Enhanced surveillance of *Clostridium difficile* infection occurring outside hospital, England, 2011 to 2013

WN Fawley [1], KA Davies [2,3], T Morris [4], P Parnell [2], R Howe [3], MH Wilcox [1,2,3], on behalf of the Clostridium difficile Ribotyping Network (CDRN) Working Group [5]

1. Public Health Laboratory Leeds, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
2. Department of Microbiology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
3. Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, United Kingdom
4. UK Anaerobe Reference Unit (UKARU), Public Health Wales, Cardiff, United Kingdom
5. The members of the working group are listed at the end of the article

Correspondence: Mark H. Wilcox (mark.wilcox@nhs.net)

Citation style for this article:
Fawley WN, Davies KA, Morris T, Parnell P, Howe R, Wilcox MH, on behalf of the Clostridium difficile Ribotyping Network (CDRN) Working Group. Enhanced surveillance of Clostridium difficile infection occurring outside hospital, England, 2011 to 2013. Euro Surveill. 2016;21(29):pii=30295. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.29.30295

Article submitted on 08 October 2015 / accepted on 00 March 2016 / published on 21 July 2016

There are limited national epidemiological data for community-associated (CA)-*Clostridium difficile* infections (CDIs). Between March 2011 and March 2013, laboratories in England submitted to the *Clostridium difficile* Ribotyping Network (CDRN) up to 10 diarrhoeal faecal samples from successive patients with CA-CDI, defined here as *C. difficile* toxin-positive diarrhoea commencing outside hospital (or less than 48 hours after hospital admission), including those cases associated with community-based residential care, with no discharge from hospital within the previous 12 weeks. Patient demographics and *C. difficile* PCR ribotypes were compared for CA-CDIs in our study and presumed healthcare-associated (HA) CDIs via CDRN. Ribotype diversity indices, ranking and relative prevalences were very similar in CA- vs HA-CDIs, although ribotypes 002 ($p \leq 0.0001$),020 ($p = 0.009$) and 056 ($p < 0.0001$) predominated in CA-CDIs; ribotype 027 ($p = 0.01$) predominated in HA-CDIs. Epidemic ribotypes 027 and 078 predominated in institutional residents with CDI (including care/nursing homes) compared with people with CDI living at home. Ribotype diversity decreased with increasing age in HA-CDIs, but not in CA-CDIs. Ribotype 078 CA-CDIs were significantly more common in elderly people (3.4% (6/174) vs 8.7% (45/519) in those aged < 65 and ≥ 65 years, respectively; $p = 0.019$). No antibiotics were prescribed in the previous four weeks in about twofold more CA-CDI vs HAs (38.6% (129/334) vs 20.3% (1,226/6,028); $p < 0.0001$). We found very similar ribotype distributions in CA- and HA-CDIs, although a few ribotypes significantly predominated in one setting. These national data emphasise the close interplay between, and likely common reservoirs for, CDIs, particularly when epidemic strains are not dominant.

Introduction

Clostridium difficile infection (CDI) has long been considered primarily to be a nosocomial disease, most notably associated with increased age, hospitalisation and antibiotic use [1]. There is, however, limited information on the epidemiology of community-associated (CA)-CDI, but data suggest that the incidence of CA-CDI could be increasing [2-4]. However, variation in reported rates may be due to varying definitions and case ascertainment bias as a consequence of suboptimal or incomplete testing of community-based patients [5]. In general, it is also known that there is marked underascertainment of the causes of diarrhoea in the community [6,7].

In conjunction with mandatory reporting of CDI cases in England [8], additional surveillance includes voluntary submission of faecal samples to a centrally funded scheme (*Clostridium difficile* Ribotyping Network (CDRN) for England and Northern Ireland), which has provided specific data on circulating *C. difficile* PCR ribotypes since 2007. CDRN now examines over a third of all reported CDI cases in England [9]. A better understanding of the epidemiology of CA-CDI is required in order to achieve improved prevention and control of cases. We have therefore augmented the national CDRN surveillance scheme to compare the patient demographics and *C. difficile* ribotypes associated with healthcare (HA)- and CA-CDI over a two-year period, March 2011 to March 2013.

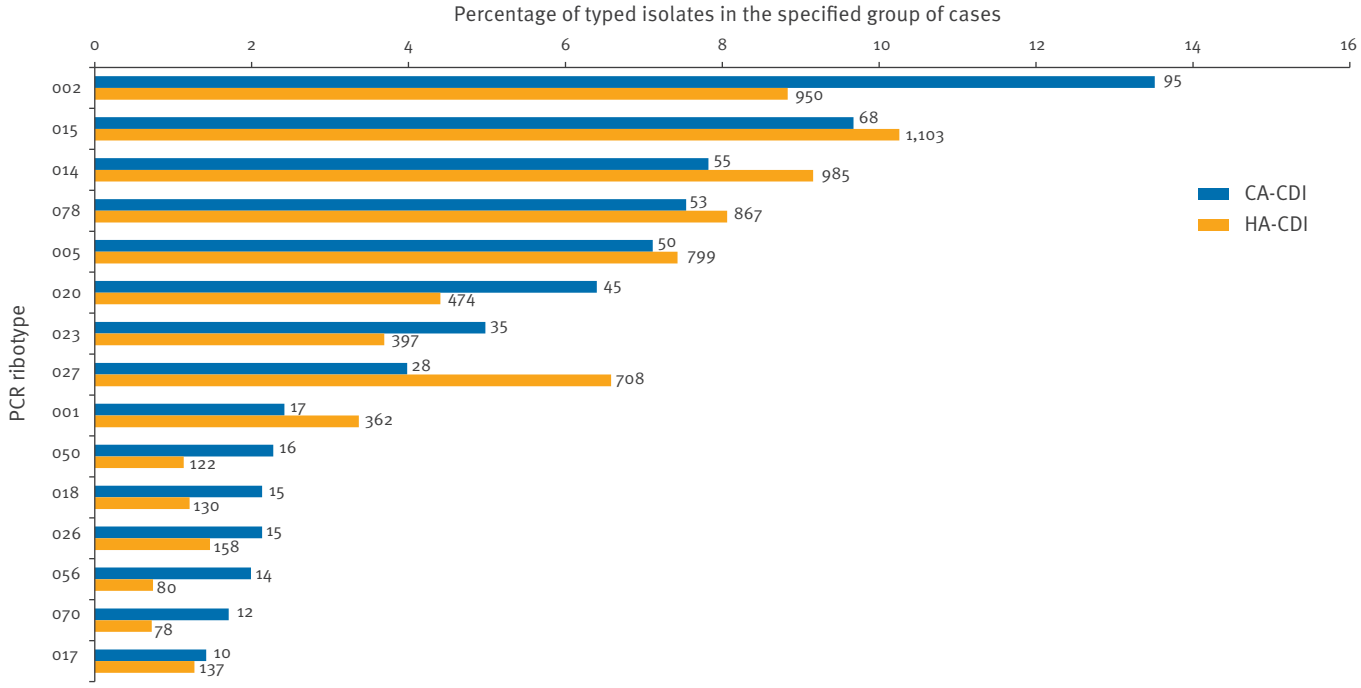
Methods

Community-associated-*C. difficile* infection surveillance scheme

During March 2011 to March 2013, hospital microbiology laboratories in England were asked to send up to 10 faecal samples to their regional CDRN laboratory from successive CDI cases who met the definition of CA-CDI: *C. difficile* toxin-positive diarrhoea (loose stools with no clear medical/surgical explanation) with onset of symptoms while outside hospital (or within the first 48 hours of hospital admission), including those cases associated with community-based residential care, and

