SURVEILLANCE REPORT

Annual Epidemiological Report for 2016

Clostridium difficile infections

Key facts

- On 1 January 2016, ECDC started the coordination of surveillance of *Clostridium difficile* infections (CDI) in acute care hospitals in EU/EEA countries. ECDC's surveillance protocol provides a standardised tool for hospitals to measure and monitor CDI incidence rates, linking epidemiological and microbiological data.
- In 2016, 20 EU/EEA countries reported CDI data to ECDC for 593 surveillance periods from 556 hospitals.
- A total of 7 711 CDI cases were reported, 5 756 of which (74.6%) were healthcare-associated (HA) CDI.
- There were 611/7 711 (7.9%) cases classified as 'recurrent' infections, and 921/5 499 (16.7%) cases which had a complicated course of infection.
- While 4 160/5 248 (79.3%) cases with known outcome were reported to have been discharged alive, 1 088/5 248 (20.7%) CDI cases had died from various causes. These include 207/5 248 (3.9%) fatal cases in which CDI was reported to have contributed to a fatal outcome.
- In 314/439 (71.5%) hospital surveillance periods, the reported diagnostic practices followed ESCMID recommendations. The mean rate of CDI testing was 42.9 stool tests/10 000 patient-days. However, the majority of hospitals tested for CDI less frequently (median: 29.6 stool tests/10 000 patient-days).
- Metronidazole resistance was reported for 26/569 (4.6%) cases with data on susceptibility, and one case of resistance to vancomycin was reported. As this percentage of metronidazole resistance is unusually high, EU/EEA countries may wish to consider confirming metronidazole and vancomycin non-susceptibility using gold standard agar dilution, thereafter performing additional analyses to characterise the transmission mechanisms.
- PCR ribotype data were available for 1 326/3 894 (34.1%) cases with enhanced case-based data. The most common PCR ribotypes were RT027 (n=303, 22.9%), RT001 (n=99, 7.5%), RT014 (n=89, 6.7%), RT078 (n=68, 5.1%), RT002 (n=56, 4.2%) and RT 020 (n=56, 4.2%).
- ECDC encourages EU/EEA countries to recruit hospitals to collect data compatible with the ECDC surveillance protocol in order to acquire standardised epidemiological and microbiological information on their own hospital CDI burden compared to other European hospitals.

Suggested citation: European Centre for Disease Prevention and Control. *Clostridium difficile* infections. In: ECDC. Annual epidemiological report for 2016. Stockholm: ECDC; 2018.

Stockholm, June 2018

Methods

This report is based on data for 2016 retrieved from The European Surveillance System (TESSy) on 21 March 2018. TESSy is a system for the collection, analysis and dissemination of data on communicable diseases.

For a detailed description of methods used to produce this report, please refer to the *Methods* chapter [1].

An overview of the national surveillance systems is available online [2].

A subset of the data used for this report will be available through ECDC's online *Surveillance atlas of infectious diseases* [3].

This surveillance report is based on *Clostridium difficile* infection (CDI) surveillance data collected by the ECDC Healthcare-Associated Infections surveillance Network (HAI-Net). The protocol specifies three permitted levels of data collection: 'minimal' (aggregate numerators and denominators); 'light' (aggregate denominators and case-based numerators) or 'enhanced' (the light option, plus directly linked, case-based microbiological data for at least the first five cases during a surveillance period). The protocol recommends that hospitals use EUCAST clinical breakpoints for interpretation of antimicrobial susceptibility test results [4,5].

ECDC started the collection of surveillance data that are compatible with the ECDC CDI surveillance protocol [5] on 1 January 2016. The surveillance data were collected through two different schemes.

1) During the start-up phase, countries were invited to report data by 31 March 2016. Data were collected using the ECDC surveillance protocol during at least one month in January–February 2016 and from at least one hospital.

2) During biannual data collection, countries were invited to upload to TESSy CDI surveillance data compatible with the ECDC surveillance protocol for hospital surveillance periods of at least three months per year. Biannual data collection enables the estimation of burden and trends; the surveillance system is not designed to detect outbreaks.

