- Samples from patients with CDI admitted from external healthcare facilities

The patient specific and disease related variables were investigated for differences between the HA and CA CDI cohorts were compared over the 10 years using the χ^2 and the Wilcoxon rank sum test. The age distributions in the two cohorts were analysed using five-year incremental age brackets. The age distributions within each cohort were examined as well as the proportion of CA *versus* HA within each age category. The ward and floor level of a patients location was at time of sample collection was available from the PAS. Correlation of incidence of HA CDI by hospital floor was completed.

Quarterly CDI rates are calculated per 10,000 BDU. This analysis approach has been recommended by the HPSC to standardise reporting and facilitate benchmarking (8). These rates were investigated using regression analysis. Beaumont's rates of CDI in the hospital per 10,000 BDU were compared to national CDI surveillance data reported by the HPSC and European CDI surveillance data reported by ECDC. The same CDI case definitions are used across all three CDI surveillance programmes (Beaumont Hospital, HPSC, ECDC) (Appendix 1). Predictor variables for CDI were investigated using a Poisson regression analysis for rates with adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CI) calculated. For continuous a Wilcoxon rank-sum test was conducted. An adjusted Cox proportional hazards regression model was used to examine time to recurrence and censored for those without recurrent CDI. Adjusted hazard ratios (HR) and 95% CI were calculated. To investigate the seasonality of CDI the monthly rates of CDI by origin for each of the ten years were used to calculate the monthly average rate for each month. The resulting trend line was investigated for significance by regression analysis. All analysis were performed using Stata version 16.1. Associations with a $p < 0.05$ were considered significant.

4.5.3 Part 3: Appraisal and review of the current CDI surveillance system

The current CDI surveillance processes in Beaumont Hospital are explained. This a narrative overview and takes into account what actions are required by members of the IPCT and when. The data collection and validation processes are also described.

5 Results

5.1 Part 1: Sample and RT overview

5.1.1 Sample overview

In total 1975 samples from 1437 patients were included. Table 1 provides a matrix of the number of samples per patient and the CDI case types assigned. This includes 904 patients with 1,045 episodes of CDI (either new or recurrent), 151 (8%) patients with 490 samples which moved between CDI and DNMCD and 382 (19%) patients with 440 samples who were DNMCD. The average number of positive samples per patient was one (range one to 11). Patients who did not move between CDI and DNMCD categories had on average one sample (average range 1 – 6 samples) whereas those who did, had on average three samples (average range 1 – 10.5 samples).

	CDI only	**DNCMD only**	**Interchangeable between CDI and DNMCD**	**Total**
Number of patients	904	382	151	1437
Number of samples	1045	440	490	1975
Median number and range of samples	1 (1 - 5)	1 (1 - 7)	3 (1 - 10.5)	1 (1 - 11)
Female	516 (57.1)	205 (53.6)	82 (54.3)	803 (55.9)
Median age – years (range)	73 (14 – 98)	77 (11- 99)	78 (35 – 97)	73 (11 – 99)

CDI, *Clostridioides difficile* infection; DNMCD, did not meet the case definition

Table 1: Number of samples per patient including patient demographics and case types assigned.

Of the interchangeable cases, 61% were CDI before DNMCND, with 39% (59 patients) the reverse. Patients who were DNMCD before CDI were mainly female (64%) with a mean age of 74 years (median 74 years, range 36 – 95 years). The mean time from DNCMD to CDI was 140 days with a median of 39 days (range 1 to 1204 days), which did not vary by sex. On review 80% of these patients went on develop HA CDI, 12% CA CDI and 9% fell into the category of being discharged 4-12 weeks from a HCF.

5.1.2 Ribotype overview

Ninety-five percent (1341) of patients had at least one sample sent for RT. A RT was not recovered for 130 (10%) of cases. Where a RT was reported, 014 and 002 predominated. Figure 2 shows the five most prevalent ribotypes identified by year. RT 014 was one of the top three RTs in all years bar 2015 and RT 002 was in the top three RT in seven of the 10 years.

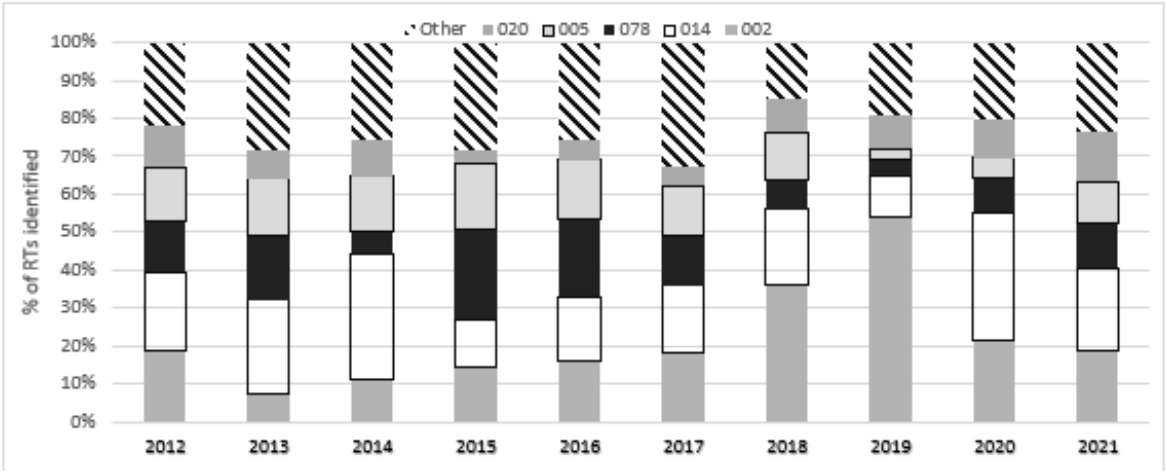


Figure 2: Frequency of most identified ribotypes by year, 2012-2021

Table 2 displays the colour coded frequency of the 10 most identified RT by year. The other dominant RT identified included 078, 005 and 015, all featuring annually in the top 10 RT, and RT 020 featured in eight of the 10 years. When reviewed by CDI origin and case type, no difference was observed between HA and CA groups for the commonest RT, i.e., 002, 014, 005, 020 and 078.

Top 10 Ribotypes	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
No. 1	RT 002 (14%)	RT 014 (13%)	RT 014 (17%)	RT 078 (12%)	RT 078 (12%)	RT 014 (13%)	RT 002 (23%)	RT 002 (40%)	RT 014 (21%)	RT 014 (14%)
No. 2	RT 014 (13%)	RT 078 (11%)	RT 005 (9%)	RT 005 (10%)	RT 002 (11%)	RT 002 (9%)	RT 014 (14%)	RT 014 (8%)	RT 002 (14%)	RT 002 (12%)
No. 3	RT 005 (11%)	RT 005 (10%)	RT 015 (9%)	RT 002 (8%)	RT 014 (9%)	RT 078 (8%)	RT 005 (9%)	RT 020 (7%)	RT 020 (8%)	RT 020 (8%)
No. 4	RT 015 (11%)	RT 015 (7%)	RT 002 (7%)	RT 011 (8%)	RT 005 (8%)	RT 015 (6%)	RT 020 (7%)	RT 056 (7%)	RT 078 (7%)	RT 005 (7%)
No. 5	RT 078 (9%)	RT 045 (7%)	RT 020 (6%)	RT 014 (7%)	RT 015 (7%)	RT 001 (5%)	RT 078 (6%)	RT 015 (4%)	RT 015 (6%)	RT 078 (7%)
No. 6	RT 020 (7%)	RT 011 (6%)	RT 012 (5%)	RT 207 (6%)	RT 017 (4%)	RT 005 (5%)	RT 015 (5%)	RT 078 (3%)	RT 005 (4%)	RT 015 (5%)
No. 7	RT 363 (5%)	RT 002 (5%)	RT 078 (4%)	RT 026 (5%)	RT 020 (4%)	RT 017 (5%)	RT 081 (3%)	RT 213 (3%)	RT 011 (4%)	RT 011 (4%)
No. 8	RT 023 (4%)	RT 012 (5%)	RT 103 (4%)	RT 015 (4%)	RT 023 (4%)	RT 026 (5%)	RT 106 (3%)	RT 005 (2%)		
No. 9		RT 020 (5%)	RT 137 (4%)	RT 070 (4%)	RT 056 (4%)		RT 213 (3%)	RT 106 (2%)		
No. 10					RT 011 (3%)			RT 021 (2%)		

Table 2: Frequency of the 10 most identified ribotypes by year, 2012-2021.

5.2 Part 2: Analysis by CDI case type

5.2.1 First episode of CDI

An overall summary table of patients with their first episode of CDI is presented in Table 3. Of the 1045 CDI cases above, four patients were admitted from another HCF and excluded from this analysis. The majority of CDI was HA (82.2%) with more females affected (OR 2.3 p<0.01). CDI testing was requested by clinicians in only 214 (22.4%) cases. Forty-six (4.8%) patients had a positive *C. difficile* laboratory results that DNMCD in the preceding 12 weeks. The mean LOS was 57.9 days (Interquartile rage (IQR) 11 to 60 days), however, this differed significantly between HA and CA cohorts (p<0.01). Patients over 70 years accounted for greater than 60% of all CDI cases but the average age of CA CDI patients was nearly 10 years younger than for HA CDI (62 years versus 71 years, p<0.01). Acute admissions (87.2%) and healthcare onset (78.5%) were observed in the majority of cases. Approximately 2% of cases developed severe CDI and the all-cause mortality rate of CDI who were inpatients was 2.6%. From 2016 to 2021 CDI treatment data was available for 551 patients (57.7% of all patients reviewed) with 300 of 451 HA CDI (66.5%) and 57 of 100 CA CDI (57.0%), respectively, being prescribed fidaxomicin. Metronidazole was prescribed for 79 (17.5%) HA-CDI and 18 (18.0%) CA-CDI, vancomycin for 70 (15.5%) HA-CDI and 25 (25.0%) CA-CDI and combination therapy of vancomycin and metronidazole for two (0.4%) HA-CDI. No combination therapy was prescribed for CA-CDI. Notably, patients who had received recent antibiotics were five times more likely to develop CDI than those who did not.

				CA vs HA CDI	
	Total Patients N (%)	**Community acquired (CA) –CDI N (%)**	**Healthcare acquired (HA) -CDI N (%)**	**Odds Ratio**	**95% CI**
New CDI	954	169 (17.79)	781 (82.21)		
Recurrent CDI	87 (9.12)	7 (8.05)	80 (91.95)		
Clinician request for *C. difficile* test	214 (22.43)	25 (14.79)	189 (24.08)	1.83	(1.16 - 2.88)
Faecal specimens tested (no CDI request) [#]	740 (77.57)	144 (85.21)	596 (75.91)		
Previous positive result that did not meet the case definition* [#]	46 (4.82)	2 (1.18)	44 (5.61)	4.96	(1.18 - 20.76)
Female[#]	541 (56.71)	122 (72.19)	419 (53.38)	2.27	(1.57 - 3.27)
Male	413 (43.29)	47 (27.81)	366 (46.62)		
Admission type					
Emergency [#]	833 (87.32)	156 (92.31)	677 (86.24)	0.52[#]	(0.29 - 0.95)
Elective	121 (12.68)	13 (7.69)	108 (13.79)		
Healthcare onset CDI[#]	749 (78.51)	26 (15.38)	723 (92.10)	64.14	(32.79 - 129.40)
Community onset CDI	205 (21.49)	143 (84.62)	62 (7.90)		
Admission Speciality					
Gastroenterology	116 (12.16)	42 (36.21)	74 (63.79)		
Medicine for the elderly	128 (13.42)	10 (7.81)	118 (92.19)		
General medicine	258 (27.04)	53 (20.54)	205 (79.46)		
Renal	121 (12.68)	17 (14.05)	104 (85.95)		
Neurosurgery	49 (5.14)	0	49 (100)		
Oncology	75 (7.86)	9 (12.00)	66 (88.00)		

General Surgery	207 (21.70)	38 (18.36)	169 (81.64)

CI: Confidence Interval
IQR: interquartile range
*Positive *C. difficile* laboratory results that did not meet CDI case definition (DNMCD) in the preceding 12 weeks
#Indicates significance, p<0.05

Table 3: Overview of HA versus CA, first CDI, 2013 to 2021

General medicine (27.04%) and general surgery (21.70%) specialities had the greatest burden of CDI patients followed by medicine for the elderly (MFTE) (13.42%). HA CDI was observed as the dominant type of CDI across all specialities with 100% of cases in neurosurgical patients, 92.19% of MFTE and 85.95% of renal patients, being HA. Gastroenterology patients (36.21%) had the highest proportion of CA CDI.

