Diarrhoea in general practice: when should a *Clostridium difficile* infection be considered? Results of a nested case-control study

M. P. M. Hensgens[1], O. M. Dekkers[2,3], A. Demeulemeester[4], A. G. M. Buiting[5], P. Bloembergen[6], B. H. B. van Benthem[7], S. Le Cessie[2,8] and E. J. Kuijper[1]

1) *Department of Medical Microbiology,* 2) *Department of Clinical Epidemiology,* 3) *Department of Endocrinology and Metabolic Diseases, LUMC, Leiden,* 4) *Stichting Huisartsen Laboratorium, Etten-Leur,* 5) *Laboratory for Medical Microbiology and Immunology of the St Elisabeth Hospital, Tilburg,* 6) *Laboratory of Clinical Microbiology and Infectious Diseases, Isala klinieken, Zwolle,* 7) *Centrum Infectieziektebestrijding (Centre for Infectious Disease Control; Cib), Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment; RIVM), Bilthoven and* 8) *Department of Medical Statistics, LUMC, Leiden, the Netherlands*

Abstract

Clostridium difficile infections (CDIs) are frequent in hospitals, but also seem to increase in the community. Here, we aim to determine the incidence of CDI in general practice and to evaluate current testing algorithms for CDI. Three Dutch laboratories tested all unformed faeces (12 714) for *C. difficile* when diagnostic testing (for any enteric pathogen) was requested by a general practitioner (GP). Additionally, a nested case-control study was initiated, including 152 CDI patients and 304 age and sex-matched controls. Patients were compared using weighted multivariable logistic regression. One hundred and ninety-four samples (1.5%) were positive for *C. difficile* (incidence 0.67/10 000 patient years). This incidence was comparable to that of *Salmonella* spp. Compared with diarrhoeal controls, CDI was associated with more severe complaints, underlying diseases, antibiotic use and prior hospitalization. In our study, GPs requested a test for *C. difficile* in 7% of the stool samples, thereby detecting 40% of all CDIs. Dutch national recommendations advise testing for *C. difficile* when prior antibiotic use or hospitalization is present (18% of samples). If these recommendations were followed, 61% of all CDIs would have been detected. In conclusion, *C. difficile* is relatively frequent in general practice. Currently, testing for *C. difficile* is rare and only 40% of CDI in general practice is detected. Following recommendations that are based on traditional risk factors for CDI, would improve detection of CDI.

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Corresponding author: E. J. Kuijper or M. P. M. Hensgens, Department of Medical Microbiology, Leiden University Medical Centre, PO Box 9600, 2300 RC, Leiden, the Netherlands
E-mails: e.j.kuijper@lumc.nl; **marjoleinhensgens@gmail.com**

Introduction

Clostridium difficile infection (CDI) is a common cause of hospital-acquired diarrhoea. Elderly patients with underlying diseases and recent antibiotic therapy are primarily affected, resulting in prolonged hospitalization and excess mortality [1]. Recently, CDI was reported as an emerging disease outside healthcare facilities [2]. Currently, more than a quarter of all CDI is estimated to be acquired in the community [3]. In contrast to nosocomial CDI, patients in the community are younger, antibiotics are less frequently used and routes of exposure are often unknown. Consequently, over a third of these patients have no known risk factors for CDI [4,5]. This makes recognition of CDI problematic, especially because *C. difficile* is not widely tested for in general practitioners' practices [6].

In 2009 a guideline was introduced in the UK, stating that all cases of diarrhoea among patients aged ≥2 years in the community should be tested for *C. difficile* unless good clinical or epidemiological reasons not to are present [7]. Diarrhoea is common in general practice, reaching incidences of 200 per 10 000 person years [8,9], which makes comprehensive testing

costly. Consequently, the UK guideline was modified in 2012 and advised testing of all diarrhoeal samples of elderly patients or patients with risk factors [10]. In most countries, including the Netherlands and the USA, guidelines for general practitioners still state that *C. difficile* should be suspected in patients with a recent hospitalization or antibiotic use [11,12], which may result in missed diagnoses.

