Advances in Experimental Medicine and Biology 1050
Advances in Microbiology, Infectious Diseases and Public Health

Paola Mastrantonio
Maja Rupnik *Editors*

Updates on *Clostridium difficile* in Europe

Advances in Microbiology, Infectious Diseases and Public Health Volume 8

Springer

Advances in Experimental Medicine and Biology

Volume 1050

Advances in Microbiology, Infectious Diseases and Public Health

This book series focuses on current progress in the broad field of medical microbiology, and covers both basic and applied topics related to the study of microbes, their interactions with human and animals, and emerging issues relevant for public health. Original research and review articles present and discuss multidisciplinary findings and developments on various aspects of microbiology, infectious diseases, and their diagnosis, treatment and prevention.

The book series publishes review and original research contributions, short reports as well as guest edited thematic book volumes. All contributions will be published online first and collected in book volumes. There are no publication costs.

Advances in Microbiology, Infectious Diseases and Public Health is a subseries of *Advances in Experimental Medicine and Biology*, which has been publishing significant contributions in the field for over 30 years and is indexed in Medline, Scopus, EMBASE, BIOSIS, Biological Abstracts, CSA, Biological Sciences and Living Resources (ASFA-1), and Biological Sciences. 2016 Impact Factor: 1.881

More information about this series at http://www.springer.com/series/13513

Paola Mastrantonio • Maja Rupnik
Editors

Updates on *Clostridium difficile* in Europe

Advances in Microbiology, Infectious Diseases and Public Health Volume 8

Springer

Editors
Paola Mastrantonio
Former Research Director in the
Department of Infectious Diseases
National Institute of Health (ISS)
Rome, Italy

Maja Rupnik
Department for Microbiological
Research
National Laboratory of Health,
Environment and Food (NLZOH)
Maribor, Slovenia

ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISSN 2365-2675 ISSN 2365-2683 (electronic)
Advances in Microbiology, Infectious Diseases and Public Health
ISBN 978-3-319-72798-1 ISBN 978-3-319-72799-8 (eBook)
https://doi.org/10.1007/978-3-319-72799-8

Library of Congress Control Number: 2016935504

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The chapters of this book were planned to cover the most important issues to be addressed in the study of infections due to *Clostridium difficile*, a microorganism still feared not only as the cause of nosocomial diarrhea related to protracted antibiotic administration but more and more frequently of diarrheal diseases unrelated to the hospital environment, including those affecting animals. In the last decades, a growing number of clinicians, microbiologists, and epidemiologists have investigated this topic, as evidenced by the large amount of scientific publications still in an upward trend over the years. In particular, this book has been focused on the clinical and experimental activities carried out in Europe for a better knowledge of this pathogen and its molecular characteristics, associated pathologies, and possible transmission routes, as well as to build up preventive and diagnostic strategies and efficacious therapeutic approaches for the treatment of *C. difficile* infection (CDI).

Thanks also to the foundation of the European Study Group on *C. difficile* (ESGCD) in 2000, in the framework of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European clinicians and researchers, together with experts from all over the world, were able to consolidate the already existing, positive collaboration that led in recent years to the establishment of a European network for the epidemiological surveillance, the molecular characterization, and the evaluation of the antibiotic resistance profile of the clinical isolates, with obvious advantages for the continuous updating of the treatment strategies of CDI. To emphasize the positive role of this study group in the fight against *C. difficile* infection, an invited chapter written by both the current and the past president of ESGCD has been included at the end of this book.

We are grateful to all the authors for their significant contributions to the book. In our view and intention, they ideally represent also the work of many other European experts in this field who did not get involved on this occasion for obvious limits of space.

Rome, Italy — Paola Mastrantonio
Maribor, Slovenia — Maja Rupnik

Contents

Economic Burden of *Clostridium difficile* Infection in European Countries 1
Elena Reigadas Ramírez and Emilio Santiago Bouza

The Need for European Surveillance of CDI 13
Camilla Wiuff, A-Lan Banks, Fidelma Fitzpatrick, and Laura Cottom

Diagnostic Guidance for *C. difficile* Infections 27
Monique J.T. Crobach, Amoe Baktash, Nikolas Duszenko, and Ed J. Kuijper

Ribotypes and New Virulent Strains Across Europe 45
Jeanne Couturier, Kerrie Davies, Cécile Gateau, and Frédéric Barbut

Comparative Genomics of *Clostridium difficile* 59
Sandra Janezic, Julian R. Garneau, and Marc Monot

Cellular Uptake and Mode-of-Action of *Clostridium difficile* Toxins 77
Panagiotis Papatheodorou, Holger Barth, Nigel Minton, and Klaus Aktories

***Clostridium difficile* Biofilm** 97
Claudia Vuotto, Gianfranco Donelli, Anthony Buckley, and Caroline Chilton

European Practice for CDI Treatment 117
Fidelma Fitzpatrick, Mairead Skally, Melissa Brady, Karen Burns, Christopher Rooney, and Mark H. Wilcox

Antibiotic Resistances of *Clostridium difficile* 137
Patrizia Spigaglia, Paola Mastrantonio, and Fabrizio Barbanti

Probiotics for Prevention and Treatment of *Clostridium difficile* Infection 161
Lorena Valdés-Varela, Miguel Gueimonde, and Patricia Ruas-Madiedo

Faecal Microbiota Transplantation as Emerging Treatment in European Countries 177
Marcello Maida, James Mcilroy, Gianluca Ianiro, and Giovanni Cammarota

Immunization Strategies Against *Clostridium difficile* 197
Jean-François Bruxelle, Séverine Péchiné, and Anne Collignon

Non-human *C. difficile* Reservoirs and Sources: Animals, Food, Environment 227
Cristina Rodriguez Diaz, Christian Seyboldt, and Maja Rupnik

The ESCMID Study Group for *Clostridium difficile*: History, Role and Perspectives 245
John E. Coia and Ed J. Kuijper

Erratum E1

Index 255

The original version of this book was revised. Due to a different technical process the source lines were set differently in the original version and have now been corrected. An erratum to this book can be found at https://doi.org/10.1007/978-3-319-72799-8_15

Adv Exp Med Biol - Advances in Microbiology, Infectious Diseases and Public Health (2018) 8: 1–12
https://doi.org/10.1007/978-3-319-72799-8_1

Published online: 29 January 2018

Economic Burden of *Clostridium difficile* Infection in European Countries

Elena Reigadas Ramírez and Emilio Santiago Bouza

Abstract

Clostridium difficile infection (CDI) remains a considerable challenge to health care systems worldwide. Although CDI represents a significant burden on healthcare systems in Europe, few studies have attempted to estimate the consumption of resources associated with CDI in Europe. The reported extra costs attributable to CDI vary widely according to the definitions, design, and methodologies used, making comparisons difficult to perform. In this chapter, the economic burden of healthcare facility–associated CDI in Europe will be assessed, as will other less explored areas such as the economic burden of recurrent CDI, community-acquired CDI, pediatric CDI, and CDI in outbreaks.

Keywords

C. difficile infection · Economic costs · Economic burden · Length of stay · Europe

1 Introduction

In this chapter, the economic burden of healthcare facility-associated *Clostridium difficile* infection (CDI) in Europe will be assessed, as will other less explored areas such as recurrent CDI (R-CDI), community-acquired CDI, pediatric CDI, and CDI in outbreaks.

Despite advances in the diagnosis and treatment of CDI and prevention efforts to reduce the incidence of CDI, the disease remains a significant challenge to health care systems worldwide

E. Reigadas Ramírez (✉)
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Medicine Department, School of Medicine, Universidad Complutense de Madrid (UCM), Madrid, Spain

Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain
e-mail: helenrei@hotmail.com

E.S. Bouza (✉)
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Medicine Department, School of Medicine, Universidad Complutense de Madrid (UCM), Madrid, Spain

Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

CIBER de Enfermedades Respiratorias (CIBERES CB06/06/0058), Madrid, Spain
e-mail: emilio.bouza@gmail.com

(Dubberke and Olsen 2012; Bouza 2012). From an economic point of view, CDI increases patient healthcare costs as a result of extended length of hospital stay (LOS), re-admission, laboratory tests, and medication (Wiegand et al. 2012; Gabriel and Beriot-Mathiot 2014; Nanwa et al. 2015). *C. difficile* infection is costly, not only to third-party payers and hospitals, but also to society as a whole (McGlone et al. 2012).

Most of the existing literature is from the United States, where an in silico economic model, reported in 2012, suggested that the annual US economic burden of CDI would be $496 million from a hospital perspective, $547 million from a third-party payer perspective, and $796 million from a societal perspective (McGlone et al. 2012). Regrettably, few published studies have attempted to estimate the consumption of resources associated with CDI in Europe (Wiegand et al. 2012) and it has been estimated that the annual cost of CDI in Europe is €3 billion per year (Jones et al. 2013); consequently, approaches that can reduce CDI-associated resource use and costs are of interest.