Patients 34 years or younger were as likely to have CA CDI as HA CDI with HA CDI becoming more likely as age increased (Figure 3a). Patients aged under 65 years accounted for a 46% of CA CDI (versus under 65s accounting for 29% of the HA CDI cohort) (Figure 3b). In the age categories between 35 and 65 years the average odds ratio of HA CDI was 3.8 (versus CA CDI). This figure is skewed by the data for the 55 to 59 age category where HA CDI was seven times that of CA CDI, proportions comparable only to those in the 80+ age category. A review of this patient age-group revealed that males and females were equally affected (~50%) as well as the patient specialties including surgical (22%), renal (19%) and neurosurgical (18%).

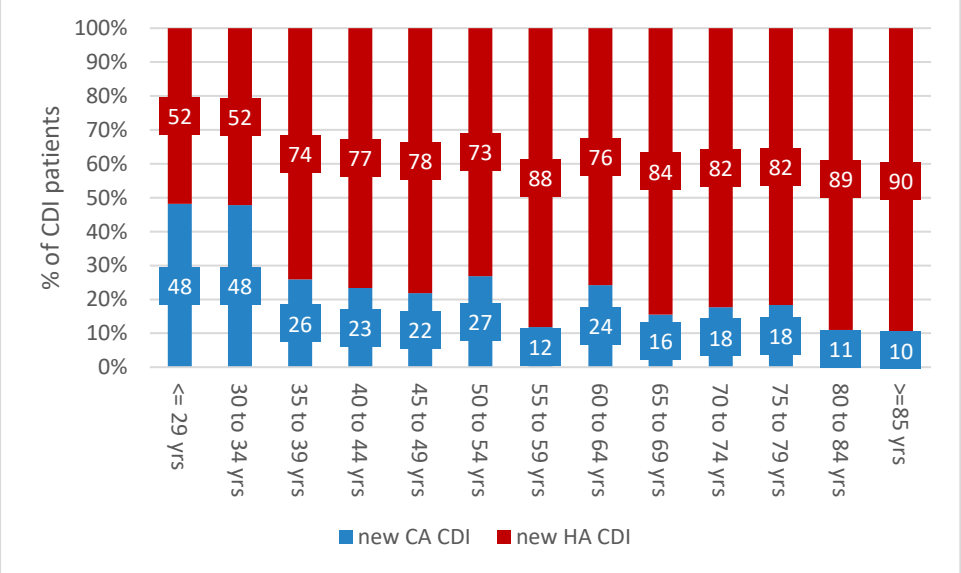


Figure 3a: Percent of first CDI by age group and origin

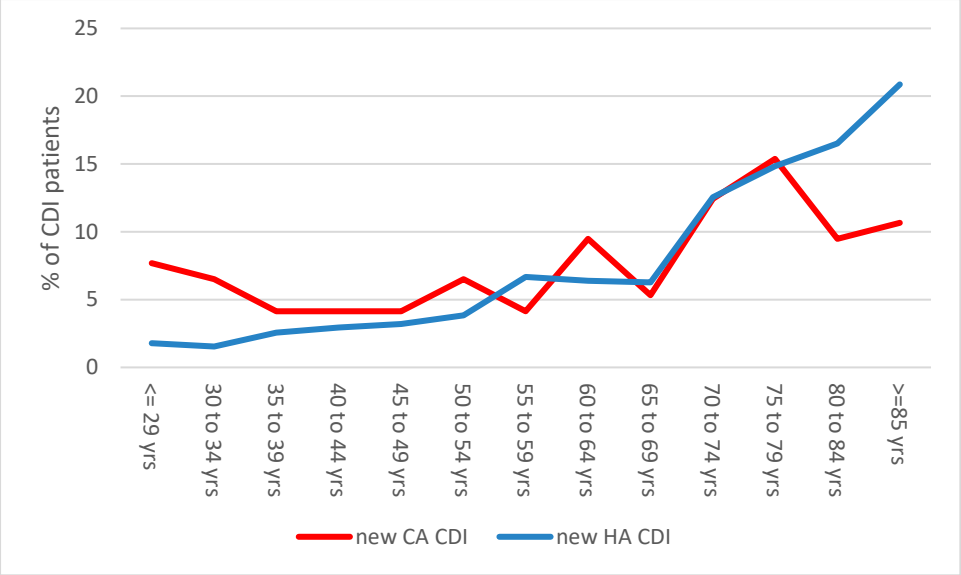


Figure 3b: Number of first CDI by origin and age group

The physical location of patients with new HA CDI was used a proxy measure of the proximity between patients in the hospital. Figures 4a – d show the trends of patient location at time of sample collection by hospital floor and year. Beaumont Hospital has patient accommodation over five floors including a lower ground floor. Most inpatient wards are located from the ground floor up. Trend analysis show that wards located on the first and third floors had an increasing trend in the number of HA CDI. The specialty of wards of these floors includes most specialties such as neurosurgery, renal, oncology, medical, surgical and MFTE. Wards located on the second and fourth floors appear to show declining trends which was more obvious on the fourth floor. The second floor is home to general medicine and MFTE. The fourth-floor houses renal and general surgical patients. An increase over all four floors can be seen to have occurred in 2019 during when a hospital wide outbreak of RT002 was managed within the hospital. None of the trends observed were found to be significant.