Although the need to characterize patients with CDI in the community is high, few studies focused on clinical presentation and additional characteristics of this patient group [5,13]. Additionally, studies often select diagnosed (and therefore recognized) patients only. Therefore, we decided to describe the occurrence of CDI in a laboratory-based cohort study, testing for *C. difficile* irrespective of whether the general practitioner requested *C. difficile* testing. Using this design, we aimed to determine the incidence of toxigenic *C. difficile* and to characterize patients with CDI. Additionally, we aimed to evaluate and guide current diagnostic algorithms.

Methods

Study design

The study was set in three medical microbiological laboratories: Stichting Huisartsen Laboratorium (Etten-Leur), the Laboratory for Medical Microbiology and Immunology of the St Elisabeth Hospital (Tilburg) and the Laboratory for Clinical Microbiology and Infectious Diseases of the Isala klinieken (Zwolle). These laboratories supply microbiological services to 832 general practices with together 2 810 830 patients. All general practitioners (GPs) were aware the study was being performed; two GPs declined participation and were not included in the study. Between 4 October 2010 and 31 January 2012, all unformed stool samples of patients aged ≥2 years, submitted by GPs, were prospectively tested for the presence of *C. difficile* toxin irrespective of whether the GP requested testing for *C. difficile*. Samples were excluded when a patient (i) had a prior positive test or (ii) was tested within the previous 30 days. An unformed stool was defined as 'taking the shape of the container' [14].

Patients with a positive test for *C. difficile* toxin were defined as CDI. Using a nested case-control design, patients with CDI were matched for age (±5 years) and sex to two control patients. Control patients were selected from the cohort of toxin-negative patients and tested negative at most 1 week before the case patient. If a control patient was not available at that time, the first patient after the index date (date of CDI case) was selected. The study protocol was approved by the LUMC Medical Review Ethics Committee.

Definitions and data collection

We collected basic demographic data of all tested patients. One laboratory (Etten-Leur) additionally registered whether the *C. difficile* test was specifically requested by the GP. This was used to evaluate whether CDI testing was requested in current practice.

After obtaining permission of the GP, questionnaires were sent to CDI patients and sampled controls. We contacted subjects by mail or telephone to request return of the questionnaire; this was done up to six times. Questions focused on medication and contact with infants or healthcare in the 3 months before diarrhoea, comorbidity in the year before diarrhoea, travelling history and proximity to other patients with diarrhoea. Frequency, viscosity and presence of bloody diarrhoea were ascertained at the height of the diarrhoeal episode. All variables, except for abdominal pain and fever, which were deemed too subjective, were included in univariate analysis. Follow-up of patients with CDI was done after 6 months by asking the GP about the initiated treatment for CDI, presence of relapses or death.

Stool examinations

The presence of toxin producing *C. difficile* was assessed by a cell cytotoxicity assay in Tilburg, which is still regarded as the reference standard [15,16]. The two other laboratories used an enzyme immunoassay (EIA) for toxins A and B (Premier toxins A&B, Meridian, Bioscience Inc., Cincinnati, OH, USA).

Upon the request of the general practitioner, faeces were tested for diarrhoeal pathogens other than *C. difficile*. These pathogens were tested using local available tests (all PCR). Testing was possible for: bacterial pathogens (*Salmonella* spp., *Shigella* spp. and *Campylobacter* jejuni/coli), parasitic pathogens (*Cryptosporidium*, *Giardia lamblia* and *Entamoeba histolytica*) or viruses (norovirus) in all three laboratories. Additional tests were available upon request or if deemed clinically relevant based on patient data (data not shown). All microbiological results, including the result of the *C. difficile* toxin test, were reported to the GP.

Stool samples that were positive for *C. difficile* in the initial test were cultured and isolates were typed with PCR ribotyping [17]. When an isolate could not be obtained, a PCR on the *tcdB* gene was performed on faeces to confirm the presence of toxigenic *C. difficile* [18].

