ORIGINAL ARTICLE

# Multihospital Outbreak of *Clostridium difficile* Ribotype 027 Infection: Epidemiology and Analysis of Control Measures

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OBJECTIVE. To report a large outbreak of *Clostridium difficile* infection (CDI; ribotype 027) between June 2007 and August 2008, describe infection control measures, and evaluate the impact of restricting the use of fluoroquinolones in controlling the outbreak.

DESIGN. Outbreak investigation in 3 acute care hospitals of the Northern Health and Social Care Trust in Northern Ireland.

INTERVENTIONS. Implementation of a series of CDI control measures that targeted high-risk antibiotic agents (ie, restriction of fluoroquinolones), infection control practices, and environmental hygiene.

RESULTS. A total of 318 cases of CDI were identified during the outbreak, which was the result of the interaction between *C. difficile* ribotype 027 being introduced into the affected hospitals for the first time and other predisposing risk factors (ranging from host factors to suboptimal compliance with antibiotic guidelines and infection control policies). The 30-day all-cause mortality rate was 24.5%; however, CDI was the attributable cause of death for only 2.5% of the infected patients. Time series analysis showed that restricting the use of fluoroquinolones was associated with a significant reduction in the incidence of CDI (coefficient, −0.054; lag time, 4 months; $P = .003$).

CONCLUSION. These findings provide additional evidence to support the value of antimicrobial stewardship as an essential element of multifaceted interventions to control CDI outbreaks. The present CDI outbreak was ended following the implementation of an action plan improving communication, antibiotic stewardship, infection control practices, environmental hygiene, and surveillance.

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*Clostridium difficile* is the primary cause of nosocomial infectious diarrhea, causing significant morbidity and increasing healthcare costs.[1] In recent years, a change in virulence of prevalent *C. difficile* strains has been associated with the occurrence of a number of outbreaks with increased severity and significant mortality.[2-6] This change involved the emergence of a new strain, referred to as PCR ribotype 027.[2,3] The increased virulence of *C. difficile* ribotype 027 is associated with mutations to the *tcdC* gene, which interferes with the downregulation of toxins A and B (the main *C. difficile* virulence factors), leading to the production of high levels of these toxins.[3,5,7] The first case of *C. difficile* infection (CDI) due to ribotype 027 that was recognized in the Republic of Ireland was reported in 2005 in a patient with diarrhea transferred from a hospital in the United Kingdom (UK).[8] In Northern Ireland, a survey of *C. difficile* ribotypes was undertaken between September and December 2006; no cases of CDI ribotype 027 were identified.[2] In June 2007, however, the first case of infection due to this ribotype was reported in the Antrim Area Hospital. The index patient was of advanced age and had multiple comorbidities. Ribotyping was requested because of the severity of the patient's illness. Subsequently, a rise in the incidence of CDI was noted in 3 acute care hospitals within the Northern Health and Social Care Trust (hereafter, "the Trust"), with an accompanying increase in the reported number of cases of *C. difficile* ribotype 027

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infection. In recognition of higher than expected numbers of cases of CDI, the Trust declared an outbreak in January 2008. The objectives of this article are to report the occurrence of a large multihospital outbreak of CDI due to ribotype 027 in Northern Ireland, to describe infection control practices, and to evaluate the impact of restricting the use of fluoroquinolones by utilizing time series analysis.[9-11]

## METHODS

As this work was considered a case review and outbreak investigation, ethical approval and the approval of the Trust's research and development department were not required; the study has been registered with the research and development department.

### Setting and Study Period

The Trust consists of 4 acute care hospitals (907 beds) and 4 rehabilitation/palliative care hospitals (141 beds). The investigation consisted of 2 components: (1) a description of the CDI outbreak and the infection control measures applied during the outbreak (June 16, 2007 through August 31, 2008) and (2) a retrospective ecological analysis that involved collecting monthly data on the usage of antibiotics and the incidence of CDI over a 5.5-year study period (January 2004 through June 2009). The former component included only 3 affected acute care hospitals (Antrim Area Hospital [411 beds], Mid-Ulster Hospital [124 beds], and Whiteabbey Hospital [130 beds]) and 2 rehabilitation/palliative care facilities (Braid Valley Hospital [36 beds] and Moyle Hospital [45 beds]). The latter component included only the affected acute care hospitals.