Although antibiotics are a key component of therapy for CDI, they currently represent a minimal cost in the overall budget for CDI management, and the main extra associated cost reported in most studies is the extended LOS attributable to CDI (Wiegand et al. 2012; Asensio et al. 2013, 2015; Wilcox et al. 1996; Hubner et al. 2015).

CDI-related costs are also likely to increase as the population ages. In a systematic European meta-analysis on clinical and economic burden, the authors reported that the incremental cost of CDI may have increased by £1857–£4266 (27–93%) over a 12-year period (Wiegand et al. 2012). In a review by Kuijper et al., the potential cost of CDI was estimated to be €3 billion/year and is expected to almost double over the next four decades, assuming a European Union population of 457 million inhabitants (Kuijper et al. 2006).

The reported extra costs attributable to CDI vary widely according to the definitions, design, and methodologies used (Ghantoji et al. 2010; Wiegand et al. 2012). Most studies do not separate the costs of resources due to CDI from those generated by the underlying disease. Therefore, comparisons need to be made with caution and limited to results obtained in a similar manner.

A clearer understanding of the healthcare and economic burden of CDI is of value to hospital administrators, infection prevention teams, and persons involved in antimicrobial stewardship programs, who can use this key information to determine the appropriate degree of investment in infection control measures and in other priority areas.

Future studies should follow standard methodology, include other indirect cost perspectives such as societal and patient perspectives, and examine poorly explored populations, such as individuals with community-acquired CDI.

2 Economic Burden of Hospital-Acquired CDI in European Countries

A wide range of CDI costs in Europe have been reported, ranging from €5798–€11,202/episode (Wiegand et al. 2012). Data are only available from six European countries (Ireland, England, Wales, Germany, Spain, and Italy). Table 1 summarizes CDI costs by study and country.

2.1 Primary Episodes

The economic burden of primary episodes in Europe is reviewed below by region, as defined by EuroVoc. The most abundant literature comes from Western Europe, followed by Southern Europe.

2.1.1 Western Europe

A recent study conducted in a tertiary referral hospital in Ireland during August 2015 showed that the total incremental cost of CDI was €75,680, with a mean cost of €5820 per patient (Ryan et al. 2017).

Table 1 Summary of European *Clostridium difficile* infection costs by study and country

Author (year)	Country or region	CDI cases examined	Study population	Study period	Cost
Ryan et al. (2017)	Ireland	N = 13	Healthcare CDI	August 2015	€5820/CDI
Al-Eidan et al. (2000)	Ireland	N = 87	Healthcare CDI	1994–1995	£2860/CDI
Wilcox et al. (1996)	England	N = 50	Healthcare CDI	1994–1995	£4107/CDI
Wilcox et al. (2017)	United Kingdom	N = 128	Healthcare CDI, recurrences	2012–2014	£6294/CDI
					£7539/recurrent CDI
Vonberg et al. (2008)	Germany	N = 116	Healthcare CDI	2006	€7147/CDI
Hubner et al. (2015)	Germany	N = 43	Healthcare CDI	2010	€5262.96/CDI
Grube et al. (2015)	Germany	N = 2767	Healthcare CDI, recurrences	2011	€4132/CDI as primary diagnosis
					€19,381/CDI as secondary diagnosis
					€20,755/recurrent CDI
Le Monnier et al. (2015)	France	N = 1097	Healthcare CDI, recurrences	2011	€9575/CDI (€6056 CDI as primary diagnosis/€11,251 CDI as secondary diagnosis)
					€9625/recurrent CDI
Asensio et al. (2013)	Spain	N = 7601	Healthcare CDI, recurrences	2012	€3901/CDI
					€4875/first recurrent CDI
					€5916/second recurrent CDI
Asensio et al. (2015)	Spain and Italy	N = 232 (Spain)	Healthcare CDI, recurrences, children	2011–2013 (adults)	€4265/CDI case (Spain)
		N = 145 (Italy)		2006–2012 (pediatrics)	€14,936/adult CDI case (Italy)
					€17,714/recurrent CDI case (Italy)
					€3545/pediatric CDI case (Italy)

Another study conducted in Ireland established the mean cost per treated case of CDI in terms of bed occupancy, laboratory requests, and treatment to be £4577 (2010 GBP) (Al-Eidan et al. 2000).

It has been estimated that the cost for CDI is €5000–€15,000 per case in England (Kuijper et al. 2006). The earliest data on economic burden from England were communicated by Wilcox et al. (1996), who performed a study in geriatric wards. Cases and controls were matched for age, sex, and distribution of the main diagnoses. The total identifiable increased cost of CDI was £6986 in 2010 GBP.

A retrospective multicenter study analyzed a sample of 12 large, public, acute-care hospitals in France representing 5.82% of the cumulative annual number of patient-days spent in public acute-care hospitals in France in 2011 (Le Monnier et al. 2015). The costs of CDI incurred by public insurance and by the hospital itself (euros) were based on full unit cost per diagnosis-related group in hospitals at 2010 values. The annual incidence of CDI based on laboratory reporting was estimated at 3.74 cases per 10,000 patient-days. In cases where CDI was the primary diagnosis, the mean cost per stay was €6056 (median €4410) and the cumulative cost for the whole set of stays observed in 2011 for the 12 hospitals was €823,656. In patients where CDI was considered a secondary diagnosis, the mean extra cost adjusted for age, sex, and diagnosis-related groups in cases without CDI was €11,251 (median: €8822) per stay (Le Monnier et al. 2015). The extrapolated annual nationwide cost of CDI in 2011 in France was €163.1 million.

A single-center retrospective analysis of data from patients with nosocomial CDI carried out over a 1-year period at a teaching hospital in Germany showed an additional cost of €5262/case (Hubner et al. 2015).

Another single-center German study showed that costs for CDI patients were significantly higher than for their matched controls (median: €7147) (Vonberg et al. 2008). A large multicenter study conducted in 37 German hospitals based on data from the German DRG system analyzed 2767 CDI cases grouped according to whether CDI was a primary or secondary diagnosis (Grube et al. 2015). For comparison, non-CDI cases from the same hospitals during the same year were matched using propensity score matching.

Patients from the primary diagnosis group (n = 817) showed a mean cost per case of €4132 (€536 more than controls), while the secondary diagnosis group (n = 1840) had costs of €19,381 (€13,082 for controls) (Grube et al. 2015). The authors extrapolated their data and declared that CDI generates a yearly cost burden of €464 million for the German healthcare system.

2.1.2 Southern Europe

Evidence regarding the impact of CDI on healthcare resources in southern Europe is generally scarce. In the case of Spain, few studies have assessed the economic burden of CDI. An economic model analysis performed in 2012 by Asensio et al.(Asensio et al. 2013) assessed the cost of CDI in adult patients (≥18 years) treated with metronidazole or vancomycin from the perspective of the Spanish National Health System Service. The resources used in clinical practice were obtained through a Delphi panel of Spanish clinicians with expertise in CDI. Unit costs (€2012) were obtained from Spanish sources.

This study estimated that 7601 episodes of CDI occur annually in Spain (incidence of 17.1 episodes/year/10,000 hospital discharges) with an estimated annual cost to the Spanish National Health System Service of €32,157,093. The cost per episode of CDI was €3901 for initial or primary CDI episodes.

More recently, another study assessed the impact of CDI on hospital resources and costs in both Spain and Italy (Asensio et al. 2015). Each patient was matched with two randomly selected uninfected controls in the same institution. Data were collected for 232 adult infected patients and 426 matched non-infected patients in Spain (n = 106) and Italy (n = 126). CDI-associated costs were due to excess hospitalization. The difference in LOS between the two countries resulted in a significant variation in costs.

Hospitalization costs attributable to CDI in Spain were €4265 per patient for all patients, €2882/patient for patients aged ≤65 years, and €4885 for those aged >65 years (Asensio et al. 2015).

For Italy, the total cost attributable to CDI was €14,023 per patient for all patients. The cost was €15,668 for those aged ≤65 years and €13,862 for those aged >65 years, with the difference in cost being due to differences in LOS (21 vs. 19 days, respectively). The authors estimated a cost of CDI in Italy of €32,371 per 10,000 patient-days (Asensio et al. 2015).

A recent multicenter Italian cost analysis study has been performed in hospitalized patients from the hospital's perspective (Poli et al. 2015). This study showed that the mean total incremental cost for a patient with CDI was €3270 per case.

2.2 Recurrent Episodes

One of the first studies to assess the cost of recurrent CDI in an European country was a Spanish study in which the cost of the initial CDI episode was estimated to be €3901, the cost of the first recurrence was €4875, and that of the second recurrence was €5916 (Asensio et al. 2013).

