Open Forum Infectious Diseases

MAJOR ARTICLE

Community-Onset *Clostridioides Difficile* Infection in Hospitalized Patients in The Netherlands

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Background. *Clostridioides difficile* infection (CDI) is increasingly reported in the community. The aim of this study was to analyze characteristics of hospitalized patients with community-onset CDI (CO-CDI).

Methods. In the Netherlands, 24 hospitals (university-affiliated and general hospitals) participate in the sentinel CDI surveillance program. Clinical characteristics and 30-day outcomes of hospitalized patients >2 years old diagnosed with CDI are registered. Samples of these patients are sent to the national reference laboratory for polymerase chain reaction ribotyping. Data obtained for this surveillance from May 2012 to May 2018 were used to compare CO-CDI with hospital-onset (HO)-CDI episodes.

Results. Of 5405 registered cases, 2834 (52.4%) were reported as HO-CDI, 2174 (40.2%) were CO-CDI, and 339 (6.3%) had onset of symptoms in another healthcare facility (eg, nursing home). The proportion of CO-CDI increased over the years and was lower during winter months. Hospitalized patients with CO-CDI were younger (63.8 vs 68.0 years, $P < .001$) and more often females (53.0% vs 49.6%, $P = .02$) than patients with HO-CDI. Median time between onset of symptoms and CDI testing was longer in CO-CDI (4 vs 1 day, $P < .001$). Similar ribotypes were found in CO-CDI and HO-CDI, but ribotype 001 was more frequent among HO-CDI, whereas ribotype 023 was more frequent in CO-CDI. Six of 7 (85.7%) surgeries due to CDI, 27 of 50 (54%) ICU admissions due to CDI, and 48 of 107 (44.9%) of CDI-associated deaths were attributable to CO-CDI.

Conclusions. Our study demonstrates that patients hospitalized with CO-CDI contribute substantially to the total number of CDI episodes and CDI-associated complications in hospitals, stressing the need for awareness and early testing for CDI in community and outpatient settings and also in patients admitted from community with diarrhoea. Surveillance programs that also target nonhospitalized CDI patients are needed to understand the true burden and dynamics of CDI.

Keywords. *Clostridioides difficile*; *Clostridium difficile* infections in humans; surveillance.

Clostridioides difficile, formerly named *Clostridium difficile* [1], is a Gram-positive, anaerobic bacterium. Once a subject encounters *C difficile* spores, colonization and subsequent establishment of asymptomatic carriership or progression to symptomatic *C difficile* infection (CDI) is possible, especially when the gut microbiota is altered and protective humoral immunity is diminished [2, 3]. During the last decades, *C difficile* epidemiology has changed, and outbreaks due to so-called "hypervirulent" strains were reported in many countries [4]. Although CDI is often a healthcare-associated disease, it has recently been recognized that onset of symptoms is often in the community, after hospital discharge. Moreover, community-associated CDI, in patients without recent hospital admission, is increasingly recognized [5, 6]. In response to the outbreaks in the beginning of this millennium, many countries implemented compulsory or voluntary surveillance programs, to monitor CDI incidence rates and circulating ribotypes [7]. In the Netherlands, a voluntary CDI surveillance program has been implemented since 2009. Data from this sentinel surveillance program were used to compare characteristics and outcomes between patients with reported community-onset symptoms and patients with hospital-onset of symptoms.

MATERIALS AND METHODS

The Dutch sentinel CDI surveillance program is conducted by the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (RIVM) in collaboration with the Leiden University Medical Centre, where the national *C difficile* reference laboratory is housed. Between 2012 and 2018, 24 acute care hospitals located across the country have been participating in the voluntary surveillance, both university-affiliated hospitals (n = 6) and general hospitals (n = 18). In these hospitals, all CDI cases in hospitalized patients >2 years old are registered. Patients who are not admitted

Received 29 November 2018; editorial decision 19 November 2019; accepted 25 November 2019.

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DOI: 10.1093/ofid/ofz501

to the hospital, but treated as outpatients or by their general practitioner, are not included in our surveillance program. Each year, an annual report is compiled, which can be found on the website of the RIVM [8]. For this analysis, all patients registered for the Dutch sentinel CDI surveillance from May 2012 to May 2018 were considered.

Definitions

Definitions valid for our surveillance program were also used for this study and are shown in Table 1.

Data Collection

Clinical characteristics of all CDI cases were collected via a web-based questionnaire by the local medical microbiologist or infection control practitioners. Collected data included age, gender, date of sample submission, location of symptom onset (ie, community, hospital, nursing home, or other healthcare facility), severity of CDI, and 30-day outcomes. Antibiotic use at the moment of hospital admission or during admission preceding the submission of the stool sample was also registered (in terms of yes/no).

