

Survey of *Clostridium difficile* infection surveillance systems in Europe, 2011

A Kola ¹, C Wiuff ², T Akerlund ³, BH van Benthem ⁴, B Coignard ⁵, O Lyytikäinen ⁶, D Weitzel-Kage ¹, C Suetens ⁷, MH Wilcox ^{8,9}, EJ Kuijper ¹⁰, P Gastmeier ¹, on behalf of members of ECDIS-Net ¹¹

1. Charité - Universitätsmedizin Berlin, Germany
2. Health Protection Scotland, Glasgow, United Kingdom
3. Swedish National Institute of Public Health, Solna, Sweden
4. Center for Infectious Diseases Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
5. Institut de Veille Sanitaire, Saint-Maurice Cedex, France
6. National Institute for Health and Welfare, Helsinki, Finland
7. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
8. Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
9. University of Leeds, Leeds, United Kingdom
10. Leiden University Medical Center, Leiden, the Netherlands
11. The members of ECDIS-Net are listed at the end of the article

Correspondence: Axel Kola (axel.kola@charite.de)

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To develop a European surveillance protocol for *Clostridium difficile* infection (CDI), existing national CDI surveillance systems were assessed in 2011. A web-based electronic form was provided for all national coordinators of the European CDI Surveillance Network (ECDIS-Net). Of 35 national coordinators approached, 33 from 31 European countries replied. Surveillance of CDI was in place in 14 of the 31 countries, comprising 18 different nationwide systems. Three of 14 countries with CDI surveillance used public health notification of cases as the route of reporting, and in another three, reporting was limited to public health notification of cases of severe CDI. The CDI definitions published by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Centre for Disease Prevention and Control (ECDC) were widely used, but there were differing definitions to distinguish between community- and healthcare-associated cases. All CDI surveillance systems except one reported annual national CDI rates (calculated as number of cases per patient-days). Only four surveillance systems regularly integrated microbiological data (typing and susceptibility testing results). Surveillance methods varied considerably between countries, which emphasises the need for a harmonised European protocol to allow consistent monitoring of the CDI epidemiology at European level. The results of this survey were used to develop a harmonised EU-wide hospital-based CDI surveillance protocol.

Introduction

Since 2000, a considerable increase in the number of *Clostridium difficile* infections (CDIs) leading to substantial morbidity, mortality and attributable costs has been observed, at least in North America and Europe [1]. Changes in the epidemiology of CDI have been mainly attributed to the emergence of a new hyper-virulent strain called PCR ribotype 027, causing numerous outbreaks in North America and Europe [2,3] and, to a lesser extent, PCR ribotype 078 [1,4,5]. In addition, patients not previously considered to be at risk for the disease (e.g., without recent antibiotic therapy or hospitalisation) have also been described [1,6-8]. The European CDI study (ECDIS), initiated and funded by the European Centre for Disease Prevention and Control (ECDC), showed that the incidence of CDI varied from hospital to hospital [9]. In 2008, a weighted mean incidence of 4.1 cases (range: 0.0–36.3) per 10,000 patient-days per hospital reported by the ECDIS study was almost 70% higher than that reported in a previous European surveillance study in 2005 (2.45 cases per 10,000 patient-days per hospital, range: 0.13–7.1) [9,10]. ECDIS also revealed the contribution of strains other than PCR ribotype 027 and that some of these strains, notably PCR ribotypes 015, 018 and 056, could cause severe CDI.

In response to the emerging problems associated with *C. difficile*, an ECDC working group published background information about the changing epidemiology of CDI, CDI case definitions and surveillance recommendations [2]. To support European Union (EU)/European

TABLE

Characteristics of European *Clostridium difficile* infection surveillance systems, 2011 (18 surveillance systems from 14 countries)