Figure 1

Top 15 *Clostridium difficile* PCR ribotypes from cases of community-associated *C. difficile* infection (n = 703) and hospital-associated *C. difficile* infection[a] (n = 10, 754), England, March 2011–March 2013



CA: community-associated; CDI: *Clostridium difficile* infection; HA: hospital-associated.

Ribotype proportions are expressed as percentages of the total number of ribotyped *C. difficile* isolates from cases within the CA-CDI and HA-CDI datasets. The number of isolates of each ribotype are indicated at the end of the bars.

[a] HA-CDI data were obtained from the *Clostridium difficile* Ribotyping Network (CDRN).

those without discharge from hospital within the previous 12 weeks [10,11]. More than 90% of (about 150) laboratories were following national (two-stage testing) guidance for CDI diagnosis. All faecal samples submitted were accompanied by a brief patient-based questionnaire (anonymised) that was completed at the local microbiological testing laboratory. The questionnaire recorded demographic data, details of hospitalisation, residency in a care/nursing home, and antibiotic exposure (from patient records where available). Only the first half of the patient's residential post code was collected to permit potential geographical mapping, while retaining anonymity. *C. difficile* was cultured at the receiving CDRN laboratory. If the sample was *C. difficile* culture-negative then another case was recruited prospectively. All *C. difficile* isolates were centralised at the CDRN Reference Laboratory in Leeds, England, and referred to the UK Anaerobe Reference Unit (UKARU) in Cardiff, Wales, for PCR ribotyping. Demographic and typing data were analysed at the CDRN Reference laboratory, Leeds.

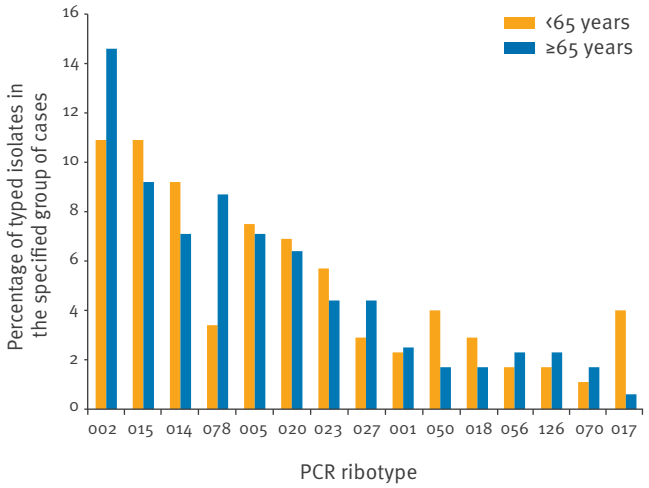
C. difficile culture, identification and PCR ribotyping

C. difficile isolates were recovered from faecal samples at by culture on modified Brazier's cycloserine-cefoxitin-egg yolk agar (Laboratory M, Bury, United Kingdom (UK)) without egg yolk and supplemented with 5 mg/L lysozyme (CCEYL) for 48 hours at 37°C in an anaerobic atmosphere. *C. difficile* isolates were identified by their characteristic smell and colony morphology, fluorescence under long-wave UV light and a latex agglutination test for *C. difficile* somatic antigen (Oxoid Ltd, Basingstoke, UK).

PCR ribotyping was performed at UKARU as described previously [12]. Briefly, DNA was extracted from overnight cultures of *C. difficile* using Chelex 100 resin (BioRad, Hemel Hempstead UK). The 16S-23S intergenic spacer regions were amplified using primers P3: 5'-CTG GGG TGA AGT CGT AAC AAG G-3' and P5: 5'-GCG CCC TTT GTA GCT TGA CC-3'. DNA fragments were concentrated before electrophoresis and resolved using 3% Metaphor agarose (Cambrex Bioscience, Rockland, United States (US)).

Figure 2

The 15 most frequently identified *Clostridium difficile* PCR ribotypes from cases of community-associated *C. difficile* infection by age (< 65 years (n = 174) and ≥ 65 years (n = 519)), England, March 2011–March 2013



Ribotype proportions are expressed as percentages of the total number of ribotyped *C. difficile* isolates from cases who were under 65 years-old and those aged 65 years or more.

Cases of healthcare-associated *Clostridium difficile* infection

Comparative data for presumed HA-CDI cases (onset of symptoms ≥ 48 hours after admission to a healthcare facility or with onset of symptoms in the community within 12 weeks following discharge from a healthcare facility) [10,11] occurring during the same period were obtained from the results of routine CDRN testing. *C. difficile* culture and ribotyping was performed at regional CDRN laboratories, with data collated by the CDRN Reference Laboratory in Leeds. In order to check the accuracy of the classification of routine CDRN cases as HA-CDI, demographic data were collected for all submitted samples in one region (Yorkshire and Humber).

Statistical methods

Univariate analyses were used to compare differences between categories using chi-squared test or Fisher's exact test (where sample size was small, i.e. less than 5, or less than 10 if only one degree of freedom). Median ages were compared by Mann–Whitney test. Ribotype diversity within groups was assessed using Simpson's index, with 95% confidence intervals (CIs) demonstrating variance within groups. Univariate analyses were performed using SPSS version 19, and diversity analyses using PAST version3.

Results

A total of 113 laboratories across England, all serving both hospitals and the community, referred 703 *C. difficile* toxin-positive (and *C. difficile* culture-positive) faecal samples from individual CA-CDI cases between March 2011 and March 2013 (i.e. median of six samples per laboratory, range: 1–25). The collected samples were approximately equally distributed over the two-year period. A dataset of 11,479 CDRN records, for the same period, were used as presumed HA-CDI cases for comparison with CA-CDI cases. CA-CDI cases were predominantly female, elderly (≥ 65 years of age) and resident in their own home (Table).

The most frequently identified ribotype causing CA-CDI was RT002 (95/703; 13.5%) (Figure 1).