Microbiological Analyses

At each participating hospital, CDI was diagnosed per local protocol. Diagnostic strategies changed over the years. In May 2013, 58% of participating hospitals relied on stand-alone Tox A/B enzyme immune-assay (Tox A/B EIA), whereas 26% of hospitals relied on a stand-alone nucleic acid amplification test (NAAT). By May 2017, 54% of the participating hospitals had switched to the use of an ESCMID-recommended algorithm (either NAAT or glutamate dehydrogenase [GDH] EIA followed by confirmatory Tox A/B EIA or Tox A/B and GDH EIA as a first step optionally followed by NAAT or toxigenic culture) [9], whereas 33% of hospitals now (2017) relied on NAAT as stand-alone assay. Cultured *C difficile* isolates identified by matrix-assisted laser desorption/ionization time-of-flight analyzer (MALDI-TOF) or fecal samples (if no culture was performed at the local hospital) were sent to the national reference laboratory. At the national reference laboratory, samples were recultured on *C difficile* selective agar supplemented with cefoxitin amphotericin B and cycloserine (CLO medium; bioMérieux), with and without ethanol shock pretreatment [10]. After incubation in an anaerobic environment at 37°C for 48 hours, suspicious colonies were tested by an in-house GDH polymerase chain reaction (PCR) to confirm the presence of *C difficile* [10]. Polymerase chain reaction ribotyping was performed as previously described [11]. At the moment, the national reference laboratory is able to recognize 263 different ribotypes and collaborates with Leeds University hospital (Dr. Warren Fawley and Prof. Dr. Mark Wilcox) to expand the collection with clinical relevant types.

Table 1. Definitions Used in This Study

CDI	*Clostridioides difficile* infection. Diarrhea OR toxic megacolon in combination with a test positive for *C difficile* toxins or toxigenic *C difficile* and no alternative explanation for the diarrhea, or evidence of pseudomembranous colitis diagnosed by endoscopy, surgery or histopathology
Severe CDI	CDI with (1) bloody diarrhea, (2) pseudomembranous colitis, (3) dehydration and/or hypoalbuminemia (<20 g/L) or (4) fever >38.0°C and leukocytosis (>15.0 × 10^9/L)
Community-onset CDI (CO-CDI)	CDI in all patients who had onset of symptoms at home and were admitted because of or with these symptoms, regardless of whether there had been a previous hospital admission or not
Hospital-onset CDI (HO-CDI)	CDI in all patients who developed symptoms during hospital admission and were consequently diagnosed with CDI
Outbreak	>2 isolates of the same type detected less than 7 days apart in one hospital either with onset of symptoms on the same ward, or accompanied by an increased CDI monthly incidence within the hospital
Recurrence	A CDI episode occurring between 2 to 8 weeks after a previous episode
Complicated course	If ICU admission or surgery due to CDI or any mortality including CDI attributable mortality within the first 30 days after CDI diagnosis occurred
CDI attributable mortality	Mortality in a CDI patient in the absence of other comorbidities that would normally have led to death

Abbreviations: CDI, *Clostridioides difficile* infection; ICU, intensive care unit.

Statistical Analysis

Characteristics between patients with community-onset CDI (CO-CDI) and hospital-onset CDI (HO-CDI) were compared with *t* test, χ^2 test, or Mann-Whitney *U* test where appropriate. *Clostridioides difficile* infection incidence and HO-CDI incidence were calculated as the number of cases per 10 000 patient-days. The proportion of patients with CO-CDI and HO-CDI was calculated, also over the different years and seasons. Five hospitals (2 university-affiliated and 3 general hospitals) from different regions in the Netherlands with monthly admission data available were selected to study seasonal trends in CDI and HO-CDI for the years 2012/2013, 2014/2015, 2016/2017, and 2017/2018. A logistic regression analysis with CO-CDI as outcome variable and year, respectively, and season as covariate was performed to determine whether there was any annual or seasonal variation. For this regression analyses, 2 groups were created: all patients with CO-CDI were counted as such, and patients with HO-CDI or onset in another healthcare facility were counted as non-CO-CDI. Patients with missing location of onset were excluded for this analysis. In addition, a logistic regression analysis with CO-CDI as outcome variable was performed with age, gender, recurrence (yes/no), season, and year as covariates to determine factors independently associated with CO-CDI. A sensitivity analysis was performed in which the definition of CO-CDI was extended to include all patients who developed CDI symptoms within the first 2 days of hospital admission.

$P < .05$ were considered statistically significant. All analyses were performed using STATA SE statistical software, version 15.1 (StataCorp, College Station, TX).

RESULTS

Between May 2012 and May 2018, a total of 5405 CDI cases were registered in 24 participating hospitals. The annual mean incidence of CDI in hospitalized patients was 3.11 cases per 10 000 patient-days, ranging from 3.06 to 3.26 cases per 10 000 patient-days over the 5 years. The mean incidence of HO-CDI was 1.63 (95% confidence interval [CI], 1.57–1.69) and ranged from 1.75 (95% CI, 1.59–1.92) in 2012–2013 to 1.53 (95% CI, 1.39–1.68) in 2017–2018. During the 6-year period, the prevalence of the so-called hypervirulent PCR ribotype 027 decreased from 3.4% (95% CI, 2.0–4.8) in 2012–2013 to 0.6% (95% CI, 0.1–1.1%) in 2016–2017. In this sentinel surveillance program, only 1 outbreak (7 patients) due to ribotype 027 was reported over the study period, in May 2013. Other outbreaks reported during the study period were due to ribotype 001 (2 outbreaks), ribotype 015 (1 outbreak), and ribotype 826 (1 outbreak) [12]. The outbreaks affected 3 to 33 patients (median 4.5 patients). Of 5405 episodes, location of CDI symptoms onset was missing for 58 episodes. Of the remaining 5347 episodes, 2174 (40.2% of total) were CO-CDI, 2834 (52.4%) were HO-CDI, and 339 (6.3%) had onset of symptoms in a healthcare facility other than a hospital (162 in a nursing home and the other 177 not specified). Over the years, the proportion of CO-CDI increased from 35.4% in 2012–2013 to 44.9% in 2017–2018 (Figure 1). In univariate analysis, the proportion of CO-CDI cases was significantly higher in the last 4 years compared to the first year of the study period: odds ratio (OR) = 1.24 (95% CI, 1.01–1.51) for 2014–2015, OR = 1.28 (95% CI, 1.05–1.56) for 2015–2016, OR = 1.22 (95% CI, 1.00–1.48) for 2016–2017, and OR = 1.43 (95% CI, 1.17–1.75) for 2017–2018, respectively. During winter months, the proportion of HO-CDI was 60.7%: this fell to 53.1% in spring, 51.3% in summer, and 52.2% in autumn (data from 1045 CDI cases from 5 hospitals) (Figure 2). The seasonal variation in proportions of HO-CDI, CO-CDI, and episodes with onset in another healthcare facility over the years is shown in Figure 3. In univariate analysis, the proportion of CO-CDI was significantly lower in winter compared to the 3 other seasons: OR = 1.28 (95% CI, 1.10–1.49) for spring, OR = 1.42 (95% CI, 01.22–1.66) for summer, and OR = 1.27 (95% CI, 1.08–1.48) for autumn.

