

# *Clostridium difficile* infection in Europe

— A CDI Europe Report —



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## Foreword by the European Hospital and Healthcare Federation

Healthcare-associated infections, including *Clostridium difficile* infection (CDI), are a paramount concern for hospitals across Europe and addressing them is essential to safeguard patient safety and to ensure the highest quality of care.

The health sector is a high-risk area because adverse events, arising from treatment rather than disease, can lead to death, serious damage, complications and patient suffering. International research has underlined the need for, and the possibility of, reducing the number of adverse events. Tools are now available to help reduce the number and consequences of adverse events. More fundamentally, the health sector should be designed and operated in a way that allows errors and adverse events to be prevented, detected or contained and that facilitates compliance with safety procedures.

The first step in this process should be the establishment of a culture of patient safety throughout the entire health system, with the routine use of risk management. A precondition for risk management is an open and trusting working environment with a culture that focuses on learning from near misses and adverse events, as opposed to one that concentrates on 'blame and shame' and punishment.

Hospitals and healthcare settings already have procedures in place to ensure patient safety. However, much more needs to be done, in particular in the field of healthcare-associated infections and, more precisely, CDI – a prominent infection in Europe.

Pascal Garel  
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European Hospital and Healthcare Federation (HOPE)



# 1. INTRODUCTION: CDI – WHAT IS THE PROBLEM?

*Clostridium difficile* infection (CDI), an infection of the large intestine, is the leading cause of healthcare-associated diarrhoea in Europe.<sup>1,2</sup> CDI is usually a consequence of antibiotic use and most cases occur in the elderly.<sup>2</sup> In severe cases CDI can cause serious bowel conditions that can be life threatening.<sup>2,3</sup> CDI is common in hospitals and is increasingly recognised by experts as a problem in the community.<sup>2,4</sup> In addition to its impact on individual patients, CDI accounts for a substantial drain on healthcare resources and costs.<sup>3,5</sup> However, in many countries, CDI remains under-recognised by health policymakers and managers, healthcare professionals and the public.

Healthcare-associated infections (HAIs) are a major healthcare priority and a focus of current European and national strategies to improve patient safety.<sup>6,7</sup> As a prominent HAI, CDI must be considered within these strategies and the resulting intervention programmes to prevent and control HAIs.

This report presents an overview of the clinical and economic burden of CDI, highlights the current deficiencies in CDI management in Europe, and proposes strategies to address these within the framework of relevant ongoing EU health policy initiatives where European-level action can add value.

This first Section explains how CDI occurs, how common it is and what impact it has on patients and health systems in Europe.

## Introducing CDI EUROPE

CDI Europe is an expert-led initiative focused at the healthcare policy level with the aim to translate research on CDI into meaningful policy responses to help raise awareness of CDI, improve and standardise disease surveillance and reporting, promote a better standard of care for CDI management across Europe (including diagnostic testing, therapy, and infection control and prevention), and ultimately to improve patient outcomes.

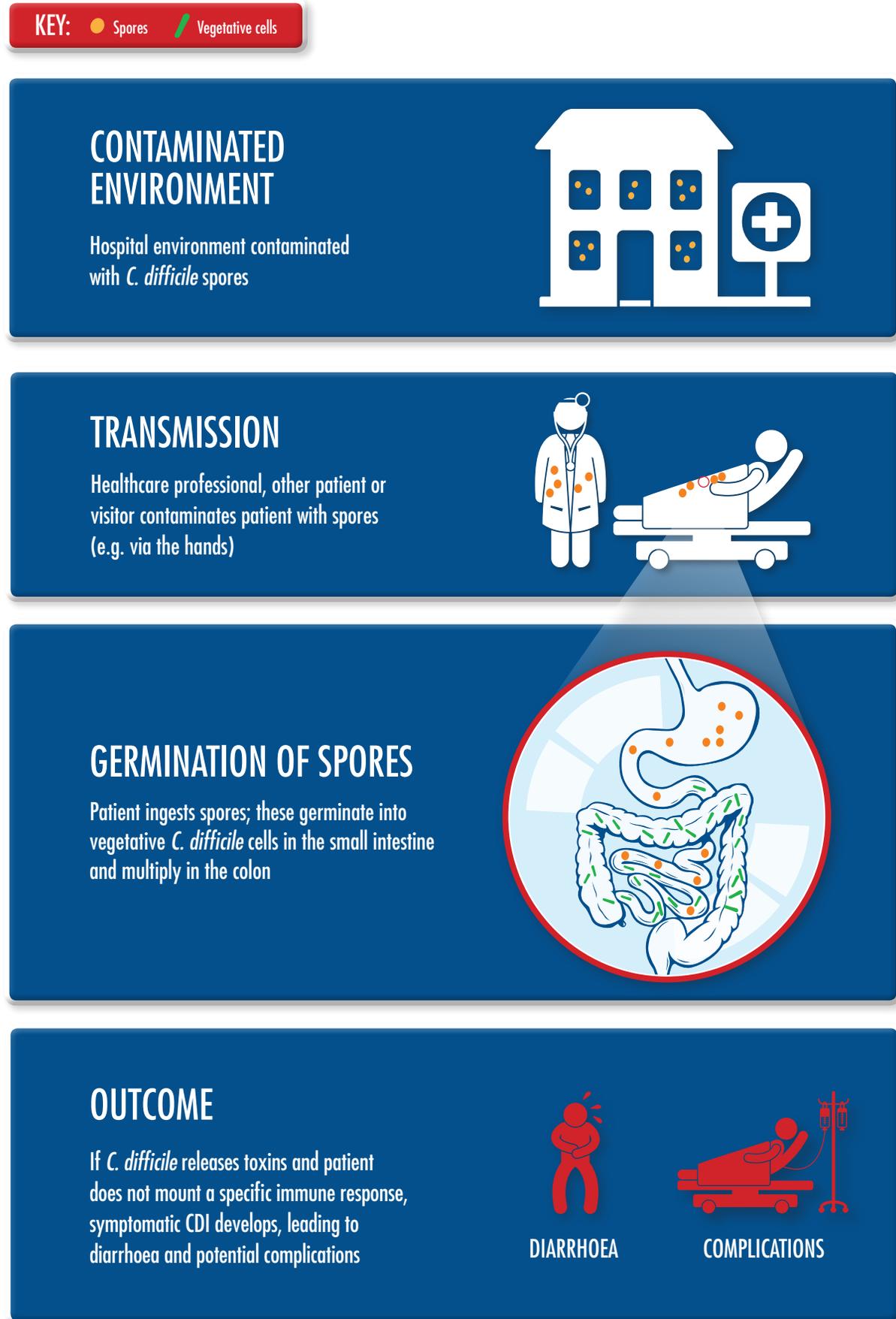
This effort is not intended to duplicate the important projects of the European Centre for Disease Prevention and Control (ECDC), i.e. the ECDC-funded European CDI Surveillance Network (ECDIS-Net) project, and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), but rather to supplement the work taking place in academic circles and further the reach of the outputs from these and other important initiatives. CDI Europe is supported by Astellas Pharma Europe Ltd.

## 1.1 How does CDI occur?

**CDI is an intestinal infection caused by the *C. difficile* bacteria:** *C. difficile* exist as active bacteria that can cause infection, and as dormant seed-like structures called 'spores'. The spores can live for months in the environment, for example on surfaces in hospitals, and can be transmitted to patients from the environment or from the hands of contaminated healthcare workers (Figure 1).<sup>2</sup> CDI develops when people swallow the spores which transform into active (or 'vegetative') bacteria in the bowel. These bacteria can then multiply and colonise the bowel, especially if bacteria that normally live there (and which protect against bowel infections) have been disrupted by the recent use of antibiotics.<sup>2</sup>

Not everyone colonised with *C. difficile* develops symptoms of CDI. Symptomatic infection can occur if the colonising *C. difficile* is of a type (or 'strain') that produces toxins that cause diarrhoea and inflammation of the large bowel, and if the patient does not mount a specific immune response against these toxins. *C. difficile* strains that do not produce toxins are not considered to cause disease (i.e. are 'non-pathogenic'), and patients who do mount an immune response against the toxins may not show CDI disease symptoms.<sup>2</sup>

Figure 1: Transmission, development and outcomes of *Clostridium difficile* infection (CDI) in the hospital.



## 1.2 How common is CDI?

**CDI can be common in some hospitals across Europe:** CDI accounts for approximately 60% of gastrointestinal infections, which in turn represent approximately 9% of all HAIs.<sup>8</sup> CDI is currently two to four times more common than HAIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA),<sup>8,9</sup> which have been a leading public health concern for many years.

It is difficult to estimate how common CDI is across Europe because of a lack of standardised national surveillance schemes. Reported CDI incidence rates vary widely, which may reflect variations in how cases are diagnosed, recorded and reported (see Section 5). As a first step in addressing this problem, the ECDC funded the large, international European CDI Study (ECDIS) in 2008.<sup>10</sup> Overall, CDI was estimated to occur in 1 in 435 hospital admissions per hospital. This figure varied markedly between hospitals and countries, from zero to one in every 36 admissions (Figure 2). Using an alternative measure, CDI was estimated to occur in approximately 4 patients per 10,000 patient-days per hospital (ranging between countries from zero to 19 patients per 10,000 patient-days).<sup>10</sup>

The number of CDI cases that occur in Europe can also be roughly estimated using data from England, where hospitals must report all CDI cases. In 2011–12, following a national programme to reduce CDI (Section 5), 18,005 cases of CDI were reported in England among individuals aged 2 years and over.<sup>11</sup> This represents 0.035% of the population,<sup>12</sup> which when extrapolated to Europe<sup>13</sup> suggests that approximately 172,000 CDI cases may occur each year across the 27 countries of the European Union (EU). Of note, the current UK incidence might not be representative across Europe. For example, CDI may be more common in countries that have not instituted national CDI campaigns.

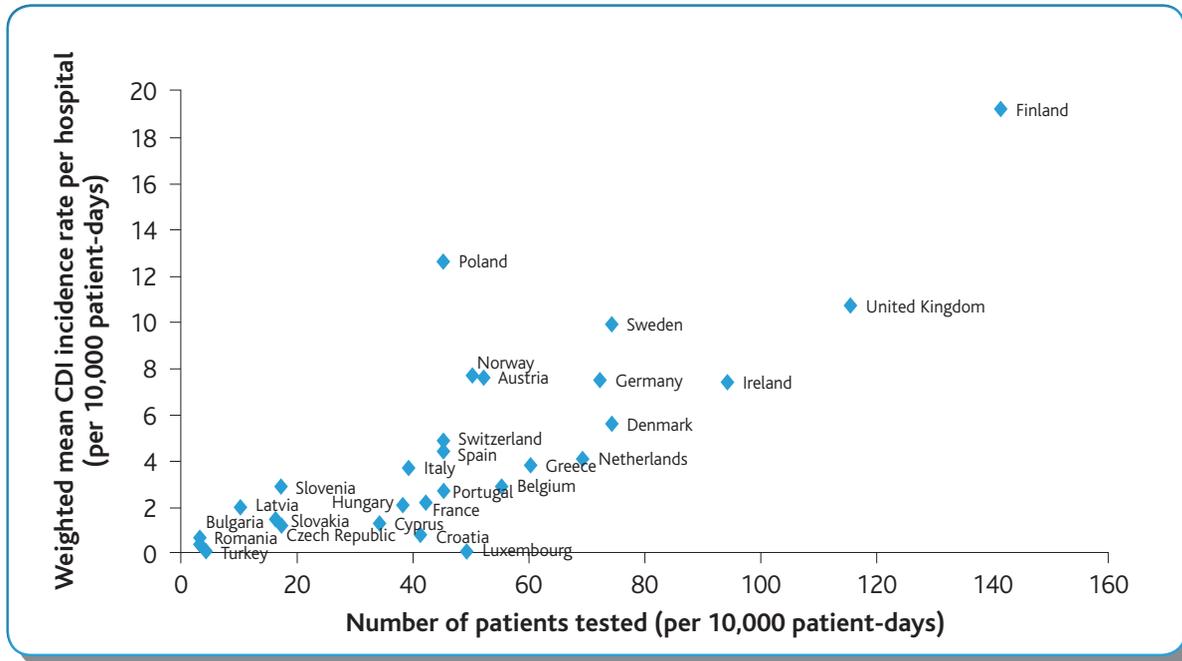
The incidence of CDI has been reported to be rising in some European countries<sup>14–17</sup> and the United States.<sup>18</sup> Moreover, in recent years there have been outbreaks across Europe of particularly severe CDI associated with increased morbidity and mortality. This has resulted from the spread of a specific type of *C. difficile* known in Europe as O27, identified using an analysis called polymerase chain reaction ribotyping.<sup>4,19</sup> Certain other 'ribotypes' found in Europe are also associated with a complicated course of CDI.<sup>10</sup> Despite this possible association between some *C. difficile* types with more severe disease and outbreaks, it is important not to focus on types, but on CDI in general.<sup>20</sup>