### Microbiology and Pharmacy Data

The monthly incidence of CDI was obtained from the clinical microbiology information system over the study period. Data duplication was eliminated by using data for only the first test result positive for *C. difficile* if there was more than 1 positive test result within 28 days, as this was considered a single episode. Within the hospital laboratory, clinical samples were processed according to routine microbiologic procedures. All assays for *C. difficile* toxins A and B in feces from patients with colitis-like symptoms were performed in the microbiology laboratory at Antrim Area Hospital using an enzyme-linked immunoabsorbant assay (Premier). Isolates of putative *C. difficile* were referred to the Anaerobe Reference Laboratory at the University Hospital of Wales, Cardiff, for confirmation and typing.

Prior to December 2007, ribotyping was requested on the basis of medical assessment of clinical severity. From the beginning of December 2007, all *C. difficile* toxin–positive samples were cultured anaerobically, and those yielding growth of putative *C. difficile* were sent for ribotyping. PCR ribotyping was performed according to the method described by others,[12] and the banding patterns produced were assigned to the PCR ribotyping library.[13]

Prior to January 2008, in accordance with government guidelines, the testing of feces from all patients 65 years of age and older with diarrhea was the routine practice. The testing of feces for patients at least 2 years of age and younger than 65 years of age was done at physician request; toxin assays were done twice per day. Following the declaration of the outbreak in January 2008, diarrheal stool from all patients 12 years of age and older was tested; toxin assays were done twice per day and when requested by the physician.

For the purpose of this investigation, CDI was defined as being present if a patient had a toxin-positive test plus diarrhea (defined as an increased number [2 or more] of watery or liquid stools [ie, type 6 or 7, according to the Bristol Stool Scale][14] that is greater than normal for the patient, over a period of 24 hours). CDI was classified as severe if any of the following criteria were present: white blood cell count greater than 1,500 cells/mm$^3$, temperature higher than 38.5°C, acutely rising blood creatinine (eg, an increase of more than 50% above baseline), and evidence of severe colitis (abdominal signs and radiologic findings). Clinical signs were obtained by retrospective chart review using a standardized form. Cases of CDI were classified as follows:[15] (1) hospital-associated *C. difficile* disease was considered present in any patient with CDI symptom onset more than 48 hours after admission to the hospital or any patient with CDI symptom onset up to 48 hours after admission to a hospital, provided that symptom onset was less than 4 weeks after the last discharge from a hospital; (2) community-associated *C. difficile* disease was considered present in any patient with CDI symptom onset up to 48 hours after admission to a hospital, provided that symptom onset occurred more than 12 weeks after the previous discharge from a hospital; (3) indeterminate *C. difficile* disease was considered present in any case patient that did not fit any of the above criteria.

The following epidemiological case definition was used for the outbreak: patients with a positive *C. difficile* toxin test result from June 16, 2007 and compatible symptoms who were inpatients in the affected hospitals when the sample was obtained. The case definition includes case patients up to August 31, 2008. This case definition was chosen to include the first confirmed case of infection with *C. difficile* ribotype 027, which occurred on June 16, 2007; the outbreak was declared over in August 2008. The criteria for declaring the end of the outbreak were (1) a sustained reduction in the number of new cases of CDI each month to the level that could have been regarded as the Trust's baseline before the outbreak commenced, (2) a reduction in the number of case patients with ribotype 027 newly acquired in the hospital environment, (3) no evidence of patient-to-patient transmission, and (4) evidence of successful implementation of the agreed control measures.

To assess relationships existing between antibiotic use and the incidence of CDI, the monthly quantities of each antibiotic delivered for patient care to each ward of the affected acute care hospitals were obtained from the hospital phar-

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macy information system. These quantities were converted into defined daily doses (DDDs) following the recommendations of the World Health Organization.[16]

### Antibiotic Restriction Policy

The Trust had guidelines for the empirical treatment of all major clinical infectious syndromes. In January 2008, the empirical use of fluoroquinolones was restricted, with the exceptions of treatment for epididymo-orchitis, prostatitis, pelvic inflammatory disease, orbital cellulitis, and cellulitis in patients with penicillin allergy. Otherwise, use of a restricted antibiotic required exemption by a medical consultant, with monitoring by the hospital pharmacy in consultation with the Consultant Medical Microbiologist.