- Twenty EU/EEA countries reported data for 593 hospital surveillance periods in 2016, from 556 hospitals with over 264 000 beds, covering over 24 million patient-days (Table 1). All hospitals used the ECDC CDI surveillance protocol, except for 203 hospitals in France and all hospitals in Belgium (n=129) and Finland (n=13), which used national surveillance protocols that are compatible with the ECDC protocol. Additionally, Romania reported that at least 25 hospitals had used the ECDC surveillance protocol, although these data were unavailable for this report.
- The majority of the hospitals were primary (n=136) or secondary (n=175) acute care hospitals (Table 2). Almost all (129/131; 98.5%) hospitals without information on hospital type were in Belgium. The specialised hospitals (n=35) were in Croatia, France, Hungary and Poland. The reported specialisations included long-term care, palliative care and rehabilitation.
- All hospitals participated in one surveillance period, except for 36 hospitals in Hungary and one hospital in Slovakia which provided data for two hospital surveillance periods in 2016. There were 308/593 (52.0%) hospital surveillance periods that lasted for three months; 113 hospitals performed continuous surveillance, including all participating hospitals in Finland, Malta and the Netherlands (n=15). Austria, Greece, Ireland, Italy and Lithuania only participated during the start-up phase of surveillance (n=9 hospitals).
- The catchment population of the hospital in Malta is more than 85% of the national population.
- The 'minimal' surveillance option was used during 233 hospital surveillance periods and included 203 hospitals in France; the 'light' surveillance option was used during 99 hospital surveillance periods; the 'enhanced' option was used during 261 hospital surveillance periods and including 118 hospital surveillance periods in Belgium.

Epidemiology

In 2016, 20 countries reported 7 711 CDI cases, 5 756 of which (74.6%) were healthcare-associated (HA) CDI; 1 955 CDI cases (25.4%) were either community-associated (CA) or of unknown origin (Table 3). Case-based data were available for 6 183/7 711 (80.2%) cases. In hospitals that provided case-based data, the mean proportion of cases that were male was 44.9%, and the median age was 75.0 years.

The crude incidence density of HA CDI was 2.4 cases/10 000 patient-days. For 126/593 (21.2%) hospital surveillance periods, no HA CDI case was reported. The median hospital incidence density of HA CDI was 2.9 cases per 10 000 patient-days. The mean CDI incidence was the highest in tertiary care hospitals (5.8 cases/10 000 patient-days; 95% CI: 3.6–7.8 cases/10 000 patient-days; Table 2) and the lowest in primary care hospitals (2.8 cases/10 000 patient-days; 95% confidence interval (95% CI): 2.1–3.5 cases/10 000 patient-days; p=0.001; Table 2). Estonia, Lithuania and Poland reported the highest HA CDI incidence densities (Table 3). The crude incidence density of CA CDI was 0.8 cases/10 000 patient-days, with the highest rates reported by Estonia, France and Poland (Table 3).

There were 611/7 711 (7.9%) CDI cases that were classified as recurrent infections; 921/5 499 (16.7%) CDI cases were reported to have followed a complicated course of infection, such as admission for CA CDI, admission to an intensive care unit, surgery for toxic megacolon, or death. Information on CDI outcome was available for 5 248/7 711 (68.1%) cases, 4 160 of which (79.3%) were discharged alive and 1 088 (20.7%) died from any cause. For 207/5 248 (3.9%) cases with information on CDI outcome, death was reported to be 'possibly' or 'definitely' related to CDI, while death was reported to have been unrelated to the CDI in 622/5 248 (11.9%) cases. Notably, 357 (13.9%) of 2 577 cases with a reported McCabe score were indicated to have had a 'rapidly fatal underlying disease', i.e. the attending physician expected the patient to survive for less than a year.

For 4 208/4 918 (85.6%) HA CDI cases, the origin of the CDI was reported to be the current hospital, while 362/4 918 (7.4%) cases were reported to have originated from another hospital and 103/4 918 (2.1%) originated from a long-term care facility (LTCF). There were 1 904/3 042 (62.6%) cases reported to have had a healthcare admission in the three months prior to the present hospital admission; 1 657 of these cases (87.0%) had been admitted to a hospital and 121 (6.4%) cases had been admitted to a LTCF.

Microbiology

ESCMID-recommended diagnostic algorithms [6,7] were used during 314/439 (71.5%) hospital surveillance periods, whereas less optimal algorithms were used during 125 (28.5%) periods. There were 62 980 stool tests for CDI reported, 5 691 of which (9.0%) were positive. While the mean rate of CDI testing was 42.9 stool tests/10 000 patient-days, the median rate was 29.6 stool tests/patient-days, as many hospitals tested relatively infrequently.