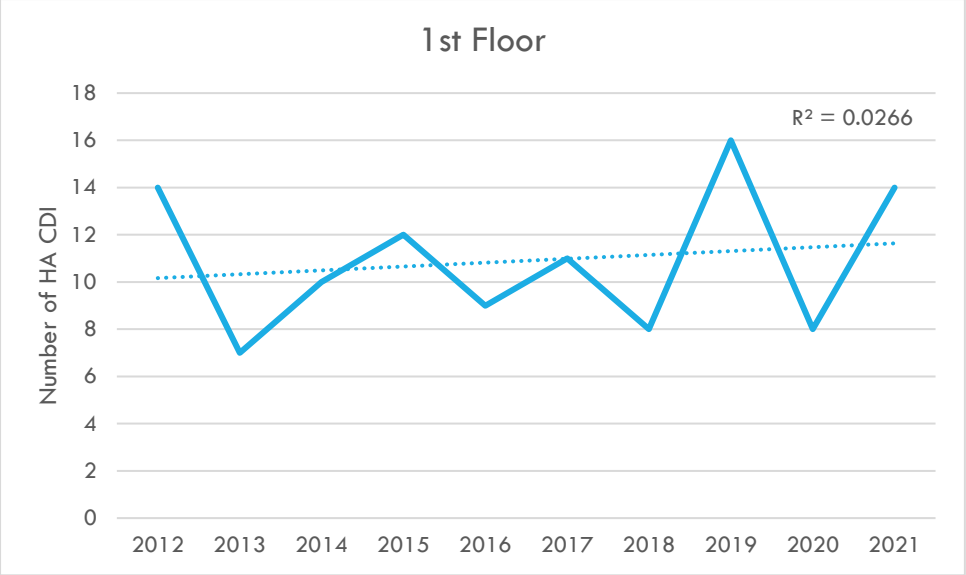


Figure 4a: The number and trendline of HA CDI on the 1st floor by year

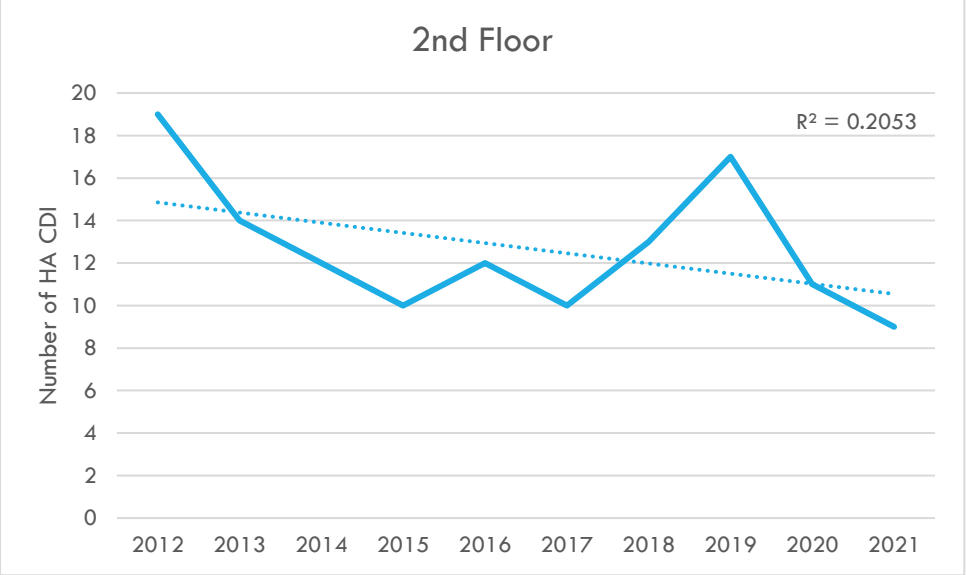


Figure 4b: The number and trendline of HA CDI on the 2nd floor by year

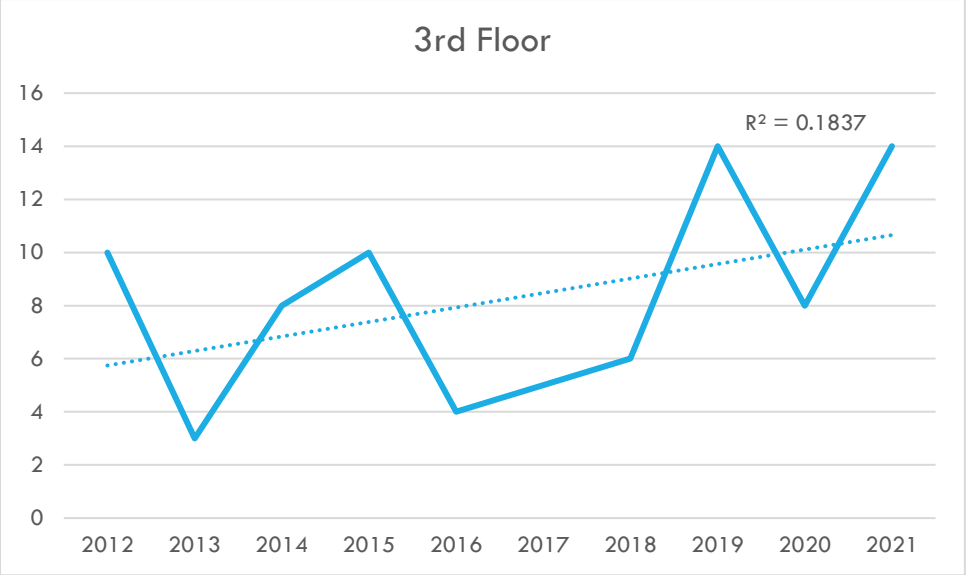


Figure 4c: The number and trendline of HA CDI on the 3rd floor by year

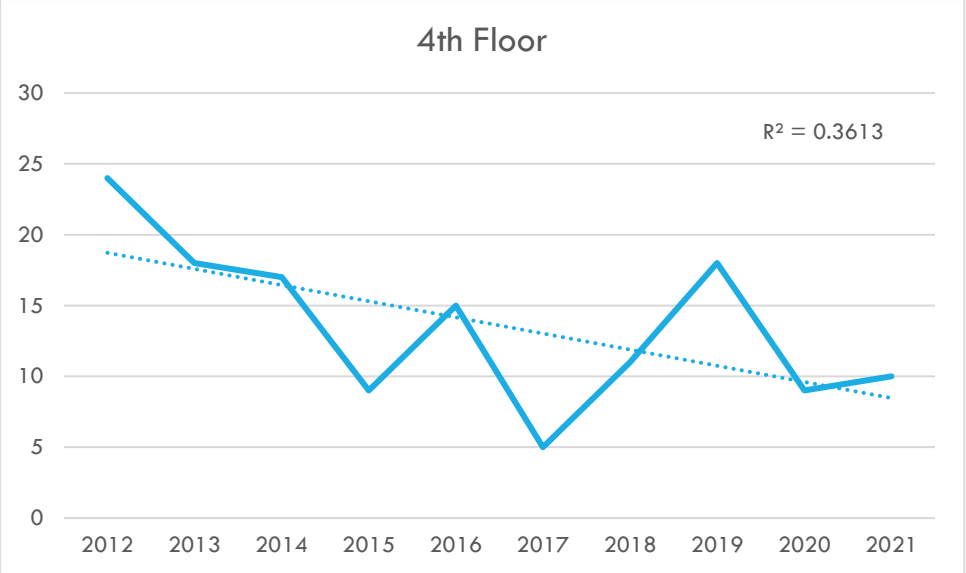


Figure 4d: The number and trendline of on HA CDI on the 4th floor by year

C.I – Confidence Interval

Poisson regression analysis and adjusted IRRs investigating risk factors for new CDI cases are presented in Table 4. HA-CDI and an emergency admission significantly increased the IRR for new CDI. Surgical and general medical patients had CDI rates comparable with MFTE, with significantly less CDI in neurosurgical patients. Wilcoxon rank-sum tests indicated that age ($p<0.01$, C.I. 0.03 – 0.05) and LOS ($p<0.01$, C.I. 1.66 – 5.5) were significantly associated with first CDI ($p<0.01$, C.I. 1.66 – 5.5).

	Adjusted incidence rate ratio (IRR)	*95% CI*
Clinician request for *C. difficile* test[#]	0.73	(0.63 – 0.85)
Faecal specimens tested (no CDI request)		
Previous positive result*[#]	0.45	(0.33 – 0.60)
Female	0.92	(0.81 – 1.05)
Male		
Admission type[#]		
Emergency	1.56	(1.28 – 1.89)
Elective		
Healthcare onset CDI[#]	1.37	(1.12 – 1.67)
Admission Speciality		
Gastroenterology	0.79	(0.61 – 1.02_
Medicine for the elderly	-	-
General medicine	1.19	(0.96 – 1.49)
Renal	0.79	(0.62 – 1.02)
Neurosurgery[#]	0.64	(0.45 – 0.90)
Oncology	0.76	(0.56 – 1.01)
General Surgery	0.94	(0.75 – 1.18)

*Positive *C. difficile* results in the 12 weeks prior to onset of first CDI
- Reference group
[#]Indicates significance, p<0.05

Table 4: Poisson regression analysis (adjusted IRR and 95% CI) investigating risk factors for the first episode of CDI

5.2.2 CDI Recurrence

The rate of CDI recurrence was 9.1% (n=87, one severe CDI) with a 1.5|1.0 female to male ratio and an average age of 74.4 (IQR 68 - 85 years). No patient with recurrent CDI was known to have died. Of the 87 patients, 68 (78.16 %) had one recurrent episode and 19 (21.84%) had two or more. The

majority (92%) of recurrent HA CDI represented the first episode of CDI. Cox regression analysis showed the use of fidaxomicin as first line CDI treatment significantly reduced the hazard ratio in recurrent CDI patients to 0.54 (p<0.01, C.I. 0.3 -0.9). No other significant factors were identified.

5.2.3 Incidence and seasonality of CDI

The annual number of new patients identified with CDI ranged from 100 patients in 2017 to 236 patients two years later in 2019. Figure 5 displays the quarterly rates of HA and CA CDI over the 10-year period. A decrease in both HA and CA is evident between 2012 and 2016 (CA R^2=0.43, p>0.01, C.I. -0.19 – 0.05, HA R^2 =0.517, p<0.01, C.I. -0.18 - -0.06)). Between 2017 and 2021 there was an increase in CA CDI, most marked in 2021 (p<0.01, C.I. 0.03 – 0.23). When reviewed as a 10-year period the quarterly rate of CDI irrespective of case type, did not vary significantly (CA CDI: mean 4.3 per 10,000 BDU R^2=0.0064 per 10,000 BDU, p<0.6, C.I -0.02 – 0.04; HA CDI: mean 3.2 per 10,000 BDU, $R^2$0.0079, p=0.59, C.I. -0.04 – 0.2).

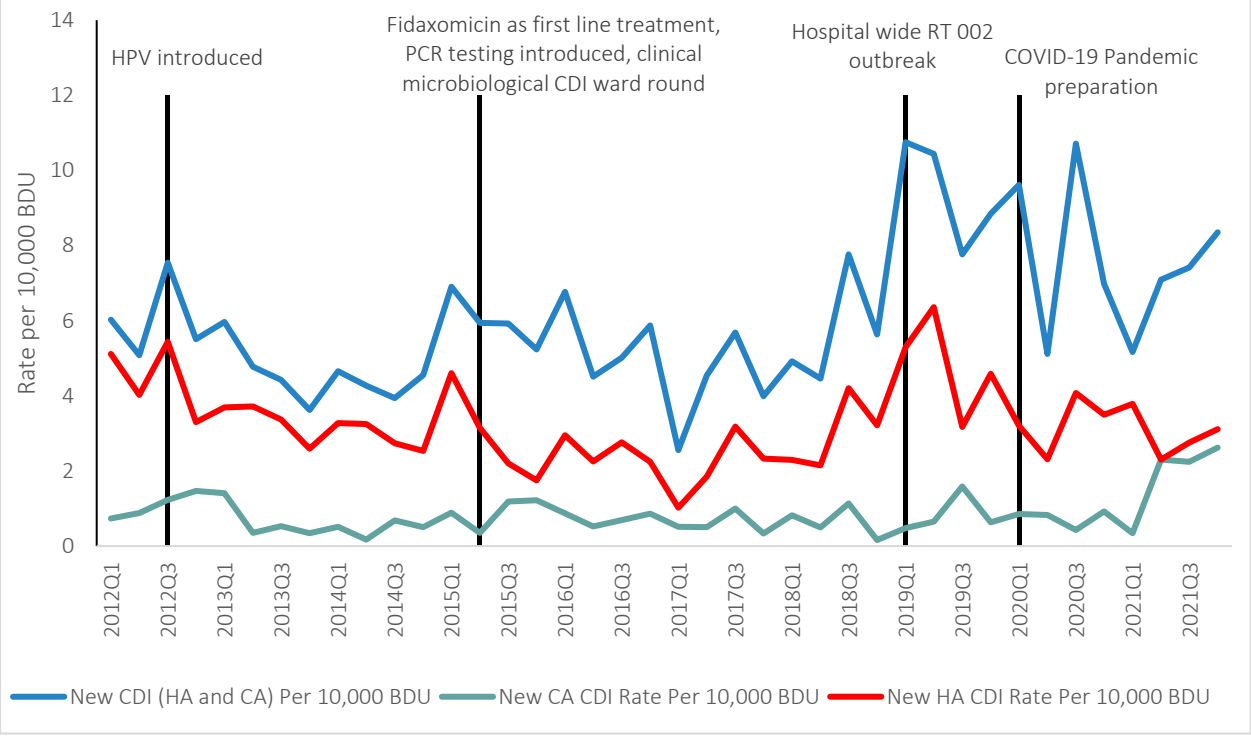


Figure 5: Rates of CDI by quarter, overall and by origin, per 10,000 BDU, and, key time point events, 2012 to 2021

The highest annual rate for CDI was in 2019 (9.4 per 10,000 BDU) when HA CDI peaked in the study period at 4.8 per 10,000 BDU. The lowest annual rate was observed in 2017 at 2.7 per 10,000 BDU when the HA-CDI rate was 2.1 per 10,000 BDU. The second lowest rate was in the preceding year, 2016, when these rates were 3.3 and 2.6 respectively. The CDI quarter 1 and 2 CDI rates were the

highest recorded at 10.8 and 10.4 per 10,000 BDU. This was reflected in HA CDI, accounting for on average 55% of cases and quarterly rates peaking at 5.3 and 6.4 per 10,000 BDU. This quarterly data was submitted to the enhanced CDI surveillance programme co-ordinated by colleagues at the HPSC during the study period. Figure 6 shows the overall quarterly national rate of new CDI for Tertiary Hospitals comparted to that of Beaumont Hospital during the study period. The average rate of new HA-CDI for tertiary hospitals was 2.7 per 10,000 BDU. This ranged from 2.2 during several quarters during 2015, 2016, 2020 and 2021 to 3.5 in Q4 2019. Data is also collated at a European level by ECDC and is the largest repository of standardised European CDI data however only 2017 data was available at the time of writing. Figures 7a and 7b illustrate the crude incidence of CDI of these 23 countries at that time was 3.48 cases per 10,000 patient days, the majority HA-CD (60.9%, crude incidence density was 2.12 cases per 10,000 patient-days).

The lowest rate of CDI was in 2017 (overall 4.2 CDI per 10,000 BDU, HA 2.1 per 10,000 BDU). During the first two quarters of this year the overall rate of CDI was 2.6 and 4.5 per10,000 BDU, respectively, with rates of HA CDI at its lowest points, accounting for 40% of cases during these periods (Q1 HA CDI 1.0 per 10,000 BDU and Q2 HA CDI 1.9 per 10,000 BDU). In 2021 the annual rate of CA CDI peaked at 1.9 per 10,000 BDU and despite a continued decrease in the rate of HA CDI for a second consecutive year.