Data analysis

Incidence rates of diarrhoea and intestinal pathogens were calculated using the total number of person years at risk, which was calculated by multiplying the general practice population (the number of people serviced by the participating general practitioners, according to their patient list) by

the period of study participation (between 12 and 15 months).

Patients with *Clostridium difficile* infection and matched controls were compared using univariate conditional logistic regression. Results were displayed as matched odds ratios (mOR) with a 95% confidence interval (95% CI). Subsequently, all factors with a p-value of <0.10, except for symptoms, were included in multivariable analysis. Although these variables were complete in >92% of the CDI patients and controls, we used multiple imputation to account for missing values in multivariate analysis. This method is appropriate when predictors of the missing data are available (missing at random; MAR) [19]. All potential predictors of missing data, potential predictors of the outcome and the outcome itself were included in the imputation procedure. To include the matched variables (age and gender; both dichotomous) in the multivariate analysis, we performed case-control weighting [20]. This was possible due to the fact that the case-control study was nested in a cohort. Weights were determined by prevalence, age (continuous variable) and sex distribution of patients and controls compared with the original cohort. In patients, weights varied only marginally (between 1.2 and 1.4), because 78% of the diagnosed CDI patients participated in the case-control study. Weights of controls varied between 17 and 112 (mean 41), emphasizing the large sampling fraction and the relative over-representation of elderly patients due to matching.

Evaluation of testing strategies

We evaluated the current diagnostic practice of general practitioners by evaluating the samples for which the GP requested testing for *C. difficile*. This method was compared with the current advice in the Netherlands, the current advice in the UK and the former advice in the UK. The percentage of diarrhoeal patients that required testing according to the aforementioned recommendations, was calculated by using the prevalence of clinical characteristics in our weighted population of diarrhoeal patients and controls (e.g. prevalence of patients with antibiotic use or prior admission was calculated because these patients required *C. difficile* testing according to current Dutch recommendations). In the population that required testing, we determined the percentage of CDI (e.g. among patients with prior antibiotic use or an admission, 8% were CDI positive). Additionally, we determined the percentage of CDI patients that would have been tested by the algorithm (e.g. 60% of all CDI patients occurred in the group of patients with prior antibiotic use or an admission).

We used SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and STATA software package 10.1 (StataCorp, College Station, TX, USA) for our analyses.

Results

During the study period, 12 714 unformed stool samples met the study's inclusion criteria (Fig. 1). The incidence of diarrhoea in which investigation of faeces was requested was 44 per 10 000 person years. Patients were on average 41.3 years old and the majority was female (57.4%) (Table 1).

Incidence of *C. difficile* infection

Of 12 714 stool samples, 194 (1.5%) were positive for *C. difficile* (incidence of 0.67 per 10 000 patient years). In Tilburg, a cell cytotoxicity assay (considered as reference standard) was used to diagnose CDI. Here, 54 tests were found to be positive among 3009 diarrhoeal samples (1.8%; 103 per 10 000 patient years).

Ninety-nine per cent of the stool samples were also tested for the presence of pathogens other than *C. difficile* (12 566/12 714), which were identified in 21.9% (2786/12 714) of all samples: in 22.1% of the CDI-negative samples (2763/12 520) and in 11.8% (23/194) of the CDI-positive samples. The most frequently found co-pathogen in CDI-positive samples was *Campylobacter coli/jejuni* (n = 10; 5%). In total, *Campylobacter coli/jejuni* and *Giardia lamblia* were found in 8.3% (1056/12 714; 3.67 per 10 000 person years) and 3.6% (454/12 714; 1.58 per 10 000 person years) of all samples, respectively. *Salmonella* spp. was found in percentages similar to *C. difficile*: 1.6% (198/12 714; 0.69 per 10 000 person years).