The ECDC surveillance protocol recommends that hospitals report antimicrobial susceptibility results according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, or otherwise EUCAST epidemiological cut-off values (ECOFFs), Clinical and Laboratory Standards Institute (CLSI) breakpoints or national breakpoints, or the measured minimal inhibitory concentration (MIC) and testing method. Moxifloxacin resistance was reported for 363/523 (69.4%) cases with data on susceptibility, and one case of vancomycin resistance, identified using an E-test, was reported.

Metronidazole resistance was reported for 26/569 (4.6%) cases with data on susceptibility. All 26 cases had the MIC for metronidazole measured using E-test. The reported MICs exceeded the EUCAST clinical breakpoint (>2mg/L), which is based on ECOFFs, but none exceeded the CLSI breakpoint (≥32mg/L). Slovakia reported 13 cases with metronidazole-resistant isolates, also measured using E-test. However, these isolates were found to be metronidazole susceptible when retested by a central reference laboratory using agar dilution [8], which is considered the gold standard.

PCR ribotype data were available for 1 326/ 3 894 (34.1%) cases with enhanced case-based data. The most common PCR ribotypes were RT027 (n=303, 22.9%), RT001 (n=99, 7.5%), RT014 (n=89, 6.7%), RT078 (n=68, 5.1%), RT002 (n=56, 4.2%) and RT 020 (n=56, 4.2%). National or regional reference laboratories provided PCR ribotyping for 1 346/3 825 (35.2%) cases and antimicrobial susceptibility testing for 571/3 018 (65.2%) cases. The surveillance protocol does not allow for collection of data on whether there is local capacity for these tests.

Table 1. Participating hospitals and CDI testing frequency by country, EU/EEA, 2016

Country	Hospitals				Stool tests		
	No. of hospitals	No. of hospital surveillance periods [a]	No. of beds	No. of patient-days	Median No. of stool tests for CDI / 10 000 patient-days	Median no. of CDI-positive stool tests/10 000 patient-days	Median % of CDI-positive stool tests that were positive for CDI
Austria	1	1	1 990	42 630	98.1	2.8	2.9
Belgium	129	129	43 843	10 224 812	ND	ND	NA
Croatia	26	26	11 826	2 064 560	19.6	2.5	14.2
Czech Republic	19	19	11 945	924 021	36.1	3.2	10.2
Estonia	4	4	3 107	49 010	87.6	13.4	10.8
Finland	13	13	5 538	1 547 016	98.3	ND	NA
France	203	203	44 401	3 056 445	39.0	2.6	7.9
Greece [b]	2	2	1 480	72 535	45.9	4.1	7.8
Hungary	58	94	82 281	3 714 597	19.7	4.0	22.5
Ireland [b]	1	1	820	19 894	166.9	9.6	5.7
Italy [b]	2	2	1 800	43 724	55.3	4.0	9.9
Latvia [b]	1	1	866	20 609	28.1	4.4	15.5
Lithuania [b]	3	3	4 191	98 530	21.9	3.6	35.0
Malta	1	1	1 029	298 878	73.5	2.7	3.6
Netherlands	1	1	882	119 998	179.0	6.8	3.8
Poland	46	46	21 581	485 479	29.0	5.6	18.2
Slovakia	36	37	18 529	1 116 805	31.0	2.5	8.3
Slovenia	3	3	3 894	82 307	36.2	3.3	9.1
Spain	4	4	3 248	78 018	63.4	4.3	6.5

Country	Hospitals				Stool tests		
	No. of hospitals	No. of hospital surveillance periods [a]	No. of beds	No. of patient-days	Median No. of stool tests for CDI / 10 000 patient-days	Median no. of CDI-positive stool tests/10 000 patient-days	Median % of CDI-positive stool tests that were positive for CDI
UK–Scotland	3	3	1 456	78 014	64.8	2.9	4.5
EU/EEA	**556**	**593**	**264 707**	**24 137 882**	**45.3** [c]	**4.6** [c]	**2.9** [d]

NA – not applicable; ND – no data; UK – United Kingdom; [a] hospitals had one or more surveillance periods per year, each ranging from a minimum duration of 3 months to 12 months; [b] hospitals only collected surveillance data during the start-up phase of data collection; [c] crude mean; [d] crude percentage ((no. of CDI-positive stool tests for CDI/no. of stool tests for CDI) × 100).