CA-CDI cases were significantly more likely than HA-CDIs to be due to ribotype 002 ($p \leq 0.0001$). Although not as commonly isolated, ribotypes 020 and RT056 were also significantly more likely to be found in CA-CDI cases than in HA-CDI cases ($p = 0.009$ and < 0.0001 respectively). Ribotypes known to be associated with enhanced pathogen virulence and poor clinical outcome (078 and 027) were fourth and eighth most frequently identified ribotypes in CA-CDI cases, respectively. Notably, ribotype 027 was found significantly more often in HA-CDI cases than in CA-CDI cases ($p = 0.01$). With the exceptions noted above, comparison of ribotypes causing CA- and HA-CDI showed a very similar ranking and prevalence distribution (Figure 1).

Cases referred to the national CDRN service (additional surveillance in conjunction with mandatorily reported CDI cases) were presumed to represent HA-CDIs. As these could conceivably contain CA-CDIs, however (for example, examined as part of outbreak investigations), we sought to compare the ribotype prevalences for CDRN-referred cases from one region in England (Yorkshire and Humber), comprising 14 distinct hospitals, with known low-level community-based testing, with those for the remainder of the CDRN-referred cases in England during the same study period. All ribotype frequency pairs were within plus or minus 1.9% of each other, with the exception of ribotype 027 (6.6% (708/10,754) CDRN England, 17.8% (265/1,489) CDRN Y and H); this discrepancy was due to hospital-based outbreaks of 027 in the Y and H region.

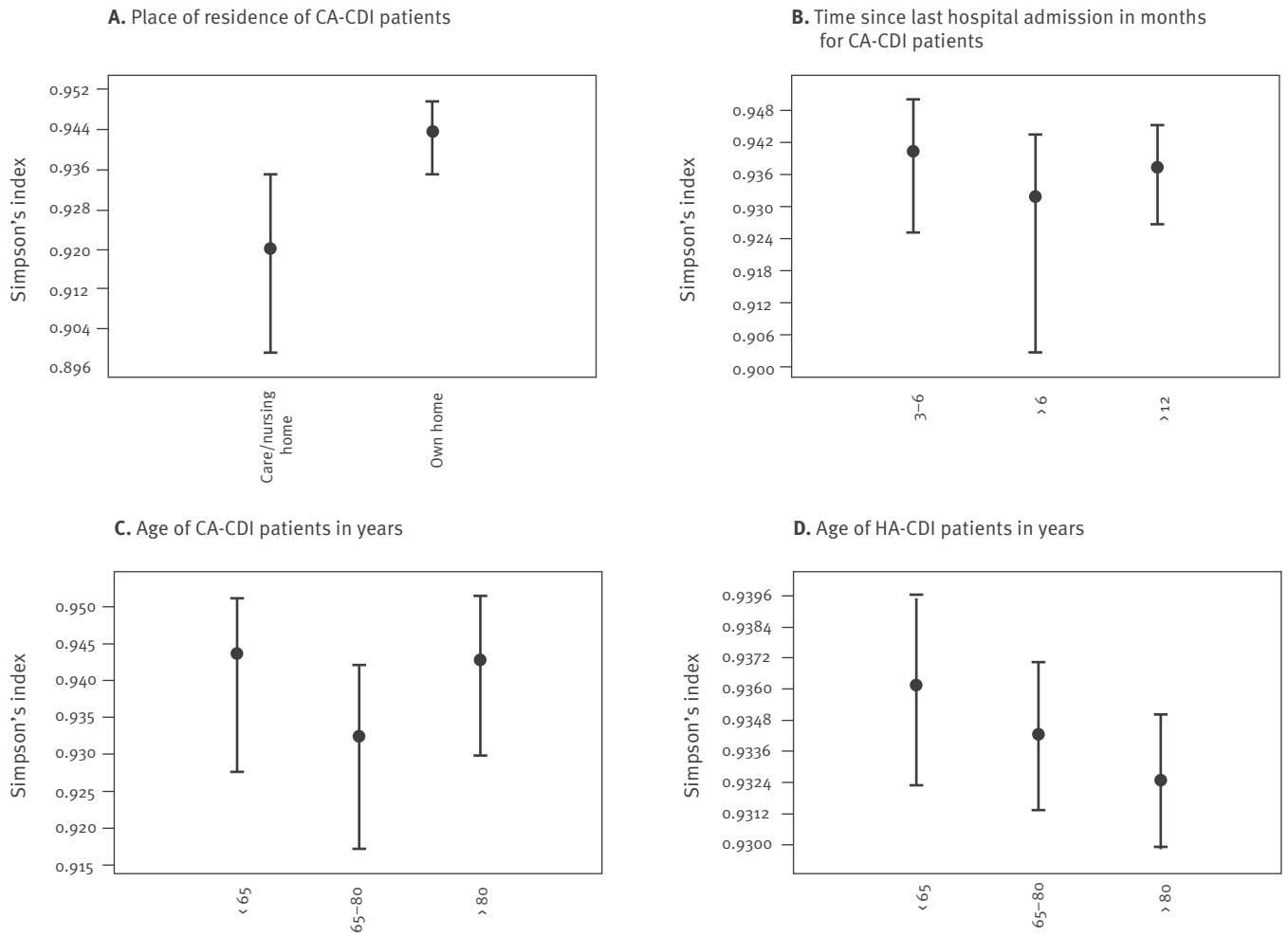
Age of cases

Three quarters of the CA-CDI cases (519/693) were aged ≥ 65 years. Frequencies of the most prevalent ribotypes (top 15) found in the study are shown with respect to patient age in Figure 2.

The prevalence of ribotype 078 in cases of CA-CDI was significantly higher in elderly patients (3.4% (6/174) vs 8.7% (45/519) in those aged < 65 vs ≥ 65 years, respectively; $p = 0.019$). Similarly, ribotype 027 prevalence increased from 2.9% (5/174) to 4.4% (23/519) in elderly patients with CA-CDI, rising further to 5.6% (15/269) in those over 80 years of age, although this trend was not statistically significant. Proportions of cases with CA-CDI with ribotype 002 were found to increase with age, but again this was not statistically significant.

Figure 3

Diversity of *Clostridium difficile* PCR ribotypes (Simpson's indices) for cases of community-associated *C. difficile* infection by (A) place of residence (n = 650), (B) time since last hospital admission (n = 627), (C) age (n = 693), and (D) for cases of hospital-associated *C. difficile* infection by age (n = 10,041)[a], England, March 2011–March 2013



CA: community-associated; CDI: *Clostridium difficile* infection; HA: hospital-associated.

The whiskers represent the 95% confidence intervals around the point estimate of the index.

[a] Hospital-associated *C. difficile* infection data were obtained from the Clostridium difficile Ribotyping Network (CDRN).