CDI vs controls with diarrhoea

Within the cohort of 12 714 samples, we performed a nested case-control study. One hundred and fifty-two of 194 CDI patients (78%) completed the questionnaire and were matched for age and gender to 304 controls. Participating CDI patients were on average 52.3 years old (standard deviation 22.5); 61% of them were female. Symptoms of diarrhoea started in the community in 94% (n = 143). Three patients (2%) developed symptoms in a long-term care facility and six (4%) developed diarrhoea during hospitalization but were diagnosed after discharge. Compared with controls, CDI patients more often had severe symptoms (bloody stools, watery or frequent diarrhoea), underlying diseases, prior hospitalization and prior use of antibiotics (univariate analysis; Table 2). A third of the CDI patients (n = 58; 39%) did not use antibiotics nor were previously hospitalized; 14% of the CDI patients (n = 22) had no underlying diseases, hospitalization or medication use prior to diarrhoea. CDI patients reported abdominal pain and fever in 77% and 31%, respectively; controls reported these symptoms in 75% and 20%, respectively.

Six variables had a p-value of <0.10 in univariate analysis and were possible predictive factors of CDI. These were included in multivariate analysis together with age and gender. Age ≥50 years, an underlying disease in the year before start of diarrhoea and hospitalization in the preceding 3 months and cancer in the preceding year had a strong association with CDI. Antibiotic use in the preceding 3 months had the strongest association with CDI (Table 3).

Performance of testing algorithms

According to data from one laboratory (Etten-Leur), general practitioners request a test for CDI in 7% of submitted samples (543/8338). These samples included 40% of all diagnosed CDI patients in this study. Currently, the advice regarding testing for *C. difficile* in general practice in the Netherlands is to test all patients with diarrhoea and recent antibiotic use or hospitalization. As 18% of the patients in the study recently used antibiotics or were hospitalized, this advice would lead to testing of 18% of all diarrhoeal patients, detecting 61% of all CDI patients. In the United Kingdom, all diarrhoeal patients aged ≥65 years or patients with recent antibiotic use or a recent hospitalization are advised to be tested. Implementing this strategy in our study population would result in detection of two-thirds of all CDI patients, whereas it would require testing 31% of all diarrhoeal samples.

Confirmation of *C. difficile*

Of the 152 patients with CDI, the presence of *C. difficile* could be confirmed by PCR ribotyping or a positive *tcdB* PCR in 68% (n = 103). Types 002 and 078 (both n = 11; 11%) were most frequently found; type 001 (8%), 005 (6%), 014 (8%), 015 (9%) and 126 (4%) were other frequently found PCR ribotypes. The virulent type 027 that caused many outbreaks in hospitals [21] was isolated in one patient with frequent relapses and prior long-term hospitalization. Thirty-five stool samples were not available for confirmation testing. The majority of the CDI patients in the case-control study had *C. difficile* as the only detected pathogen (130 of 152; 86%).

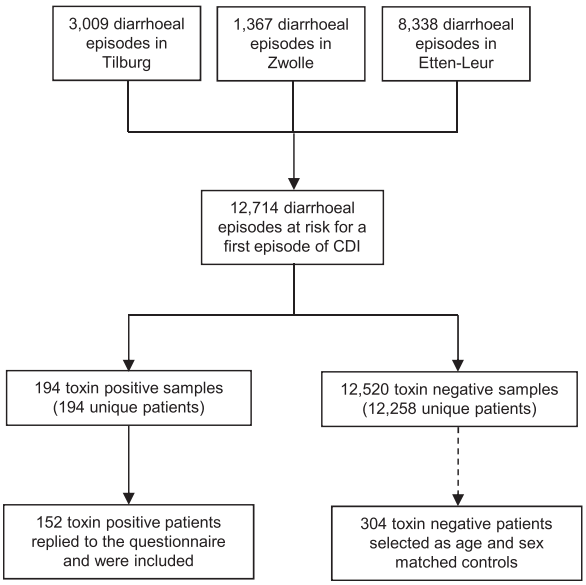

FIG. 1. Patient inclusion chart.