### DEFINING HEALTHCARE AND COMMUNITY CDI

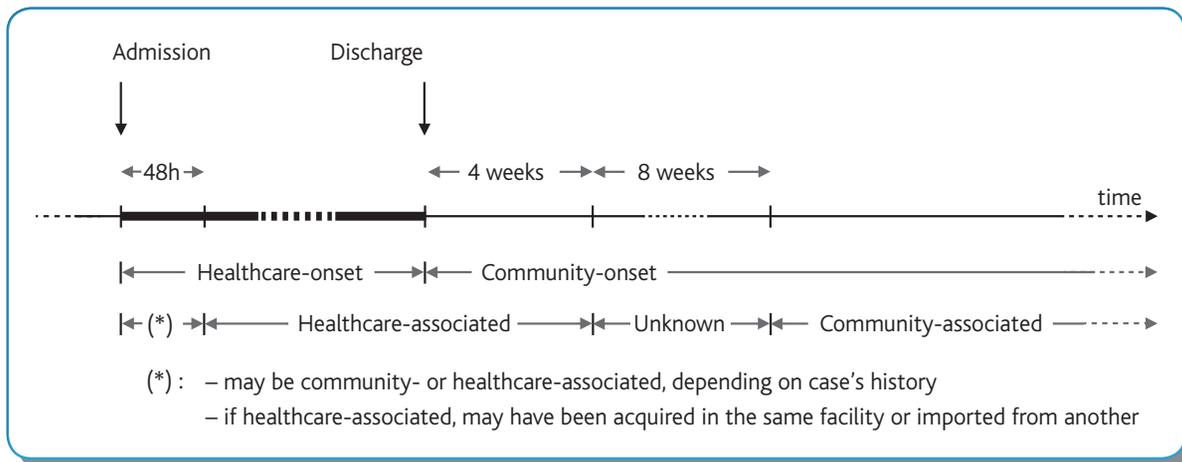
CDI usually occurs in association with the provision of healthcare. However, the site where the symptoms begin might not be the same as where the infection was acquired, because patients move between the hospital and community settings and there is a delay between *C. difficile* colonisation and symptomatic infection. For example, the onset of CDI after discharge from hospital may account for almost 2% of all re-admissions occurring within the following 12 weeks.<sup>22</sup> Therefore, CDI is defined in epidemiological studies according to where the onset of symptoms occurs (healthcare facility or community), and whether the infection is associated with the healthcare or community settings, as determined by the patient's recent admission or discharge history (Figure 3).<sup>3</sup>

- **Healthcare-onset** CDI: symptoms start during a stay in a healthcare facility
- **Healthcare-associated** CDI: symptoms start at least 48 hours after admission to, or within 4 weeks of discharge from, a healthcare facility
- **Community-onset** CDI: symptoms start in a community setting, outside healthcare facilities
- **Community-associated** CDI: symptoms begin outside a healthcare facility and without a discharge from a facility within the previous 12 weeks, or within 48 hours of admission to a facility without residence in a facility within the previous 12 weeks.

**Figure 2:** Estimated incidence rates of *Clostridium difficile* infection (CDI) in hospitals, and the frequency of CDI testing, in Europe in 2008.<sup>10</sup> This figure illustrates that CDI incidence rates are related to how many patients were tested. In general, countries that tested more patients had higher rates of CDI. Low rates of CDI appear to be related to a lack of testing for the infection.



**Figure 3:** Definitions of *Clostridium difficile* (CDI) according to its origin and site of onset.<sup>3</sup>



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**CDI is an increasing problem in the community:** Relatively few data are available on community-associated CDI because little systematic surveillance is performed in this setting. However, around 14% of cases of CDI tested in the ECDIS study were community-associated, i.e. they occurred in patients who had not been admitted to a healthcare facility in the previous 12 weeks.<sup>10</sup> Each year, approximately 20–30 cases of community-associated CDI occur for every 100,000 individuals in the population.<sup>21</sup> Some recent studies in the United States suggest that community-associated CDI is becoming increasingly common.<sup>22,23</sup> In the UK, CDI rates have decreased in recent years as a result of a comprehensive national intervention programme (see Section 5). However, the fraction of cases that were community-associated doubled from 7% in 1997/1998 to 13% in 2009/10.<sup>24</sup> In Ireland, approximately one-fifth of CDI cases are now reported to originate in the community.<sup>25</sup> Outbreaks of CDI have not yet been reported in the community in Europe, but this remains a possibility. In Australia, there was a sudden increase in community-associated CDI cases in 2011–12 caused in particular by a newly recognised strain, associated with severe infection, known as type 244.<sup>26</sup>

***In the UK, the fraction of CDI cases that were community-associated doubled between 1997/1998 and 2009/10.<sup>24</sup>***

**CDI is common in nursing homes:** Although CDI is expected to be a leading form of infection among elderly nursing home residents, little is known about this because CDI testing is not widely performed and no systematic surveillance programme is underway in this setting. In Ireland, the proportion of CDI cases occurring or originating in nursing homes has increased in recent years to 13%,<sup>25</sup> although the change in the proportion of community-attributed cases could in part reflect differences in ascertainment methods. In Germany, approximately one in 20 nursing home residents tested were colonised with *C. difficile*,<sup>27</sup> while in the Netherlands a quarter of residents in nine homes had CDI.<sup>28</sup> Living in a nursing home was an independent risk factor for CDI in another study.<sup>29</sup> Nursing home outbreaks often remain unrecognised and may even cause secondary clusters of CDI in neighbouring hospitals.<sup>28</sup>

### 1.3 Who is at risk of CDI?

The principal factors that increase the risk of CDI are well established:

- **Recent use of antibiotics:**<sup>10,29–31</sup> Patients are at a 7- to 10-fold increased risk of CDI during antibiotic therapy and for the first month after antibiotics are stopped. They remain at almost a 3-fold higher risk even at 3 months after the end of therapy<sup>30</sup>
- **Advanced age** (over 65 years):<sup>10,31</sup> Almost two-thirds of patients with CDI in the ECDIS study were aged 65 years or more<sup>10</sup>
- **Chronic underlying illness:** CDI is a particular risk in patients with kidney disease, those treated for cancer, and in other groups whose immunity against infections is compromised, e.g. owing to organ or stem cell transplantation or HIV infection<sup>32,33</sup>
- **Recent hospitalisation:**<sup>29,30</sup> Hospitalisation is important because it brings together several risk factors, including exposure to antibiotics and *C. difficile* spores and a susceptible, elderly population.<sup>2</sup> Living in a nursing home may also independently increase the risk of CDI.<sup>29</sup>

These risk factors are especially important in hospitalised patients and nursing home residents. They are also risk factors for CDI acquired in the community. However, patients with community-associated CDI are on average younger, more likely to be female and less likely to have underlying conditions than those with healthcare-associated CDI.<sup>23,29,34</sup> Importantly, up to half of patients with community-associated CDI have not recently used antibiotics, around two-thirds have not had recent hospitalisation, and up to one-third have neither had recent antibiotics nor a recent hospitalisation.<sup>21,35,36</sup> Therefore other risk factors may be important in the community, such as the use of proton-pump inhibitor drugs for the treatment of stomach acid reflux (heartburn) and stomach ulcers.<sup>37</sup> There is no conclusive evidence that *C. difficile* contamination of food has led to CDI, but further research on the implications on human health of *C. difficile* in livestock and food is needed.<sup>4,38</sup>

Given the variability in risk profiles, the possibility of CDI should therefore be considered in any patient with unexplained diarrhoea, especially in those aged 65 years or over.

***The possibility of CDI should be considered in any patient with unexplained diarrhoea, especially in the elderly.***

## 1.4 What are the clinical outcomes of CDI?

**CDI symptoms range from mild, self-limiting diarrhoea, to severe, life-threatening bowel complications** such as toxic megacolon and pseudomembranous colitis.<sup>39</sup> According to the ECDIS study, one in ten cases of CDI cause – or contribute to – intensive care unit (ICU) admission or death, or lead to surgery to remove part of the bowel (colectomy).<sup>10</sup> In a smaller study in one hospital in Austria, approximately half of patients with hospital-acquired CDI experienced at one least one complication – namely dehydration, bloodstream infection, toxic megacolon or recurrence of CDI.<sup>40</sup>

Studies in Europe and the US have documented the substantial clinical and economic burden of CDI.<sup>5,41</sup> However, no systematic national or European-wide study has yet been undertaken, and hence it is difficult to quantify the burden of CDI at these levels.

**Extended hospitalisation:** Most studies have found that CDI in hospitalised patients extends the period of hospitalisation, typically by around 6–21 days, as compared with uninfected patients matched for factors such as age and underlying illness.<sup>42–46</sup> CDI may also extend ICU stay among patients admitted to these facilities.<sup>47</sup>

**Recurrence:** Up to around 25% of patients treated for CDI have a recurrence of the infection within one to three months after treatment is completed.<sup>48–50</sup> Patients with recurrence are at higher risk for subsequent recurrences, leading to an exhausting cycle of repeated infections.<sup>39</sup>

**Death:** Between 3% and 30% of patients diagnosed with hospital-acquired CDI die within 30 days.<sup>5</sup> Many patients with CDI are already vulnerable (e.g. the elderly) and hence CDI cannot be assumed to be the primary cause of death. However, there is some evidence that hospitalised patients with CDI are up to three-fold more likely to die while in hospital or within 30 days of CDI diagnosis, independently of their age and underlying diseases.<sup>51–53</sup> The aforementioned ECDIS study found that CDI caused or contributed to 40% of deaths that occurred within 3 months of CDI diagnosis, corresponding to 9% of all diagnosed patients with CDI.<sup>10</sup> Other researchers have also found that the total mortality attributable to CDI among infected patients ranged from 0–80%, depending on the methods and definitions used.<sup>5,53</sup>

## **CDI caused or contributed to 40% of deaths that occurred within 3 months of diagnosis.<sup>10</sup>**

**Outcomes of community CDI:** CDI is a leading drug-related reason for admission to hospital.<sup>54</sup> However, there has been relatively little research into the outcomes of community-onset or community-associated CDI. Recently, US researchers retrospectively assessed the clinical outcomes among 157 patients over a 15-year period.<sup>55</sup> Community-acquired CDI was defined as that with symptom onset in the community or within 48 hours of hospital admission, provided this was more than 12 weeks after the last discharge from hospital; patients with 'intermediate CDI' with onset between 4 and 12 weeks after hospital discharge were also included. Of these patients:

- 40% required hospitalisation
- 20% had a severe infection
- 28% had recurrent CDI.<sup>55</sup>

During the aforementioned recent outbreak of community CDI in Australia, the type 244 strain of *C. difficile* was implicated in the death of up to 30% of infected patients.<sup>26</sup> This high rate of mortality needs to be confirmed and may be inflated owing to the unusual type of *C. difficile*.