During the study period, 953 episodes were reported to be severe CDI: 662 (69.5%) of these were CO-CDI and 331 (34.7%) of these were HO-CDI. In total, 7 patients required surgery due to CDI; 6 of 7 (85.7%) of these surgeries were performed in CO-CDI episodes. Twenty-seven of the 50 (54%) intensive care unit (ICU) admissions due to CDI was reported in CO-CDI, and 48 of 107 (44.9%) of all CDI-associated mortality could be attributed to CO-CDI episodes.

When characteristics were compared between CO-CDI and HO-CDI, we found that patients with CO-CDI were younger than patients with HO-CDI (63.8 vs 68.0 years, $P = .000$) and more often females (53.0% vs 49.6%, $P = .02$) (Table 2). Of CO-CDI episodes, 472 of 1409 (33.5%) were classified as a recurrence. In contrast, only 16.2% of patients with HO-CDI had a CDI episode in the previous 2–8 weeks ($P = .000$ compared with CO-CDI). The median time between onset of symptoms and submission of a stool sample for CDI testing was 4 days (interquartile range [IQR], 2–11) in CO-CDI patients and 1 day (IQR, 0–2) in HO-CDI patients. Antibiotics were used by 2096 of 2517 (83.3%) HO-CDI patients, and 49.5% of patients with CO-CDI were using antibiotics at admission ($P = .000$).

Clostridioides difficile infection was more frequently reported to be severe in CO-CDI episodes (30.2% vs 12.8%, $P = .000$). The percentage of patients who required an ICU admission due to CDI was comparable among the 2 groups (1.4% vs 1.0%, respectively; $P = .15$), and CDI-associated mortality was also similar (2.6% vs 2.5%, $P = .86$). However, HO-CDI episodes more often had a complicated course than CO-CDI episodes (13.8% vs 10.5%, $P = .001$), and this was mainly due to a higher overall mortality in the HO-CDI group (12.8% vs 8.7% in the CO-CDI group, $P = .000$).

In multivariate logistic regression, younger age, spring/summer/autumn season, female gender, and recurrent episode were associated with CO-CDI (Table 3). In multivariate analysis, study year was not associated with CO-CDI.

Ribotyping results were available for 4068 episodes. The most common ribotypes in CO-CDI episodes were 014/020, 078/126, and 002. The most common ribotypes in HO-CDI were 014/020, 078/126, and 001 (Figure 4). Ribotype 001 was more frequently found in HO-CDI episodes than in CO-CDI episodes (10.0% vs 6.1%, $P = .000$), and ribotype 023 was more frequently found in CO-CDI (3.5% vs 2.1%, $P = .006$). After excluding the year 2016–2017 (in which a RT001 outbreak occurred), the results remained significant. Ribotype 027 was found in 20 of 1758 (1.1%) CO-CDI samples and 42 of 2310 (1.8%) of HO-CDI samples ($P = .08$).

In the sensitivity analysis, 440 patients who developed CDI symptoms within the first 2 days of admission were categorized as CO-CDI instead of HO-CDI. Just like in the main analysis, patients with CO-CDI were younger and more often females and experienced severe and recurrent CDI more frequently (data not shown).

DISCUSSION

In this 6-year period of sentinel CDI surveillance in 24 acute care hospitals in the Netherlands, we found that 40.2% of 5405 hospitalized patients with CDI reported onset of symptoms in the community. This observation is in line with earlier studies; proportions ranging from 36% to 58% have been described, although studies in the higher range included patients with symptom onset in the first 48 hours of admission as CO-CDI [10, 13–15]. When we extended