In an Italian multicenter study including recurrences (Asensio et al. 2015), the cost attributable to recurrent CDI was €17,714 per patient,

while for patients with a single episode of CDI, the cost was €14,936. In this study, a total of 34 adult patients (12.5%) and 2 pediatric patients (10.5%) experienced a first recurrence of CDI. Three of the 34 adult patients and 1 of the 2 pediatric patients had an additional recurrence.

A French multicenter study estimated the median extra cost per stay with CDI to be €7514, i.e., approximately €9.5 million in 2011 for the 12 facilities included. The fraction of that total cost attributable to recurrences was 12.5% (Le Monnier et al. 2015). Recurrences occurring in acute-care settings were present in 12.0% of hospital stays with CDI. In addition, 9.3% (11/118) of recurrences were coded as the primary diagnosis and led to readmission of the patients, which resulted in prolonged LOS and additional medical costs.

Data from 37 German hospitals revealed high costs for recurrent CDI of €20,755 vs. €13,101 for matched controls from the same hospitals during the same year (Grube et al. 2015).

Wilcox et al. recently analyzed the impact of recurrent CDI in terms of hospital resource use and health-related quality of life associated with hospitalizations for recurrent CDI in six UK acute-care hospitals (Wilcox et al. 2017). The median cost per patient during a 28-day post-index period was £7539 for recurrent CDI and £6294 for first CDI episodes (Wilcox et al. 2017).

2.3 Length of Stay

In their review, Wiegand et al. (2012) estimated the average LOS in Europe to be 15 days. When examined by country, they found that Switzerland had the lowest LOS (12 days), followed by Belgium, France, Ireland (17 days), and Spain (18 days), while the highest LOS were observed for The Netherlands (21 days), Germany (27 days), and the UK (37 days) (Wiegand et al. 2012).

Even though LOS values are more reproducible between studies than costs, data on the excess LOS attributable to CDI are limited. Not many studies assess the attributable LOS, reporting only total LOS. It was recently suggested that, compared with newer statistical models, models that were previously used to determine the LOS attributable to CDI overestimated the additional LOS (Mitchell and Gardner 2012). Therefore, future studies must take this into account. Table 2 shows the European studies reporting LOS attributable to CDI; the mean incremental LOS attributable to CDI ranged from 4.2 to 20 days (Ryan et al. 2017).

As for recurrent CDI, the mean incremental LOS in Europe is 9.1–26 days (Asensio et al. 2013, 2015). Although data may vary, most studies agree that recurrent CDI presents longer LOS than primary episodes. In a recent study conducted in England, Wilcox et al. observed a median LOS of 21 days for recurrent CDI in contrast to 15.5 days for first episodes (Wilcox et al. 2017).

Few studies have assessed differences in extra costs between mild to moderate CDI cases and severe CDI cases. A study conducted by van Kleef et al. in a large English teaching hospital showed that severe cases had an average excess LOS which was twice that of the nonsevere cases (11.6 days [95% CI, 3.6–19.6] vs. approximately 5 days [95% CI: 1.1–9.5]) (van Kleef et al. 2014).

2.4 Distribution of Costs

The expense associated with CDI stems mainly from extended LOS. Various studies in Europe place the additional cost of LOS at 43.2–95.6% of the total extra costs of the CDI episode (Ryan et al. 2017; Asensio et al. 2013, 2015; Wilcox et al. 1996; Poli et al. 2015). Figure 1 represents the distribution of CDI costs of the above mentioned studies.

In contrast, cost for CDI antibiotics account for a low percentage of the total cost, ranging from 0.43% to 13.3% (Ryan et al. 2017; Asensio et al. 2013, 2015; Wilcox et al. 1996; Poli et al.

Table 2 Length of stay (LOS) attributable to *Clostridium difficile* by study and country

Author (year)	Country	CDI cases examined	Study population	Study period	LOS attributable to CDI (days)
Eckmann et al. (2013)	Netherlands	N = 270	Healthcare CDI	2008–2009	Mean 12.58
Ryan et al. (2017)	Ireland	N = 13	Healthcare CDI	August 2015	Mean 4.2
Al-Eidan et al. (2000)	Ireland	N = 87	Healthcare CDI	1994–1995	Mean 13
Eckmann et al. (2013)	England	N = 10,602	Healthcare CDI	2007–2009	Mean 16.09
van Kleef et al. (2014)	England	N = 157	Healthcare CDI	2012	Mean 7.2 (all CDI)
					Mean 11.6 (severe CDI)
					Mean 5.3 (non severe CDI)
Vonberg et al. (2008)	Germany	N = 116	Healthcare CDI	2006	Median 7
Eckmann et al. (2013)	Germany	N = 109,526	Healthcare CDI	2008–2010	Mean 15.47
Hubner et al. (2015)	Germany	N = 43	Healthcare CDI	2010	Mean 11.4
Le Monnier et al. (2015)	France	N = 1097	Healthcare CDI, recurrences	2011	Mean 8.9
Eckmann et al. (2013)	Spain	N = 830	Healthcare CDI	2008–2010	Mean 13.56
Asensio et al. (2013)	Spain	N = 7601	Healthcare CDI, recurrences	2012	Mean 7.4 (CDI)
					Mean 9.1 (first recurrent CDI)
					Mean 10.8 (second recurrent CDI)
Asensio et al. (2015)	Spain and Italy	N = 232 (Spain)	Healthcare CDI, recurrences, children	2011–2013 (adults)	Median 6.4 (Madrid)
		N = 145 (Italy)		2006–2012 (pediatrics)	Median 20.0 (Barcelona)
					Median 20.0 (Rome)
					Median 26.0 for first recurrent CDI case (Spain and Italy)
					Median 5.0 for pediatric case (Naples)

2015). Figure 2 illustrates the distribution of costs in patients with CDI antibiotics as percent of total cost per country. Most of these studies only include vancomycin and metronidazole as treatment for CDI, probably because they were conducted before fidaxomicin was licensed in those countries. Only one recent study conducted in Ireland included fidaxomicin as treatment for CDI.

Regarding distribution of costs for R-CDI, a recent study conducted in England observed that the cost of hospital admissions and emergency department visits accounted for more than 85%, similar to first-case CDI. The median cost for CDI-specific drugs was higher in R-CDI patients (£376/patient) than first-case CDI (£46/patient) (Wilcox et al. 2017).

3 Economic Burden of Community-Acquired CDI

Community-acquired CDI is a growing problem, and additional data are needed to accurately quantify the contribution of this subpopulation to the overall burden of CDI. Few studies provide insight on this understudied patient group (Kuntz et al. 2012; Sammons et al. 2013; Nanwa et al.