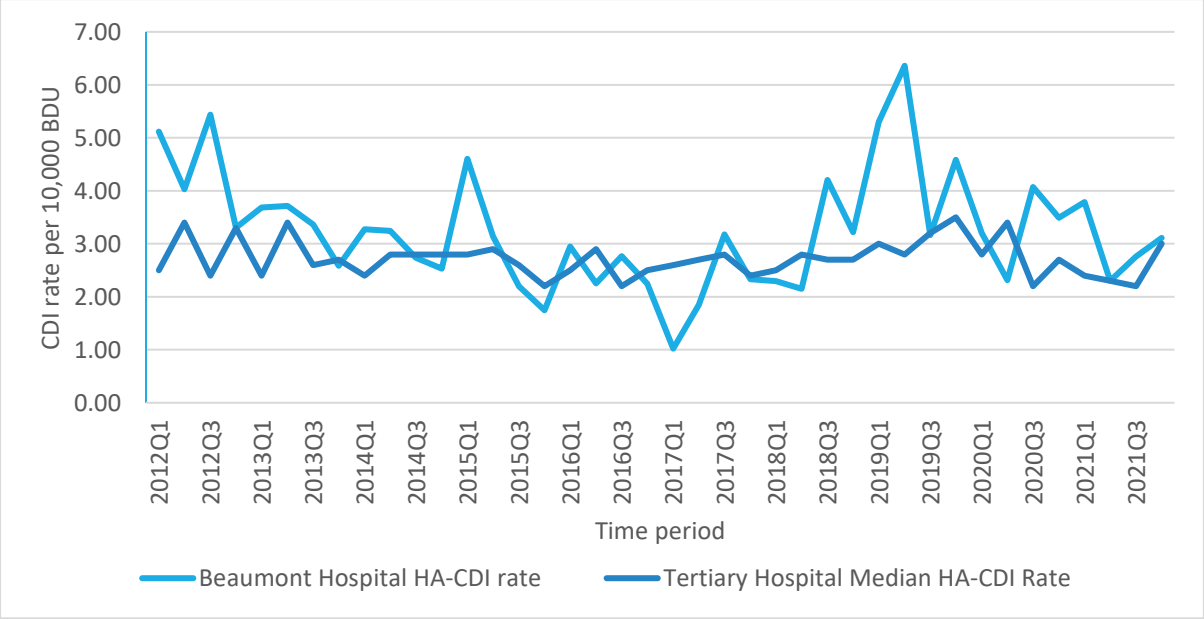
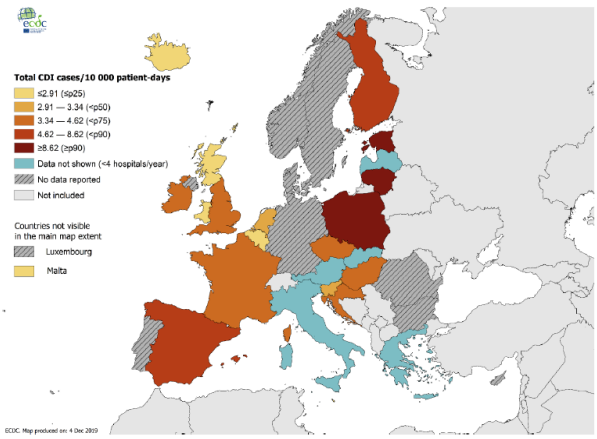


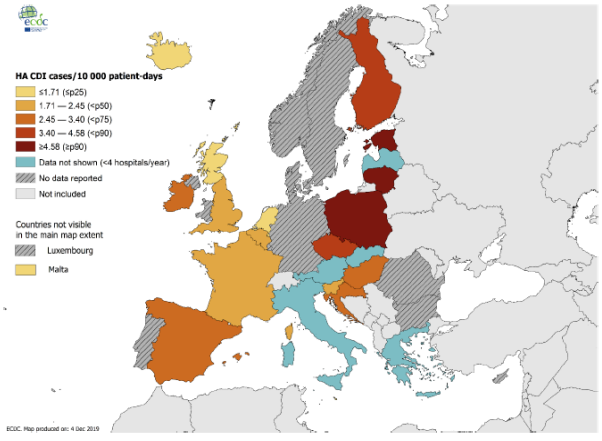
Figure 6: Quarterly national rate of new healthcare-associated (HA) CDI for Tertiary Hospitals in Ireland versus Beaumont Hospitals quarterly rate of new HA-CDI, 2012-2021 (reproduced from the Health Protection Surveillance Centre. *Clostridioides difficile* infection in Ireland 2020, Dublin: HPSC 2022.

HA-CDI – Hospital acquired *Clostridioides difficile* infection



** UK devolved administrations are shown separately.*

Figure 7 a



*Key: * UK devolved administrations are shown separately.*

Figure 7 b

Figure 7. ECDC European surveillance 2016-2017; a) crude CDI incidence density of all cases per 10,000 patient-days, b) incidence density of healthcare associated CDI (HA-CDI) per 10,000 patient-days (reproduced from European Centre for Disease Prevention and Control. *Clostridioides difficile* infections. Annual epidemiological report for 2016–2017, Stockholm: ECDC; 2022)

Figure 8 displays the annual monthly average of CDI by case type. HA CDI was on average highest in January, March, July and August with February, September and November being the lowest. The highest monthly average for CA CDI was observed in July, August and September with January, March and June having the lowest observed rates. Regression analysis indicated no obvious trends in either cohort.

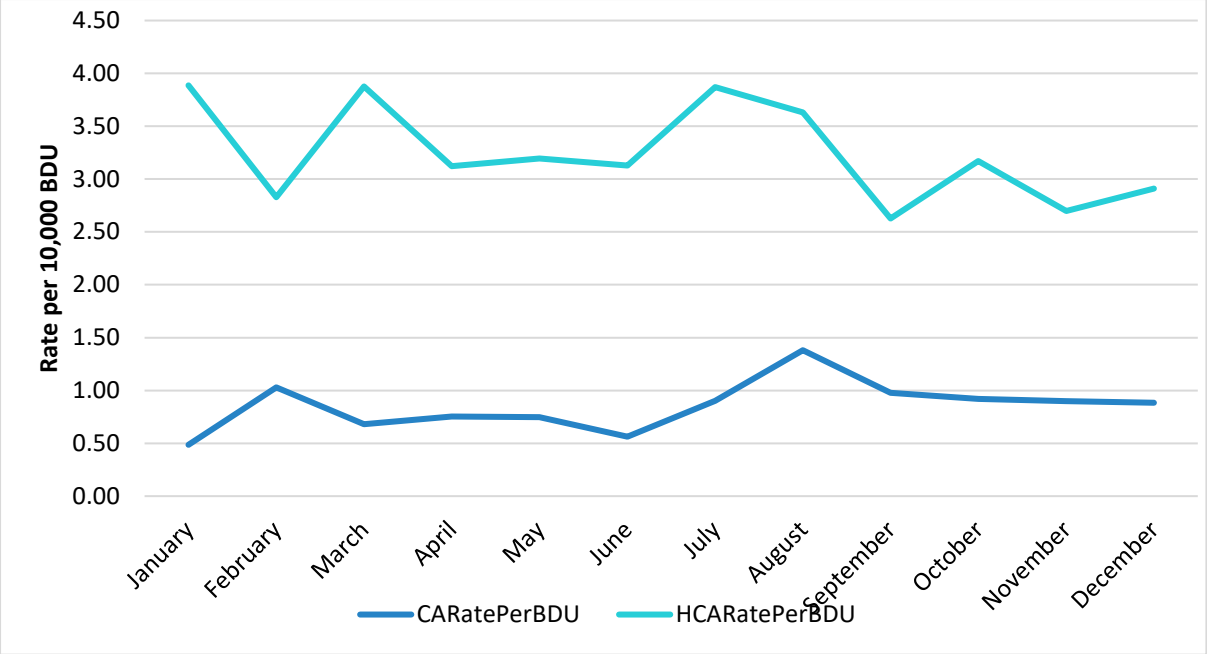


Figure 8: Average monthly rates of CDI per 10,000 BDU, 2012 to 2021

5.2.4 CDI Outbreaks

There were 27 CDI outbreaks identified and managed over the 10 years, affecting an average of 17.9 (range 2 -62 patients) over three wards. Table 5a provides a breakdown of CDI outbreaks by year and associated RT. There was no year without a CDI outbreak. In 2013, 2017, 2020 and 2021 there was only one CDI outbreak, which was confined to a single ward with an average of five patients per outbreak. The greatest burden due to CDI outbreaks was observed in 2012 (six outbreaks over six wards with 36 patients), 2015 (six outbreaks over eight wards and 21 patients) and 2019 (two outbreaks, one of which was a hospital wide with 62 patients affected). Table 5b presents by year outbreak sequentially and associated ribotypes.

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of CDI outbreaks	6	1	2	6	3	1	4	2	1	1
Number of reported cases	36	5	8	21	16	3	15	62	6	7
Number of wards affected	6	1	3	8	3	1	4	HW*	1	1
Minimum number of patients	2	n/a	2	2	3	n/a	3	4	n/a	n/a
Maximum number of patients	11	n/a	6	7	9	n/a	8	62	n/a	n/a

*HW – Hospital wide

n/a – Not applicable

Table 5a: Summary of CDI outbreaks in Beaumont Hospital by year, 2012 to 2021

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Outbreak number 1	Mixed	045	014	078	Mixed	Mixed	014	002	Mixed	Mixed
Outbreak number 2	015		003	078	078		017	Mixed		
Outbreak number 3	363		103	207	056		002			
Outbreak number 4	Mixed			070			213			
Outbreak number 5	Mixed			139						
Outbreak number 6	Mixed			Mixed						

Table 5b: Summary of CDI outbreaks by year in Beaumont Hospital

5.3 Part 3: Appraisal and review of the current CDI surveillance system

Figure 9 displays the current CDI surveillance model approach in Beaumont Hospital which is designed for weekly surveillance as the IPCT meets weekly, generally on the second working day of the week. New *C. difficile* laboratory results are automatically uploaded into the shared Access™ database. All *C. difficile* results that are PCR positive, irrespective of the EIA result, are uploaded. Each result in the database is circulated by the surveillance scientist to the IPCT in advance of the meeting.

The surveillance scientist is responsible for administration of the CDI database. This includes ensuring the data is routinely backed-up and stored in a secure, password protected location. The surveillance scientist prepares data for circulation in advance of the IPCT by reviewing recent inpatient stays, known exposures to HCF environments, duration of hospital stays to symptom onset and any known CDI history. In addition the surveillance scientist reviews any RT results received in the previous week and investigates any epidemiological links to recent CDI patients with the same RT. Potential areas of increased incidence in a clinical area, i.e., two or more *C. difficile* positive cases (irrespective of case type) or potential cross-transmission between ward areas are highlighted in advance of the IPCT meeting. Reporting of CDI data, once validated, is completed by the surveillance scientist, and includes notifying public health of all new and recurrent CDI and the provision of KPI data to national agencies. In-house communication includes presentation of CDI data to the Infection Prevention Control Committee, Hospital Directorates, and senior decision-makers throughout the hospital.

The IPCNs review all new *C. difficile* results in advance of the weekly IPCT meeting. During this process they collate information on the date of onset of symptoms, frequency of symptoms, CDI antimicrobial treatment given and isolation status of patient after *C. difficile* diagnosis. The IPCN also discusses any increased incidence with the CMT, and if needed, senior management. They also liaise and support ward staff, and if needed, activation of a CDI trigger tool. The clinical microbiologist phones all positive *C. difficile* laboratory results to the patients clinician daily and thereafter manually records patient and laboratory testing details, CDI risk factors, CDI severity, CDI antimicrobial treatment details and IPC advice in a CDI book which is kept in the clinical microbiology office. Patients with severe CDI are reviewed that day by a member of the CMT.