### Routine Infection Control Practices

The Trust's infection control policies were consistent with national and international guidelines, which included regular hand hygiene between every patient contact. All patients with a diagnosis of CDI were placed in single room or cohort contact isolation. Detergent and water were used for general ward cleaning, while detergent followed by 1,000-ppm hypochlorite solution was used for cleaning the isolation rooms on a daily basis and on discharge or transfer of the patient.

### Infection Control Practices during the Outbreak

An action plan addressing communication, infection control practices, clinical management, environmental hygiene, and surveillance was agreed to by the Outbreak Control Team (OCT). Information leaflets on the nature of CDI and the measures to control it were issued to staff, patients, and visitors. Patient care equipment and environmental cleaning in all patient care areas, which included general wards and isolation rooms, was enhanced by the introduction of an intensive cleaning including the use of vaporized hydrogen peroxide and chemical disinfection with a chlorine-releasing agent. In general wards, patient care equipment and the environment were cleaned daily and on patient discharge or transfer using a chlorine dioxide product in a one-step process; in isolation areas cleaning took place twice daily and on discharge or transfer using a two-step process: detergent followed by 1,000-ppm hypochlorite solution. An isolation ward with 8 single rooms and 4 bays, each containing 4 beds, was designated for CDI patients. All patients with laboratory-confirmed cases of CDI and patients with presumptive CDI who were unable to maintain personal hygiene were isolated; other patients with presumptive CDI were placed in open wards, with contact precautions being applied, until laboratory confirmation was received. A care bundle, the Saving Lives High Impact Intervention number 7, was reinforced Trust-wide to control the spread of CDI.[17] The latter identified 5 main key elements as being necessary to reduce the incidence of CDI: prudent antibiotic use, correct hand hygiene, environmental decontamination, personal protective equipment, and isolation and cohort nursing.[17] The Infection Control Team (ICT) monitored use of the care bundle with support from 3 senior nurses seconded from their normal duties. Hospital Site Implementation Teams (HSITs), comprising a senior manager, ward nursing and medical staff, and Hotel Services staff, were formed to ensure that the OCT action plan was implemented. The Trust infection control policies were implemented in all clinical areas, and there was an ongoing program of audit of hand hygiene practices and environmental cleanliness.

### Mortality Determination

Mortality was determined on the basis of the information provided by Northern Ireland Statistics and Research Agency from the General Register Office for registered deaths during the outbreak period. This information is based on the Medical Certificate of Cause of Death (MCCD), which is completed by a Registered Medical Practitioner who has treated the deceased in the 28 days prior to death.[18] On the MCCD, the cause of death can be included in part I (indicating that *C. difficile* infection was the disease or condition directly leading to death) or part II of the certificate (indicating that *C. difficile* was significant condition contributing to death but not related to the disease or condition causing it).

### Statistical Analysis

The $\chi^2$ test was used to determine whether there were significant differences in clinical severity and 30-day mortality between patients infected with ribotype 027 and others infected with non-027 ribotypes. This was performed using SPSS for Windows, version 17 (SPSS Institute). Autoregressive integrated moving average (ARIMA) models, using the Box-Jenkins method for analysis,[19] were used to evaluate whether relationships existed between antibiotic use and the incidence of CDI, as described elsewhere.[11] To evaluate the effect of the antibiotic restriction policy, dummy variables were created, whereby 0 and 1 represent the pre- and postintervention periods, respectively. A transfer function model that models a time series as a function of its past values and random errors was built. For each individual series, an ARIMA model was identified and fitted according to the Box and Jenkins methodology.[19] The model was identified by determining the ARIMA model orders ($p$, $d$, and $q$) using autocorrelation and partial autocorrelation. The model parameters were then estimated by the unconditional least squares method. Finally, the adequacy of the model was checked,[11] and the statistical significance of the parameters was determined. After identification of the multivariate transfer function models, the cross-correlation function was determined by estimating the correlations between the series describing antibiotic use at different time lags and the CDI series. Significance tests for parameter estimates were used to eliminate the unnecessary terms in the model. A $P$ value of .05 was considered to be statistically significant. The final model was derived by the econometric "gen-

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eral-to-specific" approach. All time series analyses were performed using EViews 6 software (QMS).