Table 2. Types of hospitals and cases of CDI in participating hospitals by type of hospital, EU/EEA, 2016

Type of hospital	No. of hospitals	No. of hospital surveillance periods [a]	No. of beds	No. of patient-days	Mean duration of participation (days)	No. of cases	Crude incidence density [b]	Mean hospital incidence density (95% CI)	p-value [c]
Tertiary care	79	86	84 825	5 807 586	94.3	2 091	3.60	5.77 (3.56 - 7.97)	Ref.
Secondary care	175	190	85 523	5 365 957	99.7	2 013	3.75	4.60 (3.50 - 5.69)	<0.001
Primary care	136	148	36 440	1 912 371	84.4	542	2.83	2.80 (2.06 - 3.54)	<0.001
Specialised	35	38	13 115	662 406	76.9	303	4.57	5.53 (3.55 - 7.52)	0.6
Unknown	131	131	44 804	10 389 562	318.6	2 761	2.66	2.79 (2.44 - 3.14)	<0.001
EU/EEA	**556**	**593**	**264 707**	**24 137 882**	**142.0**	**7 711**	**3.19**	**3.98 (3.45 – 4.51)**	**NA**

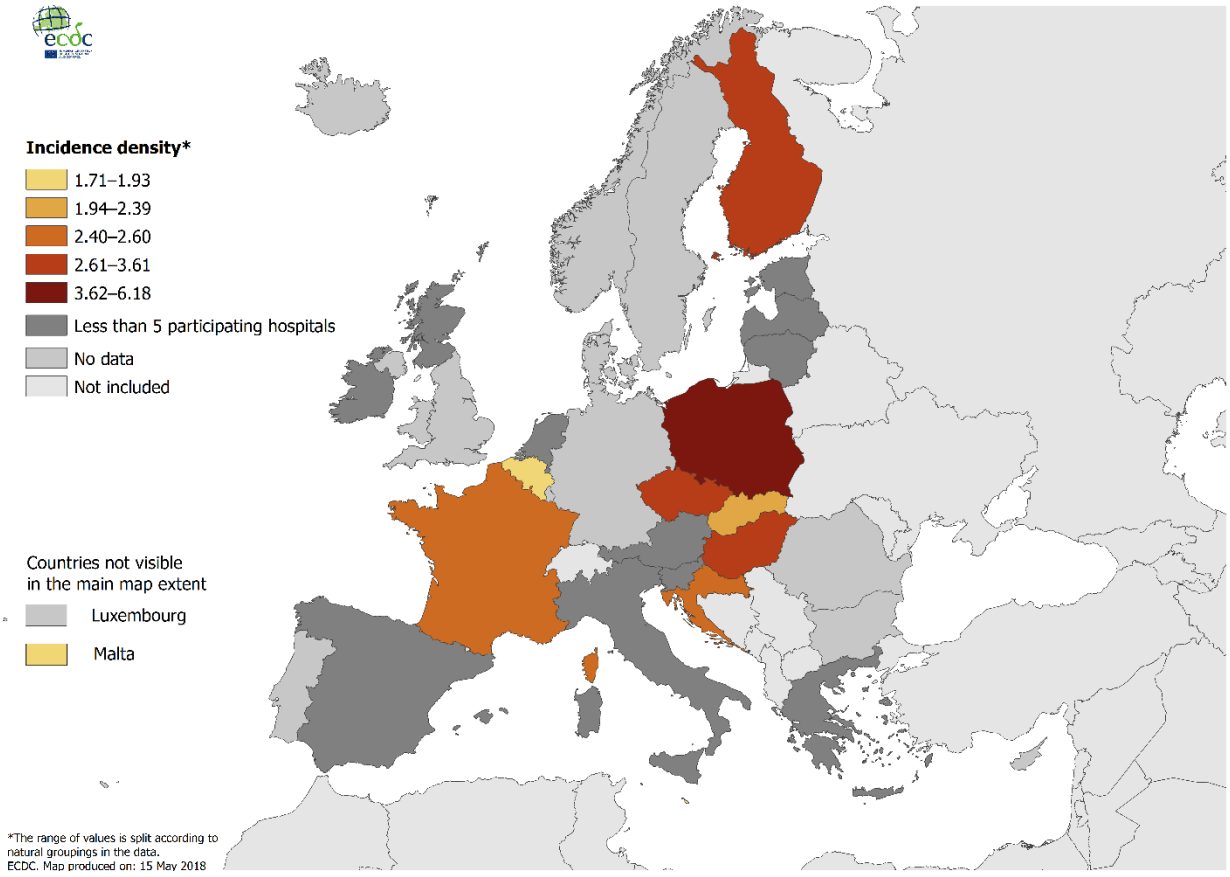
NA — not applicable; 95%CI – 95% confidence interval, calculated assuming normal distribution; [a] hospitals had one or more surveillance periods per year, each ranging from a minimum duration of 3 months to 12 months; [b] mean of hospital incidence densities, each calculated as ((no. of cases/no. of patient-days) × 10 000); [c] Poisson regression comparing mean hospital incidence densities between different types of hospitals, relative to tertiary acute care hospitals