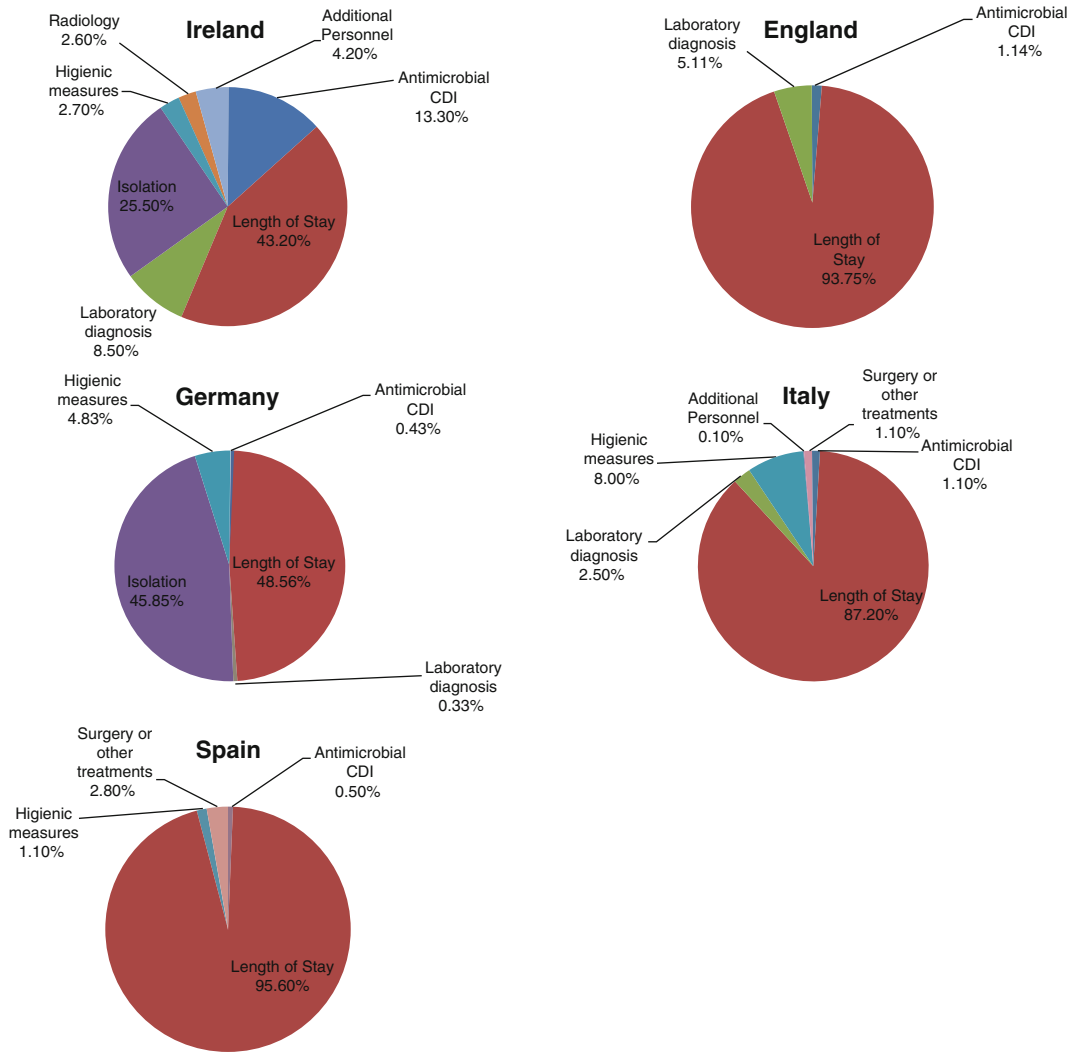

Fig. 1 Distribution of costs of *Clostridium difficile* infection

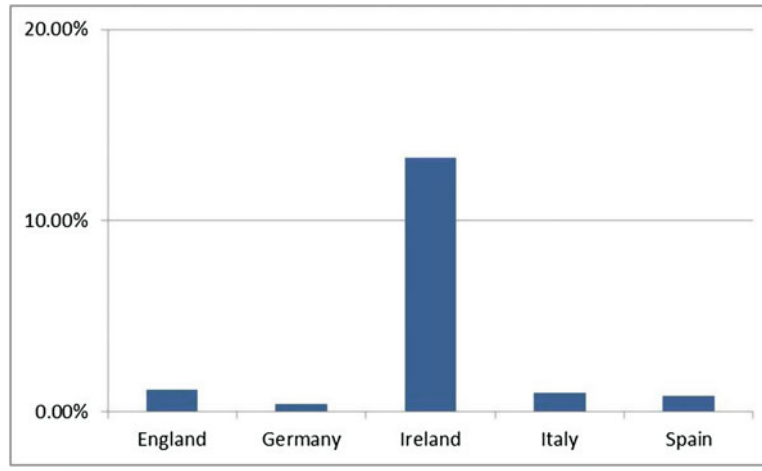

Fig. 2 Costs of antibiotics for CDI treatment as percentage of the total costs attributable to *Clostridium difficile* infection

2017), and none have been performed in European patients. In addition, across studies, the case definition of community-acquired CDI may differ depending on the time between a previous hospital admission and whether the case of CDI was an incident case (Kutty et al. 2010; Freeman et al. 2010).

The most recent and largest study is a population-based matched cohort study examining the mortality and costs of patients with community-onset CDI identified based on emergency department visits and hospital admissions in Ontario, Canada (Nanwa et al. 2017). In this study, Nanwa et al. studied 7950 subjects with community-onset CDI and found that up to 1 year after the index date, the disease was associated with 1.9- to 5.1-fold higher mean costs (CDN$10,700 in 2014) than in uninfected subjects. The largest cost components were hospitalizations and physician visits.

Differences in mortality and costs remained 3 years after index date, probably owing to recurrences of CDI, treatment failure, need for colectomy, and increased susceptibility to other conditions resulting from CDI. Mean attributable costs were higher among those aged >65 years, those infected in 2008 (year of an outbreak in Ontario caused by a particularly virulent CDI strain (Pillai et al. 2010)), and those who died within 1 year after the index date. However, this study had a major limitation, namely, the authors were not able to identify subjects whose only contact with the healthcare system was a visit to their family physician. Consequently, mortality and the economic burden of community-onset CDI per subject were likely overestimated, since all of the cases included were probably more severe.

Sammons et al. examined a cohort of children and performed a subanalysis on community-onset and hospital-onset CDI (Sammons et al. 2013). They found that patients with community-onset CDI comprised 54% of cases (2414 cases). Patients with hospital-onset CDI had significantly higher mortality rates and longer LOS than those with community-onset CDI, and mean differences in LOS and total standardized costs were 21.60 days and $93,600 for hospital-onset CDI and 5.55 days and $18,900 for community-onset CDI. Although mortality rates did not differ between those with community-onset CDI and matched unexposed subjects, community-onset CDI patients had significantly longer LOS and total hospital costs (Sammons et al. 2013).

Kuntz et al. performed a population-based study in which they identified 3067 CDIs and classified CDI by whether it was identified in the outpatient or inpatient healthcare setting (Kuntz et al. 2012). A total of 1712 (56%) were identified in the outpatient setting. These patients tended to be younger, with fewer comorbid conditions than patients with CDI identified in the inpatient setting. Eleven percent of patients with outpatient-identified CDI were hospitalized with a CDI-related diagnosis code during the follow-up period. These hospitalizations occurred, on average, 27 days after outpatient identification of CDI and lasted an average of 10 days.

As expected, the impact of CDI on healthcare utilization and cost was most notable in the setting in which the patient's infection had been identified. Outpatient care costs were higher among persons with CDI identified in the outpatient setting, with drugs representing the greatest percentage of these costs in both groups. Similarly, patients with inpatient-identified CDI had higher inpatient costs than patients with outpatient-identified CDI ($10,708.40 vs $837.40). Total costs for community-onset CDI were $1697 vs $11,315 of hospital-onset CDI (in US $2009 per patient) (Kuntz et al. 2012).

4 Pediatric Population

Data on the burden of CDI in children are even more limited and most of the literature on this topic comes from studies performed in the United States. In Italy, Asensio et al. (Asensio et al. 2015) reported separate data on the economic burden of CDI in children, although they found that the number of patients included was low (n = 19). Most cases of CDI in children were community-acquired as opposed to nosocomial.

Disease characteristics were generally comparable to those of adults, although the incidence of ulceration and bowel wall thickening was higher than in adults. The authors found that the median LOS attributable to CDI was lower than in adults (5 vs. 19 days in Rome), as was the frequency of isolation and admission to the ICU, probably because most cases were community-acquired. Therefore, although daily costs of care are higher for children than adults, the overall burden of CDI in the pediatric population in Italy is lower than in adults. The total cost attributable to CDI in pediatric patients in Naples was €3545 per patient (Asensio et al. 2015).

The only data on the economic burden of pediatric CDI in larger populations are from American studies. In their multicenter cohort study, Sammons et al. found that CDI was associated with worse outcomes among hospitalized children who were otherwise similar in the main demographic and clinical characteristics, although the difference was most pronounced in children with hospital onset disease. The presence of CDI was associated with >6-fold higher mortality rates among those with healthcare-onset CDI and resulted in significantly longer LOS and increased total hospital costs, corresponding to a mean difference in total standardized costs of $48,500 between matched exposed and unexposed patients (Sammons et al. 2013).

In another study performed in acute care hospitals in the Michigan Health and Hospital Association, children younger than 5 years of age had mean charges of $148,525, compared with $56,796 for discharges of patients who were aged ≥65 years, probably because of longer LOS: children younger than 5 years of age were hospitalized for a mean of more than 25 days per discharge vs 14.2 days for the remaining age groups reported (VerLee et al. 2012).

A large propensity score–matching analysis in 313,664 patients aged 1–18 years was performed to evaluate the influence of CDI on mortality, LOS, and costs in hospitalized surgical pediatric patients. The authors observed that after propensity score matching, the mean excess LOS and costs attributable to CDI were 5.8 days and $12,801 ($P < 0.001$), accounting for 8295 days spent in the hospital and $18.4 million (2012 USD) in annual expenditure (Kulaylat et al. 2017).

5 Economic Costs of CDI Outbreaks

Few data have been published on the costs derived from outbreaks. One of the few studies to assess this situation was that conducted in Ireland by Ryan et al. (2017). The authors collected data on LOS, diagnosis, diagnosis-related group codes at discharge, time in isolation because of CDI, additional measures because of CDI (medications, consultations, investigations, and procedures), unit costs (laboratory testing, personal protective equipment, single room accommodation, and cleaning/decontamination), and personnel time.