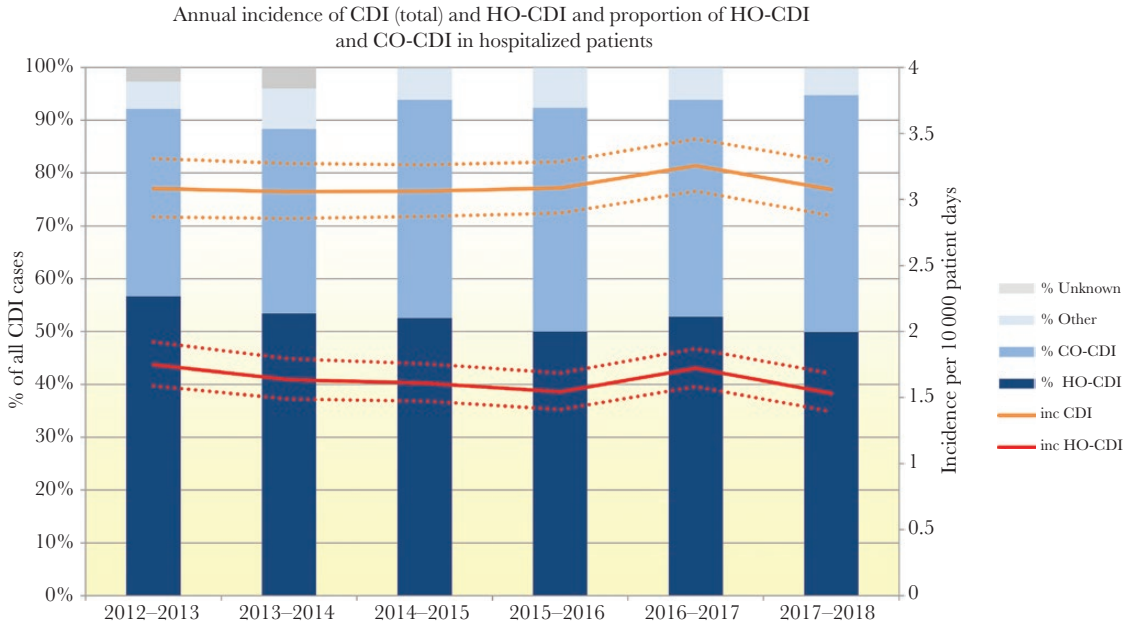

Figure 1. Proportions of hospital-onset *Clostridioides difficile* infection ([HO-CDI] dark blue), community-onset *C difficile* infection ([CO-CDI] middle blue), and episodes with onset in another healthcare facility (light blue) in hospitalized patients over the years, and incidence of CDI (total, orange line) and HO-CDI (red line) in hospitalized patients (data are from all 5405 cases, 2012–2018).

our definition of CO-CDI to all patients with symptoms in the community or within the first 2 days of admission, 48% of patients were classified as CO-CDI, and CO-CDI was thereby more frequent than HO-CDI. The incidence of HO-CDI was relatively stable over the seasons, but CO-CDI was less often observed during winter. The higher proportions in spring, summer, and autumn for CO-CDI might indicate that CO-CDI is less related to the winter peak in antibiotic use or that CO-CDI development is delayed in these patients. Antibiotic use was indeed less frequently reported in CO-CDI compared with HO-CDI. However, only antibiotic use at moment of admission was included, and no data about previous antibiotic treatment (eg, in the last 3 months) were available.

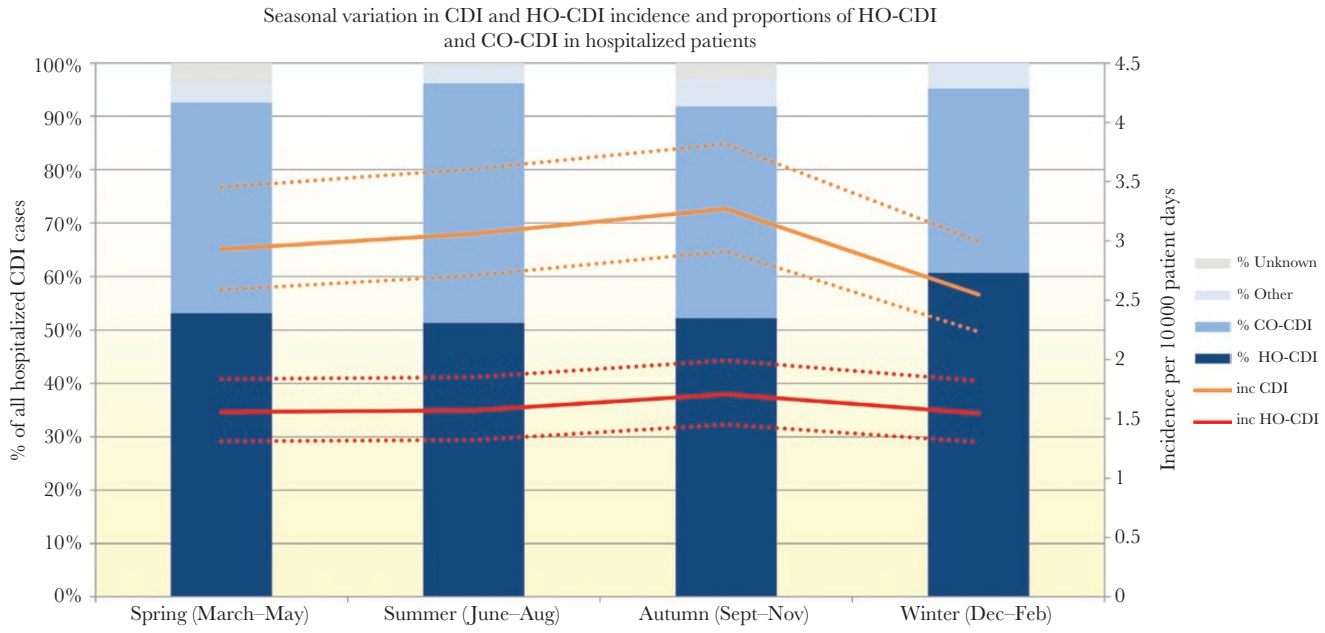

Figure 2. Proportions of hospital-onset *Clostridioides difficile* infection ([HO-CDI] dark blue), community-onset *C difficile* infection ([CO-CDI] middle blue), and episodes with onset in another healthcare facility (light blue) in hospitalized patients over the seasons, and incidence of CDI (total, orange line) and HO-CDI (red line) in hospitalized patients (data are from 5 hospitals, 1045 cases, for 2012/2013, 2014/2015, 2016/2017, and 2017/2018).