Conversely, although numbers were small, proportions of ribotypes 050, 018 and 017 were relatively larger in patients younger than 65 years than in patients 65 years and older (4.0% (7/174), 2.9% (5/174) and 4.0% (7/174) vs. 1.7 (9/519), 1.7 (9/519) and 0.6% (3/519)) respectively. However, none of these were statistically significant (Figure 2).

Median ages of cases with a particular ribotype were generally comparable for CA- and HA-CDI patients. Notably, although numbers were small, cases with CA-CDI due to ribotype 017 infection tended to be younger than corresponding HA-CDI patients (56.5 years and 75 years, respectively; p = 0.13).

Diversity of ribotypes decreased with increasing age in HA-CDI patients, while CA-CDI patients showed no such trend (Figure 3).

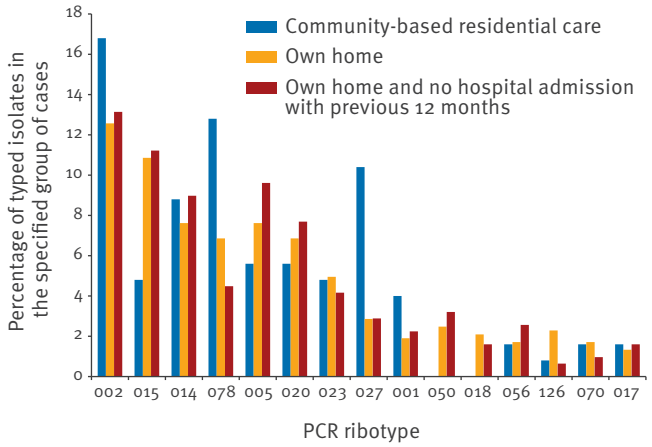
Place of residence

A fifth of the CA-CDI cases (125/525) in the study were associated with community-based residential care. Frequencies of the most prevalent ribotypes (top 15) found in the study with respect to patient residency and recent hospital admission are shown in Figure 4.

Patients with CA-CDI who were living in their own home and had no demonstrable hospital admission within the previous 12 months were classified as having no institutional or healthcare contact. Patients not residing in

Figure 4

Top 15 *Clostridium difficile* PCR ribotypes from cases of community-associated *C. difficile* infection by place of residence (community-based residential care) (n = 125) or their own home (n = 525), or their own home and no hospital admission with the previous 12 months (n=312), England, March 2011–March 2013



Ribotype proportions are expressed as percentages of the total number of ribotyped *C. difficile* isolates from patients residing in a care/nursing home, those residing in their own home, and those residing in their own home with no evidence of hospital admission with the previous 12 months.

their own home were classified as having institutional contact. Larger proportions of ribotypes 002, 078, 027 and 001 were found among patients with institutional contact. Notably, prevalences of ribotypes 027 and 078 were significantly higher in patients with institutional contact compared with those with no contact (10.4% (13/125) vs 2.9% (9/312) and 12.8% (16/125) vs 4.5% (14/312), respectively; both $p<0.001$). Conversely, ribotype 015 was identified significantly more often in patients with no institutional contact versus those with institutional contact (11.2% (35/312) vs 4.8% (6/125), respectively; $p=0.034$). Similar (but non-statistically significant) trends were also observed for ribotypes 005 and 020 CDIs. Although numbers were small, it was interesting to note that ribotypes 050 and 018 were completely absent in CA-CDI patients not residing in their own home.

The diversity of ribotypes associated with CA-CDI cases residing in their own homes per se, was markedly higher than that associated with care/nursing home residence, although this difference was not statistically signficant (Table,Figure 3).

Previous hospital stay

A quarter of CA-CDI cases (158/627) were identified as having been admitted to hospital within the previous three to six months. Frequencies of the most prevalent ribotypes (top 15) from cases in the study with respect to previous hospital stay are shown in Figure 5.

Proportions of CA-CDIs caused by ribotypes 078, 020, 023 and 027 in patients with hospital admission within the previous three to six months were higher than in those with no evidence of hospital admission within the previous year, although these differences were only significant for ribotype 078 (12.0% (19/158) vs 4.5% (18/396); $p=0.005$). Frequencies of several ribotypes, notably 002, 015 and 005, were found to be higher among patients who had no evidence of hospital admission within the previous year as compared with those admitted in the previous three to six months; only the difference in proportions of ribotype 005 was significant (9.8% (39/396) vs 2.5% (4/158); $p=0.003$). Ribotype diversity was similar for CA-CDI cases with no evidence of hospital stay within the previous year compared with those admitted in the previous three to six months (Table, Figure 3).

History of antibiotic use

History of antibiotic use was the most poorly completed part of the CA-CDI case questionnaires (47.5% (334/703) completed). For those with available antibiotic history data, CA-CDI cases were significantly more likely not to have received any antibiotics in the four weeks before their CDI episode when compared with HA-CDI cases (CDRN data) (38.6% (129/334) vs 20.3% (1,226/6,028); $p<0.0001$).

The three most common antibiotics/classes associated with CA-CDI cases were amoxicillin/clavulanic acid (16%; n = 61), amoxicillin/ampicillin (13%; n = 51) and cephalosporins (6%; n = 23); 4% (n = 14) had received a fluoroquinolone. Notably, these data do not take into account the relevant frequencies of antibiotic prescribing.

Frequencies of the most prevalent ribotypes (top 15) found in the study with respect to recent antibiotic use are shown in Figure 6.

A significantly higher proportion of ribotype 050 was associated with antibiotic use (0.78% (1/129) vs 5.8% (12/205); $p=0.013$). For all other comparisons, p was greater than 0.05.

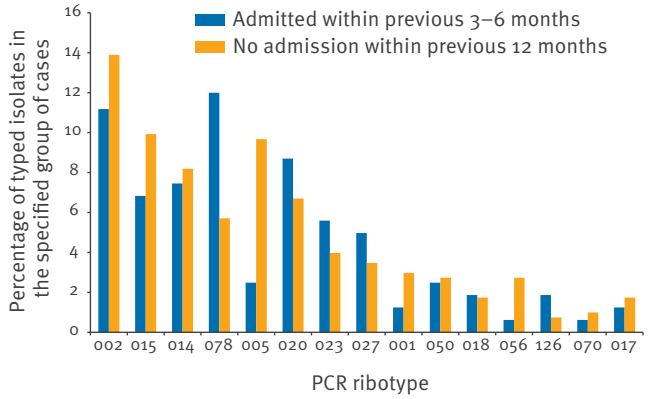
Patients with no institutional or healthcare contact and who did not receive any antibiotics in the previous four weeks, were classified as having no established risk factors for CDI. The prevalence of ribotype 002 was higher in those patients with no established risk factors when compared with those with at least one known risk factor, although this was not statistically significant (14.5% (9/62) vs 12.5% (52/415); $p=0.662$).