This study covered only a 1-month period (August 2015), during which they observed that the CDI outbreak resulted in additional costs of €46,967. The outbreak resulted in 58 bed days lost due to bed closures on the outbreak ward, with an estimated value of €34,585. Five outbreak control meetings were held, each with a mean duration of 47 min and supported by 15 h of administrative input. All meetings involved a consultant microbiologist, a senior laboratory scientist, a senior antimicrobial specialist pharmacist, an assistant director of nursing, multiple clinical nursing managers, and a number of other staff members. The mean personnel cost per meeting was €546, and the aggregate cost was €2728. The cost of outbreak-related cleaning/decontamination during August was €9654 (Ryan et al. 2017).

For the patients involved in the CDI outbreak, excluding the value of the 58 bed days lost (€34,585), costs were 30% higher (€7589 per patient) than those not involved in the outbreak during the same period (Ryan et al. 2017).

Van Beurden et al. assessed the costs of an outbreak of *C. difficile* ribotype 027 at the VU University medical center, a 750-bed tertiary care center in The Netherlands, from May 2013

to May 2014 (van Beurden et al. 2017). Several control measures were implemented, such as reinforcement of infection control, the introduction of hydrogen peroxide as disinfectant, extra cleaning, optimization of CDI diagnosis, optimization of CDI treatment, and antibiotic stewardship. Twelve meetings of the outbreak management team (consisting of five medical specialists, one infection prevention specialist, one care manager, and two co-workers from facility management) were held during the study period. Several beds had to be closed to ensure that every patient with suspected CDI was placed in contact isolation in a single room. After the implementation of these control measures, the incidence of CDI decreased to around 1.5 cases per 10,000 patient days in early 2014.

Missed revenue due to prolonged LOS among CDI patients, costs of the outbreak meetings, extra surveillance, contact isolation material (compared with the same period 1 year earlier and 1 year later), and additional microbiological diagnostics (compared with the same period 1 year earlier) were calculated directly from available data for the entire outbreak. Overall costs for additional cleaning, contact isolation, and missed revenue due to closed beds were extrapolated from the costs incurred during the previous 3 months of the outbreak. Attributable costs per item (in 2014 euros) were assessed over a 365-day period.

The total identifiable costs of this *C. difficile* outbreak were €1,222,376. Most costs (36%) stemmed from the loss of revenue resulting from decreased hospital capacity because of the increased LOS of CDI patients and the closure of multiple beds to ensure contact isolation of a single CDI patient. Twenty-five percent of the costs were from extra surveillance and the work of the department of infection control, 24% were for extra cleaning of the affected wards, 6% for extra microbiological diagnostic procedures, 3% for the outbreak meetings, and 3% for the use of extra gloves and aprons. Extra antibiotic treatment of CDI patients counted for 2% of the total costs (van Beurden et al. 2017).

As can be seen in both studies, the cost of one missed hospital admission due to closed beds or prolonged LOS is a major cost. The economic and healthcare impact of loss of revenue is very difficult to determine, and closed beds prevent inpatient accommodation, with the resultant morbidity and mortality (Singer et al. 2011). In addition, increased bed usage by medical specialties is associated with cancelled elective surgeries (Robb et al. 2004; Nasr et al. 2004).

Outbreak control generates extra work, which often relies on staff already overburdened with administrative tasks from patient care activities. Extra cleaning measures and multidisciplinary infection control teams are key elements for outbreak control (Barbut et al. 2011, 2015). Healthcare facilities should be able to assess the economic impact of an outbreak, and knowing the costs of additional measures will make it possible to establish a cost-efficient program for outbreak control, with adequate resource allocation.

It is obvious to state that accounting of LOS, cost of antimicrobial agents and other expenses of the healthcare system are unable to quantify the cost of pain, human suffering, and death.

References

Al-Eidan FA, McElnay JC, Scott MG, Kearney MP (2000) *Clostridium difficile*-associated diarrhoea in hospitalised patients. J Clin Pharm Ther 25(2):101–109

Asensio A, Bouza E, Grau S, Rubio-Rodriguez D, Rubio-Terres C (2013) Cost of *Clostridium difficile* associated diarrhea in Spain. Rev Esp Salud Publica 87(1):25–33. https://doi.org/10.4321/s1135-57272013000100004

Asensio A, Di Bella S, Lo Vecchio A, Grau S, Hart WM, Isidoro B, Scotto R, Petrosillo N, Watt M, Nazir J (2015) The impact of *Clostridium difficile* infection on resource use and costs in hospitals in Spain and Italy: a matched cohort study. Int J Infect Dis 36:31–38. https://doi.org/10.1016/j.ijid.2015.05.013

Barbut F (2015) How to eradicate *Clostridium difficile* from the environment. J Hosp Infect 89(4):287–295. https://doi.org/10.1016/j.jhin.2014.12.007

Barbut F, Jones G, Eckert C (2011) Epidemiology and control of *Clostridium difficile* infections in healthcare settings: an update. Curr Opin Infect Dis 24(4):370–376. https://doi.org/10.1097/QCO.0b013e32 834748e5

Bouza E (2012) Consequences of *Clostridium difficile* infection: understanding the healthcare burden. Clin

Microbiol Infect 18(Suppl 6):5–12. https://doi.org/10.1111/1469-0691.12064

Dubberke ER, Olsen MA (2012) Burden of *Clostridium difficile* on the healthcare system. Clin Infect Dis 55 (Suppl 2):S88–S92. https://doi.org/10.1093/cid/cis335

Eckmann C, Wasserman M, Latif F, Roberts G, Beriot-Mathiot A (2013) Increased hospital length of stay attributable to *Clostridium difficile* infection in patients with four co-morbidities: an analysis of hospital episode statistics in four European countries. Eur J Health Econ 14(5):835–846

Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, Kuijper EJ, Wilcox MH (2010) The changing epidemiology of *Clostridium difficile* infections. Clin Microbiol Rev 23(3):529–549. https://doi.org/10.1128/cmr.00082-09

Gabriel L, Beriot-Mathiot A (2014) Hospitalization stay and costs attributable to *Clostridium difficile* infection: a critical review. J Hosp Infect 88(1):12–21. https://doi.org/10.1016/j.jhin.2014.04.011

Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW (2010) Economic healthcare costs of *Clostridium difficile* infection: a systematic review. J Hosp Infect 74(4):309–318. https://doi.org/10.1016/j.jhin.2009.10.016

Grube RF, Heinlein W, Scheffer H, Rathmayer M, Schepp W, Lohse AW, Stallmach A, Wilke MH, Lerch MM (2015) Economic burden of *Clostridium difficile* enterocolitis in German hospitals based on routine DRG data. Z Gastroenterol 53(5):391–397. https://doi.org/10.1055/s-0034-1398803

Hubner C, Hubner NO, Muhr M, Claus F, Leesch H, Kramer A, Flessa S (2015) Cost analysis of hospitalized *Clostridium difficile*-associated diarrhea (CDAD). GMS Hyg Infect Control 10:Doc13. https://doi.org/10.3205/dgkh000256

Jones AM, Kuijper EJ, Wilcox MH (2013) *Clostridium difficile*: a European perspective. J Inf Secur 66(2):115–128. https://doi.org/10.1016/j.jinf.2012.10.019

Kuijper EJ, Coignard B, Tull P (2006) Emergence of *Clostridium difficile*-associated disease in North America and Europe. Clin Microbiol Infect 12(Suppl 6):2–18. https://doi.org/10.1111/j.1469-0691.2006.01580.x

Kulaylat AN, Rocourt DV, Podany AB, Engbrecht BW, Twilley M, Santos MC, Cilley RE, Hollenbeak CS, Dillon PW (2017) Costs of *Clostridium difficile* infection in pediatric operations: a propensity score-matching analysis. Surgery 161(5):1376–1386. https://doi.org/10.1016/j.surg.2016.10.020

Kuntz JL, Johnson ES, Raebel MA, Petrik AF, Yang X, Thorp ML, Spindel SJ, Neil N, Smith DH (2012) Epidemiology and healthcare costs of incident *Clostridium difficile* infections identified in the outpatient healthcare setting. Infect Control Hosp Epidemiol 33(10):1031–1038. https://doi.org/10.1086/667733

Kutty PK, Woods CW, Sena AC, Benoit SR, Naggie S, Frederick J, Evans S, Engel J, McDonald LC (2010) Risk factors for and estimated incidence of community-associated *Clostridium difficile* infection, North Carolina, USA. Emerg Infect Dis 16(2):197–204. https://doi.org/10.3201/eid1602.090953

Le Monnier A, Duburcq A, Zahar JR, Corvec S, Guillard T, Cattoir V, Woerther PL, Fihman V, Lalande V, Jacquier H, Mizrahi A, Farfour E, Morand P, Marcade G, Coulomb S, Torreton E, Fagnani F, Barbut F (2015) Hospital cost of *Clostridium difficile* infection including the contribution of recurrences in French acute-care hospitals. J Hosp Infect 91(2):117–122. https://doi.org/10.1016/j.jhin.2015.06.017