Elderly patients are particularly vulnerable to poor outcomes from CDI, including hospitalisation and death.<sup>10,55–57</sup> Other patient characteristics may also predict a poor outcome, including serious underlying diseases.<sup>55,57,58</sup> However, the data are conflicting<sup>56</sup> and a robust, evidence-based tool for the prediction of severe or complicated CDI has yet to be developed and validated.<sup>59</sup>

### **1.5 What does CDI cost?**

**CDI has a considerable impact on the healthcare system:** CDI adds significantly to the costs of patient care in hospitals, primarily because it extends hospitalisation.<sup>42,44</sup> In addition to specific therapy for the infection, CDI also necessitates revised supportive therapy for underlying conditions and infection control measures such as isolation, scrupulous hygiene and environmental disinfection (Section 4).<sup>3,60</sup> In outbreak situations, wards may need to be closed to new admissions.<sup>60</sup>

Italian researchers recently estimated that, on average, CDI acquisition during hospitalisation added almost € 14,000 per patient to the cost of hospitalisation.<sup>61</sup> Studies in the UK<sup>42</sup> and Germany<sup>44</sup> estimated costs (equivalent in 2010) of £6,986 and € 7,499<sup>5</sup> respectively, while other studies have found lower attributable costs of CDI (Table 1).<sup>43,62</sup>

In 2006, an expert group convened by the ECDC and the ESCMID Study Group for *C. difficile* estimated that CDI conferred a total direct cost to the EU of approximately € 3,000 million/year.<sup>3</sup> Assuming a 3% annual inflation rate, this approximates to € 3,700 million in 2013. These costs refer to healthcare-associated CDI and do not include the additional costs of CDI community-associated and nursing home CDI, and the 'indirect' socioeconomic costs, such as those of lost productivity and social care.

Without action by Member States, the substantial burden of CDI in Europe is anticipated to increase in line with the projected growth of the elderly population. The proportion of people aged at least 65 years is expected to reach 20% by 2020 and almost 30% by 2050.<sup>63</sup>

**Table 1. Estimated attributable hospital costs of healthcare-associated *Clostridium difficile* infection.**

Country	Year of study	Average additional cost per hospitalisation
Italy <sup>61</sup>	2009–12	€ 13,958
Finland <sup>62</sup>	2007–8	€ 2,300
Germany <sup>5,44</sup>	2006	€ 7,147 (2010 equivalent: € 7,499)
Ireland <sup>5,43</sup>	2000	£ 2,860 (2010 equivalent: £ 4,577)
UK <sup>5,42</sup>	1995	£ 4,107 (2010 equivalent: £ 6,986)

## 1.6 Summary

In summary, CDI:

- Can cause a spectrum of diseases, from mild, self-limiting diarrhoea to life-threatening complications
- Can be a common HAI in hospitals across Europe and is increasingly prevalent in the community and nursing homes, although robust data are lacking
- Is associated with recent antibiotic use, advanced age, underlying illness and recent hospitalisation. However, many patients do not fall into conventional risk groups (especially in the community) and the possibility of CDI should be considered in any patient with unexplained diarrhoea
- Extends hospitalisation, and if acquired in the community setting may necessitate hospitalisation
- May contribute to 40% of deaths occurring during the 3 months after diagnosis
- Recurs despite successful therapy in up to a quarter of patients
- Adds substantial costs to hospital care, estimated at € 3,000 million in 2006 in Europe.

### 2.1 How is CDI diagnosed?

CDI is diagnosed on the basis of clinical symptoms (e.g. diarrhoea) together with evidence of toxin-producing *C. difficile* in the stool, without evidence for another cause of diarrhoea. In some cases diarrhoea is not present because the normal passage of the bowel is disrupted. The presence of an intestinal complication called pseudomembranous colitis is also considered diagnostic of CDI.<sup>39</sup>

The ESCMID recommends that tests for the presence of toxin-producing *C. difficile* in the stool should be performed in:

- Patients with potentially infective diarrhoea who have negative tests for bacteria, parasites and viruses that commonly cause intestinal infections
- All patients with diarrhoea who have been hospitalised for more than 72 hours
- Patients with diarrhoea who have been admitted to a healthcare facility within 3 months prior to diarrhoea development.<sup>1</sup>

In addition, there should be a low threshold for testing for CDI in other patients who have symptoms, e.g. those with diarrhoea during or after the use of antibiotics and those with prior CDI.

Several different types of tests may be used.<sup>1,2</sup> The standard 'reference' tests (called cell culture cytotoxic assay and toxigenic culture) are slow and labour-intensive, and require specialised facilities and expertise. Most laboratories now use tests called enzyme immunoassays (EIAs). These detect *C. difficile* toxins or glutamate dehydrogenase (GDH; a protein produced by *C. difficile*) directly in stool samples. These are simpler and quicker than the reference tests. However, they are less accurate and their use alone results in some CDI cases being missed and some patients being incorrectly reported as having CDI.<sup>64,65</sup> Newer tests detect the *C. difficile* toxin genes. These tests pick up more cases but are relatively expensive; importantly, they do not distinguish between patients carrying *C. difficile* and those with actual CDI. In order to increase the accuracy of testing the ESCMID recommends a two-step testing protocol whereby a positive result obtained using one method is confirmed by a second test using another method.<sup>1</sup>

**The ESCMID recommends a two-step testing protocol whereby a positive result obtained using one method is confirmed using another method.<sup>1</sup>**

*C. difficile* toxin may be detected in the presence of other bowel pathogens, such as norovirus infection, although a recent study performed in The Netherlands did not show a correlation of CDI with outbreaks of viral gastroenteritis.<sup>66</sup> A better understanding is needed of the possible interaction between *C. difficile* and viruses that cause intestinal infections, including norovirus.

Important deficiencies exist across Europe in both clinical and laboratory aspects of diagnosis. These deficiencies result in many cases of CDI being missed, which has important implications for patients and healthcare systems, as discussed in the following sections.

### 2.2 Clinical diagnosis: current situation

The widely varying *C. difficile* testing rates found across Europe likely explain, at least in part, why reported CDI incidence rates also vary markedly (Section 1).<sup>10</sup> A recent nationwide study in Spain found that two out of every three episodes of CDI went undiagnosed.<sup>65</sup> The main reason for this was a lack of clinical suspicion of CDI, especially in patients aged under 65 years and those with community-acquired diarrhoea. This underscores the fact that many patients do not fall into conventional high-risk groups – especially in the community setting<sup>21,35</sup> – and hence there should be a low threshold for suspicion and testing.

***In Spain, two out of every three episodes of CDI went undiagnosed.<sup>65</sup>***

Under-diagnosis and mis-diagnosis of CDI is likely to be common in other European countries. In many countries there is an inadequate level of awareness of CDI and its risk factors among doctors and other healthcare workers.<sup>67</sup> Indeed, a recent survey found that European doctors performed significantly less well than US doctors in their knowledge of CDI.<sup>67</sup>

### **WHAT HAPPENS IF CDI CASES ARE MISSED?**

Under-diagnosis or mis-diagnosis of CDI has several important implications:

- Treatment for CDI is delayed or omitted, risking severe disease and the associated complications
- Measures to prevent the spread of the infection are not instituted, risking an outbreak affecting other patients and potentially causing ward disruption or closure
- Missed cases lead to under-recognition of the incidence of the disease
- Unnecessary and costly examinations (e.g. blood tests and scans) may be used for diagnosis.

A lack of awareness of CDI among nurses and auxiliary healthcare staff<sup>68</sup> is as important as that among doctors. As these staff members are involved in the personal care of patients they have a crucial role in recognising and reporting that patients are suffering diarrhoea, and thereby triggering testing. Patients can also play a crucial role in reporting diarrhoea to healthcare staff (Section 6).

Education of healthcare workers is particularly important in specialities where CDI is most common, including units or wards caring for the elderly and patients with cancer, kidney disease and ICUs. Conversely, all healthcare staff need to be aware of the possibility of CDI in a patient with recent exposure to antibiotics in any setting.

## **2.3 Laboratory testing: current situation**

**Laboratory procedures:** Although the ESCMID recommends a two-step protocol for *C. difficile* testing,<sup>1</sup> evidence suggests that EIA tests for *C. difficile* toxins are commonly used as a single test, resulting in cases being missed.<sup>64,65</sup> A recent survey of national laboratory capacity conducted by the European *C. difficile* infection Surveillance Network (ECDIS-Net; see box) found that variety exists across Europe in practices and volume of CDI diagnostics.<sup>69</sup> Of 31 countries providing information:

- Only 10 countries (32%) had a nationally recommended diagnostic test algorithm for CDI
- Twelve (38%) used national guidelines or recommendations with selection criteria for routine laboratory testing of CDI
- Five (16%) indicated the existence of limitations for healthcare providers to request primary CDI diagnostics in their country, including financial, technical and organisational barriers
- Fifteen (48%) indicated that there was a need for training in culture of *C. difficile* in their country.<sup>69</sup>

**Education:** The enhancement of laboratory services for *C. difficile* detection requires further efforts to improve the education of laboratory staff on the optimal current testing methods. In addition to publishing guidelines for the diagnosis and treatment of CDI,<sup>1,39</sup> the ESCMID delivers educational workshops and congress symposia on CDI.

**Nursing homes and community setting:** Services for *C. difficile* testing in these settings are often limited in terms of their availability, organisation and standardisation. This must be addressed in order to improve patient care and to assess and counter the reported increase in CDI in these settings.

## EUROPEAN CLOSTRIDIUM DIFFICILE INFECTION SURVEILLANCE NETWORK (ECDIS-NET)

The ECDIS-Net is a European Centre for Disease Control and Prevention (ECDC)-funded project implemented to enhance laboratory capacity for CDI detection and surveillance in Europe ([www.ecdisnet.eu](http://www.ecdisnet.eu)). ECDIS-Net is a multidisciplinary group of scientists working in collaboration with national public health institutes. The project aims to assess national laboratory capacity across Europe and then to improve this by:

- Establishing a European nomenclature for *C. difficile* ribotypes
- Compiling a comprehensive reference collection and database of *C. difficile* strains and providing standard strains to laboratories
- Developing a European CDI surveillance protocol and implementing educational workshops and training modules on microbiological methods for testing *C. difficile*.

The ECDC contract for the funding of ECDIS-Net runs until 2014. The maintenance of such a network, and the expansion of CDI testing services in many countries through education and capacity-building, are vital to improving CDI patient care in Europe.

**Resourcing and cost pressures:** Cost pressures are expected to be a potential barrier to the improvement of CDI diagnosis in some European countries, especially where laboratory capacity is currently most limited and requires the most development.

Importantly, health managers need to be aware that the cost of improved *C. difficile* testing is expected to be offset by the benefits of prompt and accurate diagnosis – i.e. early therapy is expected to avoid complications, limit the prolongation of hospitalisation by CDI (the main cost driver) and prevent outbreaks. According to an analysis performed by the UK Health Protection Agency, the cost in England of moving from a one-step EIA testing protocol to a two-step EIA approach (in line with recommendations<sup>1</sup>) is expected to be offset by the prevention of as few as three to six CDI cases/year per laboratory,<sup>70</sup> assuming an annual average number of 4,200 tests/year<sup>64</sup> and 70 cases/year per laboratory. With regard to individual test methods, preliminary evidence suggests that the higher cost-per-test of rapid PCR tests, as compared with cheaper conventional diagnostic methods, might be offset by a reduction in length of hospitalisation among CDI-infected patients,<sup>71,72</sup> but further controlled studies are required.