Country	Name	Participants	General remarks	Epidemiological data	Microbiological data
Austria	No name	All H/L/G	M C+P Lb+Cb only sevCDI	Total number CDI-days	RTcp AST
Belgium	National Surveillance of Infections in Hospitals (NSIH)	110 H	M P Cb Periodic (6 months a year)	HA-CDI: I (1,000 pa/6 months) Id (10,000 pd/6 months) Severe CDI: ICU-adm/death within 30 days related to CDI	TcdT (fp/sevCDI /ob) AST (fp/sevCDI /ob)
Bulgaria	BGCDISS	6 H/3 L	V C+P Lb+Cb	HA-CDI: I (10,000 pa) Id (10,000 pd)	RTcp No AST
Denmark	Surveillance of epidemic hypervirulent CD in Denmark	13 H/13 L	V C+P Lb	I (number of episodes/region)	RTag (sevCDI+ MoxR)/ob) AST
Finland-1	National Infectious Diseases Register	All L	M C+P Lb	I (100,000 inh)	RTag (sevCDI/ob) No AST
Finland-2	Finnish Hospital Infection Programme (SIRO)	12 H	V C+P Cb	HA-CDI: I (100 pa) Id (1000 pd) Severe CDI: ICU-adm/surgery/ death within 30 days related to CDI	None
Finland-3	National Hospital Discharge Register (HILMO)	57 H	M C (retrosp.) ICD 10-based	I (CDI hospitalisations/ 100,000 inh)	None
France	Healthcare acquired Infections Early warning and Response system	100 H/115 L/ 10 N	M C+P Cb only sevCDI/ob	Severe CDI: Total number I (1,000 pa) Id (10,000 pd)	RTag (sevCDI/ob) AST (sevCDI/ob)
Germany-1	CDAD-KISS	126 H	V C+P Cb	HA-CDI/severe CDI: I (100 adm) Id (1,000 pd)	None
Germany-2	SurvNet	About 2000 H	M C+P Cb only sevCDI/ ribotype 027	Severe CDI: Total number I (100,000 inh/ ICU-adm/surgery/ death within 30 days related to CDI)	RTcp (sevCDI/ob) No AST
Hungary	Epidemiological Control System and Information System (EFRIR)	35 H / 14 L	M C+P Lb+Cb	Total number	RTag (sevCDI/ob) No AST
Ireland-1	Notifiable <i>C. difficile</i> Surveillance	48 H/37 L / all G from 8 public health regions	M C+P Cb	I (100,000 inh)	None
Ireland-2	<i>C. difficile</i> Enhanced Surveillance	34 H/34 L	V C+P Cb	HA-CDI: Id (10,000 pd) Severe CDI: ICU-adm/ surgery related to CDI	None
The Netherlands	Sentinel surveillance of <i>C. difficile</i>	19 H/19 L	V C+P Lb+Cb	HA-CDI: I (CDI cases/pa) Id (CDI cases/pd)	RTag (fp) No AST
Sweden	National Laboratory-based CD Surveillance System	20 L	V C+P Lb	Total number	RTac (fp/sevCDI /ob) AST (fp)
UK-England	HCAI Data Capture System	167 NHS Acute Trusts with 1–2 H each	M C+P Lb	All types of CDI: Id (adm>65 y/1,000 pd) HA-CDI: Id (cases>2 y/10,000 pd) Severe CDI: Death within 30 days related to CDI	RTca AST (fp)
UK-Northern Ireland	Enhanced HCAI Web-based Surveillance System	28 H / 5 L / 358 GP / 240 N / 237 R	M C+P Lb	HA-CDI and CA-CDI: Total number Id (1,000 pd)	RTcp/no AST
UK-Scotland	Scottish Mandatory Surveillance Programme for CDI	23 L and 14 NHS health boards including H/N/G	M C+P Lb+Cb	HA-CDI: Id (cases≥15 y/1000 pd)	RTag (fp/sevCDI/ob) AST (fp/sevCDI/ob)

ac: acrylamide; adm: admissions; ag: agarose; AST: antimicrobial susceptibility testing; C: continuous; CA: community associated; cp: capillary; Cb: case-based; CD: *Clostridium difficile*; CDI: *Clostridium difficile* infection; fp: fixed proportion; G: general practitioners; H: hospitals; HA: healthcare associated; I: incidence; ICD-10: International Statistical Classification of Diseases 10th revision; ICU: intensive-care unit; Id: incidence density; inh: inhabitants; L: laboratories; Lb: laboratory-based; M: mandatory; MoxR: moxifloxacin resistance; N: nursing homes; ob: outbreaks; pa: patient admissions; pd: patient-days; R: residential homes; retrosp.: retrospective; RT: ribotyping; sevCDI: severe CDI; TcdC: typing of the *tcdC* gene; UK: United Kingdom; V: voluntary; y: years.

^a Iceland and UK-Wales did not reply to the web-based questionnaire.

^b Some countries had more than one surveillance system in parallel. Where relevant, they are shown with the suffixes -1, -2 and -3.

Economic Area (EEA) Member States in increasing their capacity for CDI surveillance, ECDC also initiated and funded a new project – ECDIS-Net – to develop a European surveillance protocol and enhance laboratory capacity for diagnosis and typing of *C. difficile* in EU/EEA Member States.

In 2011, a survey of existing CDI surveillance systems in European countries was performed as part of the ECDIS-Net project. The results of this survey, presented here, were later used to develop a standardised pan-European CDI surveillance protocol, which was tested in a three-month pilot study in 2013 [11]. Data collection in the ECDC-coordinated Europe-wide hospital-based CDI surveillance, using a finalised version of this piloted protocol, began on 1 January 2016 [12].