McGlone SM, Bailey RR, Zimmer SM, Popovich MJ, Tian Y, Ufberg P, Muder RR, Lee BY (2012) The economic burden of *Clostridium difficile*. Clin Microbiol Infect 18(3):282–289. https://doi.org/10.1111/j.1469-0691.2011.03571.x

Mitchell BG, Gardner A (2012) Prolongation of length of stay and *Clostridium difficile* infection: a review of the methods used to examine length of stay due to healthcare associated infections. Antimicrob Resist Infect Control 1(1):14. https://doi.org/10.1186/2047-2994-1-14

Nanwa N, Kendzerska T, Krahn M, Kwong JC, Daneman N, Witteman W, Mittmann N, Cadarette SM, Rosella L, Sander B (2015) The economic impact of *Clostridium difficile* infection: a systematic review. Am J Gastroenterol 110(4):511–519. https://doi.org/10.1038/ajg.2015.48

Nanwa N, Sander B, Krahn M, Daneman N, Lu H, Austin PC, Govindarajan A, Rosella LC, Cadarette SM, Kwong JC (2017) A population-based matched cohort study examining the mortality and costs of patients with community-onset *Clostridium difficile* infection identified using emergency department visits and hospital admissions. PLoS One 12(3):e0172410. https://doi.org/10.1371/journal.pone.0172410

Nasr A, Reichardt K, Fitzgerald K, Arumugusamy M, Keeling P, Walsh TN (2004) Impact of emergency admissions on elective surgical workload. Ir J Med Sci 173(3):133–135

Pillai DR, Longtin J, Low DE (2010) Surveillance data on outbreaks of *Clostridium difficile* infection in Ontario, Canada, in 2008–2009. Clin Infect Dis 50(12):1685–1686. https://doi.org/10.1086/653007. author reply 1686

Poli A, Di Matteo S, Bruno GM, Fornai E, Valentino MC, Colombo GL (2015) Economic burden of *Clostridium difficile* in five hospitals of the Florence health care system in Italy. Risk Manag Healthc Policy 8:207–213. https://doi.org/10.2147/rmhp.s90513

Robb WB, O'Sullivan MJ, Brannigan AE, Bouchier-Hayes DJ (2004) Are elective surgical operations cancelled due to increasing medical admissions? Ir J Med Sci 173(3):129–132

Ryan P, Skally M, Duffy F, Farrelly M, Gaughan L, Flood P, McFadden E, Fitzpatrick F (2017) Evaluation of fixed and variable hospital costs due to *Clostridium difficile* infection: institutional incentives and directions for future research. J Hosp Infect 95 (4):415–420. https://doi.org/10.1016/j.jhin.2017.01.016

Sammons JS, Localio R, Xiao R, Coffin SE, Zaoutis T (2013) *Clostridium difficile* infection is associated with increased risk of death and prolonged hospitalization in children. Clin Infect Dis 57(1):1–8. https://doi.org/10.1093/cid/cit155

Singer AJ, Thode HC Jr, Viccellio P, Pines JM (2011) The association between length of emergency department boarding and mortality. Acad Emerg Med 18 (12):1324–1329. https://doi.org/10.1111/j.1553-2712.2011.01236.x

Van Beurden YH, Bomers MK, van der Werff SD, Pompe EA, Spiering S, Vandenbroucke-Grauls CM, Mulder CJ (2017) Cost analysis of an outbreak of *Clostridium difficile* infection ribotype 027 in a Dutch tertiary care centre. J Hosp Infect 95(4):421–425. https://doi.org/10.1016/j.jhin.2016.12.019

Van Kleef E, Green N, Goldenberg SD, Robotham JV, Cookson B, Jit M, Edmunds WJ, Deeny SR (2014) Excess length of stay and mortality due to *Clostridium difficile* infection: a multi-state modelling approach. J Hosp Infect 88:213–217

VerLee KE, Finks JL, Wilkins MJ, Wells EV (2012) Michigan *Clostridium difficile* hospital discharges: frequency, mortality, and charges, 2002–2008. Public Health Rep 127(1):62–71

Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P (2008a) Costs of nosocomial *Clostridium difficile*-associated diarrhoea. J Hosp Infect 70 (1):15–20. https://doi.org/10.1016/j.jhin.2008.05.004

Wiegand PN, Nathwani D, Wilcox MH, Stephens J, Shelbaya A, Haider S (2012) Clinical and economic burden of *Clostridium difficile* infection in Europe: a systematic review of healthcare-facility-acquired infection. J Hosp Infect 81(1):1–14. https://doi.org/10.1016/j.jhin.2012.02.004

Wilcox MH, Cunniffe JG, Trundle C, Redpath C (1996) Financial burden of hospital-acquired *Clostridium difficile* infection. J Hosp Infect 34(1):23–30

Wilcox MH, Ahir H, Coia JE, Dodgson A, Hopkins S, Llewelyn MJ, Settle C, McLain-Smith S, Marcella SW (2017) Impact of recurrent *Clostridium difficile* infection: hospitalization and patient quality of life. J Antimicrob Chemother 72:2647–2656. https://doi.org/10.1093/jac/dkx174

Adv Exp Med Biol - Advances in Microbiology, Infectious Diseases and Public Health (2018) 8: 13–25
https://doi.org/10.1007/978-3-319-72799-8_2

Published online: 29 January 2018

The Need for European Surveillance of CDI

Camilla Wiuff, A-Lan Banks, Fidelma Fitzpatrick, and Laura Cottom

For surveillance systems to be useful, they must adapt to the changing environment in which they operate and accommodate emerging public health requirements that were not conceived previously.

Joseph S. Lombardo and David L. Buckeridge

Abstract

Since the turn of the millennium, the epidemiology of *Clostridium difficile* infection (CDI) has continued to challenge. Over the last decade there has been a growing awareness that improvements to surveillance are needed. The increasing rate of CDI and emergence of ribotype 027 precipitated the implementation of mandatory national surveillance of CDI in the UK. Changes in clinical presentation, severity of disease, descriptions of new risk factors and the occurrence of outbreaks all emphasised the importance of early diagnosis and surveillance.

However a lack of consensus on case definitions, clinical guidelines and optimal laboratory diagnostics across Europe has lead to the underestimation of CDI and impeded comparison between countries. These inconsistencies have prevented the true burden of disease from being appreciated.

Acceptance that a multi-country surveillance programme and optimised diagnostic strategies are required not only to detect and control CDI in Europe, but for a better understanding of the epidemiology, has built the foundations for a more robust, unified surveillance. The concerted efforts of the European Centre for Disease Prevention and Control (ECDC) CDI networks, has lead to the development of an over-arching long-term CDI surveillance strategy for 2014–2020. Fulfilment of the ECDC priorities and targets will no doubt be challenging and will require significant investment however the hope is that both a national and Europe-wide picture of CDI will finally be realised.

C. Wiuff (✉) · A.-L. Banks
Strategic Lead Microbiology, NHS National Services Scotland, Health Protection Scotland, HAI & IC Section, Glasgow, UK
e-mail: camilla.wiuff@nhs.net; alan.banks@nhs.net

F. Fitzpatrick
Department of Clinical Microbiology, The Royal College of Surgeons in Ireland, Dublin, Ireland

Department of Clinical Microbiology, Beaumont Hospital, Dublin, Ireland
e-mail: fidelmafitzpatrick@rcsi.ie

L. Cottom
Department of Microbiology, Glasgow Royal Infirmary, Glasgow, UK
e-mail: lauracottom@gmail.com

Keywords
Surveillance · Epidemiology · Standardisation · Capacity building · Collaborative effort

1 Epidemiology of CDI in Europe

Since 1978, *Clostridium difficile* has been recognised as a leading infectious cause of antimicrobial-associated diarrhoea with symptoms ranging from mild or moderate diarrhoea to pseudomembranous colitis (PMC). Until the end of the millennium interest in this pathogen was primarily in relation to health care and impact on morbidity and mortality in the elderly. However, since 2000 there has been an explosion in reports on *C. difficile* infection (CDI) as a consequence of large increases in CDI cases (and incidence), significant changes in the clinical presentation of CDI including more severe disease, occurrence of outbreaks and descriptions of new risk factors (Freeman et al. 2010). The changes in the epidemiology of CDI leading to several outbreaks in North America and Europe have mainly been attributed to the emergence of a new hypervirulent strain PCR ribotype 027 (Kuijper et al. 2006), and to a lesser extent, PCR ribotype 078 (Goorhuis et al. 2008). Ribotype 027 was associated with more severe disease, higher mortality, increased risk of relapse and higher colectomy rates (Kuijper et al. 2006; Ricciardi et al. 2007; Warny et al. 2005). However, other ribotypes of *C. difficile* also caused outbreaks and contributed to the spread of this infection in Europe and worldwide (Bauer et al. 2011).