***The cost of moving from a one-step testing protocol to a two-step approach (as recommended) is expected to be offset by the prevention of as few as three to six CDI cases/year.<sup>70</sup>***

Furthermore, rather than being simply a matter of economic resources, barriers to improving diagnostic services often reflect organisational problems (due to laboratories working independently and without standardised procedures) or educational deficiencies (with a lack of clinical suspicion among healthcare staff and laboratory expertise). Hence, these aspects should also be addressed in the development of services.

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**Limited data on new diagnostic tests:** Under current European licencing legislation, manufacturers do not need to provide independent data on the performance of tests for *C. difficile*. A review of the legislation regarding the approval processes for new tests is underway and it is hoped that this will require manufacturers to provide more robust data to support the clinical usefulness of new tests.<sup>73</sup> The problem of determining the accuracy of the many *C. difficile* tests available is compounded by the fact that the studies performed have often been too small to have sufficient power to distinguish between good and poor tests. A recent large study addressing this issue was used to formulate new national guidance on *C. difficile* testing in England.<sup>70</sup>

## 2.4 CDI Europe recommendations

The authors recommend the following actions to improve the diagnosis of CDI:

### *Awareness and clinical suspicion*

- *Managers of healthcare systems and institutions must be encouraged to assign a higher organisational priority to CDI in order to drive education programmes*
- *Awareness of the signs and symptoms of CDI, and the patients at high risk, needs to be improved among healthcare staff so that rates of testing and diagnosis are increased*
- *Education should encourage a low threshold of clinical suspicion for diagnostic testing. Many patients with CDI do not fall into conventional high-risk categories and a focus only on elderly patients receiving antibiotics will miss many cases, especially in the community*
- *Educational programmes should target nurses, nursing assistants/auxiliary healthcare staff, as well as doctors*
- *There is a need for research to develop and validate a system for predicting the risk of severe outcomes in patients with CDI.*

### *Laboratory diagnosis*

- *Healthcare systems must offer appropriate *C. difficile* testing services*
- **C. difficile* testing should be performed on stools from all patients presenting with healthcare-associated diarrhoea*
- *In the community, *C. difficile* tests should be considered in all patients who present to their general practitioner with diarrhoea and who have had recent antibiotic exposure, or are aged over 65 years, or have negative tests for other types of bowel infection. Further efforts are required to educate laboratories and to promote standardised testing according to guidelines*
- *Improved co-operation between hospitals, nursing homes and community healthcare providers is necessary in laboratory testing and in the interpretation and use of the results*
- *The impact of improved *C. difficile* testing on overall healthcare costs needs to be assessed. Managers should take into account potential savings, as well as benefits for patients, resulting from improved CDI management and avoidance of costly outbreaks*
- *The approval of new laboratory tests for *C. difficile* should be supported by robust evidence of their accuracy, clinical validity and cost-effectiveness compared with existing tests.*

### 3.1 How is CDI treated?

The treatment of CDI has changed little during the last three decades, although in recent years research has yielded newer therapeutic options. In 2009, the ESCMID published recommendations for treating CDI according to the severity of the infection.<sup>39</sup>

- Mild CDI that is clearly induced by antibiotic therapy which the patient is currently taking may be treated by stopping the antibiotic, where appropriate.<sup>39</sup> The patient is then observed closely and antibiotic therapy is restarted if necessary, using an agent with an antibacterial spectrum no broader than is necessary<sup>39</sup>
- Moderate or severe CDI is treated using antibiotics active against *C. difficile* in the intestines. There are few available options. If oral therapy is possible, an antibiotic called metronidazole is recommended for non-severe initial episodes and non-severe first recurrences. Vancomycin is recommended for severe episodes and second and further recurrences.<sup>39</sup> Since the ESCMID guidelines were developed a novel agent, fidaxomicin, has been approved for the treatment of CDI in adults<sup>74</sup>
- Surgery (colectomy) is recommended for complicated disease associated with perforation of the colon, lack of response to recommended antibiotics for CDI, toxic megacolon and when the bowel passage is severely disturbed with signs of bowel distension (ileus).<sup>39</sup>

The use of antibiotics to prevent CDI is not recommended by the ESCMID guidelines.<sup>39</sup>

Importantly, there has been little research into the factors that predict a poor outcome from CDI and so the current definition of severe CDI is based on assumptions about markers of disease severity.<sup>39</sup>

### 3.2 Current situation

**Compliance:** The ESCMID treatment guidelines are widely accepted by experts, although there is a lack of data on their implementation and on compliance among prescribers.

**Recurrence:** The main challenge in the treatment of CDI is recurrence of the infection after an initial response. Recurrence occurs in up to approximately 25% of treated patients,<sup>48-50</sup> and can represent either a relapse of the original infection, or a new infection.<sup>39,75</sup> The definition of recurrent CDI varies between different studies, resulting in contradicting percentages. Clinical failure of CDI treatment and recurrence are not usually thought to be caused by *C. difficile* being 'resistant' to the antibiotics used for treatment.<sup>2</sup> Recent data suggest that certain *C. difficile* subpopulations may exhibit a reduced susceptibility to metronidazole, but the clinical impact has not yet been assessed.<sup>76</sup> Rather, treatment failure may occur because the antibiotic does not reach sufficient concentration in the bowel or because an inflammatory response persists despite the removal of *C. difficile* from the bowel.<sup>39,77</sup>

**Recurrence of CDI occurs in up to 25% of treated patients.**<sup>48-50</sup>

Recurrent CDI is difficult to manage, the therapeutic options being essentially the same as those for an initial episode.<sup>39</sup> It is clear that the composition of the intestinal microbiota determines the individual risk to acquire CDI and to develop a recurrence. Subsequently, the transplantation of faeces from CDI-uninfected donors (via enemas or a nasogastric tube) has been used to restore the normal bowel flora and hence to break the cycle of recurrent CDI. This procedure has been shown to be effective and well-tolerated in small studies in patients.<sup>78</sup> Recently, a randomised study comparing a standard regimen of vancomycin versus duodenal infusion of donor faeces was stopped after an interim analysis showed that 81% of the patients treated with donor faeces infusion responded.<sup>79</sup> These results should stimulate research to other interventions targeting the intestinal microbiota to defend against CDI. Further controlled clinical trial data are necessary to assess the effect of faeces transplantation in patients who do need on-going antibiotic therapy and those who are immunosuppressed.

All healthcare staff caring for patients with CDI should be aware of the risk of recurrence so that patients who develop diarrhoea following therapy for CDI are tested and treated if necessary.

**Assessment of treatments:** Conventionally, the main endpoints used by clinical studies are clinical cure and recurrence. The time to resolution of symptoms and the time to return to normal activities are not well studied, even though these are important measures of disease burden. Crucially, the relationship between treatment options and mortality is poorly studied. Very large clinical studies would be required to show a significant difference between treatments on mortality and so using mortality to differentiate between treatments would be difficult.

**Parenteral therapy:** Oral therapy may not be possible in many patients for a variety of clinical reasons. Currently, there is a serious lack of options for parenteral therapy of CDI. At present, treatment options when oral therapy is impossible (depending on the disease severity) are limited to intravenous metronidazole and vancomycin instilled directly into the colon or given by a nasogastric tube.<sup>39</sup> Limited evidence from case reports suggests that intravenous tigecycline may be a potential treatment for severe or severe complicated CDI, but randomised controlled trials are required.<sup>80</sup>

**Special situations:** Further guidance is required for the treatment of CDI in special clinical situations, such as: moderate CDI in patients with poor prognosis (e.g. due to age or underlying illness); severe CDI (e.g. when surgery should be used); CDI in patients with inflammatory bowel disease; and in patients who are allergic to existing agents.

### 3.3 CDI Europe recommendations

The authors recommend the following actions to improve the treatment of CDI:

- *Awareness of, and compliance with, CDI treatment guidelines needs to be improved among healthcare professionals, in conjunction with education on diagnosis*
- *Further research is required to answer outstanding questions about optimal CDI treatment, in particular to establish the relative benefit of treatment options on mortality in CDI patients and to support improved guidance in special clinical cases where data are presently limited*
- *Existing guidelines should be updated when necessary in order to take account of new published data. Future guidelines should better define 'severe' CDI in order to guide therapy*
- *As new treatment options become available there is an increasing need for ways of identifying in clinical practice which patients will benefit from the available therapies*
- *The role of the microbiota in defending against CDI should be further explored with specific attention directed to new therapeutic interventions to prevent CDI or its recurrences.*

### 4.1 What is infection control?

Infection control refers to a collection (sometimes referred to as a 'bundle') of measures used to prevent and control the spread of HAIs. The following interventions are recommended for the prevention and control of CDI.<sup>60,81</sup>

**Antibiotic stewardship:** Most cases of CDI are associated with the use of antibiotics that disrupt the normal bacteria in the bowel and thereby allow *C. difficile* to flourish (Section 1). Since CDI is often an adverse effect of appropriate antibiotic use to treat or prevent infections, it cannot be completely prevented. However, good antibiotic stewardship is an important means of controlling CDI. Antibiotic stewardship in this context includes ensuring that antibiotics are used prudently, limiting the use of certain agents most frequently implicated with CDI, and stopping the use of antibiotics (other than those used to treat CDI) as soon as possible in patients with CDI. In general, the use of multiple antibiotics (either simultaneously or sequentially) and prolonged antibiotic administration should be minimised.

**Prompt and reliable diagnosis:** Prompt and reliable diagnosis of CDI (clinical and microbiological; Section 2) is essential so that infection control measures can be implemented and treatment started.

**Isolation or cohort nursing:** Where possible, patients with CDI should be isolated in a single room with a private toilet, or in isolation wards. If this is not possible, patients with CDI should be grouped in the same ward bay and cared for by designated healthcare staff. Healthcare staff should use gloves and gowns or aprons for contact with patients with CDI. Dedicated healthcare equipment should be used for patients with CDI. All reused equipment should be disinfected using agents that kill *C. difficile* spores.

**Hand hygiene:** Hand hygiene is crucial to reduce CDI transmission. While healthcare staff typically use alcohol-based hand-rubs, these are not effective in preventing CDI because these products do not kill *C. difficile* spores. Staff should therefore wash their hands carefully with soap and water before and after contact with patients with CDI or with surfaces that may be contaminated.

**Disinfection of the healthcare environment:** Infection control is particularly difficult for CDI because *C. difficile* spores can live for months in the environment and are not killed by standard disinfectants used for routine disinfection in hospitals. Regular disinfection (at least daily) using an agent that kills *C. difficile* spores is essential. Chlorine-based products (i.e. bleach) are currently recommended.

**Measures during outbreaks:** During outbreaks, all hygiene, decontamination and antibiotic stewardship measures should be reviewed and reinforced as necessary. Units or facilities may need to be closed and intensive cleaning performed.