Methods

National coordinators for this study were identified through the members of ECDC's Healthcare-Associated Infections surveillance Network (HAI-Net) and via representatives for the ECDIS study [9]. A link to a web-based questionnaire was sent to these national coordinators to assess the characteristics of existing CDI surveillance systems in European countries. If the national coordinators indicated that CDI was under surveillance in their country, the surveillance protocols were requested and used to augment the information obtained via the questionnaire. Information on the national CDI surveillance systems was entered using a web-based electronic form designed for the purpose of this study.

Results

Between 6 June and 15 July 2011, 33 of the 35 national coordinators approached from 31 European countries responded to the web-based questionnaire (Iceland and Wales did not respond). Four surveillance systems were excluded from further analysis, as they were not ongoing, comprehensive nationwide surveillance systems, i.e. they were completed one-off studies (two studies from Spain), only regional (Switzerland) or focused only on outbreaks (one system of the Netherlands). In 14 countries, the national coordinators indicated that surveillance of CDI was in place. Of these, surveillance protocols were available from 10 surveillance systems. Thus, 18 CDI surveillance systems from 14 European countries (Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Hungary, Ireland, the Netherlands, Sweden and three countries of the United Kingdom (UK), England, Northern Ireland and Scotland) remained available for analysis. Of the 18 surveillance systems, all but one reported national CDI rates annually.

General characteristics of *C. difficile* infection surveillance systems

An overview of the European CDI surveillance systems is given in the Table. In summary, 11/18 surveillance systems used mandatory reporting and seven used voluntary reporting of cases. The majority (16/18) of the

surveillance systems were continuous and prospective, one was periodical and prospective (Belgium), and one was retrospective (Finland-3). In three countries (Germany, Ireland, the Netherlands), two surveillance systems were run in parallel, (shown with the suffixes -1 and -2). In Finland, there were three parallel systems (Finland-1, -2 and -3). Parallel systems were also in place in the three parts of the United Kingdom that took part in the survey (England, Northern Ireland and Scotland). In Finland, Germany and Ireland, one surveillance system was limited to (legally required) public health notification of CDI cases, whereas additional systems collected laboratory-based data and enhanced epidemiological data on a voluntary basis. Public health notification of CDI was also carried out in Austria, Denmark and Hungary.

In Austria, France and Germany-2, surveillance of CDI targeted severe cases only. All surveillance systems included CDI in hospitalised patients, but 10/18 systems also included patients with community-acquired CDI. CDI case ascertainment was case-based (including clinical evaluation) in 7/18 systems, laboratory-based (relying on positive test results for toxin-producing *C. difficile*) in 5/18 systems or a combination of both in an additional 5/18 surveillance systems. Only Finland-3 used the International Statistical Classification of Diseases 10th revision (ICD-10)-based discharge coding [13] to find cases of CDI.

Definitions of *C. difficile* infection

The definitions used for CDI surveillance are summarised in the Box .

The majority (12/18) of the surveillance systems used the ECDC and CDC case definition of CDI [2,14], 4/18 used other definitions and 2/18 did not use a specific case definition (but relied instead on the diagnosis of the attending physician and a positive laboratory test result for toxigenic *C. difficile*). More detailed definitions for community-associated CDI, community-onset of healthcare-associated CDI and healthcare-onset of healthcare-associated CDI were used by 9/18 (ECDC definition: 7/9, other definitions: 2/9). Definitions differing from ECDC's for community-associated CDI, community-onset healthcare-associated CDI and healthcare-onset healthcare-associated CDI used a time point of ≥ 72 hours or > 3 days (i.e. on or after day 4 of admission) instead of ≥ 48 hours between admission and onset of symptoms to distinguish between community- and healthcare-associated CDI.

In 13/18 surveillance systems, there was a definition for severe cases of CDI (ECDC definition: 5/13, other definitions: 8/13) and in 11/18 systems, there was also a definition for recurrence of CDI (ECDC definition: 9/11, other definitions: 2/11). Definitions differing from ECDC's definition for severe/complicated course of CDI used additional criteria such as bloody diarrhoea, temperature $> 38.5^{\circ}\text{C}$, white cell count $> 15 \times 10^9/\text{L}$, decreased kidney function or hypo-albuminaemia (< 30

Box

Definitions, including surveillance system-specific definitions^a, for surveillance of *Clostridium difficile* infections