Discussion

To the best of our knowledge, this is the first large study in the UK to compare the epidemiology of CA- vs HA-CDI. In marked contrast to earlier reports, when HA-CDI was closely associated with a small range of epidemic ribotypes [1,13,14], we found very similar ribotype diversity indices for CA- and HA-CDI.

Figure 5

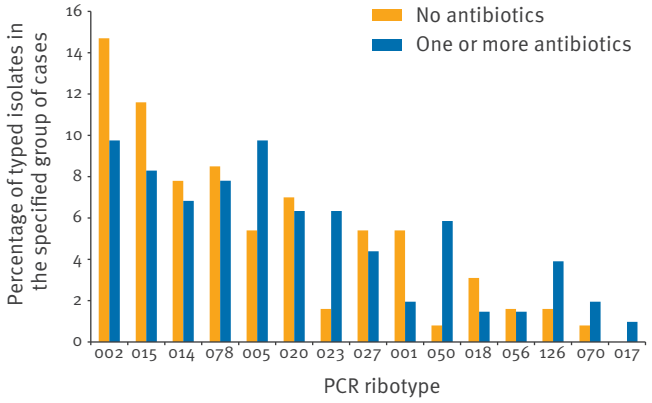
Top 15 *Clostridium difficile* PCR ribotypes from cases of community-associated *C. difficile* infection by status of previous hospital admission (within 3–6 months of their *C. difficile* infection episode (n = 158) and those with no record of hospital admission within the previous 12 months (n = 396)), England, March 2011–March 2013



Ribotype proportions are expressed as percentages of the total number of ribotyped C. difficile isolates from patients admitted to hospital within the previous three to six months and those with no evidence of hospital admission within the previous 12 months.

Figure 6

Top 15 *Clostridium difficile* PCR ribotypes from cases of community-associated *C. difficile* infection by history of antibiotic use during 4 weeks before their *C. difficile* infection episode (no antibiotics (n = 129) and one or more antibiotics (n = 205)), England, March 2011–March 2013



Ribotype proportions are expressed as percentages of the total number of ribotyped *C. difficile* isolates from patients who received no antibiotics and those who received one or more antibiotics.

Furthermore, the ranking and relative prevalences of ribotypes causing CA- and HA-CDIs were very similar. A relatively recent landmark study, using highly discriminatory whole genome sequencing (WGS), showed that the majority of CDIs occurring between September 2007 and March 2011 across a region in England did not represent case-to-case transmission of *C. difficile* [15]. Importantly, in that study, the rate of appearance of new, distinct *C. difficile* genotypes causing infections was constant, suggesting the existence of a large reservoir(s) of *C. difficile*. If correct, this would tend towards a similar distribution of ribotypes causing HA- and CA-CDI, (as found in this study) assuming that there are no powerful selection pressures or niches for particular ribotypes that could promote CDIs in one setting versus the other.

In England, a pragmatic definition has been used in national surveillance to apportion CDI cases between hospitals (symptom onset after 72 hours following admission) and the community (symptom onset in the community or within the first 72 hours following admission to hospital) [8]. However, this definition may exaggerate numbers of cases with apparent CA-CDI as it fails to take into account recent previous hospital admission. Multiple, often large outbreaks were typical around the peak incidence of CDIs in the UK in 2007–08; since then there has been a ca 70–80% decrease in case frequency [13,14] This followed intensive public health campaigns that included multiple infection prevention and control measures designed to reduce transmission of *C. difficile* and alter prescribing of antimicrobials [16]. One of the most striking aspects of this control programme was the substantial decrease in prevalence of ribotype 027 CDIs. In 2007–08, this ribotype caused more than 50% of CDIs in England referred to the CDRN; in subsequent 12-month periods the corresponding proportions were 36% (in 2008–09), 22% (in 2009–10), 13% (in 2010–11), and 9% (in 2011–12) [13]. The control of this epidemic strain, which is associated with poor clinical outcome [17,18], has been paralleled by an increased heterogeneity of ribotypes causing CDIs [13]. This observation is also consistent with the similar distributions of strains found to be causing CA-CDIs and HA-CDIs in this study. Earlier studies in Sweden (1998 and 2004) also reported similar distributions of ribotypes among nosocomial and community settings [19,20]. Such data likely reflect the close interplay between hospital and community settings at times of relatively low levels of hospital-based CDI case-to-case transmission.

While *C. difficile* ribotype distributions were similar among cases of CA- and HA-CDI in our study, there were some notable differences. CA-CDI cases were significantly more likely than HA-CDI cases to be due to ribotype 002 and (less commonly) to ribotypes 020 and 056. Conversely, ribotype 027 was found significantly more often in HA-CDI cases than CA-CDI cases. Ribotype 002 is a relatively frequent cause of HA-CDI and is among several other long-recognised ribotypes, including 015, 014, 020 and 078, which have become more common in the UK, concurrent with the demise of epidemic ribotypes such as 027, 106 and 001 [9,13].

Studies have repeatedly demonstrated a lower median age in patients with CA-CDI compared with HA-CDI [19-22]. However, we did not find a statistically significant difference. Age-related differences may be confounded

Table

Patient-based questionnaire data and *Clostridium difficile* PCR ribotype diversity (Simpson's index) for cases of community-associated *C. difficile* infection (n = 703) and cases of healthcare-associated *C. difficile* infection[a] (n = 11,479), England, March 2011–March 2013

Case characteristics Number		Cases of CA-CDI with available data Simpson's index (95% CI)			Cases of HA-CDI with available data			PCR ribotype diversity	
		Total number per category	%	Number	Total number per category	%	CA-CDI	HA-CDI[b]	
Sex	Male	234	701	33	4,855	11,289 For Simpson's, n = 9,812[b]	43	0.94 (0.92–0.95)	0.94 (0.94–0.94)
	Female	467		67	6,434		57	0.94 (0.93–0.95)	0.94 (0.94–0.95)
Age in years	‹65	174	693	25	2,805	11,387 For Simpson's, n = 10,041[b]	25	0.94 (0.93–0.95)	0.95 (0.94–0.95)
	65–80	250		36	3,843		34	0.93 (0.92–0.94)	0.94 (0.94–0.95)
	›80	269		39	4,739		42	0.94 (0.93–0.95)	0.94 (0.94–0.94)
Place of residence	Community-based residential care	125	650	19	NA	NA	NA	0.92 (0.90–0.94)	NA
	In own home	525		81	NA	NA	NA	0.94 (0.94–0.95)	NA
Previous hospital stay, from sample date	Within less than the previous 3–6 months	158	627	25	NA	NA	NA	0.94 (0.93–0.95)	NA
	Within previous 6 to 12 months	73		12	NA	NA	NA	0.93 (0.90–0.94)	NA
	No evidence of hospital stay within previous 12 months	396		63	NA	NA	NA	0.94 (0.93–0.95)	NA
Antibiotics received, within previous 4 weeks	None	129	334	39	1,226	6,028 For Simpson's, n = 5,279[b]	20	0.93 (0.91–0.94)	0.93 (0.93–0.94)
	1	134		40	2,066		34	0.94 (0.93–0.95)	0.94 (0.94–0.94)
	2	48		14	1,411		23	0.94 (0.90–0.95)	0.94 (0.94–0.94
	3 or more	23		7	1,325		22	0.91 (0.86–0.93)	0.94 (0.94–0.95)

CA: community-associated; CDI: *Clostridium difficile* infection; CI: confidence interval; HA: hospital-associated; NA: not available.