All cases of CDI over weekends are discussed at the weekly CMT handover which takes place on the first day of the working week. This multidisciplinary meeting includes the surveillance scientists and antimicrobial pharmacist but not the IPCNs. In advance of the IPCT, the CMT review clinical notes of *C. difficile* cases circulated by the surveillance scientist. Information reviewed includes date of symptom onset, frequency of symptoms, case type, CDI treatment prescribed and any follow up actions.

C. difficile is a standing agenda item at the weekly IPCT. This meeting is chaired by the consultant microbiologist on- call and attended by IPCNs, surveillance scientist, chief and/or senior medical laboratory scientist, antimicrobial pharmacist and CMT. The IPCN summarises each CDI case briefly at the meeting. Once discussions are complete, agreed case type, increased incidence, and agreed actions are documented in the minutes. After the meeting the surveillance scientist reviews and updates the CDI database to ensure the data is reflective of what has been agreed at the IPCT. The surveillance scientist also notifies any new or recurrent CDI to public health, as required by the Infectious Diseases (Amendment) Regulations 2022 [50]

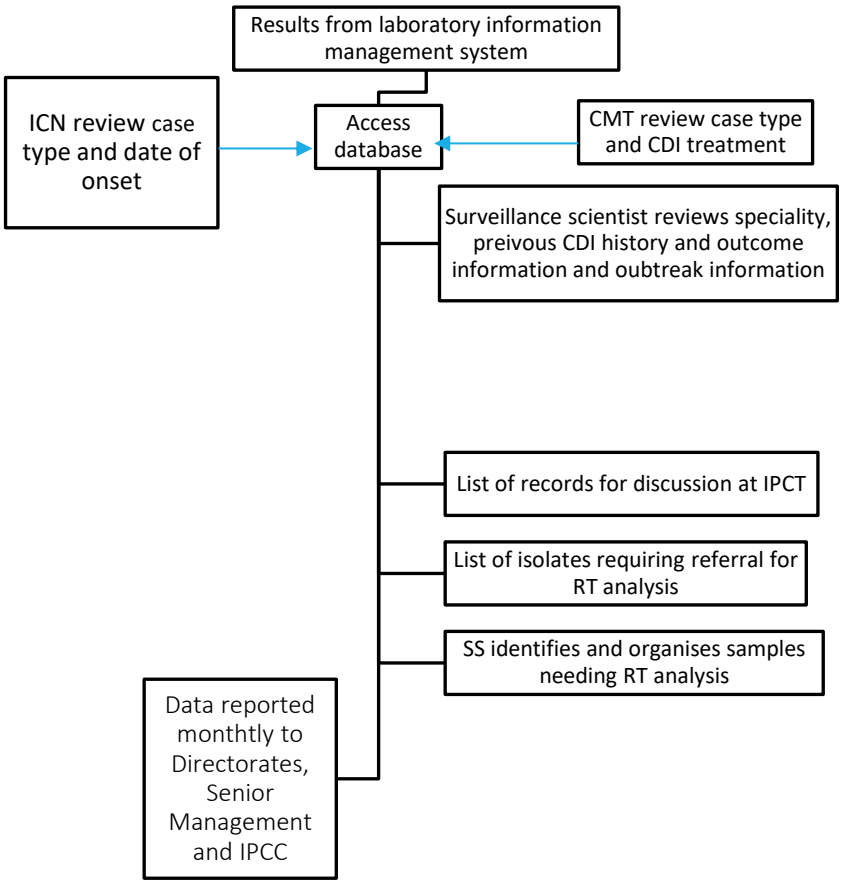


Figure 9: Overview of Beaumont Hospital's current CDI surveillance processes

IPCC – Infection Prevention Control Committee

SS – Surveillance scientist

The CDI database is validated monthly. A consultant microbiologist and surveillance scientist meet at the beginning of each month to review the previous months' data. The consultant microbiologist reviews CMT notes for any follow up details that were not available at the time of IPCT. Each record is reviewed in conjunction with the PAS and onset and origin definitions appraised for accuracy i.e., any CA cases are reassigned as HA for long-term care facility residents and the appropriate facility. The database is updated as required during this meeting. The duration of the meeting is approximately 30 minutes but this can vary depending on case load. After this meeting the surveillance scientist circulates the number and details of HA CDI to IPCT and the hospitals' senior management team, and the number of HA CDI and BDU to the HSE as part of KPI reporting requirements. Data is fed back directly to Directorates via a business intelligence data analysis and reporting tool, via monthly reports to the Senior Management Team and quarterly to the Infection Prevention Control Committee.

The characteristics of Beaumont Hospitals' current CDI surveillance systems and their fulfilment of the attributes of quality for an epidemiological surveillance system, as described by Thacker *et al.,* are set out in Table 6. Overall the current system compares well with the attributes required of such a system. The data captured is routinely monitored by members of the IPCT, the Infection Prevention and Control Committee and the Senior Management Team. The system can be adapted and changed as required. The quality control plan cycle illustrated in Figure 1 are also satisfied. This quality control plan includes standardisation, evaluation and continuous improvement of the system.

Attribute of quality	**Current Beaumont Hospital surveillance approach**	**Comments / Suggested improvements**
Sensitivity	Clinical details of all patients with *C. difficile* positive samples are reviewed at the weekly IPCT meeting. Nursing, medical and previous CDI history information as well as previous hospital admissions information are jointly reviewed and a decision as to case type, in accordance with case definitions, agreed. Any discrepancies are reviewed by the consultant on call and a final decision as to case type made by them.	Current surveillance systems are comprehensive with sufficient information available to accurately assign CDI case type as per national CDI definition.
Specificity	Clinical details of all patients with *C. difficile* positive samples are reviewed at the weekly infection prevention and control team meeting. Nursing information and medical information are reviewed jointly and a decision as to case type, in accordance with case definitions, agreed. Any discrepancies are reviewed by the consultant on call and a final decision made by them.	Current surveillance process is comprehensive with sufficient information available to accurately assign case type (or not) as per national CDI definition.

Attribute of quality	Current Beaumont Hospital surveillance approach	Comments / Suggested improvements
Representativeness	All stool samples which take the shape of the container are tested onsite daily for *C. difficile**.	Educating healthcare workers as to when they should send stool samples to the microbiology laboratory for testing is given at induction, grand rounds and by Infection Control Nurses at ward level.
Timeliness	All stool samples which take the shape of the container are tested onsite daily for *C. difficile**. Positive results are communicated daily to the clinical microbiology team, ICNs and surveillance scientist. They are then discussed weekly at the IPCT meeting. The CDI database is quality assured monthly.	Current process is sufficient to meet local and national reporting requirements.
Simplicity	Laboratory records of all *C. difficile* positive results are automatically updated into a shared access database. This database is accessible by all IPCT members. Data is extracted weekly for discussion at the IPCT. Any changes/corrections agreed at the meeting are added to the database by the surveillance scientist and final minutes reflect these changes. The database has been configured for easy usability with users accessing relevant data via toggle buttons and predefined queries.	Current systems are easily accessible by members of the IPCT.
Flexibility	The Access database can be easily modified to incorporate any new field/parameters the IPCT wish to include	Current systems are easily adaptable by surveillance

Attribute of quality	Current Beaumont Hospital surveillance approach	Comments / Suggested improvements
	in their surveillance system. The database is also mapped to business intelligence data analysis and reporting tool where directorate team members can log into and view the number of new and recurrent CDI within their directorate each month	scientist to meet the needs of the IPCT.
Acceptability	The CDI surveillance processes have been modified and updated since first implemented. The approach has been well established and is used by all members of the IPCT.	No issues or difficulties with the current surveillance systems have been reported by members of the IPCT.

Table 6: Review of the attributes of quality of Beaumont Hospitals' current CDI surveillance system

* Patients with a positive *C. difficile* sample in the preceding 14 days are not re-tested until two weeks after the date of positive sample.

CDI – *Clostridioides difficile* infection

ICN – Infection Control Nurse

IPCT – Infection prevention and control team

6 Discussion

Despite international focus and research, CDI remains a significant patient safety and IPC issue. In our institution, over the last decade, HA-CDI rates remain broadly unchanged in hospitalised patients, impacting our more vulnerable older patients with a prolonged LOS. Our policy of testing all diarrhoeal specimens for *C. difficile* despite whether a clinician requests it or not is supported by low rates of specific *C. difficile* test request, and positive results when not requested. One in ten CDI patients experienced recurrent CDI, with one in twenty having two or more episodes. Fidaxomicin CDI treatment reduced the likelihood of recurrent CDI. The recent increase in CA-CDI requires further investigation although it may reflect the impact of the COVID-19 pandemic on healthcare access and utilisation outside the hospital setting. The majority of CA-CDI and over one in twenty HA-CDI have symptom onset in the community, highlighting the need for ongoing CDI awareness efforts outside the hospital setting. The cause of observed sex differences in CA-CDI is unclear and requires further investigation.

All positive *C. difficile* results identified in Beaumont Hospital undergo multi-disciplinary review at the weekly IPCT whereby clinical and nursing information are assessed and used to assign case type. Other possible causes of a patients symptoms are out ruled before origin and onset of CDI for a patient is agreed. This has resulted in a dynamic cohort of patients, where some cases fulfil the CDI case definition and some do not (DNMCD). For those who do not meet the case definition, their symptoms either did not fulfil the definition of diarrhoea (i.e. diarrhoea is defined as three or more loose/watery bowel movements (which are unusual or different for the patient) in a 24-hour period) or another cause had been identified for the patients symptoms and did not need treatment for CDI. On review of sample results by patient, show that some patients are straightforward CDI, some change between CDI and DNMCD and some patients have never met the CDI case definition. This last group accounted for 27% of our patients and as such were never notified to public health. Such patients could be considered 'asymptomatically colonised' with *C. difficile.* There are a number of studies investigating the roles of asymptomatically colonised *C. difficile* patients and their role in the transmission pathway within the healthcare setting. It is known that asymptomatic *C. difficile* carriage occurs in up to 20 percent of hospitalised adults; these patients can shed *C. difficile* in stool but do not have diarrhoea or other clinical symptoms. Individuals who are colonised by *C. difficile* may acquire protection from progression to disease, however, by serving as a reservoir for environmental contamination, they also have the potential to contribute to transmission in

healthcare settings (55-58). These patients also add to the workload of the laboratory, CMT and IPCNs. From an IPC perspective, their sample meets the criteria for requiring a *C. difficile* test (i.e., all stool samples which take the shape of the container are screened for *C. difficile*) and as their clinician requested a faecal culture of their stool specimen, it would imply that gastrointestinal infection, is being considered as part of the diagnostic differential. Once ascertained that these patients did not have symptoms compatible with CDI and other possible infectious causes were out ruled they remain under IPC review until they are discharged. These findings could be reflective of our testing policy i.e., all diarrhoeal specimens are tested for *C. difficile* or a growing number of patients are colonised with *C. difficile.* The role of these patients in transmission pathways within the hospital was outside the scope of this project.