<p>CDI case</p> <p>A patient to whom one or more of the following criteria applies:</p> <ol style="list-style-type: none">1. diarrhoeal stools or toxic megacolon AND a positive laboratory assay for <i>C. difficile</i> TcdA and /or TcdB in stools or a toxin-producing <i>C. difficile</i> organism detected in stool via culture or other means;2. pseudomembranous colitis revealed by lower gastrointestinal endoscopy;3. colonic histopathology characteristic of CDI (with or without diarrhoea) on a specimen obtained during endoscopy, colectomy or autopsy.
<p>Differing definitions:</p> <p>Finland-1: Detection of <i>C. difficile</i> organism/DNA/RNA/toxin in a clinical sample.</p> <p>Finland-3: International Classification of Diseases (ICD)-10 codes A04.7 and K52.8 specific for <i>Clostridium difficile</i>-associated disease.</p> <p>UK-England: Diagnoses on the basis of tests for <i>C. difficile</i> toxins A and B on diarrhoeal stool samples. Positive results on the same patient within 28 days of the first specimen are regarded as a single episode. All cases are reported regardless of location of the patient at the time the specimen was taken, i.e. regardless of whether the patient was in a hospital or another setting. Diarrhoeal stools are defined as 'those that take the shape of their container'. One (unexplained) diarrhoeal episode is sufficient to qualify for a diagnosis of CDI if the laboratory test is supportive.</p> <p>UK-Northern Ireland: A patient aged two years and over from whom a diarrhoeal specimen is tested positive for <i>C. difficile</i>.</p>
<p>Community-associated CDI</p> <p>Onset of CDI outside a healthcare facility (HCF) or within 48 hours following admission to a healthcare facility without residence in/ discharge from a healthcare facility within the previous 12 weeks.</p>
<p>Differing definitions:</p> <p>Finland-2 and Germany-1: Onset of CDI in an outpatient or inpatient within 72 hours after admission to the facility.</p>
<p>Community-onset of healthcare-associated CDI</p> <p>Onset of CDI in the community within 4 weeks following discharge from a healthcare facility.</p>
<p>Healthcare-onset of healthcare-associated CDI</p> <p>Onset of CDI at least 48 hours (>48 hours) following admission to a healthcare facility</p>
<p>Complicated course of CDI (severe CDI case)</p> <p>A patient to whom any of the following criteria applies:</p> <ol style="list-style-type: none">1. admission to a healthcare facility for treatment of community-associated CDI;2. admission to an intensive-care unit for treatment of CDI or its complication (e.g. for shock requiring vasopressor therapy);3. surgery (colectomy) for toxic megacolon, perforation or refractory colitis;4. death within 30 days after diagnosis, if CDI is either the primary or a contributive cause.
<p>Differing definitions:</p> <p>Austria: CDI requiring admission to an intensive-care unit/CDI requiring surgery/fatal cases of CDI.</p> <p>Germany: Instead of 1: Readmission because of recurrent CDI (points 2–4 as above)</p> <p>France: In addition: white cell count >20 × 10³/mm³.</p> <p>Hungary: Death linked to CDI (based on death register).</p> <p>Ireland-2: 1. Admission to an intensive care unit for treatment of CDI or its complication (e.g. for shock requiring vasopressor therapy) and/ or 2. surgery (colectomy) for toxic megacolon, perforation or refractory colitis.</p> <p>The Netherlands: 1. Bloody diarrhoea and/or 2. pseudomembranous colitis and/or 3. diarrhoea in combination with dehydration and/or hypo-albuminaemia (<30 g / L) 4. temperature >38 °C and white cell count >15 × 10⁹/L.</p> <p>UK-England: Temperature >38.5 °C, white cell count >15 × 10⁹/L, decreased kidney function, or evidence of colitis.</p> <p>UK-Scotland: In addition: Endoscopic diagnosis of pseudomembranous colitis (with or without toxin confirmation) persisting CDI where the patient has remained symptomatic and toxin positive despite two courses of appropriate therapy.</p>
<p>Recurrent CDI</p> <p>An episode of CDI that occurs >2 weeks and ≤ 8 weeks following the onset of a previous episode.</p>
<p>Differing definitions:</p> <p>UK-England: A positive specimen taken more than 28 days after the initial specimen is considered a new CDI episode.</p> <p>UK-Scotland: A new episode is defined as one occurring more than 28 days after the previous onset.</p>

CDI: *Clostridium difficile* infection; UK: United Kingdom.

^a Some countries had more than one surveillance system in parallel.

Source: [2,14]. Surveillance system-specific definitions: this study.

g/L). Definitions differing from those used by ECDC for recurrent CDI used a time lapse of between two and four weeks after the previous onset to distinguish between different episodes of CDI.

Collection of *C. difficile* infection surveillance data

In 5/18 surveillance systems, data collection was done only by laboratories, in 7/18 only by infection control teams, and in 5/18 by both. One surveillance system used hospital administration data only (Finland-3). In 8/18 surveillance systems, case-based data were

collected by healthcare personnel (in 7/8 in combination with the infection control teams). In addition, general practitioners were engaged in surveillance data collection in Austria and UK-Scotland, as were public health doctors in Ireland-1. Only 3/18 surveillance systems relied solely on laboratory tests positive for CDI without additional patient data (Denmark, Finland-1, Sweden).