## RESULTS

In the affected hospitals, a marked increase in CDI incidence rates was observed in late 2007 and early 2008 (Figure 1); the mean annual CDI incidence rates, for the affected acute care hospitals for the 5 years from January 2004 to December 2008 were 0.05, 0.07, 0.08, 0.12, and 0.11 cases per 100 bed-days. The mean annual CDI incidence rates for each affected acute care hospital for these years were 0.05, 0.06, 0.09, 0.13, and 0.10 cases per 100 bed-days for Antrim Area Hospital; 0.05, 0.06, 0.07, 0.09, and 0.13 cases per 100 bed-days for Whiteabbey Hospital; and 0.06, 0.10, 0.06, 0.10, and 0.11 cases per 100 bed-days for Mid-Ulster Hospital. In 2007, the mean fluoroquinolone usage rates for Antrim Area Hospital, Whiteabbey Hospital, and Mid-Ulster Hospital were 12, 13, and 9 DDDs per 100 bed-days, respectively. In 2008 (following restrictions on the use of fluoroquinolone), the mean fluoroquinolone usage rates for these 3 hospitals was 2, 3, and 1 DDDs per 100 bed-days, respectively.

The median age of patients was 81 years, with 84% of the affected patients aged over 65 years. Of the 318 affected patients, the onset of illness occurred within 2 days after admission for 57 patients (18%). Of these 57 patients, 26 (8%) had been discharged from a Trust hospital within the 4 weeks prior to onset of CDI. A further 8 (3%) patients had been discharged from a Trust hospital between 4 and 12 weeks prior to onset of CDI. Twenty-three of the patients (7%) whose onset of symptoms occurred within 48 hours after admission had not been hospitalized in a Trust hospital in the 12 weeks before the onset of CDI. General characteristics of the affected patients ($n = 318$) during the outbreak period and a comparison of characteristics of *C. difficile* ribotype 027–infected patients and those of non-027 *C. difficile* ribotype–infected patients are shown in Tables 1 and 2, respectively.

A total of 154 of the 318 patients with CDI were identified as deceased from all causes up to October 21, 2008. One of those patients who died within 30 days was not identified by MCCD, giving a total of 155 deaths (48.7% of patients). Details of mortality rates in relation to overall mortality, mortality within 30 days, and mortality after admission are shown in Table 3. Clinical outcomes (ie, nonsevere or severe) and 30-day mortality for patients infected with ribotype 027 and for those infected with other identified ribotypes are shown in Table 4. No statistically significant differences were observed. Of the 15 patients infected with ribotype 027 identified as deceased within 30 days (Table 4), 3 had *C. difficile* mentioned on part I of the MCCD and 8 had *C. difficile* mentioned on part II; 4 had no mention of *C. difficile* on the death certificate. Of the 19 patients infected with non-027 ribotypes identified as deceased within 30 days (Table 4), 2 had *C. difficile* mentioned on part I of the MCCD, 7 had *C. difficile* mentioned on part II, and 10 had no mention of *C. difficile* on the death certificate.

The time series analysis model showed that restricting the use of fluoroquinolones by 1 DDD per 100 bed-days resulted 4 months later in a significant reduction in the incidence of CDI, by 0.054 cases per 100 bed-days (Table 5). The determination coefficient ($R^2$) of the final model was 0.66; that is, 66% of the variation in the monthly incidence of CDI over the study period was explained by the factors included in the model. A graphical representation of the relationship between the monthly use of fluoroquinolones and the monthly incidence of CDI is presented in Figure 1.