[a] HA-CDI data were obtained from the *Clostridium difficile* Ribotyping Network (CDRN).

[b] Simpson's index was calculated where a ribotype result was available.

by ascertainment bias, including testing policy in hospital versus community settings. We speculate also that differences between studies with respect to age may be driven by ribotype distribution in population cohorts. Data from our study showed that infections associated with certain ribotypes (002, 027, 078) were more common in patients aged ≥ 65 years. Notably, CA-CDIs due to ribotype 078 were ca 2.5-fold more likely to affect an individual aged ≥ 65 years. Median ages of CA-CDI cases and HA-CDI cases were very similar for infections due to ribotypes 002, 027 and 078. A Dutch study in 2008 found a significant difference in the median age of CDI cases due to ribotypes 078 and 027 (67.4 vs 73.5 years, respectively) [21]. In our study, although median age was lower for cases due to ribotype 078 (80 years), vs 82 years for ribotype 027, this difference was not statistically significant. Although numbers were small, ribotype 017-associated CA-CDIs were more than three times more likely to affect a younger individual. Additionally, the median age of patients with ribotype 017-associated CDI was significantly lower in CA-CDI patients than in corresponding HA-CDI patients, suggesting that a true association may exist between ribotype 017 infections and the younger patient in a

community setting. We also found that ribotype diversity decreased with increasing age in HA-CDI patients, while CA-CDI patients showed no such trend.

Recent US studies (2013–15) found that about a third of CDI cases were CA-CDIs [3,4,23]. However, the increasing use of nucleic acid amplification tests (NAATs) alone for the diagnosis of CDI may be confounding US data, given the clear potential for large overestimates of CDI incidence by this sensitive but poorly specific diagnostic approach [24]. Indeed, use of NAATs was found to significantly correlate with higher reported CA-CDI incidence [3]. By contrast, at the time of our study, 79% and 94% of UK hospitals in 2011–12 and 2012–13, respectively, were using an optimised method (screening test followed by a toxin test) for CDI diagnosis [24]. In the US, between 2009 and 2011, ca 40% of cases defined as CA-CDI had high-level exposure to healthcare (i.e. surgery, dialysis, emergency or urgent care visit, inpatient care with no overnight stay, or healthcare personnel with direct patient care), despite no hospital admission in the previous 12 weeks [4]. A further ca 40% had low-level healthcare exposure (i.e. an outpatient visit with a physician or dentist). Thus, only ca 20% of CA-CDI cases had no recorded healthcare contact in the previous 12 weeks. Of note, HA-CDI was taken to include cases occurring in nursing homes (and acute care hospitals or long-term acute care hospitals). There is a key issue regarding consistency between studies and healthcare systems concerning definitions of 'nursing homes'. In the US, there are more than 15,000 nursing homes, each averaging over 100 licensed beds [25]. By contrast, care homes in England (about 17,500) with nursing capability (n = ca 4,000) are about half the size of their US counterparts; typically both nursing and residential care are provided within the same facility [26-28]. In England, about 4% (ca 375,000) of the population aged over 65 years live in care/nursing homes, rising to almost 20% of those aged ≥ 85 years. Thus, a sizeable minority of elderly people live in care homes, but determining whether individuals are receiving nursing as opposed to residential care is problematic, given that care needs may fluctuate. Subjects receiving residential care are not receiving healthcare per se, but instead are helped with normal daily living activities. This highlights the dilemma of how best to categorise subpopulations resident in care homes.

A limitation of our study is that we did not ascertain the level of nursing received by CA-CDI cases in care homes. We chose to define CA-CDI cases to include non-hospital-associated cases living in care homes, noting that the great majority of residents in such settings are not receiving nursing care [26-28]. However, by examining subpopulations resident in the community in care homes, we did demonstrate a clear predominance of epidemic ribotypes, notably 027 and 001, in patients with institutional contact compared with those living in their own home. High prevalence of ribotype 027 CDIs in nursing home residents has been reported in Germany in 2012 [29], but data in this setting are limited [30]. Carriage of *C. difficile*, CDI and subsequent transmission of the pathogen are more common in elderly patients [1], and so it is not surprising that (older) patients associated with community-based residential care had a different distribution of ribotypes compared with community residents living in their own home. Furthermore, we found that CDI cases either resident in their own home or with no evidence of hospital stay within the previous 12 months were associated with higher relative diversity indices than either those residing in care homes or admitted to hospital within the previous six months. More simply, patients with less recent contact with hospitals were more likely to be affected by a more diverse range of *C. difficile* strains than those with more recent contact, presumably reflecting a lower risk of contact with epidemic strains. We did not collect information on CDI outbreaks as this was beyond the scope of the study.

While antibiotic exposure is a key risk factor for CDI [1,31-33], our study has again demonstrated that over a third of CA-CDI cases were associated with no recent history of a prescribed antibiotic, as seen in other studies [22,34-37]. Indeed, we found that CA-CDI cases were nearly twice as likely to have had no antibiotics preceding infection than HA-CDI cases ($p < 0.0001$). Certain ribotypes notably 001, 002 and 015 were more commonly associated with patients receiving no antibiotics before their infection. Such data indicate that antibiotic history might be less of a prerequisite for infection with these *C. difficile* ribotypes and alternative factors support the spread of these ribotypes in the community setting. Other risk factors associated with CA-CDI have been extensively reported, including gastric acid suppressants and contact with infants under two years-old [34,38]. However, no data currently exist to associate such factors with CDI due to ribotypes 002 and 015 in the community setting.

There is increasing evidence linking CDI to environmental sources including water and food [39-41]. Although these studies have identified clinically relevant ribotypes, notably including 078, in foodstuffs, foodborne transmission of *C. difficile* has not been demonstrated. For example, we recently found no differences between hospital and community onset of infection, or in food or environmental exposures between ribotype 078 CDI cases and those caused by other ribotypes [42]. However, conditional logistic regression modelling adjusting for age found that ribotype 078 CDI cases were markedly more likely than other cases to report prior antibiotic exposure (odds ratio: 5.1 (95% CI: 1.6–16.3); $p = 0.002$) [42]. More studies employing WGS are needed to understand the significance of community *C. difficile* reservoirs to human disease. This is probably best achieved early as new strains emerge, not least because once established it becomes more difficult to untangle true risk factors from confounding issues. The emergence of ribotype 244 in Australasia is a good example of the use of WGS to map the spread

of this new clone primarily causing CA-CDI, although a proven community reservoir remains elusive [43].