The collected data were pooled nationwide in 11/18 surveillance systems (Belgium, Bulgaria Finland-1, Finland-3, France, Hungary, Ireland-1, Ireland-2,

Sweden, UK-Northern Ireland and UK-Scotland), per district or health board in 9/18 systems (Austria, Denmark, Finland-1, Finland-3, France, Germany-2, Ireland-1, UK-Northern Ireland and UK-Scotland), per healthcare facility in 9/18 systems (Belgium, Bulgaria, Finland-2, France, Germany-1, Ireland-2, the Netherlands, UK-England, UK-Northern Ireland) and per unit within a healthcare facility in 2/18 systems (Finland-2, UK-Northern Ireland). In Finland-3 and Sweden, the collected data were also pooled per laboratory. Data about the size or type of the reporting healthcare facility were collected in 12/18 CDI surveillance systems, but not in the remaining six systems (Austria, Denmark, Finland-1, Germany-2, Hungary, Sweden). In 8/18 surveillance systems, even the speciality of the reporting unit or department was known. Most of the surveillance systems collected patient data: age and sex of CDI cases were reported in 16/18 surveillance systems, the date of onset of CDI in 13/18 systems and the date of admission in 11/18 systems. Only one surveillance system did not collect any patient data (Germany-1). Data about the history of CDI cases were collected in 6/18 surveillance systems (number of previous hospital admissions: 2/6, number of previous episodes of CDI: 4/6; recurrent CDI: 5/6) and data about the outcome of CDI (death within 30 days) were collected in 5/18 systems.

Reporting of *C. difficile* infection surveillance data

CDI surveillance results were periodically reported in 16/18 surveillance systems (ranging from daily reports in UK-Northern Ireland to annual reports in 9/18 systems); only 2/18 surveillance systems did not report the results at regular intervals (Finland-3, Germany-2). All 18 surveillance systems published their reports nationally, but in 6/18 and 3/18 surveillance systems, there were additional regional and local reports, respectively. Most (12/18) of these reports were available to the public and healthcare professionals; only 4/18 and 2/18 surveillance systems published reports that solely targeted healthcare professionals or the public, respectively. Surveillance results were stratified in 8/18 surveillance systems, mostly by geographical region (4/8) or type of healthcare facility (4/8). More details, including denominators and calculated CDI rates, are given in the Table.

Typing

Typing of *C. difficile* was performed by national reference laboratories in 13 European countries with CDI surveillance, PCR ribotyping (either agarose: 8/13, acrylamide: 1/13 or capillary gel-based: 4/13) being the preferred method. Only one reference laboratory also used *tcdC* typing (Belgium). For the purposes of surveillance, typing was done in 13/18 European surveillance systems with varying criteria for submitting strains for further typing: severe CDI (9/13), outbreaks (7/13), isolates resistant to moxifloxacin (Denmark) or a more systematic sampling design selecting (4/13), e.g. the first five strains of each semester, i.e. each half of

the year (Belgium), all strains of selected calendar periods (Sweden, UK-Scotland) or selected hospitals (the Netherlands). An overview is given in the Table. A more detailed analysis was performed by another ECDIS-Net survey in 2011 and 2014 of diagnostic and typing capacity for CDI in Europe: the results of which are also reported in this issue [15].

Susceptibility testing

There were no official recommendations for routine susceptibility testing of *C. difficile* isolates in any of the European countries taking part in ECDIS-Net, but susceptibility testing results were included in 7/18 CDI surveillance systems analysed. Conditions leading to susceptibility testing were the surveillance of antimicrobial resistance itself (5/7), severe CDI cases (4/7) or outbreaks of CDI (3/7).

Discussion

This survey showed that 14 of 31 European countries surveyed conducted some kind of CDI surveillance in 2011. The majority of the 18 existing European nationwide CDI surveillance systems were continuous and prospective, and captured CDI cases by standardised case definitions targeting the clinical symptoms of CDI and/or laboratory diagnosis of CDI, and all of them included CDI in hospitalised patients. However, there were interesting differences between these systems. In 11/18 of European countries with CDI surveillance, surveillance was mandatory, either by mandatory reporting of laboratory and/or clinically confirmed cases or by public health notification of CDI. Whether surveillance should be based on mandatory or voluntary reporting of confirmed cases is still under discussion [16-18]. Opponents of mandatory reporting argue that especially in combination with public reporting of surveillance results and financial penalties, it may lead to systematic under-reporting of cases.