#### FOCUS ON HAND HYGIENE

According to a global survey by the World Health Organization (WHO), healthcare workers perform hand hygiene procedures before patient contact in only half of occasions when this is required.<sup>82</sup> The WHO has issued international guidelines on hand hygiene and a multimodal hand hygiene improvement strategy – known as "Save lives. Clean your hands" – in hospitals and in outpatient care settings.<sup>83–85</sup>

Government support is a key feature for the success of hand hygiene campaigns.<sup>86,87</sup> By 2011, 22 European countries had undertaken (or were preparing) such campaigns.<sup>6</sup>

Hand hygiene programmes can contribute significantly to reducing the incidence of CDI. The national UK 'Cleanyourhands' campaign, launched in 2004, is part of a high profile framework of care bundles and legally binding organisational obligations, all driven by a political will to address high rates of CDI and other healthcare-associated infection (Section 5). Between 2004 and 2008, the campaign was associated with an increase in the procurement of soap by hospitals; in turn, this was independently associated with a reduction in cases of CDI.<sup>88</sup>

## 4.2 Current situation

**Compliance:** Compliance with existing CDI control and prevention measures is limited and variable both within and between countries. Evidence suggests that there is a pressing need to improve infection control procedures with respect to CDI in nursing homes, where compliance with recommendations may be particularly poor.<sup>89</sup>

The reasons for poor compliance with infection control measures are multifactorial and are likely to include:

- Insufficient governmental and organisational prioritisation of infection prevention and control
- A lack of education and awareness among healthcare staff
- Difficulty and inconvenience of current sporicidal regimens
- Resource and cost limitations, including general understaffing in wards and a lack of infection control personnel and isolation facilities.

**Governmental and organisational prioritisation:** Governmental support is a key determinant of the success of nationwide infection control improvement programmes, such as those designed to improve hand hygiene.<sup>86</sup> Governments need to be aware of the importance of CDI and to include this infection within a wider policy prioritisation of HAI prevention and control, in line with recommendations by the European Council (see box).<sup>90</sup>

***Governments need to be aware of the importance of CDI and to consider this infection within a wider policy prioritisation of HAI prevention and control.***

### EUROPEAN COUNCIL RECOMMENDATION ON HAI PREVENTION AND CONTROL

The European Council<sup>90</sup> recommended in 2009 that Member States should:

- Implement healthcare-associated infection (HAI) prevention and control measures at national or regional level, including national guidelines and recommendations, and encourage adherence to these measures using indicators and accreditation or certification processes
- Enhance infection prevention and control at the level of the healthcare institutions, in particular by encouraging institutions to have in place: an infection prevention and control programme; diagnostic and therapeutic procedures (e.g. antimicrobial stewardship); resource requirements; surveillance objectives; training and information for patients; appropriate organisational governance arrangements for monitoring of the programme; and appropriate organisational arrangements and qualified personnel.

There is some evidence that Europe is moving towards a higher priority for HAI prevention and control, with actions underway at European and national level.<sup>6,7,91</sup> By 2011, approximately two-thirds of European countries had a national or regional strategy in place for the prevention and control of HAI, and approximately three-quarters had legal requirements or professional guidelines for hospital-level governance of infection control (e.g. by dedicated committees) and operational infection control teams.<sup>6,7</sup> In some countries infection control has moved from being the responsibility of specialist services to being embedded within the infrastructure of healthcare provider organisations with an emphasis on the responsibility of all healthcare staff members.<sup>92</sup> Notably, in the UK, organisational prioritisation was driven by legislation that effectively conferred legally binding duties on hospital directors with regard to infection control.<sup>88</sup>

The challenge is to change the behaviour of healthcare staff in order to apply these interventions effectively and to improve patient safety. Means to help achieve this include:

- High profile, sustained, organisation-wide prioritisation of infection control at all levels of healthcare
- Positive leadership by management, with appropriate resourcing to effect change
- Cross-boundary collaboration of infection control personnel with other departments
- Infection control messages incorporated into communications throughout institutions
- Role modelling by senior staff, including the use of 'champions'
- Design of infection control systems to promote behaviour change.<sup>92</sup>

**Education and awareness among healthcare staff:** The European Council has recommended that Member States foster education and training of healthcare workers at the national or regional levels, defining and implementing specialised infection control training and/or education programmes for infection control staff and strengthening education on HAI prevention and control for other healthcare workers. Healthcare institutions should provide regular training for all healthcare personnel, including managers, on basic principles of hygiene and infection prevention and control. Advanced training should be given to personnel having particular tasks related to HAI prevention and control.<sup>90</sup> By 2011, most European countries had established, or were preparing, guidelines for HAI prevention and control.<sup>6</sup> However, less than one-half had mandatory infection training for all healthcare workers in healthcare institutions.

The European Council did not make any recommendations for particular HAIs, and the authors urge that CDI-specific interventions be included in strategic infection control and prevention programmes, allowing for cost savings and a reduction in the toll on resources. As an example, a multifaceted CDI-specific infection control bundle has been disseminated by the UK Department of Health.<sup>81</sup> CDI-specific performance indicators should also be employed. For example, the percentage of patients admitted to each hospital who contract CDI would be an important patient safety and quality performance indicator that could also drive awareness among patients. Protocols surrounding outbreak management and respective reporting also require attention and improvement. International benchmarking may be useful in helping to improve standards of infection control.<sup>92</sup>

***CDI-specific interventions should be included in strategic infection control and prevention programmes.***

## EUROPEAN COMMISSION HAI EDUCATION INITIATIVES

**Training Infection Control in Europe (TRICE):** The TRICE project aimed to update the information regarding infection control or hospital hygiene training in Europe. Of 33 countries surveyed in 2010, 88% had national recommendations for managing infection control/hospital hygiene and approximately 60% had a national curriculum or programme for doctors and nurses.<sup>91</sup> A consensus document on infection control/hospital hygiene core competencies has been approved by representatives of 33 countries. Effective dissemination and endorsement are now essential to ensure they have a positive impact.<sup>93</sup>

**Prevention of Hospital Infections by Intervention and Training (PROHIBIT):** This project aims to: 1) elucidate existing guidelines and practices to prevent healthcare-associated infections (HAIs); 2) identify factors affecting compliance; and 3) evaluate interventions.<sup>94</sup> Most European countries issue infection prevention and control programmes by law, but only seven provide funding for these and only three reported incentive schemes for additional infection control activities. Few countries reimburse costs attributable to HAIs, and none has a 'pay for performance' system.<sup>95</sup> Some countries still lack evidence-based national guidelines for preventing some HAIs, and accessing existing guidelines can be difficult.<sup>96</sup>

The WHO Patient Safety Curriculum Guide provides guidance on the content, implementation and assessment of infection control and prevention education given to healthcare staff.<sup>97</sup> Standards and performance indicators for the prevention and control of HAIs have been developed at the European level<sup>98</sup> and nationally in some countries.<sup>99</sup>

***CDI-specific measures, and associated performance indicators, should be added within national directives on HAI control and prevention.***

**Deficiencies of current sporicidal regimens:** Chlorine-based bleaches are inexpensive and have good activity against *C. difficile* spores. However they have an unpleasant odour, are corrosive, can cause respiratory irritation and have poor activity in dirty conditions, meaning that cleaning is required prior to disinfection.<sup>100,101</sup> New sporicidal agents are in development.<sup>100,102</sup> However, few data are available and the development and evaluation of new sporicidal agents is hampered by a lack of standard methods for testing their efficacy against *C. difficile* in hospital environments.<sup>101,103</sup>

Work is underway at European level to devise standard sporicidal tests.<sup>103</sup> National efforts will also contribute to this process. For example, a UK taskforce is also working toward an accepted standard test, and also aims to develop a network of laboratories for testing and a national laboratory quality assessment scheme.<sup>103</sup>

**Resourcing and costs:** Infection control measures represent an investment in care quality and patient safety, which are now key political and public priorities (see Section 7). Furthermore, these measures would be expected to reduce overall healthcare costs by avoiding the substantial economic burden due to HAIs. Further research is required to establish the cost-effectiveness of infection control interventions and thereby support decision-making within a context of shrinking resources.<sup>92</sup>

### 4.3 CDI Europe recommendations

The authors recommend the following actions to improve the control and prevention of CDI:

- *Improvements in CDI diagnosis and treatment are vital to infection control and prevention, as well as to optimise the standard of care for individual patients*
- *Policymakers need to support and communicate the need for CDI-specific interventions and guidance to be integrated within policies and initiatives on patient safety and HAI prevention and control*
- *Infection control should be a priority in all relevant aspects of healthcare management, including facility design and planning*
- *Improving compliance with infection control measures for all HAIs, among all healthcare staff, is crucial. Routine infection control should be encouraged through high-profile education and communications directed to all staff throughout institutions. Compliance should be audited regularly*
- *CDI-specific performance indicators should be assessed and used to help drive up patient safety and quality of care. Infection control data should ideally be publicly available. Sharing best practice internationally may help improve standards*
- *Specific protocols for cleaning and disinfection against *C. difficile* should be developed and implemented*
- *Infection control procedures in nursing homes need to be assessed and improved where necessary*
- *New, user-friendly disinfectants active against *C. difficile* are required. To help the development and evaluation of new agents, policymakers at European and national levels should support the introduction of standardised tests and laboratory services*
- *Further research is required to address outstanding questions regarding the sources of *C. difficile* contamination, modes of transmission, and the optimal, cost-effective means of infection prevention and control.*

## 5.1 What is disease surveillance?

Disease surveillance is used to monitor the epidemiology of HAIs and to evaluate and guide policies on their prevention and control. The objectives of CDI surveillance are to:

- Track trends in the epidemiology of CDI
- Increase nationwide awareness of CDI
- Provide feedback to units participating in CDI surveillance
- Analyse risk factors for infection
- Assess outcomes, e.g. complications, death and recurrence
- Obtain microbiological typing data to elucidate the epidemiology of CDI
- Provide data on the susceptibility of *C. difficile* to antibiotics used to treat CDI.

Collection of the following data is of particular importance:

**Incidence of laboratory-confirmed CDI:** CDI surveillance data must be based on microbiological data. While clinical diagnosis records (e.g. International Classification of Disease [ICD]-10 code records) are useful for assessing general trends, they may underestimate the incidence of CDI as compared with microbiological data.<sup>104</sup> Crucially, surveillance data are highly dependent on how cases of CDI are identified and defined, and on the laboratory methods used to confirm the diagnosis. CDI surveillance programmes therefore need to use the case definitions and microbiological methods recommended by expert groups under the auspices of ECDC and/or ESCMID.<sup>1,3</sup> These definitions are not perfect and will require ongoing refinement.

The two main measures used to estimate the frequency of a disease are its prevalence (the percentage of patients with the disease at a point in time) and incidence (the number of cases occurring in a population over a specified time period). Prevalence data provide a useful 'snapshot' of the burden of CDI, but incidence rates are more useful for assessing risk factors and outcomes, and for planning prevention programmes.<sup>105</sup>

**Distribution of *C. difficile* polymerase chain reaction (PCR) ribotypes:** Data on the distribution of ribotypes helps scientists to understand the spread of *C. difficile*. In addition, certain ribotypes (e.g. 027, 018 and 056) are associated with a higher risk of severe or complicated CDI<sup>10,19</sup> and hence the distribution of these forms provides important data on the disease burden. There is evidence that the prospective measurement of which ribotypes are causing CDI can help infection control teams to combat epidemic strains. In England and the Netherlands, the implementation of a national ribotyping service was associated with control of the epidemic *C. difficile* ribotype 027 strain,<sup>106,107</sup> and coincided with a marked reduction in the CDI incidence and related mortality.<sup>107</sup>

**Clinical outcomes:** Ideally, surveillance data on CDI epidemiology should be linked with clinical outcomes of CDI, e.g. mortality, ICU admission, surgery, death and recurrence.

## 5.2 Current situation

**Implementation and standardisation of surveillance:** The European Council recommended in 2009 that Member States should establish or strengthen HAI surveillance systems at regional, national and healthcare institution levels. Where appropriate, authorities should use the surveillance methods and indicators recommended by ECDC and the case definitions agreed at Community level.<sup>90</sup> Most European countries have now established HAI surveillance systems for public hospitals.<sup>6,95</sup> The Council did not specify which HAIs should be subject to such surveillance systems, and the authors urge that CDI should be included.