Outbreaks caused by PCR ribotype 027 were first reported in Europe in England and the Netherlands followed by a series of reports from several other European countries (Kuijper et al. 2007); and, by 2008 a total of 16 countries had reported this ribotype, including outbreaks in nine countries (Kuijper et al. 2008). However, the reasons for its emergence and rapid global spread remained unexplained until the genomes of a global collection of *C. difficile* 027 isolates from hospital patients between 1985 and 2010 was sequenced. Phylogenetic analysis showed that two separate lineages of 027, FQR1 and FQ2, had emerged in North America within a short period of time, after acquiring the same fluoroquinolone resistance mutation, of which one spread throughout the United States (US), South Korea and Switzerland and the other spread more widely across continents throughout Europe and Australia (He et al. 2013). Isolates obtained prior to the emergence of these two lineages were not associated with any hospital outbreaks, suggesting that they represented pre-epidemic lineages of ribotype 027. These findings highlighted the important role of selective pressure from flouroquinolone use in the evolution and spread of these two lineages in healthcare settings and highlighted the interconnectedness of the global healthcare systems due to human travel.

In the 2011/2012 European Centre for Disease Prevention and Control (ECDC) acute hospital point prevalence survey of hospital-acquired infection (HAI) *C. difficile* was the most frequently reported pathogen associated with healthcare associated gastrointestinal disease in European hospitals(accounting for 48% of all gastrointestinal disease) (ECDC 2013a). Based on this data it was estimated that 152,905 new cases of CDI occur every year in Europe with an incidence of 30 cases per 100,000 population. CDI was associated with considerable short or long term disability, and 8382 deaths per year (Cassini et al. 2016). In addition, CDI occurred increasingly in persons in the community without typical risk factors such as antimicrobial treatment and recent hospitalisation (Bauer et al. 2009; Wilcox et al. 2008) (Fig. 1).

2 Development of European CDI Guidance

In response to the changing epidemiology of CDI in Europe and North America, the European Study Group on *C. difficile* (ESGCD) published a standardised approach to detect, monitor and control CDI (Kuijper et al. 2006). In the following year, evidence-based guidance on infection prevention and control measures to limit the

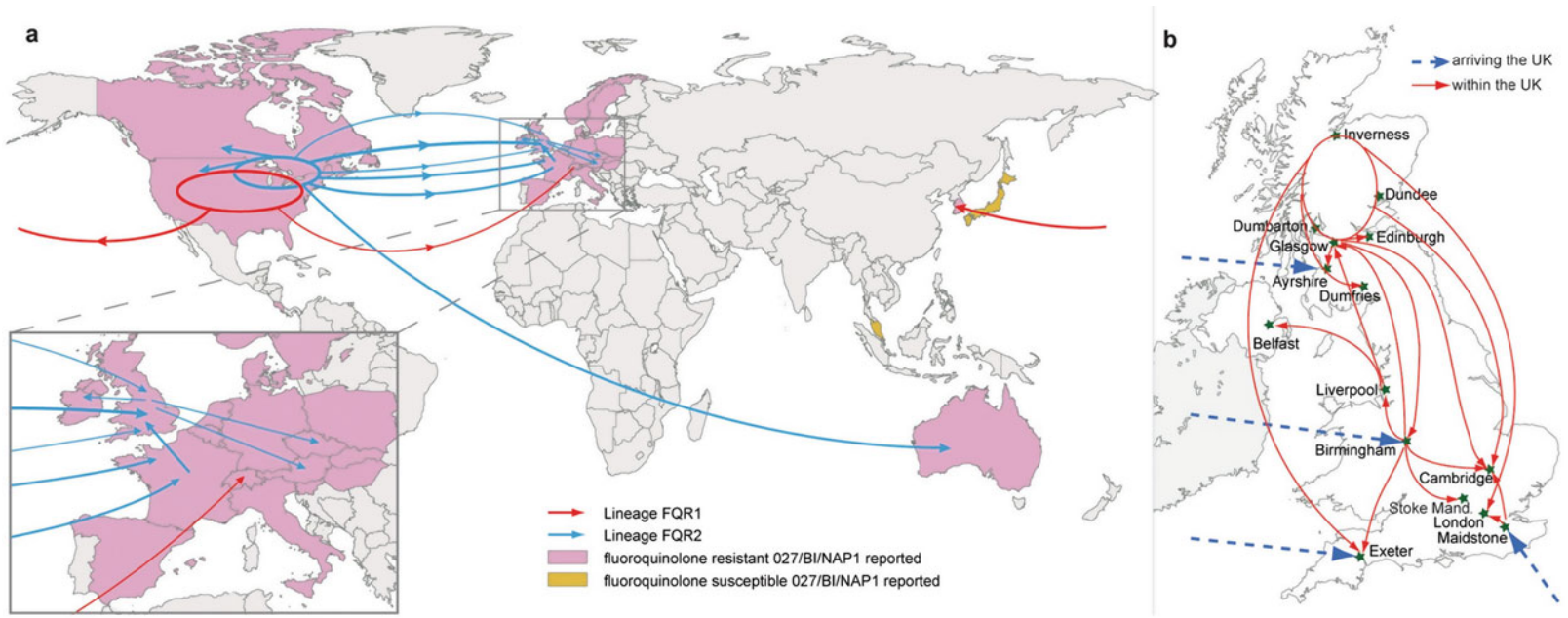

Fig. 1 Global transmission events of *C. difficile* PCR ribotype 027 (with permission from authors). Arrows indicate individual introductory transmission events of FQR1 and FQR2 (He et al. 2013)

spread of CDI was also developed. In this context CDI surveillance was identified as one of the ten most important measures in preventing and controlling CDI. Surveillance allows continuous monitoring and identification of increases in incidence and severity of disease at an early stage in order to implement changes in practice and monitor the impact of infection prevention and control efforts (Vonberg et al. 2008).

Timely feedback of surveillance data and its interpretations not only to the clinical and infection prevention and control teams but also to senior management, governing boards and administrators via the established communication system is considered essential to preventing and control CDI in hospitals (Commission. 2006). However, when CDI emerged as a serious threat to public health and patient safety at the start of this millennium, comparison of the burden of CDI between healthcare facilities and countries was problematic for a number of reasons. This included suboptimal case ascertainment and inconsistent patient sampling, inadequate laboratory diagnosis and use of non-standardised denominators for calculation of incidence rates. Standardisation of laboratory testing methodology and adherence to agreed surveillance definitions is needed for accurate monitoring of trends in hospitals and other healthcare settings (and for comparison between hospitals in their country and between countries). The suite of guidance documents on CDI diagnostics, infection prevention and control and treatment developed by ESGCD and supported by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), has provided the evidence platform for the development of European surveillance of CDI now undertaken and coordinated by ECDC (ECDC 2017) (Fig. 2).

3 Approaches to Diagnosing and Monitoring Cases of CDI

In the 1990s, a large number of diagnostic tests for *C. difficile* became commercially available, including faecal culture on selective media, detection of GDH (glutamate dehydrogenase) a non-specific antigen, direct detection of toxin A and B from stool using enzyme immune assay or cytotoxicity assay (Delmee 2001) but system-wide or national surveillance programmes remained rare. In 1993, a French multicentre point prevalence study identified *C. difficile* from 11.5% of 3921 diarrhoeal stool cultures sent to 11 microbiology laboratories (Barbut et al. 1996). Stool assays for toxin A and B became quickly the main clinical test for diagnosing CDI while stool cultures were used mainly for epidemiological investigations (Kelly and LaMont 1998). However, the majority of the available testing methods were associated with either low sensitivity or specificity, or both (see also Chap. 4), and some required culture facilities. Moreover, at that time there was no consensus across Europe in terms of diagnostic testing and surveillance due to the lack of guidance.

In 2002, the ESGCD carried out a survey of 212 laboratories in eight countries (B, DK, F, NL, G, I, SP, GB) to obtain an overview of diagnostic methods used and to estimate the average incidence of CDI across Europe (Barbut et al. 2003). A high proportion (87.7%) of laboratories performed *C. difficile* diagnosis on a routine basis, although laboratories in smaller hospitals often relied on sending samples to a bigger centre. Laboratory methods used in the surveyed hospitals included direct toxin detection (93%), culture (55%), glutamate dehydrogenase (GDH) (5.9%) but testing strategies (i.e. application of standalone tests vs. combination of tests) varied considerably between laboratories and between countries. Moreover, criteria for investigation for CDI

Vision, priorities and targets

By 2020, strong, harmonised and efficient European surveillance systems will serve the Member States, the European Commission and public health professionals by providing relevant data for the effective prevention and control of communicable diseases while minimising the burden on the Member States.