Six months follow-up

Of 122 CDI patients with known follow-up (80.3%), the majority (n = 96; 78.7%) was treated for the infection: monotherapy with metronidazole was most frequently used (n = 85; 88.5%); six patients were treated with vancomycin (6.3%), three with a combination of both (3.1%). Thirty patients (24.6%) had recurrent diarrhoea within 6 months, which was confirmed by a positive toxin test in 36.7%. Within

TABLE 1. Age, gender and incidence of intestinal pathogens in unformed stool samples with a test request from the general practitioner

	Samples (N = 12 714)				
	No. of cases	% of all samples	Rate per 10 000 person years (95% CI)		No. of samples tested
Female gender	7302	57.4			
Age, mean (±SD)	41.3 (23.2)				
Diagnosed pathogens					
Campylobacter coli/jejuni	1056	8.3	3.67	(3.45–3.90)	10 598
Giardia lamblia	454	3.6	1.58	(1.44–1.73)	8954
Salmonella spp.	198	1.6	0.69	(0.60–0.79)	10 598
Clostridium difficile	194	1.5	0.67	(0.58–0.78)	12 714
Shigella spp.	114	0.9	0.40	(0.33–0.47)	10 598
Cryptosporidium	107	0.8	0.37	(0.31–0.45)	8954
Norovirus	75	0.6	0.26	(0.21–0.32)	1374
Entamoeba histolytica	2	0.0	0.01	(0.00–0.02)	6720
Pathogen other than *C. difficile*	2786	21.9	9.68	(9.33–10.05)	12 566

All samples were tested for *C. difficile*, whereas other pathogens were tested upon request of the general practitioner. All laboratories used a PCR to detect the pathogens: *Campylobacter* [35,36], *Salmonella* [36,37], *Shigella* [38], *Giardia lamblia* [39–41], *Cryptosporidium* [39,40], *Entamoeba histolytica* [39,40] and Norovirus [42].

TABLE 2. Clinical characteristics of CDI patients and matched control patients, analysed with conditional logistic regression analysis

Characteristics	CDI cases (*N* = 152)		Controls (*N* = 304)		Crude analysis		
	N	%	*N*	%	mOR	95% CI	p-Value
Symptoms							
Bloody stools	36	25.2	44	15.7	1.82	1.07–3.09	0.03
Watery diarrhoea	119	78.3	207	68.1	1.71	1.08–2.71	0.02
Frequency of diarrhoea >8 times	68	44.7	75	24.9	2.39	1.59–3.61	<0.01
Time to visit GP <1 month	96	64.5	165	56.3	1.40	0.94–2.10	0.10
Medication							
Antibiotics	82	55.0	49	16.6	8.15	4.57–15.5	<0.01
Other medication	92	60.5	166	56.1	1.26	0.81–1.98	0.31
PPI/antacid	43	29.1	60	21.1	1.59	0.99–2.55	0.06
Statin	25	16.9	40	14.1	1.38	0.74–2.58	0.31
NSAID	11	7.4	24	8.4	0.80	0.37–1.73	0.57
DM	10	6.8	19	6.7	1.03	0.46–2.28	0.95
Immunosuppression	11	7.4	12	4.2	1.72	0.74–4.02	0.21
Diuretics, antihypertensives	47	30.9	76	25.2	1.48	0.87–2.53	0.15
Underlying diseases							
Any disease	90	59.2	120	39.7	2.64	1.66–4.20	<0.01
Circulatory system diseases	18	11.8	34	11.3	1.09	0.54–2.19	0.81
Respiratory system diseases	24	15.8	26	8.6	1.90	1.08–3.36	0.03
Cancer	10	6.6	7	2.3	3.60	1.21–10.7	0.02
Environment							
Previous admission	28	18.4	21	7.0	3.16	1.67–5.99	<0.01
Family member with diarrhoea	7	4.8	23	8.0	0.58	0.25–1.35	0.20
Infant <2 years old	40	27.6	97	32.2	0.75	0.47–1.20	0.23
Visited foreign country							
In western world	16	15.4	43	18.4	0.79	0.40–1.56	0.50
Outside western world	15	14.4	41	17.5	0.77	0.38–1.58	0.48

The crude analysis was done by univariate conditional logistic regression, which takes into account the matched factors 'age' and 'gender'. Variables with a p-value <0.10 (*n* = 9) supplemented with age and sex were included in the multivariate analysis (Table 3).