***CDI should be included within national HAI surveillance systems.***

There are marked variations between countries in the development of national-level CDI surveillance. The expert recommendations for surveillance developed under the auspices of ECDC and the ESCMID Study Group for *C. difficile* are widely accepted by experts, but the extent of their implementation within existing surveillance systems is unclear. By mid-2011, 15 European countries reported having national or regional networks for CDI surveillance.<sup>7</sup> National surveillance systems in some countries (e.g. UK<sup>70,108</sup> and Belgium<sup>34</sup>) use standardised case definitions, ribotyping services and mandatory reporting, but these features exist to various degrees in other countries (Table 2). Surveillance systems are relatively under-developed in certain Eastern Europe countries, resulting in a particular lack of data in this region. However, the fact that there are no data does not mean there is no problem.

**Table 2: Characteristics of *Clostridium difficile* infection (CDI) surveillance systems in selected European countries.**

Country	National surveillance CDI in place	Standardised methods among labs	Clinical data collected	Mandatory data reporting	Ribotyping available
Denmark	✓	✗	✓	✓	✓
France	✓	✗	✗	✓	✓
Germany	✓	✗	✗	✗	✓
Hungary	✓	✓ <sup>1</sup>	✓	✓ <sup>2</sup>	✓ <sup>2</sup>
Ireland	✓	✗	✓	✓	✗
Netherlands	✓	✗	✓	✗	✓
Slovenia	✗	✗	✗	✓ <sup>3</sup>	✓
United Kingdom	✓	✓	✓	✓	✓

Information provided by authors of this report.

<sup>1</sup> Often diagnosis is not requested.

<sup>2</sup> Selected data.

<sup>3</sup> Notifiable infectious disease (within specification of causative agents of diarrhoea).

## ECDC: EUROPEAN-LEVEL HAI SURVEILLANCE

**Antimicrobial Resistance and Healthcare-Associated Infections programme:** This aims to improve surveillance of antimicrobial resistance, antimicrobial consumption and HAI. Other roles include providing evidence-based guidance and reviews; providing training; supporting Member States activities; and co-ordinating the annual European Antibiotic Awareness Day on 18 November.<sup>109</sup>

- Healthcare-Associated Infections Network (HAI-Net): HAI-Net collects surveillance data on surgical site infections and HAIs in intensive care units (ICUs). It also co-ordinates point prevalence surveys and supports capacity building for CDI surveillance via ECDIS-Net<sup>109</sup>
- Epidemic intelligence information system (EPIS): This allows exchange of information on HAIs and antimicrobial resistance<sup>109</sup>
- ECDIS-Net: ECDIS-Net aims to enhance laboratory capacity for CDI detection and surveillance in Europe (see Section 2)
- HAIs in European Long-Term care facilities (HALT): This study surveyed HAIs in long-term facilities in 2010. A follow-up study (HALT-2) will be performed in 2013.<sup>110</sup>

**European Surveillance System (TESSy):** All EU countries submit data on communicable diseases to TESSy.<sup>111</sup> This system was launched in 2008 and its key aims are data analysis and production of outputs for public health action.

Staff responsible for identifying and reporting CDI cases must understand the importance of accurately identifying CDI cases according to standard definitions. This is especially important for staff groups among whom there is particular under-recognition of CDI. Training of laboratory staff is also crucial, as shown by educational deficiencies identified by ECDIS-Net (Section 2). Evidence from the UK illustrates the difficulty in changing laboratory practices to comply with recommendations.<sup>112</sup>

**Ribotyping:** According to an ECDIS-Net survey, 22 of 31 (71%) European countries have at least one laboratory performing typing of *C. difficile*. Typing was performed at a national reference laboratory in approximately half of countries, and in 14 (of 20) the typing was nationally/officially funded.<sup>69</sup> Eighteen countries (58%) declared a need for training in PCR-ribotyping. Therefore, the majority of countries have the capacity to perform typing for outbreaks and/or surveillance, but restrictions exist in several countries.

#### **Reporting surveillance data**

As of 2011, 17 countries reported having systems for the timely detection and reporting of CDI; data reporting was mandatory (rather than voluntary) in 12 countries.<sup>7</sup> Mandatory reporting is preferable, as this provides a more robust and transparent data set. Furthermore, mandatory surveillance helps to build public confidence in the compliance of hospitals with recommendations for infection control. However, the introduction and interpretation of mandatory data reporting, especially in conjunction with penalties for high CDI rates, may lead to conflicts of interests for institutions. The implementation of systematic surveillance is likely to increase the detection rate of CDI, owing to improvements in case recognition and laboratory diagnosis and regardless of any true change in the incidence of CDI. Hospitals reporting high CDI rates may therefore face criticism or penalties as a result of successfully implementing recommended surveillance procedures.<sup>113</sup> Local surveillance data must therefore be interpreted carefully, taking into account testing procedures<sup>114</sup> and other factors (e.g. the types of wards included).

## **NATIONAL CDI PROGRAMMES CAN REDUCE CDI: CASE STUDY FROM ENGLAND**

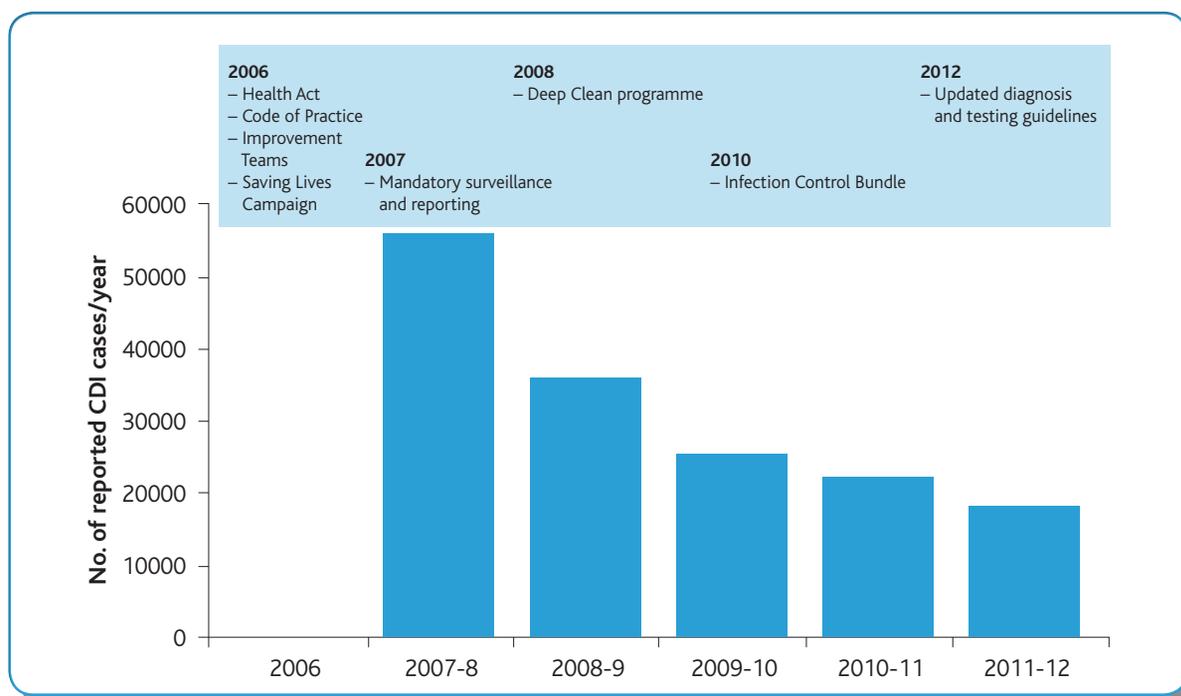
In England in 2006, 55,635 cases of CDI were reported among patients aged 65 years or older alone.<sup>11</sup> The following measures to tackle CDI were introduced from 2006 onwards as part of a suite of actions to combat healthcare-associated infections (HAIs):<sup>115</sup>

- **Legislation:** New legislation required hospital directors to ensure that infection control measures are in place, under guidance later provided by a Code of Practice.<sup>116</sup> This legislation was strongly associated with a reduction in CDI cases, as well as in the incidence of bloodstream infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>88</sup>
- **Intervention package:** A programme of interventions,<sup>115</sup> including the Cleanyourhands and Saving Lives campaigns, and visits by Department of Health improvement teams, was implemented. A specific infection control care bundle for CDI was provided in 2010<sup>81</sup>
- **Mandatory surveillance and reporting:** Since 2007, all acute hospitals in England have been required to report all cases of CDI (based on a standard case definition) in patients aged 2 years and over.<sup>11</sup> Clinical and microbiological data are submitted online and are used to produce monthly and annual statistics and epidemiological reports. In 2013, a new web-based reporting system for CDI and other HAIs will be introduced<sup>117</sup>
- **Diagnosis and testing guidelines:** In 2012, updated guidance was issued on the standard CDI case definition and laboratory testing protocols<sup>70</sup>
- **Ribotyping network:** The *C. difficile* Ribotyping Network (CDRN) is a centrally-funded network of laboratories that hospitals can access to investigate situations where there is increased frequency or severity of CDI in order to optimise management of the infection locally.<sup>108</sup> This CDRN used a similar basis to the network founded in The Netherlands in 2004, which has been expanded with continuous sentinel surveillance in 20 hospitals to monitor changes in the epidemiology and distribution of circulating polymerase chain reaction ribotypes.<sup>118</sup>

#### **Mandatory targets and achievements to date**

- All hospital trusts are given mandatory targets for CDI reduction
- The annual number of reported cases of CDI in all patients aged 2 years and over has fallen by 68% from 55,498 in 2007–2008 to 18,005 in 2011–12 (Figure 4)<sup>11</sup>
- The government has issued new CDI targets for each institution in England in 2012–13 that nationally represent a further reduction of 26% in acute hospitals and 18% in primary health providers.<sup>119</sup>

**Figure 4:** Number of reported cases of *Clostridium difficile* infection (CDI) in England (patients aged 2 years and over) during mandatory surveillance and reporting,<sup>11</sup> together with a timeline of infection control interventions.<sup>115</sup>



**Nursing home and community surveillance:** CDI surveillance data are particularly lacking in nursing homes and the community setting. No European country has yet implemented systematic national surveillance in these settings. This is important because CDI acquired in these settings: 1) can be severe and in some cases cause hospitalisation; 2) may be increasingly common in some countries, or represent an increasing proportion of total CDI cases; 3) represents a reservoir of CDI that is interrelated with hospital infection; and 4) is poorly studied with regard to its epidemiology (e.g. ribotype distribution) (Section 2). CDI in these settings is under-recognised by healthcare professionals and the public.

In England, a new mandatory surveillance scheme instituted between October 2011 and March 2012 required all Trusts to submit 10 faecal samples from patients with community-acquired CDI. Analyses will determine the ribotype distribution of the causative strains and the demographic characteristics of the infected patients.<sup>120</sup> The extension of CDI surveillance into the independent healthcare sector has also been recommended by the expert committee responsible for advising the UK government on HAIs.<sup>121</sup>

**CDI in children:** Although some studies have found high or increasing *C. difficile* positive test results in children, the clinical significance of these is unclear because children are more likely than adults to be colonised without showing CDI symptoms.<sup>4</sup> However, paediatric patients with underlying diseases are at risk of CDI.<sup>122</sup> Further research is therefore required into the epidemiology and clinical significance of CDI in children.<sup>4,73</sup>

### 5.3 CDI Europe recommendations

The authors recommend the following actions to improve CDI surveillance:

- *CDI must be considered a 'targeted infection type' for which healthcare institution surveillance should be supported at the European and national levels*
- *All European countries should institute national-level surveillance systems for hospital-acquired CDI. These should utilise standardised case definitions and laboratory tests according to current recommendations. Ribotyping services should be available, as strain typing is important for outbreak investigations. However, surveillance should not focus on certain so-called 'hypervirulent' types. Data reporting should ideally be mandatory and public. Countries setting up such systems may benefit from the experience of others that have successfully implemented and evaluated such systems*
- *Surveillance systems should be developed for community and nursing home CDI. The application of clear, standardised definitions of CDI in each setting will be important in order to provide comparable data across studies*
- *The European Commission should provide on going support for ECDIS-Net in order to facilitate European-level surveillance, involving national and international capacity building and education for CDI testing services.*

### 6.1 What does patient empowerment mean in CDI?

Patients and the general public have important roles to play in reducing the incidence and impact of HAIs, including CDI. These include:

- Reporting unexplained diarrhoea (either their own, or that of persons they are caring for) to healthcare staff so that laboratory tests for CDI can be performed, where appropriate
- Understanding the need for infection control and prevention measures (especially hand hygiene) and supporting these measures as patients, hospital or nursing visitors, or carers
- Adhering to treatment courses for CDI, especially in community
- Reporting recurrence of diarrhoea following treatment for an earlier episode
- Communicating with healthcare providers to improve health outcomes.