The most common RTs in our study are similar to those previously reported and with the exception of the RT002 outbreak in 2019, the most common circulating RT were generally stable (4, 59-61). Ribotypes 014 and 002 dominated in our patient population. Other common ribotypes observed annually included the hyper virulent RT 078, which remains an IPC priority as well as 005, 015 and 020. Over the decade under study there was a notable absence of RT027. This differs to what was reported by a Pan-European study where RT 027 was the dominant RT between 2012 and 2016 (59). Our CA-CDI cohort is not a true representation of CA-CDI in our community as our study was confined to hospitalised patients. However, the similarity of dominant RTs between HA-CDI and CA-CDI groups raises questions as to the exposure and interaction of CA-CDI patients with healthcare facilities and the reliability of traditional CDI origin case definitions. These definitions rely on an overnight hospital stay for HA-CDI case classification and with increasing numbers of patients receiving day-case based care in a hospital setting, these may require review (13). A limited number of studies were identified during the literature review which suggested day five of hospital admission as a possible cut off for assigning CA CDI. These findings were backed by strong statistical evidence using positive predictive and negative predictive values as well as sensitivity and specificity analyses. However, international CDI cases definitions continue to use the 48-hour rule for assigning HA- and CA-CDI status. This approach, currently employed by Beaumont Hospitals IPCT, also overlooks cohorts of patients attending HCFs in an outpatient capacity with CDI reported for these groups as CA- CDI, as per case definition. In the light of the similarity of dominant RT in both the HA and CA groups in our study, an in-depth review of patient healthcare exposures as well as further molecular epidemiology of *C. difficile* isolates are required to investigate our "CA"-CDI cohort further to inform decision making regarding case definitions of CDI origin.

International guidelines recommend testing all diarrhoeal specimens for CDI irrespective of clinician request (9). Indeed, the majority of inpatient CDI cases would have been missed if we had not adopted a universal testing approach. In a European study of 20 countries, it was estimated that hospital-based CDI may be underestimated by 23%, equating to 74 missed CDI cases daily (61). CDI under-diagnosis presents a significant transmission risk, especially in hospitals such as ours with predominant multi-bedded wards and shared bathrooms. Patients with DNMCD in the previous 12 weeks appeared to be protected against subsequent CDI. This may reflect colonisation with nontoxigenic *C. difficile* which can prevent subsequent CDI or an increased awareness of CDI among clinical staff who may be more focussed on improving antimicrobial stewardship efforts in these particular patients (60). One in five of our patients had CO-CDI (the majority CA-CDI) and were diagnosed first when admitted to hospital. While CDI diagnosis outside hospital presents unique challenges (e.g., viral causes of diarrhoea predominate, off-site laboratories requiring specimen transport arrangements, and difficulties accessing some CDI treatment information outside the hospital setting), it is important that in following the COVID-19 pandemic, CDI remains a focus in all healthcare settings.

Poisson regression analysis and adjusted IRRs showed that increased length of stay, increased age, recent antibiotic exposure, and acute admission were all significant risk factors for new CDI. Increasing age is a widely reported CDI risk factor, and as in our study, patients with CA-CDI tend to be younger (62). We employed five-year age groups in our data analysis approach. When reviewing the origin of CDI within age groups it was observed that patients age less than 29 years were as likely to acquire HA CDI as CA CDI. However, in the older age groups the risk of HA CDI increases exponentially, with the exception of the 55 to 59 years group where 88% of cases were HA CDI. This group had an OR for HA CDI of 6.1, comparable only to the 80+ age group. When age groups are examined by CDI origin it is clear that CDI is more common in older age groups in both the CA and HA cohorts up until 80 years. In the CA CDI group only 10 % of cases occurred in the 80 to 84 age group (versus 17% of HA CDI) and 11% in the >85 years (versus 21% of HA CDI). This could be reflective of the living circumstance of patients in these age groups, with them being more likely to be a long-term care resident.

The association of sex and infectious diseases has been described for a range of infections with differences associated with chromosomal, hormonal, biological and social factors (63, 64). Sex differences in CDI hospitalisation rates and in colonisation with non-toxigenic *C. difficile*/CDI risk have been described previously (65, 66). In the Netherlands, hospitalised patients with CO-CDI tended to be younger (63 vs 68 years) and female (53%) (67). Likewise, in a US population-based study, CA-CDI patients tended to be younger (median age 50 vs 73 years) and more likely to be female (76%) (68). Being female was one of the most common CDI risk factors for new CDI in a recent systematic review, however, the reasons behind this are unclear. In our study, significant sex differences in CA-CDI but not HA-CDI were found. Differences by sex in health seeking behaviour and healthcare utilization may be one reason for this discrepancy, although further investigation is required (69, 70).

Given the increase in CA-CDI observed in 2021, the higher proportion of female patents (72% of cases) in this cohort and also the similarity of RTs identified with the HA-CDI demographic, further investigation into the attributes and risk factors of CA-CDI patients would be helpful to better understand the epidemiology of CDI in the community. More current information concerning residential status (i.e. may have recently become a long term care resident but medical records not as yet updated), as well as any exposure to a healthcare setting in the weeks leading up to their CDI onset, would help provide clarity as to the origin of their infection. Our CA-CDI data is limited to those patients who required admission to the hospital. It does not reflect those patients with milder CA-CDI who did not require admission.

General medical and surgical patients had CDI rates similar to MFTE, which likely reflects the hospital catchment area. In contrast CDI was significantly less common in the neurosurgical population. As with many infectious diseases, CDI displays a seasonal pattern peaking in spring with a reduction in summer/autumn (71). This can be attributed to increased antibiotic prescribing during winter 'flu' season. While no significant trend was evident in this cohort, the trend largely mirrored the winter into spring pattern reported elsewhere. The seasonal pattern of HA-CDI observed in our study may also reflect medical staff changeover periods (January and July), when new staff take time to become familiar with the hospitals' IPC and antimicrobial stewardship policies. Without further investigation the seasonal pattern of CA-CDI peaking in summer/autumn is difficult to explain.

Onset location of CDI types did not always align with the origin of infection. We found 8% of HA CDI with community onset and 15% of CA CDI with hospital onset. Overall 21.5% of case had community onset of symptoms, irrespective of origin. Education amongst primary care teams is important to ensure that CDI is part of the differential when investigating diarrhoeal symptoms, particularly when the patient has been recently discharged from a HCF. A review of HA CDI by ward location within the hospital showed some interesting trends. Both the first and thirds floors of Beaumont Hospital are home to a variety of specialties and appear to have experienced an increasing trend in HA CDI. Wards on the second and fourth floors appear to show a fall in cases with these floors home to general medical, MFTE, renal and surgical patients. The average LOS differed significantly between the HA (67.1 days) and the CA (14.6 days), with HA CDI adding a significant burden to the hospital not only in terms of patient flow but also cost (2).

One in ten CDI patients experienced recurrent CDI (rCDI), with one in twenty having two or more episodes (72). It should be noted that Beaumont Hospital is a tertiary referral hospital. As such the reported CDI recurrent rate does not account for patients who were discharged outside the Hospitals catchment area. We found that fidaxomicin as first line CDI treatment reduced the likelihood of rCDI. The recent increase in CA-CDI requires further investigation though it may reflect the impact of the COVID-19 pandemic on healthcare access and greater utilisation of healthcare outside the hospital setting (73). The majority of CA-CDI and over one in twenty HA-CDI have symptom onset in the community, highlighting the need for ongoing CDI awareness efforts outside the hospital setting. The cause of observed sex differences in CA-CDI is unclear and requires further investigation.

In comparison to the first episode of CDI, rCDI is associated with significantly higher healthcare costs and prolonged hospital stay (7). Rates of rCDI vary with ribotype, although are generally 15-30% (74). An initial rCDI is a risk factor for further episodes of rCDI. Risk factors for rCDI in hospitalised patients include prior/current antimicrobials, older age, and LOS (total and LOS pre-CDI) (75). Ten percent of our patients developed rCDI which was generally HA, with a fifth having two or more rCDI episodes. Fidaxomicin as first line CDI treatment was the only significant factor that reduced the likelihood of rCDI in our patients. This has been reported in other studies and was one factor favouring fidaxomicin as first line CDI therapy in recent European guidelines (76). The management of multiply

rCDI is less well defined especially in Ireland where there is not ready access to faecal microbiota transplantation, a widely acceptable treatment for rCDI with resolution rates exceeding 90% (77).

HA CDI and outbreaks of HAI within a hospital can be reflective of a variety of factors including environmental, staffing, infrastructure, and resources. There were changes in Beaumont Hospital over the study period, not only in its approach to CDI prevention but also in terms of the complexity of service provision (78). The number and extent of CDI outbreaks over the 10 years varied year to year with no year unaffected by a CDI outbreak. In 2019 the impact of the RT 002 outbreak is evident in the HA CDI rate of 5.1 reported to the HSE that year, one of the highest reported by the hospital to date (4). The unpredictability of outbreaks in general pose great difficulty to patients and hospital management alike. Control measures can include bed and ward closures, and postponement of non-acute procedures (2, 79). Little of the patient experience of HA CDI has been reported (80).

The annual rate of new CDI in the hospital ranged during the study period from 2.7 per 10,000 BDU in 2017 to 9.4 per 10,000 BDU in 2019. The lowest rate of new HA-CDI was in 2017 (2.1 per 10,000, BDU). At that time both the HPSC and the ECDC reported similar rates (2.0 and 2.12 per 10,000 BDU). The greatest burden of new CDI in the hospital was observed in 2019 (new HA-CDI rate; 4.8 per 10,000). While data available from the ECDC is limited, data from the HPSC show the highest reported median HA-CDI figure for tertiary hospitals was 3.5 per 10,000. It must be considered that rates reported by National and European agencies do not provide for different testing approaches or facility type. Despite rigorous local CDI IPC and antimicrobial stewardship programmes, the overall HA-CDI rate has not changed whereas CA-CDI is at its highest in a decade. When the microbiology department moved to the more sensitive testing algorithm of *C. difficile* tcdB PCR and if positive, enzyme immunoassay (EIA) for *C. difficile* toxin in Q2 2015, no increase in cases of CDI was observed. This underpins the importance of two step approach to and universal screening of stool samples for *C. difficile* in addition to our robust multi-disciplinary approach to CDI surveillance. The COVID-19 pandemic brought significant changes to the Irish healthcare service and to our hospital. Despite initial reported decreases in CDI (81), HA-CDI has increased back to pre-pandemic levels along with hospital activity, a similar experience of that reported by Xia *et al.*in a Canadian hospital (42). The recent increase in CA-CDI may be accounted for by a number of potential factors including delays in diagnosis (patients experiencing difficulty accessing primary healthcare; healthcare providers having reduced access to *C. difficile* testing because of the focus on SARS-CoV2 testing), the increased incidence of respiratory illness and antimicrobial prescribing after relaxation of lockdown measures,

increased CDI risk and/or factors such as frailty and comorbidity as a consequence of lockdowns (e.g., delays in diagnosis and management because of healthcare access difficulties). Education amongst primary care teams is important to ensure that CDI is part of the differential when investigating diarrhoeal symptoms, particularly when the patient has been recently discharged from a healthcare facility.