An important issue for surveillance purposes is the definition of CDI cases. These definitions should be valid, specific, easily understood, generally applicable and meet the requirements of different clinical settings, ideally across borders. Moreover, they should allow the comparison of local, regional, national and international infection rates [19]. The definitions proposed by the study group for *C. difficile* of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and ECDC [2] are in agreement with those of the United States Centers for Disease Control and Prevention (CDC) [2,14]. Most of the European CDI surveillance systems adhere to these definitions, but difficulties are encountered in differentiating between community- and healthcare-associated cases of CDI. Some surveillance systems do not make any distinction between the two types of cases (for instance, when only laboratory data are used), while others use different time points for differentiating between the two. Stratification of community-associated and healthcare-associated CDI cases may permit recognition of changes in epidemiology, e.g. an increase in the

number of community-associated cases of CDI possibly caused by 'hypervirulent' *C. difficile* strains [1,20,21]. For feasibility reasons, the definitions of community- and healthcare-associated cases of CDI could be simplified, e.g. by adjusting the threshold time between the two types of cases to three days or later instead of 48 hours. However, regardless of the threshold used, variable proportions of CDI cases defined as community-associated CDI cases may in fact be linked to recent hospitalisation.

In order to meet the ECDC CDI case definitions, most surveillance systems used laboratory reporting and identification of CDI cases by attending healthcare personnel and/or infection control practitioners; few relied solely on laboratory test results. Only one of the Finnish surveillance systems used ICD-10 coding of CDI supplied by hospital administrations. In comparison with surveillance using CDI case definitions, surveillance using ICD coding has shown to be less sensitive [22,23]. In Finland, three different surveillance systems for CDI are run in parallel and so may compensate for their respective limitations.

All surveillance systems reporting hospital-associated CDI cases express CDI rates as incidence rate (per number of patient admissions within a given surveillance period) or incidence density (per number of patient-days). However, different orders of magnitude are used (100 or 1,000 admissions and 1,000 or 10,000 patient-days). Apart from that, surveillance systems only reporting the total number (i.e. community-associated and hospital-associated combined) of CDI cases mostly calculate the incidence per number of inhabitants; only a few exceptions just give the cumulative number of CDI cases. According to published recommendations and for better comparison, the incidence density of healthcare-associated and community-associated CDI should be expressed per 10,000 patient-days and 100,000 inhabitants, respectively [14,19].

More than half of the European CDI surveillance systems presented their findings pooled, i.e. without any further stratification. Unfortunately, only a few surveillance systems provided sender-specific analyses. This would, however, be very important to inform interventions at local level and may help to reduce infection rates [24].

Microbiological data may be an important supplement to epidemiological surveillance data and allow deeper insights into epidemiological changes. In our survey, however, strain typing and susceptibility testing were mainly restricted to outbreaks of CDI or severe cases of CDI; only a few surveillance protocols included typing or susceptibility testing on a regular basis. Although lacking the discriminatory power to study outbreaks, PCR ribotyping is the most adopted *C. difficile* typing methodology in European reference laboratories. International standardisation of ribotyping methods would allow comparability and reproducibility between

countries. Capillary-based ribotyping offers the opportunity to achieve these aims, as results are easier to interpret and to exchange than those of conventional agarose-based ribotyping [25-27].

The main limitations of microbiological testing for *C. difficile* are financial, and shipment of strains to reference laboratories for typing may be hampered by the fact that many laboratories perform toxin testing alone and do not culture *C. difficile*.

Published recommendations of ECDC and the United States Centers for Disease Control and Prevention (CDC) are that CDI surveillance should be conducted for at least all inpatients to monitor healthcare-associated CDI, and healthcare-associated CDI rates should be expressed as number of cases per 10,000 patient-days [2,14]. A standardised European CDI surveillance protocol should be used to allow meaningful intercountry comparisons of CDI incidence rates and for follow-up of the epidemiology of CDI at European level. Special emphasis should be given to the harmonisation of definitions of community-associated and healthcare-associated CDI, inclusion criteria for patients and CDI cases, criteria for typing *C. difficile* strains, denominator data, epidemiological case-based data and case-finding methods. In order to integrate microbiological test results into CDI surveillance, more frequent culture of *C. difficile* is required, and typing methods should be standardised. Harmonised systematic surveillance at national and European level is more likely to facilitate the identification of epidemiological changes and the optimal control of CDI. As a result of this survey, ECDC published a harmonised EU/EEA-wide hospital-based CDI surveillance protocol in May 2015 [12].

Members of ECDIS-Net (national coordinators)