Informing patients and the public about CDI can help them to achieve these roles and to empower patients to make informed choices between healthcare providers based on publicly reported quality indicators.

Indeed, patient empowerment is a key aspect of the European Council's Recommendations to the Commission for improving patient safety.<sup>90</sup> According to these Recommendations, Member States should empower and inform citizens by:

- Involving patient organisations and representatives in the development of policies and programmes on HAIs and patient safety at all appropriate levels
- Disseminating information to patients on patient safety standards and measures in place to reduce or prevent errors and harm, complaints procedures, and available means of remedy and redress
- Considering the development of core competencies in patient safety, namely the core knowledge, attitudes and skills required to achieve safer care for patients.<sup>90</sup>

### 6.2 Current situation

**Public awareness about HAIs and CDI:** Members of the public in Europe recognise that there are risks associated with healthcare, and HAIs are the most widely anticipated adverse events.<sup>123</sup> According to the 2009 Eurobarometer survey:

- Nearly half of respondents felt they could be harmed by healthcare in their country
- Approximately six out of 10 respondents felt that HAIs are either fairly likely or likely to occur when receiving healthcare in their own country
- There is uncertainty about which body is responsible for patient safety.<sup>123</sup>

HAIs are repeatedly the subject of media headlines in Europe and CDI is among the leading HAIs in such coverage.<sup>95</sup> However, little is known about the public's understanding of the risk of CDI, owing to a lack of research in this area.<sup>124</sup> Limited evidence suggests there may be gaps in the public's understanding of the condition, e.g. on the link between CDI and antibiotic use.<sup>125</sup>

***Approximately six out of 10 respondents felt that HAIs are either fairly likely or likely to occur when receiving healthcare in their own country.<sup>122</sup>***

Almost half of surveyed Europeans reported that they would seek help from a lawyer if they were harmed while receiving healthcare in their own country.<sup>122</sup> The costs of litigation due to clinical negligence are a substantial and increasing drain on healthcare resources, although this may be under-recognised. In the UK, the number of litigation claims involving infections caused by MRSA – an important cause of HAIs – has decreased significantly as the incidence of these infections was driven down by national interventions. A reduction in claims involving CDI has not yet been observed.<sup>126</sup>

The European Council has recommended that Member States should provide objective and understandable information about the risk of HAIs, the measures implemented by the healthcare institution to prevent them, and how patients can help to prevent those infections.<sup>90</sup> Specific information on prevention and control measures should be given to patients who have a HAI. In 2012, the European Commission reported that there is still room for improvement in patient empowerment with regard to HAIs.<sup>6,7</sup> As CDI requires particular infection control measures, the authors urge all authorities to ensure that CDI is included in patient education.

### ***CDI should be included in patient education on HAIs.***

**CDI education programmes:** The ECDC provides some information on CDI ([www.ecdc.europa.eu](http://www.ecdc.europa.eu)) and is active in initiatives such as European Antibiotic Awareness Day. At a national level, many countries have undertaken efforts to change public attitudes and behaviour with regard to antibiotics.<sup>127</sup> Sustainably increasing awareness and knowledge levels among the public is challenging. Evaluations of educational programmes designed to change beliefs and behaviour with regard to antibiotics suggest that poster campaigns have a low likelihood of success.<sup>127</sup> Multi-faceted interventions that combine patient and physician education are more likely to be effective.<sup>128</sup> According to the Eurobarometer 2010 survey, Europeans consider television to be the main source of information regarding adverse events in healthcare, followed by newspapers and magazines, and friends and family<sup>122</sup> (Figure 5).

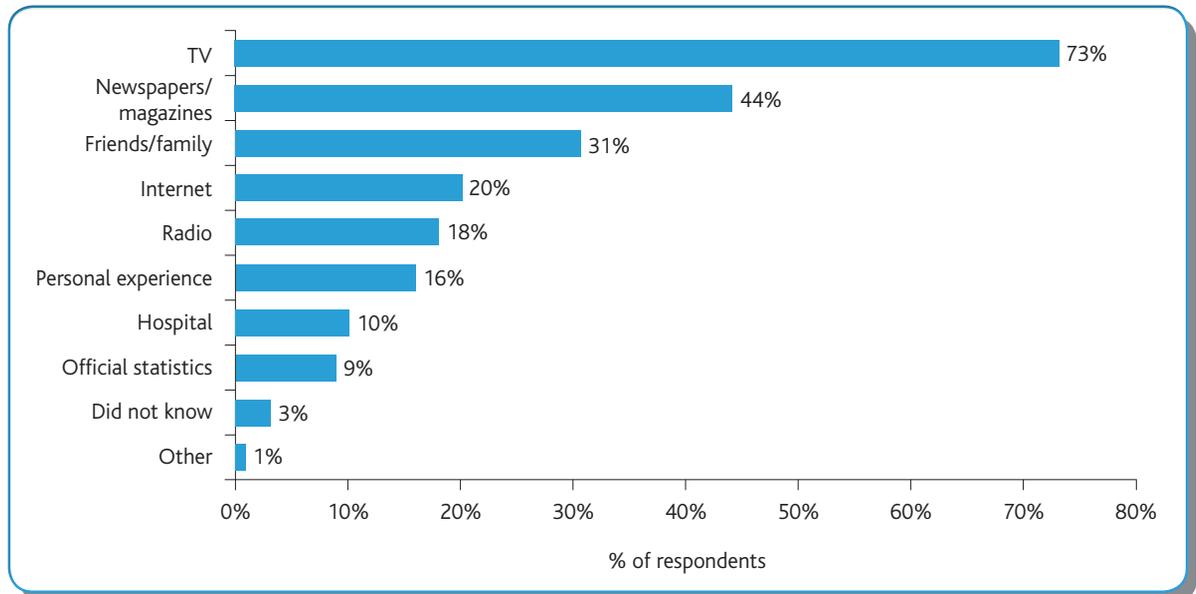
Key messages regarding CDI for patients and the public include:

- CDI is a bowel infection that can develop in some people who take antibiotics
- CDI is particularly common in elderly people
- Diarrhoea is the main symptom of CDI, although it is not always present
- In severe cases CDI can cause serious bowel problems
- Anyone with severe or prolonged diarrhoea should consult their doctor
- Patients who develop diarrhoea while in hospital should report this to a nurse or doctor
- Washing hands carefully with soap and water can help to reduce the risk of catching and spreading CDI
- Hospitals may take precautions to help control CDI and it is important to follow these if you are asked to do so as a patient or visitor.

**Patient advocacy:** Patient support and advocacy groups are active in HAI, including CDI (e.g. [www.cdifff-support.co.uk](http://www.cdifff-support.co.uk)), and these have contributed to raising infection control concerns in the media and at the political level.<sup>95</sup> However, these groups are few in number and they tend to be concentrated in a handful of countries. This may be because CDI occurs across medical specialties and in both hospital and community settings, and because awareness of the condition is limited in many countries, especially where CDI surveillance and data reporting are limited.

CDI awareness among the public could be improved by the collaboration of CDI experts with European and national-level patient organisations representing groups at particular risk of CDI (e.g. elderly, chronic kidney disease and cancer).

**Figure 5:** Sources of information regarding adverse events in healthcare.<sup>123</sup> Citizens (total 26,663) in 27 EU Member States were asked to name the three main information sources through which they heard about or found out about adverse events in healthcare.



European Union, Eurobarometer<sup>123</sup> ([http://ec.europa.eu/public\\_opinion/archives/ebs/ebs\\_327\\_en.pdf](http://ec.europa.eu/public_opinion/archives/ebs/ebs_327_en.pdf)). The European Union does not endorse changes, if any, made to the original data and in general terms to the original survey, and such changes are the sole responsibility of the author and not the EU.

### 6.3 CDI Europe recommendations

The authors recommend the following actions to develop patient empowerment with respect to CDI:

- *Measures to help improve education and awareness of CDI among the general public need to be included within public health education programmes*
- *Educational collaboration between CDI experts and patient organisations representing groups at risk of CDI should be supported at European and national levels to improve CDI awareness and encourage better communication with healthcare professionals*
- *Patients and visitors should be encouraged to comply with infection prevention precautions within hospitals and nursing homes, especially concerning patient isolation and hand hygiene.*



### 7.1 Introduction: HAIs and patient safety

The European Commission estimates that 8–12% of patients admitted to hospital suffer adverse effects while receiving healthcare.<sup>129</sup> Some effects may be minor, while others can result in permanent injury, additional and extended hospitalisations, and even death.<sup>97</sup> Poor patient safety severely compromises public health and confers a high economic burden on limited healthcare resources.<sup>90</sup> Patient safety is therefore a dominant international healthcare concern within the European Commission, the WHO and healthcare professional organisations,<sup>6,97,129</sup> and among the general public.<sup>123</sup> International efforts to improve patient safety have included the European Union Network for Patient Safety (EUNetPaS), which aimed to facilitate development of patient safety programs in Member States ([www.eunetpas.eu](http://www.eunetpas.eu)).

***"HAIs ... are among the most frequent and potentially harmful causes of unintended harm..."<sup>129</sup>***

HAIs are a leading form of healthcare-associated adverse events. ECDC has estimated that HAIs occur in one out of 20 hospitalised patients (i.e. in 4.1 million patients a year) and result in 37,000 deaths each year.<sup>90</sup> In 2008, the European Commission estimated conservatively that HAIs account for € 5,480 million in hospital costs and € 1,370 million in lost productivity among patients.<sup>130</sup> As a consequence, the prevention and control of HAIs is a principal aim of European Commission patient safety initiatives.<sup>90</sup> The proposed European Commission Health for Growth Programme for 2014–2020 also includes an objective to "reduce the burden of resistant infections and HAI".<sup>131</sup> The ongoing efforts of the European Commission to combat antimicrobial resistance, e.g. through promoting appropriate antibiotic use and surveillance of antibiotic consumption,<sup>132</sup> are also relevant to addressing the problem of CDI.

The European Council recommended in 2009 that Member States should develop a national strategy incorporating prevention and control of HAIs into national public health objectives.<sup>90</sup> Measures recommended by the Council cover HAI prevention and infection control, education of healthcare staff and patients, disease surveillance and research.

CDI is an important HAI in terms of its impact on patients and healthcare systems (Section 1) and it is a component of care quality and patient safety. Evidence suggests that CDI is at least twice as common as MRSA infections in hospitals,<sup>9,11</sup> which have been the focus of considerable concern and strategic public health interventions. Some countries (e.g. the UK) have already implemented sustained and successful national strategies specifically to control CDI. However, CDI is under-recognised within European policy on HAIs and at the national level in most EU Member States. A potential consequence of this is that necessary actions to improve the diagnosis, treatment and control of CDI, and to prepare for outbreaks of the infection, may be omitted from HAI strategies.