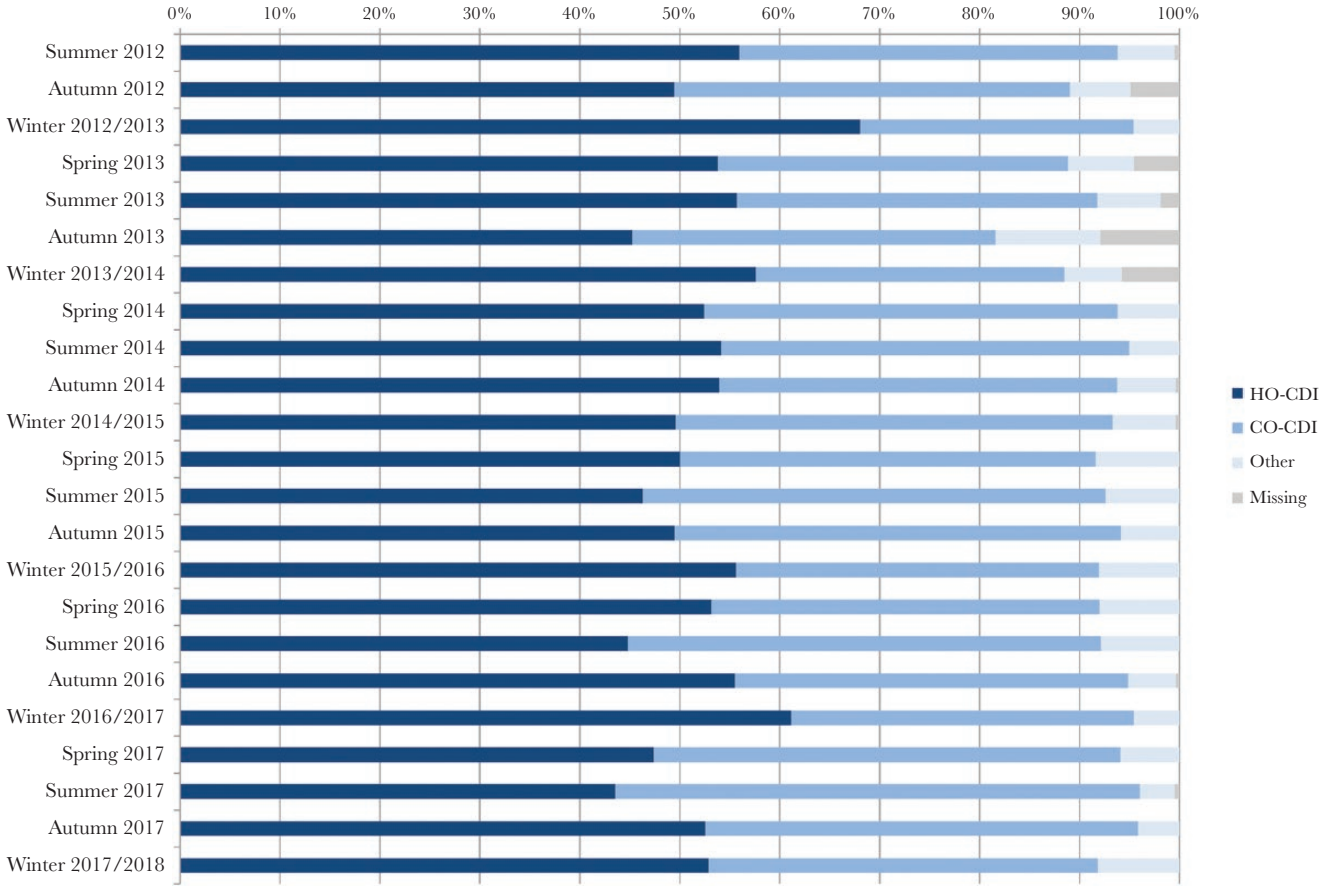

Figure 3. Proportions of hospital-onset *Clostridioides difficile* infection (HO-CDI), community-onset *C difficile* infection (CO-CDI), and episodes with onset in another healthcare facility over the seasons and years in hospitalized patients (data are from 5186 cases, 2012–2018).

In our study, we only analyzed hospitalized patients, because this is the targeted group of our CDI surveillance program, similar to surveillance programs in many other countries. Therefore, our cohort consisted of all patients with HO-CDI and patients with CO-CDI who were subsequently admitted to the hospital. It is understandable that mostly patients with severe or difficult-to-treat CO-CDI were admitted to the hospital. The restriction to admitted patients introduces collider

Table 2. Characteristics of CDI Episodes in CO-CDI (n = 2174) and HO-CDI (n = 2834)