When it comes to developing, implementing and refining CDI surveillance processes within the hospital setting in Ireland, there are limited resources available. The HPSC provides a data capture form and a protocol for completion of this form ("Protocol for Completion of Enhanced Surveillance) (13). There is however no 'gold standard' which to follow to implement an effective and standardised CDI surveillance process. The database described here was developed very much on an *ad hoc*, local needs basis. The success of our CDI surveillance programme in Beaumont Hospital has always depended on the co-operation and engagement of IPCT colleagues. The database was designed to ensure it was user friendly and adaptable to the needs of the IPCT while following the key elements of a good surveillance system (as described by the CDC)(10). We have developed an active approach to CDI data capture based on a standardised method and application of case definitions. Strong communication is key to the integration of systems, applications, data, and people. The process is semi-automated with *C. difficile* positive laboratory results automatically imported into the database. From there the data collected is routine and the Access™ provides a means to collate and capture this information. The data collected exceeds what is required by the national enhanced CDI programme. That said, the data collected is routine, and necessary to ensure best patient practice and inform local IPC decisions. Thacker *et al,* has listed the attributes of quality of for an epidemiological surveillance system that include: 1) sensitivity; 2) specificity; 3) representativeness; 4) timeliness; 5) simplicity; 6) flexibility; and 7) acceptability (11). Having reviewed the steps (Table 6) used in Beaumont Hospitals weekly CDI surveillance, it is apparent that all seven attributes are satisfied and that the IPCT is committed, as described in its mission statement to "*reduce the risk of infection"* to patients attending the hospital by producing robust, reliable data to inform and guide its decision-making process. Any new or change in requirements of the database are discussed and agreed at the weekly IPCT. The Surveillance Scientist will then change the database and user interface as needed to ensure a streamline approach to data collection is maintained.

The data captured via the CDI database is used to produce monthly, quarterly and annual reports. This information is reported monthly to members the Senior Management Team and to the Infection Prevention Control Committee which meets quarterly. The data is also fed back directly to Directorates via a business intelligence data analysis and reporting tool. Given the timely availability of robust, standardised CDI data, the IPC are empowered to make recommendations at ward and hospital level. In terms of the day to day running of the hospital this ensures that any increased incidence of CDI is monitored and outbreak control teams convened if necessary. At a broader level this data is used for planning of resources year to year such as rolling ward based programmes focusing on decanting and infrastructure updating.

Our findings underpin the importance of using prospective surveillance to provide local information in real time for multi-disciplinary action and testing all diarrhoeal specimens for *C. difficile* irrespective of request. CDI remains a significant patient safety issue and in the pandemic era requires ongoing focus. The convergence of CA and HA RTs, as well as a proportion of CDI patients with community onset, question the traditional view of nosocomial CDI with CA CDI requiring further review and research to trace circulating RTs between HCFs and the community.

Limitations to this study include its single site, inclusion of only hospitalised patients, lack of follow-up of patients after discharge which may have impacted on our recurrent CDI rates, lack of detailed patient comorbidity and outcome data and with no information of antimicrobial resistance of isolates. Detailed information on hand hygiene or antimicrobial stewardship audits were not included, nor the impact of DNMCD patients on the hospital environment (82). However, the strength of this study is the robustness and consistency of the analysed data. All patients with a positive *C. difficile* result were prospectively assessed by a multi-disciplinary group resulting in real time allocation to case type using national CDI case definitions which were subsequently agreed weekly by the IPCT, *C. difficile* RT was performed on all patients by the same UK laboratory over the study period and the CDI database was quality assured monthly on an ongoing basis. In addition, the surveillance approach explored in this research could be used and adapted by IPCTs in other HCFs as the software used to develop the system described, Access™, is widely available and can be tailored to local surveillance needs.

7 Conclusions

These findings underpin the importance of using consistent, robust, prospective surveillance to provide reliable local information in real time for multi-disciplinary action. The study also highlights the importance of testing all diarrhoeal specimens for *C. difficile* irrespective of request. CDI remains a significant patient safety issue and in the pandemic era requires ongoing focus. The convergence of CA and HA RTs, as well as an increasing proportion of CDI patients with community onset, question the traditional view of nosocomial CDI with CA CDI requiring further review and research to trace circulating RTs between healthcare facilities and the community.

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9 Appendices

Appendix 1: CDI definitions

Case type		
New case of CDI	A patient (two years or older) is considered a new CDI case when one or more of the following criteria apply:	Diarrhoeal (three or more loose/watery bowel movements (which are unusual or different for the patient) in a 24-hour period or a toxic megacolon with either: • A positive laboratory assay for *C. difficile* toxin A (TcdA) and/or toxin B (TcdB) in stools or • 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
	A patient with a subsequent episode of CDI meeting the criteria above, with onset of symptoms more than eight weeks after the onset of a previous episode	
Recurrent case of CDI	A patient with an episode of CDI that occurs within eight weeks following the onset of a previous episode provided that CDI symptoms from the earlier episode resolved with or without therapy	
Did not meet case definition *C. difficile*	*C. difficile* identified from stool specimen however clinical symptoms at time of review were not consistent with the 'new' CDI case definition	
Unknown CDI case type	Information on clinical symptoms could not be ascertained by either Clinical Microbiology or Infection Prevention and Control	
Severe case of CDI	This is a CDI patient to whom any of the following criteria apply: - Admission to an intensive care unit for treatment of CDI or its complications (e.g., for shock requiring vasopressor therapy) - Surgery (colectomy) for toxic megacolon, perforation, or refractory colitis	

Origin		**Origin facility**
Community associated	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	N/A*
	Onset of symptoms within 48 hours following admission to a healthcare facility without residence in a	N/A

	healthcare facility within the previous 12 weeks (healthcare-onset, community-associated)	
Healthcare associated	Onset of symptoms at least 48 hours following admission to a healthcare facility (healthcare-onset, healthcare-associated)	Nursing home / LTCF[%] Other hospital This hospital ^Indeterminate
	Onset of symptoms in the community within four weeks following discharge from a healthcare facility (community-onset, healthcare-associated)	Nursing home / LTCF Other hospital This hospital ^Indeterminate
Discharged 4-12 weeks from healthcare facility	Patient was discharged from a healthcare facility between four and 12 weeks before the onset of symptoms	N/A
No information available on origin of infection		N/A N/A
Onset		**Onset facility**
Community onset	Symptoms start in a community setting, outside healthcare facilities N/A	N/A
Healthcare onset	Symptoms start during a stay in a healthcare facility	Nursing home / LTCF Other hospital This hospital
No information available	If no information was available on location of patient at onset of symptom	N/A

* N/A = Not applicable

% LTCF = Long term care facility

^ Facility “Indeterminate” is used for patients transferred between different healthcare facilities prior to onset of symptoms and associated origin facility of infection could not be clearly identified

Appendix 2: Average age (years) of Beaumont Hospital patients by specialty and year, non-CDI versus CDI patients

Age

	All patients								CDI								Difference non-CDI versus CDI							
Year	BH	Renal	Oncology	Neurosurgery	MFTE*	Surgery	Medical	Gastroenterology	BH	Renal	Oncology	Neurosurgery	MFTE*	Surgery	Medical	Gastroenterology	All	Renal	Oncology	Neurosurgery	MFTE*	Surgery	Medical	Gastroenterology
2012	55.2	56.9	57.4	45.9	71.8	48.1	60.3	60.1	67.4	63.8	48.0	55.3	78.9	67.0	71.3	67.0	12.2	6.9	-9.4	9.4	7.1	18.9	11.0	6.9
2013	56	57.3	58.6	46.3	72	49.1	60.5	62.3	69.9	64.3	70.7	40.3	75.0	70.0	74.3	62.4	13.9	7.0	12.1	-6.0	3.0	20.9	13.8	0.1
2014	55.8	57	58.7	46.2	75.3	49.1	59.1	59.6	68.5	58.3	61.7	66.3	83.0	69.3	77.5	60.1	12.7	1.3	3.0	20.1	7.7	20.2	18.4	0.5
2015	56.7	58.7	57.9	46.2	77.1	50.6	59.3	60.5	70.9	70.5	50.0	53.2	83.2	71.7	70.7	78.3	14.2	11.8	-7.9	7.0	6.1	21.1	11.4	17.8
2016	57.6	59.6	58.6	47	76.4	51.2	60.1	61	72.3	60.3	68.6	60.7	88.3	70.8	76.6	76.7	14.7	0.7	10.0	13.7	11.9	19.6	16.5	15.7
2017	58.1	59.2	59.9	46.6	76.2	52.2	60.6	60.8	64.4	68.1	56.0	41.3	81.7	72.8	60.8	57.1	6.3	8.9	-3.9	-5.4	5.5	20.6	0.2	-3.7
2018	58.4	59.2	58.1	47	76.6	52.5	61.2	61.5	70.7	58.9	68.3	52.8	80.6	73.7	70.4	67.6	12.3	-0.3	10.2	5.8	4.0	21.2	9.2	6.1
2019	59	58.9	58.5	47.7	75.6	53.5	62.4	61	70.5	75.6	63.2	53.1	82.4	70.1	73.9	60.8	11.5	16.7	4.7	5.4	6.8	16.6	11.5	-0.2
2020	60.1	59.6	60.1	51.6	75.7	55.3	61.8	60.4	71.4	65.8	58.7	59.5	82.0	73.9	73.0	68.1	11.3	6.2	-1.4	7.9	6.3	18.6	11.2	7.7
2021	60.6	59.5	60.8	53.2	75.5	55.9	62	60.6	69.3	73.7	55.5	52.2	81.0	69.6	71.1	63.1	8.7	14.2	-5.3	-1.0	5.5	13.7	9.1	2.5
Mean	57.75	58.59	58.86	47.77	75.22	51.75	60.73	60.78	69.5	65.9	60.1	53.5	81.6	70.9	71.9		11.8	7.3	1.2	5.7	6.4	19.2	11.2	5.3
Minimum	55.2	56.9	57.4	45.9	71.8	48.1	59.1	59.6	64.4	58.3	48.0	40.3	75.0	67.0	60.8		6.3	-0.3	-9.4	-6.0	3.0	13.7	0.2	-3.7
Maximum	60.6	59.6	60.8	53.2	77.1	55.9	62.4	62.3	72.3	75.6	70.7	66.3	88.3	73.9	77.5		14.7	16.7	12.1	20.1	11.9	21.2	18.4	17.8

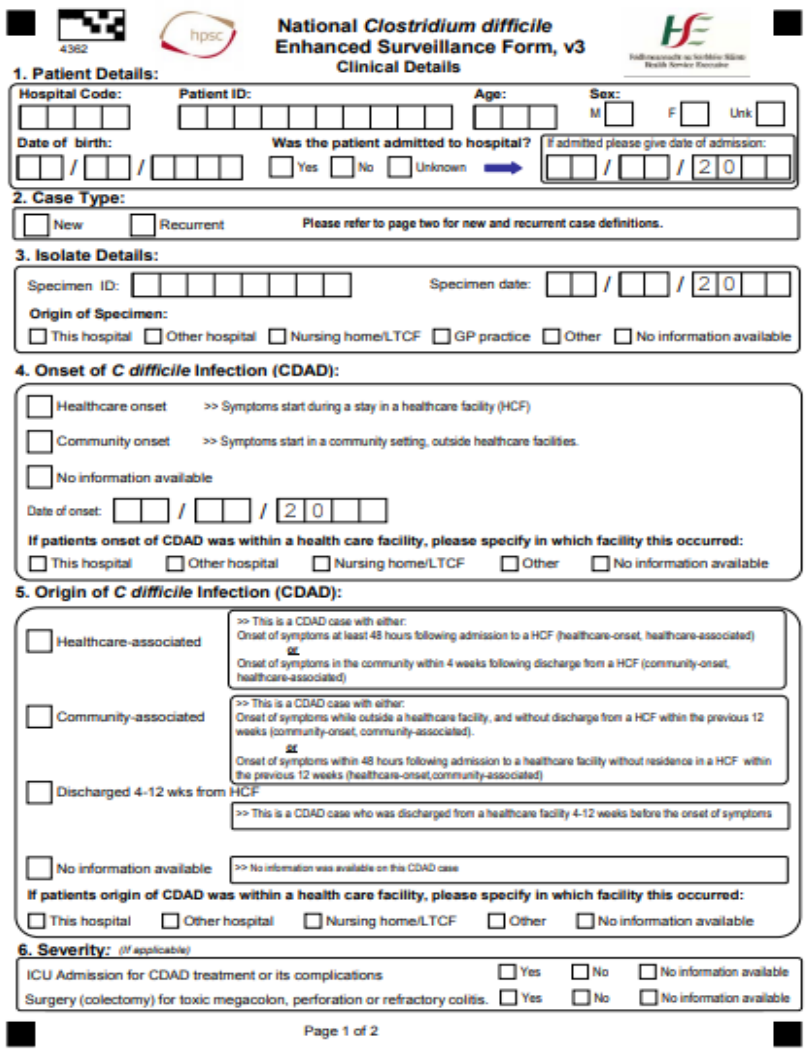
*MFTE Medicine For The Elderly

Appendix 3: Average length of stay (days) of Beaumont Hospital patients by specialty and year, non-CDI versus CDI patients