## DISCUSSION

Recent reports of CDI outbreaks of greater severity and significant mortality associated with *C. difficile* ribotype 027 have

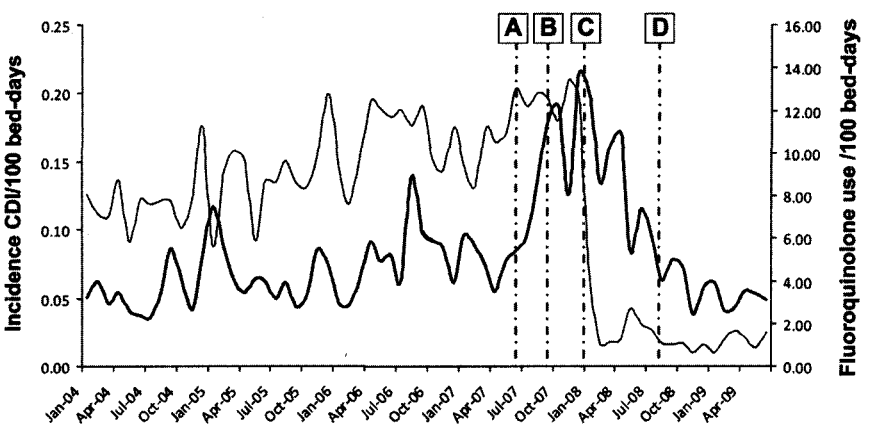


FIGURE 1. Comparison of the monthly incidence of *Clostridium difficile* infection (CDI; *thick line*) and fluoroquinolone usage rate (*thin line*) at Antrim Area Hospital, Mid-Ulster Hospital, and Whiteabbey Hospital, January 2004 through June 2009. *A*, Admission of a patient with CDI ribotype 027 in June 2007. *B*, Laboratory results for this patient reported to the Northern Health and Social Care Trust. *C*, CDI outbreak declared; infection control measures and a fluoroquinolones restriction policy introduced. *D*, Outbreak declared over.

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TABLE 1. General Demographic and Clinical Characteristics of Patients with *Clostridium difficile* Infection (CDI) during the Outbreak Period (June 16, 2007, through August 31, 2008)

| Characteristic | Value |
|---|---|
| Median age (IQR), years[a] | 81 (71–87) |
| >65 years old | 266/318 (84) |
| Male sex | 120/318 (38) |
| Female-to-male ratio | 1.7 : 1 |
| LOS, median (IQR), days | |
| In hospital | 36 (16–72) |
| In hospital prior to first positive CDI toxin test | 11 (2–32) |
| In hospital from first positive CDI toxin test to discharge | 19 (8–36) |
| Onset of illness within 2 days after admission | |
| Any status | 57/318 (18) |
| Discharged from a Trust hospital within 4 weeks prior to onset of CDI | 26/318 (8) |
| Discharged from a Trust hospital 4–12 weeks prior to onset of CDI | 8/318 (3) |
| Not hospitalized in a Trust hospital in the 12 weeks prior to onset of CDI[b] | 23/318 (7) |
| Comorbidity score[c] at admission, median (IQR) ($n$ = 263) | 1 (0–2) |
| Type of ward admission | |
| Medical | 216/258 (84) |
| Surgical | 37/258 (14) |
| ICU | 5/258 (2) |
| Normal residence | |
| Nursing or residential home | 63/258 (24) |
| Long-stay hospital facility | 5/258 (2) |
| Own home | 190/258 (74) |
| Ribotyping results | |
| Samples sent for ribotyping[d] | 213/318 (67) |
| Samples failed to grow or were not able to be ribotyped | 39/213 (18) |
| Samples ribotyped | 174/213 (82) |
| Ribotype identified | |
| Ribotype 027 | 71/174 (41) |
| Non-027 ribotype | 103/174 (59) |
| Ribotype 001 | 24/174 (14) |
| Ribotype 078 | 20/174 (12) |
| Others | 59/174 (34) |
| Clinical events in the 12 weeks prior to diagnosis | |
| Receipt of antibiotics[e] | 238/261 (91) |
| Receipt of proton pump inhibitors | 160/268 (60) |
| Gastrointestinal surgery | 14/269 (5) |
| Receipt of immunosuppressive therapy | 23/263 (9) |
| Receipt of prolonged laxative therapy | 78/259 (30) |
| Admission to hospital | 132/256 (52) |

NOTE. Data are proportion (%) of patients, unless otherwise indicated. ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; Trust, Northern Health and Social Care Trust.

[a] Only completed and available records were included for each variable.

[b] It was not possible to establish whether any of these patients had been in a hospital of another trust in the 28 days before onset of CDI.

[c] Comorbidity was scored using the Charlson Index as described by others.[20]

[d] The ribotyping of all *C. difficile* isolates started only in late 2007 and early 2008.