Characteristics	CO-CDI	HO-CDI	*P* Value
Mean age (SD)	63.8 (20.5)	68.0 (17.5)	<.001
Male (%)	1021/2173 (47.0)	1429/2834 (50.4)	.02
Previous CDI <8 weeks (%)	472/1409 (33.5)	304/1575 (16.2)	<.001
Median days onset symptoms-sample submission (IQR)	4 (2–11)	1 (0–2)	<.001
Severe CDI (%)	622/2057 (30.2)	331/2262 (12.8)	<.001
Colitis	97/2057 (4.7)	47/2593 (1.8)	<.001
Dehydration	321/2057 (15.6)	164/2429 (6.3)	<.001
Bloody diarrhea	170/2057 (8.3)	40/2593 (1.5)	<.001
Fever	207/2057 (10.1)	135/2593 (5.2)	<.0001
Complicated Course (%)	197/1879 (10.5)	331/2392 (13.8)	.001
Surgery due to CDI	6/1879 (0.3)	1/2392 (0.04)	.03
ICU admission due to CDI (%)	27/1879 (1.4)	23/2392 (1.0)	.15
CDI-associated 30-day mortality (%)	48/1879 (2.6)	59/2392 (2.5)	.86
Overall 30-day mortality (%)	164/1879 (8.7)	307/2392 (12.8)	<.001

Abbreviations: CO-CDI, community-onset *Clostridioides diffcile* infection; HO-CDI, hospital-onset *C difficile* infection; IQR, interquartile range; SD, standard deviation.

Table 3. Multivariate Analysis of Variables Associated With CO-CDI

Variable	Odds Ratio (95% CI)
Age (Each Year Increase)	0.99 (0.98–0.99)
Gender	
Male	1 (reference)
Female	1.19 (1.03–1.36)
Recurrence	
No	1 (reference)
Yes	2.08 (1.78–2.44)
Season	
Winter	1 (reference)
Spring	1.43 (1.18–1.74)
Summer	1.57 (1.29–1.92)
Autumn	1.26 (1.04–1.54)
Year	
2012–2013	1 (reference)
2013–2014	0.76 (0.57–1.01)
2014–2015	1.01 (0.77–1.31)
2015–2016	0.96 (0.73–1.24)
2016–2017	0.94 (0.72–1.21)
2017–2018	1.03 (0.79–1.34)

Abbreviations: CI, confidence interval; CO-CDI, community-onset *Clostridioides difficile* infection.

bias, a specific form of selection bias. Included patients were either patients with HO-CDI or patients with severe or recurrent CO-CDI, necessitating admission. Patients with mild or moderate CO-CDI are therefore underrepresented in the cohort. Despite this limitation, we think that our study demonstrates several important findings.

The majority (65.3%) of severe CDI episodes in hospitalized patients had a community-onset. This demonstrates that although we do not know which proportion of CO-CDI episodes requires hospital admission, their share in severe cases in the hospital is substantial. *Clostridioides difficile* infection-related complications were often reported in CO-CDI episodes: the majority (6 of 7, 85.7%) of all surgery due to CDI could even be attributed to CO-CDI episodes. A direct comparison of CO-CDI versus HO-CDI episodes shows that in these hospitalized CO-CDI episodes, CDI was more often reported to be severe and that CDI attributable mortality was comparable between CO-CDI and HO-CDI. However, it is unclear to what extent these observations would change if all CO-CDI episodes would have been included. For example, a recent US study, in which both inpatients and outpatients were enrolled (instead of only patients with CO-CDI and subsequent hospital admission), did find a higher disease severity in patients with HO-CDI, on the contrary [16].

Patients with CO-CDI were younger and more often females than patients with HO-CDI, and we thereby confirm findings from previous studies [13, 14, 17]. The younger age in CO-CDI may reflect younger mean age in the community than in the hospital, but once more indicates that not all patients with CDI have the traditional risk factors such as age >65 years. The higher proportion of females in the CO-CDI group has been suggested to be a reflection of a more care-seeking behavior in females compared with males and, therefore, a higher chance of being diagnosed and hospitalized with CDI [17, 18]. Similar to other studies [13], the median delay between onset of symptoms and submission of a stool sample was higher in CO-CDI (median 4 days) than in HO-CDI (1 day) in our cohort. Of note, the delay may both be caused by a patient's delay in seeking medical attention and lack of clinical CDI suspicion by healthcare workers.

During the study period, CDI was found at an endemic rate with a low rate of RT027 and only a few (mostly limited) outbreaks, thereby minimizing the impact of hospital outbreaks on the proportions of CO-CDI versus HO-CDI and minimally impacting retrieved ribotypes in both groups. Although similar ribotypes were identified in CO-CDI and HO-CDI, ribotype 001 was more frequently found in HO-CDI. Polymerase chain reaction ribotype 001 is one of the most common types found in the Dutch surveillance program (ranging from 3.4% to 10.2% in the last 5 years). On the other hand, RT023 was more frequently found in CO-CDI. RT023 contains all 3 toxins (TcdA, TcdB, and CDT) and was recently reported to be associated with severe disease (Shaw HA, Preston MD, Vendrik KEW et al., unpublished observations, 2019). However, a community source for RT023 has not been identified yet and among asymptomatic *C difficile* carriers, RT023 is not frequently found, making them an unlikely reservoir for RT023 (Crobach MJT, manuscript in preparation) [19].