Table 3. Incidence of CDI cases in participating hospitals, by country and by type of CDI, EU/EEA, 2016

Country	No. of hospitals	No. of hospital surveillance periods [a]	Healthcare-associated CDI		Community-associated CDI or unknown origin		Total CDI	
			N	Mean hospital incidence density [b]	N	Mean hospital incidence density [b]	N	Mean hospital incidence density [b]
Austria	1	1	7	1.64	5	1.17	12	2.82
Belgium	129	129	1 861	1.93	831	0.84	2 692	2.78
Croatia	26	26	450	2.60	130	0.75	580	3.35
Czech Republic	19	19	229	3.42	38	0.45	267	3.87
Estonia	4	4	23	12.93	3	1.88	26	14.81
Finland	13	13	518	3.61	71	0.70	589	4.31
France	203	203	588	2.52	507	1.60	1 095	4.12
Greece [c]	2	2	15	3.10	6	1.03	21	4.12
Hungary	58	94	1 297	3.18	196	0.47	1 493	3.65
Ireland [c]	1	1	6	3.02	2	1.01	8	4.02
Italy [c]	2	2	10	2.27	2	0.50	12	2.76
Latvia [c]	1	1	7	3.40	0	0.00	7	3.40
Lithuania [c]	3	3	59	7.88	6	0.78	65	8.66
Malta	1	1	51	1.71	24	0.80	75	2.51
Netherlands	1	1	26	2.17	7	0.58	33	2.75
Poland	46	46	261	6.18	56	1.40	317	7.58
Slovakia	36	37	292	2.39	52	0.49	344	2.88
Slovenia	3	3	18	2.60	6	0.79	23	3.40
Spain	4	4	23	3.01	10	1.25	33	4.26
UK-Scotland	3	3	15	1.99	3	0.56	18	2.54
EU/EEA	556	**579**	**5 756**	**2.38** [d]	**1 955**	**0.81** [d]	**7 711**	**3.19** [d]

[a] Hospitals had one or more surveillance periods per year, each ranging from a minimum duration of 3 months to 12 months; [b] mean of hospital incidence densities, each calculated as (no. of cases/no. of patient-days × 10 000); [c] hospitals only collected surveillance data during the start-up phase of data collection; [d] crude incidence density calculated as (no. of cases in all participating hospitals/no. of patient-days in all participating hospitals × 10 000).

Figure 1. Healthcare-associated CDI cases per 10 000 patient-days in participating hospitals by country, EU/EEA, 2016



Source: Country reports from Austria, Belgium, Croatia, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Poland, Slovakia, Slovenia, Spain, UK–Scotland.

Outbreaks and other threats

No multi-national CDI outbreaks were reported to ECDC in 2016.

Discussion

During the first year of ECDC-coordinated CDI surveillance, over two thirds of EU/EEA countries participated, highlighting the perception of the importance of CDI by those working at the national level in EU/EEA countries. Participation of a hospital in national surveillance is also an indication of its commitment to controlling CDI. For example, in Poland, 46 of 795 acute care hospitals participated in 2016, almost all of which used the 'enhanced' surveillance option. In 2017, Lithuania initiated mandatory surveillance of all its hospitals, using the 'enhanced' option.