Austria: F. Allerberger, AGES - Institut für medizinische Mikrobiologie und Hygiene, Wien; Belgium: M. Delmée, University of Louvain, Brussels; Bulgaria: K. Ivanova, R. Vatcheva-Dobrevska, National Centre for Infectious and Parasitic Diseases, Sofia; Croatia: B. Matica, Public Health Institute Dr A. Štampar, Zagreb; Cyprus: P. Maikanti-Charalampous, Nicosia General Hospital, Nicosia; Czech Republic: O. Nyč, Hospital FN Motol Prague, Prague; Denmark: K.E.P. Olsen, Statens Serum Institut, Copenhagen; Estonia: M. Jyrna-Ellam, North Estonia Medical Centre, Tallinn; Finland: O. Lyytikäinen, S. Mentula, A. Virolainen, THL (National Institute for Health and Welfare), Helsinki; France: F. Barbut, Hôpital Saint-Antoine, Paris; B. Coignard, C. Eckert, Institut de Veille Sanitaire, Saint-Maurice Cedex; Germany: T. Eckmanns, Robert Koch-Institut, Berlin; L. von Müller, University of Saarland Medical Centre, Homburg; Greece: E. Malamou-Lada, M. Orfanidou, G. Gennimatas General Hospital, Athens; Hungary: E. Nagy, Faculty of Medicine, University of Szeged, Szeged; Ireland: F. Fitzpatrick, Health Protection Surveillance Centre, Dublin; Italy: P. Mastrantonio, Istituto Superiore di Sanità, Rome; Latvia: A. Balode, Pauls Stradins Cilincal University hospital, Riga; Liechtenstein: M. Ritzler, Labormedizinisches Zentrum Dr. Risch, Schaan; Lithuania: J. Miculevičienė, National Public Health Surveillance Laboratory, Vilnius; Luxembourg: M. Perrin, Laboratoire National de Santé (LNS), Luxembourg; Netherlands: B. van Benthem and D. Notermans, Center for

Infectious Disease Control, Bilthoven; E.J. Kuijper, Leiden University Medical Centre, Leiden; Norway: A. Ingrebretsen, Rikshospitalet University Hospital, Oslo; Poland: H. Pituch, Medical University of Warsaw, Warsaw; Portugal: M.A. Sousa Oleastro, Departamento de Doenças Infecciosas Instituto Nacional de Saúde Dr Ricardo Jorge, Lisboa; Romania: D. Lemeni, Cantacuzino Institute, Bucharest; Slovakia: K. Kramarova, E. Novakova, Comenius University, Jessenius Faculty of Medicine, Martin; Slovenia: M. Rupnik, Institute of Public Health, Maribor, J. Kolman, National Institute of Public Health, Ljubljana; Spain: E. Bouza, M. Marin, L. Alcalá, Hospital General Universitario Gregorio Marañón, Madrid; Sweden: T. Åkerlund, O. Aspevall, Public Health Agency of Sweden, Solna; Switzerland: A.F. Widmer, S. Erb, University Hospital, Basel; Turkey: B. Levent, Refik Saydam National Public Health Agency, Ankara; United Kingdom - England: M. Wilcox, Leeds Teaching Hospitals NHS Trust, Leeds; United Kingdom - Northern Ireland: P. Rooney, Belfast City Hospital, Belfast; United Kingdom - Scotland: C. Wiuff, Health Protection Scotland, Glasgow, J. Coia, Scottish Microbiology Reference Laboratories, Glasgow.

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Conflict of interest

Mark H Wilcox: received research work fees, and/or consulting fees and/or lecture fees from Actelion, Cubist, Astellas, Merck, Optimer, Sanofi-Pasteur, Summit, Astra-Zeneca, Cerexa, Nabriva, Novacta, Novartis, Pfizer, Corporation Roche, The Medicines Company, VH Squared, Abbott, biomerieux, Da Volterra, European Tissue Symposium, Basilea, and Alere (paid to the department), and a clinical trial consultancy from Durata.

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All other authors: none declared.

Authors' contributions

The survey was designed by AK, DWK and PG, with support of BHB, BC, OL, JS and CW. EJK and MHW were the principle coordinators of ECDIS-Net, using support of CS from ECDC. AK and DWK performed data collection and data analysis, PG supervised data collection and data analysis. AK wrote the manuscript together with CW. All co-authors reviewed the manuscript.