TABLE 3. Multivariable analysis using weighted logistic regression analysis

Factors	MVA		
	OR	95% CI	p-value
Age ≥50	1.41	0.79–2.52	0.25
Gender	1.18	0.70–1.99	0.53
Antibiotics	6.88	3.97–11.9	<0.01
PPI/antacid	1.10	0.56–2.08	0.77
Any disease	1.80	1.00–3.23	0.05
Respiratory system diseases	1.25	0.51–3.06	0.63
Cancer	4.04	1.47–11.1	<0.01
Previous admission	1.66	0.75–3.68	0.21

In the multivariate analysis (MVA) we included all possible predictive factors for CDI with a p-value of <0.10 according to the crude analysis and 'age' and 'gender'. Symptoms were not included in the MVA. We adjusted the variables in this table for age, gender, antibiotics, PPI/antacid, respiratory system diseases, cancer and previous admission. The variable 'any disease' was not adjusted for 'respiratory system diseases' and 'cancer' as these variables were included in 'any disease'.

6 months, six CDI patients (3.9%) were hospitalized because of diarrhoea and four died (2.6%). In one patient (0.6%) CDI contributed to the cause of death.

Discussion

Incidence of CDI in general practice

This study determined the incidence of *C. difficile* in a large sample of microbiological test requests from general practitioners. One out of 66 diarrhoeal episodes was positive for *C. difficile* (1.5%), which was comparable to the incidence of *Salmonella* spp. Earlier studies reported similar incidences of CDI (1.5–2.1% [4,5]; 0.7–2.5 per 10 000 person years [2,5,9,22–27]), with the exception of a study from the UK that reported virtually no CDI in general practice [28]. The latter UK study confirmed our relatively low rate of salmonellosis (1.8 per 10 000 patient years using faecal culture), but should be interpreted with caution because exclusion criteria such as recent travel and diarrhoeal illness lasting over 2 weeks resulted in the analysis of 45% (991/2203) of all diarrhoeal episodes. Although we included all diarrhoeal samples that were sent to a laboratory, the incidence of CDI in our study could be underestimated if diarrhoeal samples of patients with CDI were not sent to a laboratory and the disease had a self-limiting course.

Our study included 12 714 diarrhoeal episodes and showed that CDI is relatively common among diarrhoeal stool samples and should be included in the differential diagnosis of infectious diarrhoea in general practice.

When should we consider CDI and request a test?

Dutch GPs are advised to test all patients with prior antibiotic use or hospitalization for CDI. Currently, GPs do not follow these recommendations and test only 7% of all diarrhoeal patients, detecting 40% of all CDI patients. This large proportion of undiagnosed patients with CDI is in our opinion undesirable, as all CDI patients had diarrhoeal complaints and nine patients (5.8%) experienced a complicated course (hos-

pitalization or death within 6 months). A similar course was observed in community-based studies [5,26]; however, as most CDI patients in these studies were treated for CDI, we expect the number of complicated courses to be higher when CDI is undiagnosed and therefore untreated. In our study, complicated courses were also experienced by patients without traditional risk factors (3/9; 33.3%), which underlines the necessity for diagnosis.

Because testing of all unformed stool samples, as was the former UK advice, requires a large budget, this is currently probably not achievable in most laboratories and general practices. Our study confirms that well-known risk factors for nosocomial CDI (antibiotic use and hospitalization) are present in only 61% of the patients with CDI in the community. As shown in multivariate analysis, the clinical presentation of patients with CDI differs from other causes of diarrhoea, as they frequently have bloody stools, watery diarrhoea and many stools daily. Therefore, we suggest including clinical symptoms in a future prediction model for CDI. For now, we recommend following current Dutch guidelines or the current UK advice in the Netherlands. This would result in detection of 61% or 72% of all CDI, respectively, which would clearly outperform current practice.