In summary, while there were examples of ribotypes that significantly predominated in CA- or HA-CDIs, we found very similar ribotype diversity indices, ranking and relative strain prevalences in these two groups. Ribotype 002 was associated with CA-CDI, and there was a clear predominance of epidemic ribotypes, notably 027 and 001, in patients associated with community-based residential care compared with those living in their own home. CA-CDI cases were nearly twice as likely to have had no antibiotics preceding infection than corresponding HA-CDI cases during the same period. Our nationally sourced data emphasise the close interplay between hospital and community settings, particularly when there are relatively low levels of hospital-based case-to-case transmission of *C. difficile* and thus less dominance of epidemic *C. difficile* clones.

CDRN Working Group members

Rohini J. Manuel, Derren Ready, Michael Shemko (Public Health Laboratory London, Barts & The London Hospital Trust, London, UK); Peter M. Hawkey, Katie Hardy (Public Health Laboratory West Midlands, Heart of England NHS Foundation Trust, Birmingham, UK); Andrew Birtles, Kirsty Dodgson (Public Health Laboratory North West, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK); Martin D. Curran, Margaret Dixon (Public Health Laboratory East, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK); Barbara Dowling, Andrew Sails (Public Health Laboratory North East, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK); Stephen M Green (Public Health Laboratory South East, University Hospital Southampton NHS Foundation Trust, Southampton, UK); Jiancheng Zhang (Public Health Laboratory South West, University Hospitals Bristol NHS Foundation Trust, Bristol, UK).

Acknowledgements

We are grateful to NHS microbiology laboratories in England for CA-CDI specimen submission, and to staff of the CDRN and UKARU for isolate referral and PCR ribotyping associated with this study.

The study was funded by Public Health England.

Conflict of interest

MHW has received grants from Abbott, Actelion, Alere, Astellas, Biomerieux, Cerexa, Cubist, Da Volterra, European Tissue Symposium, Merck, Sanofi-Pasteur, Summit, The Medicines Company, Qiagen.

WNF, KAD, TM, PP and RH: none declared.

Authors' contributions

WNF, RH and MHW designed the study, with support from the CDRN working group. TM performed PCR ribotyping. PP was responsible for sample logistics and data collection, with support from the CDRN working group in their respective regions. WNF, KAD and MHW analysed data and wrote the report. All authors reviewed drafts of the report.

References

1. Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, et al. The changing epidemiology of Clostridium difficile infections. Clin Microbiol Rev. 2010;23(3):529-49. DOI: 10.1128/CMR.00082-09 PMID: 20610822
2. Gupta A, Khanna S. Community-acquired Clostridium difficile infection: an increasing public health threat.Infect Drug Resist. 2014;7(7):63-72.PMID: 24669194
3. Lessa FC, Mu Y, Winston LG, Dumyati GK, Farley MM, Beldavs ZG, et al. Determinants of Clostridium difficile Infection Incidence Across Diverse United States Geographic Locations. Open Forum Infect Dis. 2014;1(2):ofu048. DOI: 10.1093/ofid/ofu048 PMID: 25734120
4. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, et al. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. JAMA Intern Med. 2013;173(14):1359-67. DOI: 10.1001/jamainternmed.2013.7056 PMID: 23780507
5. Hensgens MP, Dekkers OM, Demeulemeester A, Buiting AG, Bloembergen P, van Benthem BH, et al. Diarrhoea in general practice: when should a Clostridium difficile infection be considered? Results of a nested case-control study. Clin Microbiol Infect. 2014;20(12):O1067-74. DOI: 10.1111/1469-0691.12758 PMID: 25040463
6. Wheeler JG, Sethi D, Cowden JM, Wall PG, Rodrigues LC, Tompkins DS, et al. Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. BMJ. 1999;318(7190):1046-50. DOI: 10.1136/bmj.318.7190.1046 PMID: 10205103
7. Tam CC, Rodrigues LC, Viviani L, Dodds JP, Evans MR, Hunter PR, et al. Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. Gut. 2012;61(1):69-77. DOI: 10.1136/gut.2011.238386 PMID: 21708822
8. Public Health England (PHE). CDI mandatory surveillance. London: PHE. [Accessed 24 Aug 2015]. Available from: https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-quarterly-epidemiological-commentary
9. Public Health England (PHE). Clostridium difficile Ribotyping Network for England and Northern Ireland. Biennial report (2013-2015). London: PHE; 2016. Lasted accessed 24 August 2015.
10. McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK, Ad Hoc Clostridium difficile Surveillance Working Group. Recommendations for surveillance of Clostridium difficile-associated disease.Infect Control Hosp Epidemiol. 2007;28(2):140-5. DOI: 10.1086/511798 PMID: 17265394
11. 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. DOI: 10.1111/j.1469-0691.2006.01580.x PMID: 16965399
12. Stubbs SL, Brazier JS, O'Neill GL, Duerden BI. PCR targeted to the 16S-23S rRNA gene intergenic spacer region of Clostridium difficile and construction of a library consisting of 116 different PCR ribotypes.J Clin Microbiol. 1999;37(2):461-3.PMID: 9889244
13. Wilcox MH, Shetty N, Fawley WN, Shemko M, Coen P, Birtles A, et al. Changing epidemiology of Clostridium difficile infection following the introduction of a national ribotyping-based surveillance scheme in England. Clin Infect Dis. 2012;55(8):1056-63. DOI: 10.1093/cid/cis614 PMID: 22784871
14. Brazier JS, Raybould R, Patel B, Duckworth G, Pearson A, Charlett A, et al. Distribution and antimicrobial susceptibility patterns of Clostridium difficile PCR ribotypes in English hospitals, 2007-08. Euro Surveill. 2008;13(41).pii:19000
15. Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, et al. Diverse sources of C. difficile infection identified on whole-genome sequencing. N Engl J Med. 2013;369(13):1195-205. DOI: 10.1056/NEJMoa1216064 PMID: 24066741
16. Health Protection Agency (HPA). Clostridium difficile infection: How to deal with the problem. London: HPA; 2008. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/340851/Clostridium_difficile_infection_how_to_deal_with_the_problem.pdf
17. Miller M, Gravel D, Mulvey M, Taylor G, Boyd D, Simor A, et al. Health care-associated Clostridium difficile infection

in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. Clin Infect Dis. 2010;50(2):194-201. DOI: 10.1086/649213 PMID: 20025526