Consolidating surveillance, increasing its efficiency and enhancing the outputs and their impact

- Target 1: Critical evaluation of indicator-based EU surveillance.
- Target 2: Machine-to-machine reporting to TESSy in use by a majority of Member States.
- Target 3: Data processing is semi-automated while retaining a high quality, enabling ECDC routine surveillance outputs to be timelier, more easily available, user-customisable and thus perceived to be more useful by stakeholders.
- Target 4: The complementarity and synergy between indicator-based and event-based surveillance is improved.
- Target 5: ECDC and the Member State experts routinely communicate European surveillance findings through peer-reviewed scientific journals and other channels to better inform disease prevention and control as well as public health decision-making.

Developing standards, improving data quality and sharing best practice in surveillance

- Target 6: European surveillance standards agreed and implemented.
- Target 7: The European surveillance network culture promotes systematic learning from the example of the high-quality data providers.
- Target 8: Surveillance data quality assurance policies are in place at EU and Member State level.
- Target 9: The quality of European surveillance data has improved sufficiently to enable the routine application of time-series analysis, spatial analysis and other advanced statistical methods, where appropriate, to better monitor, understand and predict epidemiological trends of communicable diseases in Europe.

Promoting use of surveillance data

- Target 10: European event-based surveillance detects, assesses and monitors communicable disease threats to public health in near-real time.
- Target 11: European surveillance data are used to identify and monitor risk groups, where appropriate.
- Target 12: European surveillance data are used to monitor and evaluate prevention programmes against agreed indicators.
- Target 13: European surveillance data generate hypotheses for further scientific investigation and influence the EU research agenda.

Strengthening capacity in surveillance

- Target 14: ECDC works effectively with the European Commission, World Health Organization and other Agencies to promote the development of a European policy environment that supports maintenance and development of effective Member State surveillance systems and avoids overlap or duplication.

Controlling expansion

- Target 15: Routine molecular surveillance of selected pathogens is fully established at European level.
- Target 16: Relevant alternative data sources for surveillance and early threat detection have been fully explored (usefulness, data quality, potential for record linkage, etc.) and, if found to add value, are ready to be used.

Monitoring implementation of the strategy

- Target 17: The implementation of this long-term surveillance strategy is monitored and reported to the Member States on an annual basis.

Fig. 2 Targets in the ECDC long-term surveillance strategy for 2014–2020 (ECDC 2013b)

varied extensively with 58% of laboratories only testing for CDI if specifically requested by a physician while 40.7% of laboratories routinely tested for CDI when specific criteria (determined by the microbiologist) were met; most commonly loose or watery stools (40.3%), stools from patients with a history of antibiotic therapy (45.5%) and stools from nosocomial diarrhoea (57.1%). Within most countries the proportion of laboratories that used criteria for investigating CDI also varied between countries (ranging from 13% to 67%); only in the United Kingdom (UK), testing was routinely done according to specific criteria determined by the microbiologist (in 95% of laboratories). Ability to type *C. difficile* was infrequent with only 10.7% of laboratories reporting experience with typing. The inconsistent approach to diagnosing and typing CDI, including variation in the criteria for testing, laboratory methodology and strategy for testing and possible bias in the study (by inclusion of only the most responsive laboratories) raised concern of under-ascertainment due to un-diagnosed and mis-diagnosed cases and inaccurate estimates of the overall burden of disease and highlighted the need for international guidance.

The ESCGD review of the emergence of CDI in North America and Europe (Kuijper et al. 2006) specified for the first time a case definition for CDI, (including healthcare and community association), provided advice on optimal diagnostic testing and recommended that each member state should develop systematic and comprehensive surveillance systems in order to detect, monitor and respond to changes in the epidemiology of CDI, and in particular PCR ribotype 027 at both national and European levels. Following 2006 national surveillance systems were developed or expanded in countries across Europe.

In 2011, the European *C.difficile* Infection Surveillance Network (ECDIS-net) surveyed the national surveillance systems through a web-based questionnaire and reviewed extant surveillance protocols at the time. Fourteen countries were found to have a total of 18 surveillance systems in place (of which some had more than one data collection system) (Kola et al. 2016). The majority of the European surveillance systems were continuous and prospective; and 11/18 used mandatory reporting while seven used voluntary reporting. Key features of the surveillance systems varied widely with considerable variation in case definitions data collection methods, reporting and availability of reference typing. In total, 12/18 countries used the ECDC/ Centers for Disease Control and Prevention (CDC) case definitions, nine used the ECDC definitions for community associated and healthcare associated CDI while the remainder had different cut-off for healthcare association (including $\geq$48 h, $\geq$72 h, $>$3 or 4 $\geq$days after admission). Thirteen systems had a definition for severe disease while 11 had a definition for recurrence but both definitions varied between countries. Despite the increasingly recognised role of CDI in community settings only two countries (Austria and Scotland) engaged General Practitioners in their surveillance systems. Descriptive enhanced patient data were only collected in 6/18 systems and death within 30 days in five. Reference typing was performed routinely in 13/14 countries using various different criteria for submission including the presence of severe CDI, outbreaks or a more systematic periodic collection of a representative sample of cases. Finally, the reporting of the CDI burden varied widely with the use of a non-standardised denominators and stratification by geographical region, healthcare facility or laboratory making comparisons over time and between regions and facilities difficult (Kola et al. 2016).

Although, the overall capability and capacity for monitoring CDI has increased tremendously across Europe between 2003 and 2011, as of today there is still scope for improvement in diagnostic and surveillance setups in the majority of European countries.

4 Diagnostic Capability: A Pre-requisite for Surveillance

The attention given to diagnostic procedures and surveillance of CDI varied widely between countries. In 2008, with the support of ECDC a Europe-wide survey (involving 106 laboratories in 34 countries) assessed the epidemic preparedness and current CDI epidemiology aiming to ultimately build capacity for diagnosis and surveillance of CDI in each country (Bauer et al. 2011). The frequency of testing varied between countries from 3 to 141 CDI tests conducted per 10,000 patient days; and a correlation between testing rate and CDI incidence was identified (resulting in North European countries reporting the highest incidence rates). When a subset of *C. difficile* isolates were typed centrally (in Leiden, NL), a higher than expected diversity of PCR ribotypes was observed with ribotypes 001, 014/020, and 078 ribotype being the most prevalent and 027 being only the 6th most common type (4.8% of examined isolates).

Optimum laboratory diagnosis of CDI depends on testing patients at the correct time using appropriate testing methodology and strategy. A point prevalence study in multi-centre setting in Spain evaluated 988 unformed stools (from 897 patients) found 66% of CDI episodes were undiagnosed or misdiagnosed due to lack of clinical suspicion (48%) or due to using a non-sensitive test (19%) (Alcala et al. 2012). In the Europe-wide point prevalence study (EUCLID) 3800 unformed stools (from >450 hospitals in 20 countries) were tested using the recommended two-step diagnostic algorithm. In total, 25% of samples had not been tested due to lack of clinical suspicion and 23% of patients had been misdiagnosed due to using an inadequate laboratory test. It was estimated that on a single day 82 patients with diarrhoea due to *C. difficile* in hospitals across Europe were not diagnosed due to lack of suspicion (Davies et al. 2014). In addition, only 32% of participating hospitals used the optimum diagnostic method at the first measurement (in 2011–2012) whereas this had improved at the second measurement (in 2012–2013) when 48% used the optimum method.

These two recent studies highlighted again variation in awareness and capability and capacity to diagnose, sub-type, report, collect patient risk factor data and monitor CDI across Europe and as a consequence the true burden of CDI and distribution of ribotypes is unclear.

5 Benefits of Mandatory Surveillance: Experiences from United Kingdom

Prior to the year 2000, data on *C. difficile* was collected on a voluntary basis. In the UK, a steady increase in laboratory reports was observed during the 1990s (Department of Health and Health Protection Agency 2008; Health Protection Scotland 2006). In England, this was suggested to reflect a failure to implement guidelines published in 1994, as well as the result of increased testing and awareness of CDI, and an increase in community-associated CDI (Department of Health and Health Protection Agency 2008).

The increasing CDI rates and emergence of ribotype 027 precipitated the implementation of mandatory national surveillance of CDI by England, Wales and Northern Ireland in 2004, and by Scotland in 2006. Initially, the surveillance programmes included only those aged 65 years and above, but have since expanded to include all ages except the very young (Pearson 2009; Health Protection Scotland 2010). Between 2003 and 2007, several large hospital outbreaks of CDI occurred, involving ribotype 027 (two in England and one in Scotland), which brought CDI to the public attention (Healthcare Commission 2006; The Vale of Leven Hospital Inquiry 2014). Among the many key findings and recommendations contained within the critical reports that followed was an acknowledgement of a lack of appropriate surveillance mechanisms, both locally and nationally, that could have identified an outbreak, and the need for formal communication channels to be in place to allow information on CDI numbers and severity to be quickly disseminated. These major incidents were quickly followed by the setting of national targets within the UK to reduce CDI rates by 30% (Duerden 2011; Scottish Government 2012).