References

- 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
- 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
- Honda H, Dubberke ER. The changing epidemiology of Clostridium difficile infection. *Curr Opin Gastroenterol.* 2014;30(1):54-62. DOI: 10.1097/MOG.000000000000018 PMID: 24285002
- 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
- Goorhuis A, Debast SB, van Leengoed LA, Harmanus C, Notermans DW, Bergwerff AA, et al. Clostridium difficile PCR ribotype 078: an emerging strain in humans and in pigs? *J Clin Microbiol.* 2008;46(3):1157-8, author reply 1158. DOI: 10.1128/JCM.01536-07 PMID: 18326836
- Chernak E, Johnson CC, Weltman A, McDonald LC, Wiggs L, Killgore G, et al. Centers for Disease Control and Prevention (CDC). Severe Clostridium difficile-associated disease in populations previously at low risk--four states, 2005. *MMWR Morb Mortal Wkly Rep.* 2005;54(47):1201-5. PMID: 16319813
- 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
- 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
- Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, et al. ECDIS Study Group. Clostridium difficile infection in Europe: a hospital-based survey. *Lancet.* 2011;377(9759):63-73. DOI: 10.1016/S0140-6736(10)61266-4 PMID: 21084111
- Barbut F, Mastrantonio P, Delmée M, Brazier J, Kuijper E, Poxton I, European Study Group on Clostridium difficile (ESGCD). Prospective study of Clostridium difficile infections in Europe with phenotypic and genotypic characterisation of the isolates. *Clin Microbiol Infect.* 2007;13(11):1048-57. DOI: 10.1111/j.1469-0691.2007.01824.x PMID: 17850341
- van Dorp SM, Kinross P, Gastmeier P, Behnke M, Kola A, Delmée M, et al. Standardised surveillance of Clostridium difficile infection in European acute care hospitals: a pilot study, 2013. *Euro Surveill.* 2016;21(29):30293. DOI: 10.2807/1560-7917.ES.2016.21.29.30293
- European Centre for Disease Prevention and Control (ECDC). European Surveillance of Clostridium difficile infections. Surveillance protocol version 2.2. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1402
- World Health Organization (WHO). International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Geneva: WHO; 2010.
- McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kuty 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
- van Dorp SM, Notermans DW, Alblas J, Gastmeier P, Mentula S, Nagy E, et al. Survey of diagnostic and typing capacity for Clostridium difficile infection in Europe, 2011 and 2014. *Euro Surveill.* 2016;21(29):30292. DOI: 10.2807/1560-7917.ES.2016.21.29.30292
- Goldenberg SD, Price NM, Tucker D, Wade P, French GL. Mandatory reporting and improvements in diagnosing Clostridium difficile infection: an incompatible dichotomy? *J Infect.* 2011;62(5):363-70. DOI: 10.1016/j.jinf.2011.03.007 PMID: 21439999
- Fridkin SK, Olmsted RN. Meaningful measure of performance: a foundation built on valid, reproducible findings from surveillance of health care-associated infections. *Am J Infect Control.* 2011;39(2):87-90. DOI: 10.1016/j.ajic.2011.01.002 PMID: 21356430
- McKibben L, Fowler G, Horan T, Brennan PJ. Ensuring rational public reporting systems for health care-associated infections: systematic literature review and evaluation recommendations. *Am J Infect Control.* 2006;34(3):142-9. DOI: 10.1016/j.ajic.2005.09.006 PMID: 16630978
- Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Society for Healthcare Epidemiology of America, Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America

- (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-55. DOI: 10.1086/651706 PMID: 20307191
20. McDonald LC, Killgore GE, Thompson A, Owens RC, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med*. 2005;353(23):2433-41. DOI: 10.1056/NEJMoa051590 PMID: 16322603
 21. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet*. 2005;366(9491):1079-84. DOI: 10.1016/S0140-6736(05)67420-X PMID: 16182895
 22. Dubberke ER, Butler AM, Yokoe DS, Mayer J, Hota B, Mangino JE, et al. , Prevention Epicenters Program of the Centers for Disease Control and Prevention. Multicenter study of surveillance for hospital-onset *Clostridium difficile* infection by the use of ICD-9-CM diagnosis codes. *Infect Control Hosp Epidemiol*. 2010;31(3):262-8. DOI: 10.1086/650447 PMID: 20100085
 23. Dubberke ER, Butler AM, Nyazee HA, Reske KA, Yokoe DS, Mayer J, et al. , Centers for Disease Control and Prevention Epicenters Program. The impact of ICD-9-CM code rank order on the estimated prevalence of *Clostridium difficile* infections. *Clin Infect Dis*. 2011;53(1):20-5. DOI: 10.1093/cid/cir246 PMID: 21653298
 24. Gastmeier P, Sohr D, Schwab F, Behnke M, Zuschneid I, Brandt C, et al. Ten years of KISS: the most important requirements for success. *J Hosp Infect*. 2008;70(Suppl 1):11-6. DOI: 10.1016/S0195-6701(08)60005-5 PMID: 18994676
 25. Indra A, Huhulescu S, Schneeweis M, Hasenberger P, Kernbichler S, Fiedler A, et al. Characterization of *Clostridium difficile* isolates using capillary gel electrophoresis-based PCR ribotyping. *J Med Microbiol*. 2008;57(Pt 11):1377-82. DOI: 10.1099/jmm.0.47714-0 PMID: 18927415
 26. Fawley WN, Knetsch CW, MacCannell DR, Harmanus C, Du T, Mulvey MR, et al. Development and validation of an internationally-standardized, high-resolution capillary gel-based electrophoresis PCR-ribotyping protocol for *Clostridium difficile*. *PLoS One*. 2015;10(2):e0118150. DOI: 10.1371/journal.pone.0118150 PMID: 25679978
 27. Knetsch CW, Lawley TD, Hensgens MP, Corver J, Wilcox MW, Kuijper EJ. Current application and future perspectives of molecular typing methods to study *Clostridium difficile* infections. *Euro Surveill*. 2013;18(4):20381. PMID: 23369393

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