[e] Mostly amoxicillin-clavulanic acid (145/261 patients; 56%), piperacillin-tazobactam (81/261 patients; 31%), macrolides (69/261 patients; 26%), and fluoroquinolones (46/261 patients; 18%).

focused attention on the changing epidemiology of this pathogen. The objectives of this research were to report (in line with recent recommendation on outbreak investigations)[21] a large multihospital outbreak of infection due to *C. difficile* ribotype 027 in Northern Ireland, to describe infection control practices, and to evaluate the impact of restricting the use of fluoroquinolones to control the outbreak. The majority of patients affected during the outbreak were exposed to 1 or more risk factors, such as host factors (eg, advanced age and comorbidities),[3,22] exposure to factors that disrupt the normal

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TABLE 2. Characteristics of Patients with *Clostridium difficile* Ribotype 027 Infection and Patients with Non-027 Ribotype Infection during the Outbreak Period (June 16, 2007, through August 31, 2008)

| Characteristic | Ribotype 027 infection | Non-027 ribotype infection |
|---|---|---|
| Median age (IQR), years | 82 (75–87) | 82 (72–88) |
| Male sex | 23/67 (34) | 35/95 (37) |
| LOS, median (IQR), days | | |
| In hospital | 37 (17–76) | 37 (25–81) |
| In hospital prior to onset of CDI | 10 (3–25) | 12 (3–31) |
| In hospital following first onset of CDI to discharge | 24 (9–55) | 22 (10–42) |
| Comorbidity score at admission, median (IQR) (ribotype 027, $n = 54$; other ribotypes, $n = 74$) | 1 (0–2) | 1 (1–3) |
| Normal residence | | |
| Nursing or residential home | 10/40 (25) | 22/73 (30) |
| Long-stay hospital facility | 1/40 (3) | 1/73 (1) |
| Own home | 29/40 (73) | 50/73 (69) |
| Clinical events in the 12 weeks prior to diagnosis | | |
| Receipt of antibiotics | 45/45 (100) | 71/76 (93) |
| Receipt of proton pump inhibitors | 22/44 (50) | 41/78 (53) |
| Gastrointestinal surgery | 3/45 (7) | 5/78 (6) |
| Receipt of immunosuppressive therapy | 4/41 (10) | 6/77 (8) |
| Receipt of prolonged laxative therapy | 15/39 (38) | 20/75 (27) |
| Admission to hospital | 19/35 (54) | 38/70 (54) |

NOTE. Data are proportion (%) of patients, unless otherwise indicated. Only completed and available records were included for each variable. CDI, *C. difficile* infection; IQR, interquartile range; LOS, length of stay.

protective intestinal microflora (ie, broad-spectrum antibiotics),[23-25] the use of gastric acid–suppressive agents,[26-28] and poor infection control practices (eg, relating to the healthcare environment, and healthcare workers' compliance with hand hygiene).[3,29] Auditing of compliance for adequate environmental cleanliness and antibiotic stewardship before the outbreak occurred showed that these practices were suboptimal.[30,31]

The analysis of the ribotyped *C. difficile* isolates (during the outbreak period) showed that ribotype 027 was the most frequently identified strain (41% of isolates), highlighting the predominance of this ribotype in the outbreak. The 30-day all-cause mortality rate observed in this outbreak (24.5%) was similar to that in other outbreaks.[32-34] However, CDI was the attributable cause of death for 2.5% of the *C. difficile*–infected patients who died within 30 days. Although a number of studies have reported on the contribution of ribotype 027 to greater disease severity and mortality,[35-38] our analysis showed no statistically significant difference in the 30-day mortality and clinical severity between patients infected with ribotype 027 and patients infected with non-027 ribotypes. This finding could be related to the patients' different susceptibility profiles—which patients were affected by exposure to one or more of the previously mentioned risk factors—and the impact of the isolation ward in maximizing clinical management skill and experience. A single group of clinicians and nurses were looking after CDI patients in the designated isolation ward. This may have led to the development of high levels of skill in the clinical assessment and management of people with CDI and the ability to react more quickly to the clinical impact of CDI ribotype 027 to mitigate its effect. Of note is that 12% of the non-027 ribotype isolates were *C. difficile* ribotype 078, an emerging strain that was reported as having mechanisms for toxin hyperproduction similar to those of ribotype 027.[2] The assessment of comparative clinical severity between patients infected with *C. difficile* ribotype 027 and those infected with other ribotypes requires further investigation with a larger sample size to allow the construction of multivariate models, which should include other factors that may have influenced our findings, for example, age, morbidity on admission, and effects of ribotype 078 infection. Thus, a definitive conclusion in relation to this assessment was not possible, and these findings must therefore be interpreted with caution.