18. Walker AS, Eyre DW, Wyllie DH, Dingle KE, Griffiths D, Shine B, et al. Relationship between bacterial strain type, host biomarkers, and mortality in Clostridium difficile infection. Clin Infect Dis. 2013;56(11):1589-600. DOI: 10.1093/cid/cit127 PMID: 23463640
19. Karlström O, Fryklund B, Tullus K, Burman LG. A prospective nationwide study of Clostridium difficile-associated diarrhea in Sweden. The Swedish C. difficile Study Group.Clin Infect Dis. 1998;26(1):141-5. DOI: 10.1086/516277 PMID: 9455523
20. Norén T, Akerlund T, Bäck E, Sjöberg L, Persson I, Alriksson I, et al. Molecular epidemiology of hospital-associated and community-acquired Clostridium difficile infection in a Swedish county. J Clin Microbiol. 2004;42(8):3635-43. DOI: 10.1128/JCM.42.8.3635-3643.2004 PMID: 15297509
21. Goorhuis A, Bakker D, Corver J, Debast SB, Harmanus C, Notermans DW, et al. Emergence of Clostridium difficile infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. Clin Infect Dis. 2008;47(9):1162-70. DOI: 10.1086/592257 PMID: 18808358
22. Dumyati G, Stevens V, Hannett GE, Thompson AD, Long C, Maccannell D, et al. Community-associated Clostridium difficile infections, Monroe County, New York, USA. Emerg Infect Dis. 2012;18(3):392-400. DOI: 10.3201/eid1803.102023 PMID: 22377231
23. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372(9):825-34. DOI: 10.1056/NEJMoa1408913 PMID: 25714160
24. Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID). Lancet Infect Dis. 2014;14(12):1208-19. DOI: 10.1016/S1473-3099(14)70991-0 PMID: 25455988
25. United States Centers for Disease Prevention and Control (CDC). Nursing home care. CDC FastStats. Atlanta, GA: CDC. [Accessed 13 Aug 2015]. Available from: http://www.cdc.gov/nchs/fastats/nursing-home-care.htm
26. United Kingdom Care Quality Commission. Newcastle upon Tyne: Care Quality Commission. [Accessed 13 Aug 2015]. Available from: http://www.cqc.org.uk/search/services/care-homes
27. Smith P, Sherlaw-Johnson C, Ariti C, Bardsley M. Focus on: Hospital admissions from care homes. London: The Health Foundation; 2015. Available from: http://www.health.org.uk/sites/default/files/QualityWatch_FocusOnHospitalAdmissionsFromCareHomes.pdf
28. Comas-Herrera A, Wittenberg R, Pickard L. The long road to universalism? Recent developments in the financing of long-term care in England.Soc Policy Adm. 2010;44(4):375-91. DOI: 10.1111/j.1467-9515.2010.00719.x
29. Arvand M, Moser V, Schwehn C, Bettge-Weller G, Hensgens MP, Kuijper EJ. High prevalence of Clostridium difficile colonization among nursing home residents in Hesse, Germany.PLoS One. 2012;7(1):e30183. DOI: 10.1371/journal.pone.0030183 PMID: 22253917
30. Rodriguez C, Korsak N, Taminiau B, Avesani V, Van Broeck J, Delmée M, et al. Clostridium difficile infection in elderly nursing home residents. Anaerobe. 2014;30:184-7. DOI: 10.1016/j.anaerobe.2014.08.007 PMID: 25152228
31. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection.N Engl J Med. 1989;320(4):204-10. DOI: 10.1056/NEJM198901263200402 PMID: 2911306
32. Bignardi GE. Risk factors for Clostridium difficile infection.J Hosp Infect. 1998;40(1):1-15. DOI: 10.1016/S0195-6701(98)90019-6 PMID: 9777516
33. Furuya-Kanamori L, Stone JC, Clark J, McKenzie SJ, Yakob L, Paterson DL, et al. Comorbidities, Exposure to Medications, and the Risk of Community-Acquired Clostridium difficile Infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2015;36(2):132-41. DOI: 10.1017/ice.2014.39 PMID: 25632995
34. Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated Clostridium difficile infection.J Antimicrob Chemother. 2008;62(2):388-96. DOI: 10.1093/jac/dkn163 PMID: 18434341
35. Bauer MP, Goorhuis A, Koster T, Numan-Ruberg SC, Hagen EC, Debast SB, et al. Community-onset Clostridium difficile-associated diarrhoea not associated with antibiotic usage--two case reports with review of the changing epidemiology of Clostridium difficile-associated diarrhoea. Neth J Med. 2008;66(5):207-11.PMID: 18490799
36. Kutty PK, Woods CW, Sena AC, Benoit SR, Naggie S, Frederick J, et al. Risk factors for and estimated incidence of community-associated Clostridium difficile infection, North Carolina, USA. Emerg Infect Dis. 2010;16(2):197-204. DOI: 10.3201/eid1602.090953 PMID: 20113547
37. Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am J Gastroenterol. 2012;107(1):89-95. DOI: 10.1038/ajg.2011.398 PMID: 22108454
38. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease.JAMA. 2005;294(23):2989-95. DOI: 10.1001/jama.294.23.2989 PMID: 16414946
39. Hensgens MP, Keessen EC, Squire MM, Riley TV, Koene MG, de Boer E, et al. Clostridium difficile infection in the community: a zoonotic disease? Clin Microbiol Infect. 2012;18(7):635-45. DOI: 10.1111/j.1469-0691.2012.03853.x PMID: 22536816
40. Janezic S, Zidaric V, Pardon B, Indra A, Kokotovic B, Blanco JL, et al. International Clostridium difficile animal strain collection and large diversity of animal associated strains. BMC Microbiol. 2014;14(1):173. DOI: 10.1186/1471-2180-14-173 PMID: 24972659
41. Marsh JW, Tulenko MM, Shutt KA, Thompson AD, Weese JS, Songer JG, et al. Multi-locus variable number tandem repeat analysis for investigation of the genetic association of Clostridium difficile isolates from food, food animals and humans. Anaerobe. 2011;17(4):156-60. DOI: 10.1016/j.anaerobe.2011.05.015 PMID: 21669297
42. Cleary P, Patel B, Fawley W, Wilcox M. No association between Clostridium difficile ribotype 078 infection and food, animal or environmental exposures: matched case-case study. 9th Healthcare Infection Society International Conference. 16-18 November 2014; Lyon, France. Abstract available from: https://www.his.org.uk/files/1214/1831/1509/Poster_abstracts_for_HIS_Website_Nov_2014.pdf
43. Eyre DW, Tracey L, Elliott B, Slimings C, Huntington PG, Stuart RL, et al. Emergence and spread of predominantly community-onset Clostridium difficile PCR ribotype 244 infection in Australia, 2010 to 2012. Euro Surveill. 2015;20(10):pii=21059. DOI: 10.2807/1560-7917.ES2015.20.10.21059 PMID: 25788254

License and copyright