In 2010, ECDC initiated the ECDIS-Net project to develop and test a pilot protocol for the surveillance of CDI in European acute care hospitals. In May–November 2013, 14 European countries used the pilot protocol. Of these, eight countries (Belgium, Estonia, Finland, France, Hungary, the Netherlands, Poland and UK–Scotland) performed surveillance throughout 2016, two countries (Austria and Romania) only participated during the start-up phase in 2016, and four countries (Denmark, Germany, Norway and Serbia) did not participate in 2016. The 37 hospitals that participated in the pilot surveillance period in 2013 were mostly tertiary care hospitals. The incidence of HA CDI that these hospitals recorded in 2013 during the pilot surveillance period (interquartile range: 2.0–6.6 cases per 10 000 patient-days) was similar to that reported in 2016 during ECDC-coordinated surveillance (median: 2.6 cases per 10 000 patient-days) [9].

CDI cases reported in 2016 contributed to significant morbidity and case fatality. Notably, many hospitals tested stools for CDI relatively infrequently and so these data may be an underestimate of the true CDI burden in Europe [7].

The 2011—2012 ECDC point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use in European acute care hospitals also identified *C. difficile* as the 8th most frequently-reported microorganism.

However, there were differences between countries in the proportion of gastrointestinal infections that were reported to be CDI, which suggests variation in the sensitivity of CDI detection [10]. Even so, a comparison of these CDI data with other data in TESSy indicated that HA CDI has the 8th highest disease burden of any infectious disease under surveillance at the European level in terms of disability-adjusted life years per 100 000 population [11].

In almost all participating countries, the sample of hospitals that participated in 2016 was not representative of hospitals in the country. Still, the aggregate data confirm expected findings. For example, due to differences in patient case mix, CDI incidence was expected to be higher in tertiary care and specialised hospitals than in other hospitals. Also, the most commonly reported PCR ribotype was RT027, demonstrating that virulent strains can and have become established in Europe.

A survey of 39 laboratory sites in 22 European countries in 2011–2012 identified metronidazole resistance in only <0.2% isolates [12], as had another study of 73 hospital sites in 26 European countries in 2008 [13]. None of the 37 hospitals in the 2013 pilot surveillance reported metronidazole-resistant isolates. In 2016, 4.6% *C. difficile* isolates were reported by participating EU/EEA countries as being resistant to metronidazole. However, all these metronidazole-resistant isolates were reported as having been identified using E-test, rather than the agar dilution method (gold standard). Slovakia had reported 13 isolates that were metronidazole-resistant according to E-test results, but subsequently all confirmed as metronidazole-susceptible, following agar dilution testing by a central reference laboratory.

ECDC provides microbiological support to CDI surveillance through a framework contract with a consortium led by Leiden University Medical Centre (Netherlands) in collaboration with the University of Leeds (United Kingdom), the National Reference Laboratory for *C. difficile* in France, and the national public health institutes of Austria (AGES) and the Netherlands (RIVM). Activities of the consortium include the development of standard operating procedures for diagnostics and typing, external quality assessment (EQA) exercises for PCR ribotyping, as well as typing services for *C. difficile* isolates that were not typable at national level or showed an unusual phenotype, such as a MIC of ≥2mg/ml for metronidazole.

Public health implications

During its first year, ECDC-coordinated surveillance of CDI detected a noteworthy morbidity and case fatality of CDI in the participating EU/EEA countries. While the variation in the reported HA CDI rates between the participating hospitals and countries may be attributable to differences in sampling and testing practices, it highlights that the CDI burden in Europe can be reduced. Increasing the national coverage of hospital-based CDI surveillance will improve the national and EU/EEA estimates of the burden of CDI.

The cornerstones of CDI prevention and control in healthcare facilities remain appropriate microbiological testing practices, participation in epidemiological surveillance, standard and contact precautions with special emphasis on hand hygiene, use of personal protective equipment and environmental disinfection, antimicrobial stewardship and education (healthcare workers, CDI cases and hospital visitors) regarding CDI prevention [14].

As ESCMID-recommended diagnostic practices have a high diagnostic accuracy, their use will permit hospitals and EU/EEA countries to better measure their true CDI burden [6]. Typing *C. difficile* using a common nomenclature for *C. difficile* subtypes, particularly for PCR ribotyping, will permit the detection of *C. difficile* strains with known notoriety, identification of strains with uncommon virulence, and monitoring for the establishment or control of virulent strains across Europe [15].

The apparent emergence of metronidazole resistance is of concern, since a new mechanism has been found, occurring in both animal and human isolates of *C. difficile* [16]. EU/EEA countries should consider confirming metronidazole and vancomycin resistance of *C. difficile* isolates by agar dilution methods, performed by a reference laboratory, and additional investigations to elucidate the transmission mechanisms.

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