The investigation showed temporal relationships between the use of certain antibiotic classes and the incidence of CDI. Restricting the use of fluoroquinolones was associated with a significant reduction in the incidence of CDI, confirming fluoroquinolones as high-risk agents.[25,39] In addition, the analysis showed that the use of amoxicillin-clavulanic acid and macrolides was also positively correlated with the incidence of CDI. However, second- and third-generation cephalosporins did not appear as significant variables in the model, since their usage rate was already very low within the Trust. The control of antibiotics within the Trust has been scrutinized over a long period of time.[40] This analysis led to more robust guidance on the use of antibiotics to be developed and introduced in the study site hospitals in 1995, with a significant

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TABLE 3. Mortality Rates of the Affected Patients during the *Clostridium difficile* Infection (CDI) Outbreak (June 16, 2007, through August 31, 2008)

| Variable | No. (%) of patients ($n$ = 318) | | |
|---|---|---|---|
| | Mortality within 30 days | Mortality after 30 days | Overall mortality[a] |
| *C. difficile* mentioned on MCCD | 38 (11.9) | 13 (4.0) | 51 (16.0) |
| *C. difficile* recorded in part I of the MCCD | 8 (2.5) | 5 (1.5) | 13 (4.1) |
| *C. difficile* recorded in part II of the MCCD | 30 (9.4) | 8 (2.5) | 38 (11.9) |
| Total, all causes | 78 (24.5) | 77 (24.2) | 155 (48.7) |

NOTE. MCCD, Medical Certificate of Cause of Death.

[a] The 30-day and the after-30-day mortality rates grouped together.

revision in 1999 specifically to restrict the use of broad-spectrum cephalosporins in response to an outbreak of CDI, as there was strong association with the use of these agents.[41] All antibiotic usage policies were regularly reviewed and updated.

Importantly, it has been emphasized that an approach combining optimal infection control practices with antimicrobial stewardship is required in order to interrupt transmission and successfully control CDI outbreaks.[25,42,43] The current CDI outbreak ended after the implementation of a series of controlling measures that targeted high-risk antibiotic agents (ie, restricting the use of fluoroquinolones), infection control practices, and environmental hygiene; this was achieved through the extended ICT and HSIT ensuring that ward staff understood their role in controlling the outbreak. The implementation of the infection control and environmental hygiene measures was uniform among the affected hospitals, with the exception of the isolation ward, which was established only in Antrim Area Hospital. This isolation ward received patients from all hospitals within the Trust when they were fit to be transferred; patients unfit for transfer were isolated in single rooms in their admitting hospitals. Auditing of the compliance for adequate environmental cleanliness[30] and antibiotic stewardship (data provided by the European Surveillance of Antimicrobial Consumption network [ESAC] May 2009 survey) following the declaration of the outbreak showed a remarkable improvement in these practices. The ESAC 2009 survey results showed that compliance with the Antrim Area Hospital antibiotic guidelines was 70%, while a previous audit for compliance with the hospital guidelines in surgical wards (in 2006) showed a lower compliance rate (31%).[31] Similarly, external audits of environmental cleanliness (January 2008) showed that all hospitals within the Trust improved their compliance scores for adequate environmental cleanliness. Antrim Area Hospital scored 89% in a January 2008 audit, while in a previous audit (January 2007), the hospital score was 77%.[30] These results may provide an indication that the implementation of the outbreak-controlling measures was successful. Nevertheless, as the emergence of CDI is multifactorial, it is difficult to determine the relative contributions made by infection control measures and antimicrobial stewardship. This remains an area that needs further investigation.