	All patients								CDI								Difference non-CDI versus CDI							
Year	BH	Renal	Oncology	Neurosurgery	MFTE*	Surgery	Medical	Gastroenterology	BH	Renal	Oncology	Neurosurgery	MFTE*	Surgery	Medical	Gastroenterology	All	Renal	Oncology	Neurosurgery	MFTE*	Surgery	Medical	Gastroenterology
2012	9.9	6.9	8	10.2	30.3	7.2	11	13.2	58.8	31.8	16.5	32.1	178.5	45.2	55.1	67.4	48.9	24.9	8.5	21.9	148.2	38.0	44.1	54.2
2013	9.2	6.8	8.7	10.2	29.5	6.5	9.8	11.2	61.1	31.5	21.6	27.7	100.2	39.8	89.4	27.0	51.9	24.7	12.9	17.5	70.7	33.3	79.6	15.8
2014	9.4	6.9	10.1	9.2	28.9	7.1	9.1	9.7	62.4	46.9	17.0	25.0	98.6	56.2	80.7	75.3	53.0	40.0	6.9	15.8	69.7	49.1	71.6	65.6
2015	9.5	6.4	11.7	10.3	27.8	7.1	9	9.7	61.4	52.0	25.5	67.5	69.8	52.4	93.6	29.3	51.9	45.6	13.8	57.2	42.0	45.3	84.6	19.6
2016	9.1	6.2	12.4	10	23.3	6.8	8.7	10	51.6	28.9	37.6	15.3	76.0	77.0	44.7	35.1	42.5	22.7	25.2	5.3	52.7	70.2	36.0	25.1
2017	9.3	6.5	11.5	9.7	20.2	6.9	9.4	9.2	42.5	52.7	32.0	22.0	85.7	38.7	31.5	35.1	33.2	46.2	20.5	12.3	65.5	31.8	22.1	25.9
2018	9.7	6.7	13.1	9.5	20.1	7	10.2	9.5	76.2	51.5	31.9	66.8	161.7	78.1	42.2	28.2	66.5	44.8	18.8	57.3	141.6	71.1	32.0	18.7
2019	9.9	6.4	12.3	10.6	21.1	7.2	10.4	8.9	66.5	49.7	49.0	35.5	206.3	37.6	44.5	20.5	56.6	43.3	36.7	24.9	185.2	30.4	34.1	11.6
2020	9.1	5.9	11.2	10	16.7	6.8	9.5	8.5	62.0	39.3	48.9	74.0	240.5	28.6	32.0	23.2	52.9	33.4	37.7	64.0	223.8	21.8	22.5	14.7
2021	9.4	6.1	10	11.5	16.1	7.1	9.8	9.2	31.5	29.3	26.0	35.7	62.5	31.6	29.8	13.0	22.1	23.2	16.0	24.2	46.4	24.5	20.0	3.8
Mean	9.45	6.48	10.9	10.12	23.4	6.97	9.69	9.91	57.4	41.3	30.6	40.2	128.0	48.5	54.3	35.4	47.9	34.9	19.7	30.0	104.6	41.6	44.6	25.5
Minimum	9.1	5.9	8	9.2	16.1	6.5	8.7	8.5	31.5	28.9	16.5	15.3	62.5	28.6	29.8	13.0	22.1	22.7	6.9	5.3	42.0	21.8	20.0	3.8
Maximum	9.9	6.9	13.1	11.5	30.3	7.2	11	13.2	76.2	52.7	49.0	74.0	240.5	78.1	93.6	75.3	66.5	46.2	37.7	64.0	223.8	71.1	84.6	65.6

*MFTE Medicine For The Elderly

Appendix 4: Enhanced C. difficile Surveillance Form, provided by the HPSC



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hpsc

National *Clostridium difficile* Enhanced Surveillance Form, v3
Clinical Details

HSE

1. Patient Details:

Hospital Code: | Patient ID: | Age: | Sex: M F Unk

Date of birth: / / | Was the patient admitted to hospital? Yes No Unknown → If admitted please give date of admission: / / 20

2. Case Type:

New Recurrent **Please refer to page two for new and recurrent case definitions.**

3. Isolate Details:

Specimen ID: | Specimen date: / / 20

Origin of Specimen:

This hospital Other hospital Nursing home/LTCF GP practice Other No information available

4. Onset of *C difficile* Infection (CDAD):

Healthcare onset >> Symptoms start during a stay in a healthcare facility (HCF)

Community onset >> Symptoms start in a community setting, outside healthcare facilities.

No information available

Date of onset: / / 20

If patients onset of CDAD was within a health care facility, please specify in which facility this occurred:

This hospital Other hospital Nursing home/LTCF Other No information available

5. Origin of *C difficile* Infection (CDAD):

Healthcare-associated
>> This is a CDAD case with either:
Onset of symptoms at least 48 hours following admission to a HCF (healthcare-onset, healthcare-associated)
or
Onset of symptoms in the community within 4 weeks following discharge from a HCF (community-onset, healthcare-associated)

Community-associated
>> This is a CDAD case with either:
Onset of symptoms while outside a healthcare facility, and without discharge from a HCF within the previous 12 weeks (community-onset, community-associated).
or
Onset of symptoms within 48 hours following admission to a healthcare facility without residence in a HCF within the previous 12 weeks (healthcare-onset,community-associated)

Discharged 4-12 wks from HCF
>> This is a CDAD case who was discharged from a healthcare facility 4-12 weeks before the onset of symptoms

No information available
>> No information was available on this CDAD case

If patients origin of CDAD was within a health care facility, please specify in which facility this occurred:

This hospital Other hospital Nursing home/LTCF Other No information available

6. Severity: *(if applicable)*

ICU Admission for CDAD treatment or its complications Yes No No information available

Surgery (colectomy) for toxic megacolon, perforation or refractory colitis. Yes No No information available

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Definitions of *Clostridium difficile* Infection:

***A confirmed Clostridium difficile* - associated disease (CDAD) case is a patient two years or older, 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 edoscopy.

- 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**

Case Type:

New Case of CDAD:

A new case of CDAD is either:

A. The first episode of CDAD

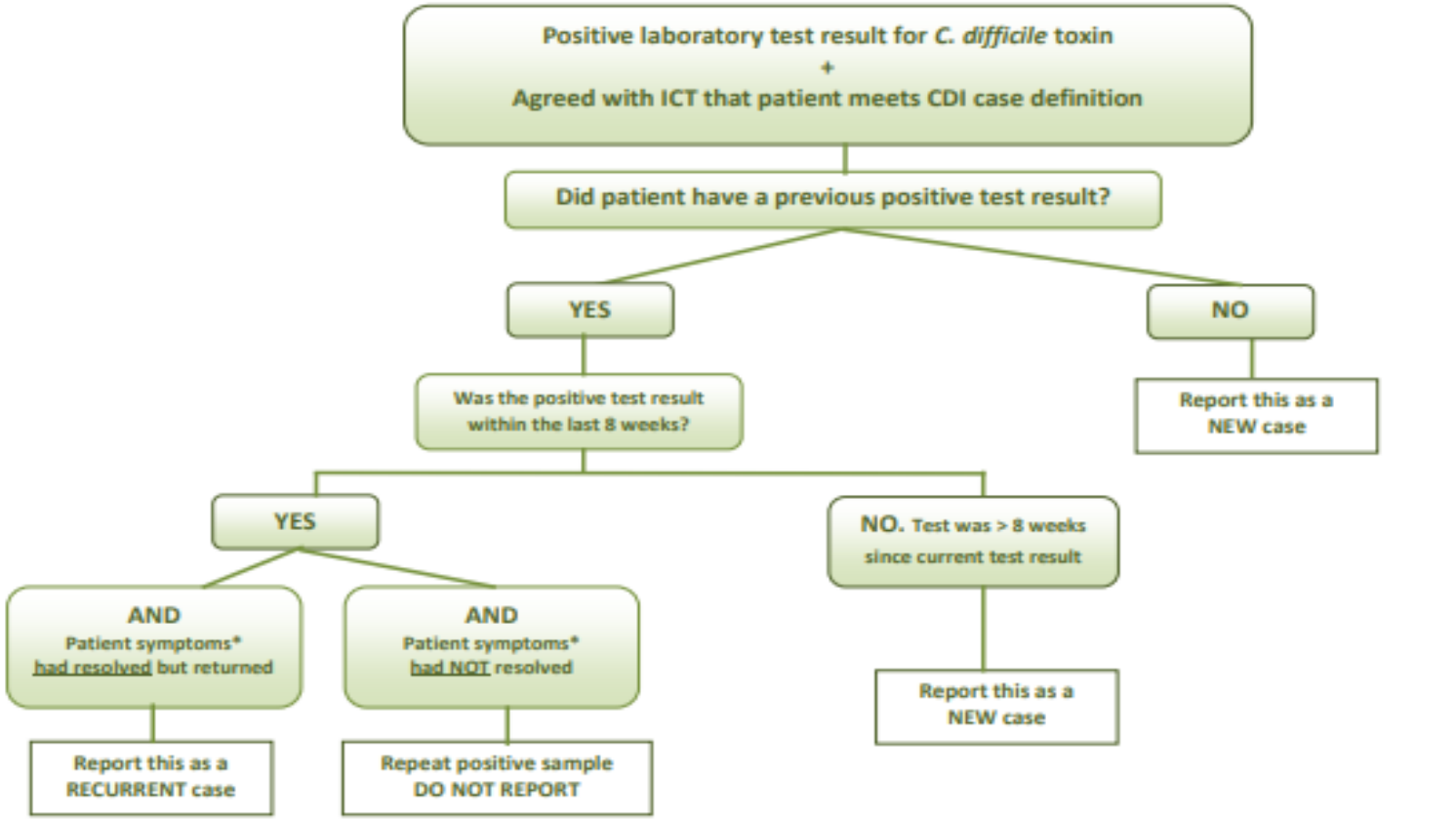
OR

B. A subsequent episode of CDAD with onset of symptoms **more than 8 weeks** after the onset of a previous episode.

Recurrent Case of CDAD:

A recurrent case of CDAD 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.**

Appendix 5: Algorithm to Determine CDI Case Type, provided by the HPSC



*If a patient's symptoms are not available then if the specimen collected date is ≤14 days of a previously notified specimen collection date, treat this as a repeat positive specimen.

Appendix 6: Algorithm to Determine Origin of CDI, provided by the HPSC