The proportion of CO-CDI seemed to be increasing over the years, although this was not significant in multivariate analysis. It is unfortunate that in the Dutch CDI surveillance, no information about previous healthcare contact is registered. Therefore, we do not know whether the reported (increasing) CO-CDI cases were due to (an increase in) true community-acquired cases (CA-CDI, defined as CDI and no previous healthcare admission within the previous 12 weeks) or community-onset healthcare facility-associated cases (CO-HCFA-CDI, defined as CDI with onset of symptoms in the community or within 48 hours of admission and a healthcare admission within the previous 4 weeks) [7, 20, 21]. In the Netherlands, the mean length of stay (LOS) in hospitals has dropped from 8.5 days in 2000 to 5.2 days in 2012, and it remained relatively stable from 2012 onwards. Because hospital LOS has decreased over the years, adverse events including hospital-acquired CDI (HA-CDI) presenting as diarrhea with a community onset may increasingly become apparent only after discharge. Studies have shown that HA-CDI is especially frequently reported within the 4 weeks after discharge [15, 18] when patients have been exposed to *C difficile* spores in the hospital environment [22] and possible inpatient and postdischarge antibiotic treatment may have led to a disruption of the protective microbiota.

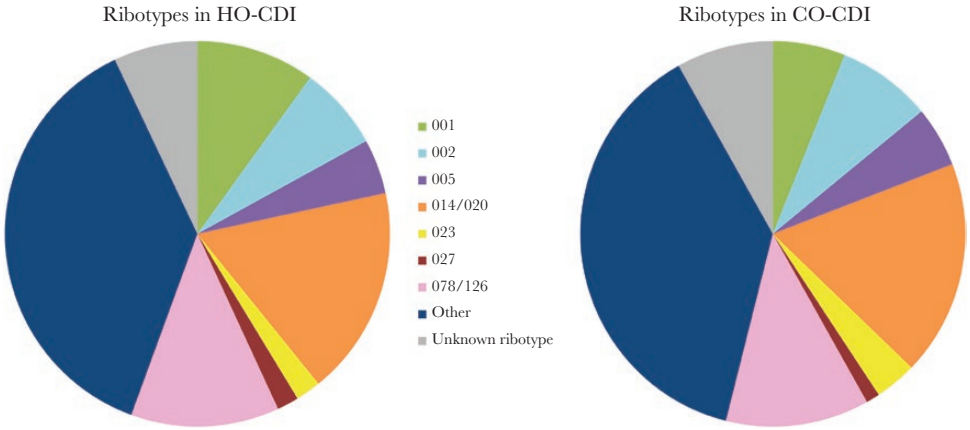

Figure 4. Ribotype distribution in hospital-onset *Clostridioides difficile* infection (HO-CDI) (left) and community-onset *C difficile* infection (CO-CDI) (right) in hospitalized patients (data from 4068 samples with polymerase chain reaction ribotyping result available, 2012–2018: 1758 CO-CDI episodes and 2310 HO-CDI episodes).

A large-scale US study including data from 2000 to 2007 demonstrated that HA-CDI was the reason for readmission in 1.8% of 170 995 readmissions and was thereby even more reported than HA-CDI that occurred during the initial admission, suggesting that most HA-CDI cases may now be occurring after discharge [18]. Another US study performed in 2011 confirmed that a large proportion of HA-CDI occurs postdischarge, by demonstrating that of 188 900 HA-CDI cases, 57% had onset of symptoms during hospitalization, whereas 43% developed symptoms in the community [23]. Of note, a large proportion of these HA-CDI cases (31%) were due to the NAP1/RT027 strain, which may have been a major reason why many patients developed CDI after being exposed to *C difficile* during admission. In addition, in Denmark, 46% of HA-CDI cases registered in 1 Capital Region in Denmark in 2010–2015 had community-onset of symptoms [24]. However, lower proportions of CO-HA-CDI have been reported in other studies [16, 25], indicating local differences in frailty of the studied population, hospital LOS, CDI awareness in the hospitals or community, circulating ribotypes, and differing healthcare systems. Besides the reported increase in HA-CDI occurring postdischarge, CA-CDI incidence has also been reported to have increased over the last years [26]. The reported rate of CA-CDI in hospitalized patients was 14% in a European study in 2008 [27]. In 2016, 5756 of 7711 (74.6%) of episodes registered for European CDI surveillance led by European Centre for Disease Prevention and Control (ECDC) were HA-CDI, whereas the remainder were either CA-CDI or CDI of unknown origin [28]. It is interesting to note that CA-CDI is often reported in patients who lack specific risk factors for CDI [5, 29]. Whether the increase in CA-CDI is a true increase, or also partly determined by a higher awareness of CDI in the community in patients without typical risk factors, is difficult to ascertain.

CONCLUSIONS

In conclusion, in an endemic CDI setting, we found that 40% of hospitalized CDI patients reported community-onset symptoms. A substantial proportion of CDI complications is caused by CO-CDI. Therefore, healthcare workers, especially general practitioners, should be aware of CDI (recurrences) with onset of symptoms in the community and consider CDI testing. Because only hospitalized CDI patients are included in our (and many other including ECDC) sentinel surveillance programs, the importance of CO-CDI (which includes both CA-CDI and CO-HA-CDI) as a public health concern remains unclear. Therefore, we think that additional studies in the community and amongst outpatients are needed to elucidate this.