The study has some limitations. First, although analysis of data included both nosocomial cases of CDI in Trust hospitals and other CDI cases, the percentage of patients who had not been hospitalized in a Trust hospital in the 12 weeks prior to onset of CDI was only 7% (Table 1). These patients were

TABLE 4. Clinical Outcome and 30-Day Mortality for Patients Identified with *Clostridium difficile* Ribotype 027 Infection and Patients with Non-027 Ribotype Infection during the Outbreak Period (June 16, 2007, through August 31, 2008)

| Variable | Proportion (%) of patients | | $P$[a] |
|---|---|---|---|
| | Ribotype 027 infection | Non-027 ribotype infection | |
| Clinical severity at date of first CDI-positive sample | | | .836 |
| Nonsevere | 34/46 (74) | 74/98 (76) | |
| Severe | 12/46 (26) | 24/98 (24) | |
| Clinical severity at worst point during this episode | | | .297 |
| Nonsevere | 26/39 (67) | 68/90 (76) | |
| Severe | 13/39 (33) | 22/90 (24) | |
| 30-day mortality | | | .713 |
| Alive | 52/67 (78) | 76/95 (80) | |
| Dead | 15/67 (22) | 19/95 (20) | |

NOTE. Only completed and available records were included for each variable. CDI, *C. difficile* infection.

[a] Statistically significant at $P < .05$.

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TABLE 5. Estimated Multivariate Time Series Analysis Model for the Impact of Restricting the Use of Fluoroquinolones on the Monthly Incidence of *Clostridium difficile* Infection (CDI) ($R^2 = 0.66$)

| Term | Lag time, months[a] | Coefficient ± SE[b] | *T* ratio | *P* |
|---|---|---|---|---|
| Fluoroquinolone use restriction | 4 | −0.054044 ± 0.017585 | −3.073 | .0033 |
| Macrolide use | 4 | 0.002935 ± 0.000848 | 3.460 | .0010 |
| Amoxicillin-clavulanic acid | 2 | 0.001797 ± 0.000528 | 3.401 | .0012 |
| AR | 1 | 0.495220 ± 0.118818 | 4.167 | .0001 |
| MA | 3 | 0.515774 ± 0.116495 | 4.427 | <.0001 |

NOTE. AR, autoregressive term representing past incidence density of CDI; MA, moving average term representing past disturbances in the incidence density of CDI.

[a] Delay necessary to observe the effect.

[b] Size and the direction of the effect.

included in the study, as it was not possible to establish whether any of these patients had been in a hospital of another trust in the 28 days before onset of CDI. However, it is unlikely that such a low percentage (7%) can influence the findings. Second, it was not possible to rule out the possibility that there had been unrecognized cases of CDI due to ribotype 027 before June 2007. Third, the CDI mortality was determined on the basis of MCCDs, which may lack accuracy and data completeness. The Trust addressed this issue from early in the outbreak by having an independent review of case notes of toxin-positive patients who were known to have died in 2007 in the Trust (of all causes) by 2 senior clinicians, one of whom was an external gastroenterologist. *C. difficile* was reported as significant condition contributing to death more frequently in the MCCD than in the reviewed case notes. The observed differences may have influenced the findings; however, such an error in completion of the MCCD is more likely to affect infections due to all *C. difficile* ribotypes rather than being selective for a specific ribotype. Following the declaration of the outbreak in 2008, the Trust reinforced guidance on completion of MCCD and established more robust measures to monitor deaths associated with CDI using direct reporting to a senior clinician and the reviewing Infection Control Prevention team data. The Trust would note that all reported figures are provisional, pending the completion of the "Public Inquiry into the Outbreak of *C. difficile* in Northern Trust Hospitals." Finally, the assessment of the impact of restricting fluoroquinolones did not take into account the changes in infection control practices that took place as a result of the CDI outbreak. However, such parameters may contribute to the 34% of the variance in CDI rates that was not explained by the final model.

In conclusion, the occurrence of this multihospital CDI outbreak was the result of the interaction between *C. difficile* ribotype 027 being introduced into the affected hospitals for the first time and other predisposing risk factors (ranging from host factors to less than optimal compliance with hospital infection control and environmental hygiene policies) that facilitated its spread. These findings provide additional evidence to support the value of antimicrobial stewardship as an essential element of multifaceted interventions to control CDI outbreaks. The CDI outbreak was controlled by the implementation of an action plan improving communication, antibiotic stewardship, infection control practices, environmental hygiene, and surveillance.

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