Strengths and weaknesses

We are the first to provide a complete overview of incidence, clinical characteristics and testing strategies of CDI in general practitioners' practice. The size of the cohort and high participation rate (78%), and the early and thorough follow-up of the questionnaire, provide a stable base for our conclusions. Furthermore, we were able to confirm *C. difficile* with PCR ribotyping in two-thirds of the cases with a positive toxin test, which enabled us to compare types circulating in general practice with those causing disease in hospitals. Similar types were seen in general practice and hospitals in the Netherlands during the study period [29,30]. As recent evidence suggests that direct transmission of *C. difficile* between hospitalized patients is not the prime route of transmission [31], the large overlap of PCR ribotypes in both settings strengthen the hypothesis of movement of *C. difficile* between both settings.

Our study also has limitations. Firstly, we restricted our study to samples that were sent to a laboratory. Our conclusions are therefore not necessarily generalizable to settings with different testing criteria. Although Dutch GPs request laboratory diagnostics in 10–20% of gastroenteritis consultations [32] and 20–30% of the GPs in the UK request testing [9,33], testing criteria in other countries could differ. Secondly, testing strategies in our study include the 'reference standard' and an enzyme immunoassay (EIA), which has a limited negative and positive predictive value in the community [34]. Missing cases due to a false-negative toxin test could have resulted in an underestimation of the incidence of CDI. However, the incidence according to the reference standard (used in Tilburg) was even higher. The large sampling fraction in the case-control study makes it unlikely that false-negative patients were included as controls. However, false-positive cases might have occurred. In the majority of the CDI cases (n = 130, 86%) no pathogens other than *C. difficile* were found. Additionally, in 13 of the 22 CDI cases with a co-pathogen, the presence of toxigenic *C. difficile* was confirmed by PCR ribotyping. Therefore, we assume that bias due to to false-positive cases is limited. Thirdly, we would like to stress that the results of Table 4 are dependent on the test that was used. In a setting where different tests for *C. difficile* are used, sensitivity and specificity and therefore the measured incidence of CDI (and the weighted case-control analyses of Table 4) can differ. Nonetheless, our conclusion regarding present insufficient testing and suggestions for future testing are strong and will hold in a setting with a different test.

Clinical relevance

Although it has several limitations, our study illustrates that CDI should be included in the differential diagnosis of infectious diarrhoea in general practice, even when the patient was not recently using antibiotics, is young and has no comorbidity. Additionally, it highlights that current Dutch testing strategies are insufficient. We recommend following current Dutch guidelines or the current UK advice in the Netherlands, which outperform current practice without testing a large number of samples.

TABLE 4. Performance of seven different algorithms for testing diarrhoeal samples for *Clostridium difficile* in general practice

Test algorithm for CDI in diarrhoeal samples from the community	Setting	Patients tested % of all unformed stool samples	Positive results % of all tested samples	Detection of CDI % of all positives
≥2 years	Former advice UK (2009)	100	1.5	100
≥65 years, after AB use or hospitalization	Current advice UK (2012)	31	3.5	72
After AB use or hospitalization	Current advice NL	18	5.0	61
Doctor's current practice	Current practice NL	7	8.1	40

These percentages are based on the weighted analysis of all CDI patients and controls (n = 12 714). AB, antibiotic.

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Reporting

This study was reported according to the STROBE guidelines.

Details of Contributors

M. Hensgens: contributed to the collection of the data and design of study, performed all analyses and produced the first draft of the article. O. Dekkers: designed the study, contributed to the epidemiological analyses and revised drafts of the article. A. Demeulemeester: contributed to the collection of the data and coordinated the study in Etten-Leur. P. Bloembergen and A. Buiting: coordinated the study in Zwolle and Tilburg, respectively, and revised drafts of the manuscript. B. van Benthem: contributed to the design of the study and revised drafts of the manuscript. S. Le Cessie: assisted with and performed parts of the statistical analysis of the study and revised drafts of the manuscript. E. Kuijper: designed the study and revised the drafts of the article.

Transparency Declaration

None to declare.

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