Acknowledgments

We sincerely thank all infection control personnel, laboratory technicians, and medical microbiologists who contributed to this study.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of *Clostridium difficile* as *Clostridioides difficile* (Hall and O'Toole 1935) Prévot 1938. Anaerobe **2016**; 40:95–9.
2. Crobach MJ, Vernon JJ, Loo VG, et al. Understanding *Clostridium difficile* colonization. Clin Microbiol Rev **2018**; 31:e00021-17.
3. Smits WK, Lyras D, Lacy DB, et al. *Clostridium difficile* infection. Nat Rev Dis Primers **2016**; 2:16020.
4. Freeman J, Bauer MP, Baines SD, et al. The changing epidemiology of *Clostridium difficile* infections. Clin Microbiol Rev **2010**; 23:529–49.
5. Wilcox MH, Mooney L, Bendall R, et al. A case-control study of community-associated *Clostridium difficile* infection. J Antimicrob Chemother **2008**; 62:388–96.
6. Bauer MP, Veenendaal D, Verhoef L, et al. Clinical and microbiological characteristics of community-onset *Clostridium difficile* infection in The Netherlands. Clin Microbiol Infect **2009**; 15:1087–92.
7. Krutova M, Kinross P, Barbut F, et al.; survey contributors. How to: surveillance of *Clostridium difficile* infections. Clin Microbiol Infect **2018**; 24:469–75.
8. Crobach MJ, van Dorp SM, Terveer EM, et al. *Eleventh Annual Report of the National Reference Laboratory for Clostridium difficile and Results of the Sentinel Surveillance*. **2017**. Available at: https://www.rivm.nl/documenten/

eleventh-annual-report-of-national-reference-laboratory-for-clostridium-difficile-and-0. Accessed 3 December 2019.
9. Crobach MJ, Planche T, Eckert C, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection. Clin Microbiol Infect **2016**; 22(Suppl 4):S63–81.
10. Paltansing S, van den Berg RJ, Guseinova RA, et al. Characteristics and incidence of *Clostridium difficile*-associated disease in The Netherlands, 2005. Clin Microbiol Infect **2007**; 13:1058–64.
11. Bidet P, Barbut F, Lalande V, et al. Development of a new PCR-ribotyping method for *Clostridium difficile* based on ribosomal RNA gene sequencing. FEMS Microbiol Lett **1999**; 175:261–6.
12. Crobach MJT, Voor In 't Holt AF, Knetsch CW, et al. An outbreak of *Clostridium difficile* infections due to new PCR ribotype 826: epidemiologic and microbiologic analyses. Clin Microbiol Infect **2018**; 24:309.e1–4.
13. Tan XQ, Verrall AJ, Jureen R, et al. The emergence of community-onset *Clostridium difficile* infection in a tertiary hospital in Singapore: a cause for concern. Int J Antimicrob Agents **2014**; 43:47–51.
14. Viseur N, Lambert M, Delmee M, et al. Nosocomial and non-nosocomial *Clostridium difficile* infections in hospitalised patients in Belgium: compulsory surveillance data from 2008 to 2010. Euro Surveill **2011**; 16:pii:20000.
15. Kutty PK, Benoit SR, Woods CW, et al. Assessment of *Clostridium difficile*-associated disease surveillance definitions, North Carolina, 2005. Infect Control Hosp Epidemiol **2008**; 29:197–202.
16. Reveles KR, Pugh MJV, Lawson KA, et al. Shift to community-onset *Clostridium difficile* infection in the national Veterans Health Administration, 2003-2014. Am J Infect Control **2018**; 46:431–5.
17. Fellmeth G, Yarlagadda S, Iyer S. Epidemiology of community-onset *Clostridium difficile* infection in a community in the South of England. J Infect Public Health **2010**; 3:118–23.
18. Murphy CR, Avery TR, Dubberke ER, Huang SS. Frequent hospital readmissions for *Clostridium difficile* infection and the impact on estimates of hospital-associated *C. difficile* burden. Infect Control Hosp Epidemiol **2012**; 33:20–8.
19. Zomer TP, VAN Duijkeren E, Wielders CC, et al. Prevalence and risk factors for colonization of *Clostridium difficile* among adults living near livestock farms in the Netherlands. Epidemiol Infect **2017**; 145:2745–9.
20. Kuijper EJ, Coignard B, Tüll P; ESCMID Study Group for Clostridium difficile; EU Member States; European Centre for Disease Prevention and Control. Emergence of *Clostridium difficile*-associated disease in North America and Europe. Clin Microbiol Infect **2006**; 12(Suppl 6):2–18.
21. McDonald LC, Coignard B, Dubberke E, et al.; Ad Hoc Clostridium difficile Surveillance Working Group. Recommendations for surveillance of *Clostridium difficile*-associated disease. Infect Control Hosp Epidemiol **2007**; 28:140–5.
22. Norén T, Akerlund T, Bäck E, et al. Molecular epidemiology of hospital-associated and community-acquired *Clostridium difficile* infection in a Swedish county. J Clin Microbiol **2004**; 42:3635–43.
23. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med **2015**; 372:825–34.
24. Olesen B, Hallberg H, Bangsborg J, et al. A new approach to recognition of *Clostridium difficile* infections with community onset. Clin Microbiol Infect **2015**; 21:e55–6.
25. Kennedy C, Waldron C, Skally M, et al. The epidemiology of *Clostridium difficile* infection in a national kidney transplant center. Clin Transplant **2017**; 31:e12962.
26. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. Am J Gastroenterol **2012**; 107:89–95.
27. Bauer MP, Notermans DW, van Benthem BH, et al.; ECDIS Study Group. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet **2011**; 377:63–73.
28. European Centre for Disease Prevention and Control. Healthcare-associated infections: *Clostridium difficile* infections. In: ECDC. Annual Epidemiological Report for 2016. Stockholm: ECDC; **2018**.
29. Kuntz JL, Chrischilles EA, Pendergast JF, et al. Incidence of and risk factors for community-associated *Clostridium difficile* infection: a nested case-control study. BMC Infect Dis **2011**; 11:194.