***CDI is at least twice as common as MRSA infections in hospitals.***

## 7.2 Integrating CDI into HAI strategies

The authors urge policymakers and other stakeholders to ensure that CDI-specific measures are included within the strategic patient safety and HAI intervention programmes at European, national and institutional levels.

***CDI-specific measures should be included within the strategic patient safety and HAI intervention programmes at European, national and institutional levels.***

Priority areas that need to be considered are:

- Organisational awareness and leadership
- Implementation and audit of measures to improve CDI diagnosis, treatment and control
- Education and training of healthcare staff and the public
- Disease surveillance
- Resourcing
- Research.

**Organisational leadership:** The European Council recommends that Member States should ensure that patient safety (in which HAIs are a central concern) is embedded as a priority issue in health policies and programmes at national, regional and local levels.<sup>90</sup> Improving management and control of CDI and other HAIs requires sustained commitment and hence this should be a long-term strategic priority for institutions.<sup>129</sup>

By 2011, approximately two-thirds of European countries had a national or regional strategy in place for the prevention and control of HAI. At the level of organisations, approximately three-quarters of countries had legal requirements or professional guidelines with respect to hospital-level governance of infection control (e.g. by dedicated committees) and operational infection control teams.<sup>6,7</sup> Fewer than half of countries encourage appropriate organisational governance of infection control and prevention in nursing homes.<sup>6</sup> Most countries with a national action plan had set up mechanisms to encourage its implementation or were in the process of doing so. These measures included mandatory reporting of indicators, certification/accreditation, regulation, and financial sanctions or incentives. However, each of these mechanisms was used only by half of the countries or fewer.<sup>7</sup>

HAIs are therefore already a leading priority for hospitals in some countries owing to political initiatives instituted in response to public concern. Indeed, legislation has been used to compel hospitals to give strategic prioritisation to HAI control and prevention.<sup>115</sup> Where these kinds of pressures are not in place, organisational leaders should be incentivised based on evidence that this is an important dimension of the quality of care that not only improves patient outcomes, but also reduces hospital costs (see below).

The use of patient safety, HAI or CDI 'champions' may be a useful approach to communicate the prioritisation of infection control and prevention throughout an organisation.

**Implementation and audit of measures to improve CDI management and control:** As of 2011, 14 European countries reported having national guidelines for CDI prevention and control in hospitals, and 13 had such guidelines for nursing homes.<sup>7</sup> Healthcare policymakers and managers should ensure that evidence-based guidelines for the diagnosis, treatment and control of CDI are implemented at national and institutional levels in all countries. These should reflect the current European guidance documents published by experts under the auspices of ECDC and/or ESCMID.<sup>1,39,60</sup> Existing national guidelines may also be helpful.

Indicators of HAI burden, including CDI, are a measure of overall patient safety and quality of care. As such, they have a broad relevance for the improvement of health services across Europe, for example with regard to the European Union Directive on patient's rights in cross-border healthcare (see box). The European Council recommended that common indicators for patient safety need to be developed through co-operation between Member States and the European Commission.<sup>90</sup> In 2011, most countries had, or were developing, HAI indicators but only six countries had established public reporting of indicators on HAI prevention and control at the hospital level.<sup>7</sup>

***Indicators of HAI burden, including CDI, are a measure of overall patient safety and quality of care.***

An international consensus project has produced European quality standards and performance indicators for HAIs.<sup>98</sup> However, these do not contain any specific standards or indicators for CDI and it is possible that this infection could be overlooked when national HAI indicators are adopted. The European Union Network for Patient Safety survey found that only one European country (the UK) included the incidence of CDI as a quality indicator.<sup>133</sup> CDI should be routinely considered a marker of care quality and hence one or more CDI measures should be included among performance indicators. Relevant indicators could include the proportion of patients admitted to hospital who develop CDI and the rate of rooms properly disinfected with a sporicidal agent after a patient's discharge.

International comparison and benchmarking may also be useful in improving the quality of care for HAI, including CDI.<sup>92</sup>

### **EUROPEAN UNION DIRECTIVE ON THE APPLICATION OF PATIENTS' RIGHTS IN CROSS-BORDER HEALTHCARE**

This aims to help patients to exercise their rights to reimbursement for healthcare received in another EU country, to provide assurance about safety and quality of cross-border healthcare, and to establish formal cooperation between health systems.

Patient safety and standards and quality of care are key criteria in this legislation. Prior authorisation of cross-border healthcare may be denied by the Member States if there are serious doubts about patient safety standards and quality care.

Member States retain responsibility for providing safe, high quality, efficient and quantitatively adequate healthcare to citizens on their territory and they may choose to limit the reimbursement of cross-border healthcare for reasons relating to the quality and safety of the healthcare provided.<sup>134</sup>

The Directive is binding and has to be transposed into national law in all Member States by 25 October 2013.

**Education and training:** The European Council recommends that patient safety be embedded in the education and training of healthcare workers, including in undergraduate and postgraduate education, on-the-job training and continuing professional development.<sup>90</sup> The European public regards well trained medical staff as the number one criterion for high quality healthcare.<sup>123</sup> The WHO Patient Safety Curriculum Guide provides comprehensive guidance to aid capacity building in patient safety education.<sup>97</sup> Although many countries have taken actions to improve infection training among healthcare staff, this remains mandatory in less than half of European countries.<sup>6,7</sup>

***“It is apparent that it is feasible to define and attain new targets in the application of EU Council recommendations provided that all stakeholders (governmental institutions, universities, health care providers, managers, professionals, patients and their advocates) are engaged and support and sustain new initiatives specifically for professional training.” ECDC-funded TRICE project (see Section 4).<sup>91</sup>***

Specifically, CDI awareness and educational levels are low in many countries. Responsible authorities must ensure that healthcare staff in hospitals and nursing homes understand the risk factors and clinical signs and symptoms of CDI and the locally applied protocols for diagnostic testing, treatment and infection prevention and control (both for isolated cases and special measures in outbreak situations). In addition, implementation of the recommended ESCMID laboratory test protocol will require specific training of laboratory staff, and associated auditing.

Education of patients and the general public may also contribute to improving CDI management and control. Nationally, key facts about CDI should be included in public health awareness and education plans. Institutions should make information available to patients and visitors, with a focus on the signs and symptoms, the risk factors, what to do if CDI is suspected and – in particular – the importance of hand hygiene.

**Disease surveillance:** Disease surveillance is essential to improving the management and control of CDI across Europe. At the European level, the activities of the ECDIS-Net to develop and co-ordinate laboratory capacity across the continent require sustained support from the European Commission. Nationally, CDI should be included as a target infection type when surveillance programmes are established or strengthened according to the European Council Recommendations. National CDI surveillance systems should use the case definitions and laboratory methods recommended by ECDC and/or ESCMID.<sup>1,3,39</sup>

**Resourcing:** The European Council recommends that Member States should allocate the necessary resources for implementing the components of a national strategy on patient safety as part of the core funding for healthcare delivery.<sup>90</sup> With regard to CDI, resourcing includes the costs of training healthcare professionals and the public, CDI laboratory testing according to current recommendations, recruitment of specialist infection control staff and infection control facilities and measures (e.g. isolation facilities and recommended cleaning protocols).

As of 2011, only five European countries reported having legal requirements for a dedicated hospital budget for infection control and prevention.<sup>6</sup> Resourcing decisions are especially challenging in an era when healthcare budgets are already under pressure and there are many competing demands. However, the European Commission has estimated that the implementation of national HAI prevention and control strategies should be highly cost effective owing to reductions in HAI incidence and associated costs. Strengthened co-operation with Member States and other bodies, supported by ‘soft law’ instruments such as a Commission Communication<sup>129</sup> and Council Recommendation,<sup>90</sup> was anticipated to reduce the incidence of HAIs by 20% and to save € 1.1 billion in hospital costs and €274 million in productivity costs (see Table 3).<sup>130</sup> There is a need for further evaluation of the economic impact of infection control interventions and systems.<sup>92</sup>

**Table 3. Estimated impact of EU policy actions on costs of healthcare-associated infections (HAIs) in Europe.<sup>130</sup>**

Policy action	Reduction in HAI		Public health expenditure	Productivity costs	Cost of employing infection control staff*
	%	Cases			
Status quo			€ 5.48 billion	€ 1.37 billion	
Limited adoption	↓5%	↓225,000	↓ by €274 million	↓ by €68.5 million	↑€80 million
Greater adoption	↓20%	↓900,000	↓€ 1.10 billion	↓€274 million	↑€363 million

\*Note: Costs of surveillance and improved infrastructure were not provided.

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**Research:** Although much research into CDI has been performed in recent years, further research is needed to address outstanding questions relating to:

- How infection develops. The reasons why some *C. difficile* strains are more likely to spread and/or cause severe disease remain unclear. For example, there are many outstanding questions regarding the role of *C. difficile* spores and toxins, and that of the patient's own immune system. It is important to unravel these issues as this may lead to better treatment options and more rational use of the available drugs. Recent progress in developing powerful new typing techniques, in particular whole genome sequencing, should improve our understanding of how strains evolve and spread. Preliminary results indicate that the spread of *C. difficile* within hospitals may be more complicated than previously thought, possibly involving individuals who carry *C. difficile* in the intestinal tract asymptomatically<sup>135</sup>
- Epidemiology, including the patterns and clinical significance of particular ribotypes and the implications of CDI in livestock and food
- Mechanisms of *C. difficile* transmission in the community
- CDI diagnosis, e.g. development of more rapid, accurate and convenient laboratory tests, and tools for predicting severe/complicated disease
- CDI treatment, e.g. randomised, controlled trials with additional endpoints to better evaluate treatment effect on morbidity (e.g. time to symptom control) and mortality
- Infection control, to establish the effectiveness and cost-effectiveness of infection control interventions.

These areas should be considered for inclusion in future European Commission research programmes.

### 7.3 Conclusions

The European Commission is leading the development and implementation of European- and national-level strategic actions to improve patient safety through better control and prevention of HAIs. However, the importance of addressing CDI specifically is not recognised in these activities and this reflects a widespread under-appreciation of the burden of CDI and the opportunities for addressing this.

CDI is a component of care quality and patient safety and the authors urge health policy makers and healthcare system managers to:

- Recognise the need to address the deficiencies that exist in many European countries with regard to CDI diagnosis, treatment, control and surveillance (see recommendations)
- Ensure that CDI is taken into account during the development and implementation of international and national programmes for improving HAI control and prevention, with inclusion of CDI-specific measures as necessary
- Recognise that investing in better detection and management of CDI represents an investment in the quality of patient care, and that the costs are expected to be offset by savings in overall healthcare costs in addition to the reduced burden of illness among patients.

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## Summary of CDI Europe recommendations

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### Diagnosis

#### Awareness and clinical suspicion

*Managers of healthcare systems and institutions must be encouraged to assign a higher organisational priority to CDI in order to drive education programmes.*

*Awareness of the signs and symptoms of CDI, and the patients at high risk, needs to be improved among healthcare staff so that rates of testing and diagnosis are increased.*

*Education should encourage a low threshold of clinical suspicion for diagnostic testing. Many patients with CDI do not fall into conventional high-risk categories and a focus only on elderly patients receiving antibiotics will miss many cases, especially in the community.*

*Educational programmes should target nurses, nursing assistants/auxiliary healthcare staff, as well as doctors.*

*There is a need for research to develop and validate a system for predicting the risk of severe outcomes in patients with CDI.*

#### Laboratory diagnosis

*Healthcare systems must offer appropriate *C. difficile* testing services.*

**C. difficile* testing should be performed on stools from all patients presenting with healthcare-associated diarrhoea.*

*In the community, *C. difficile* tests should be considered in all patients who present to their general practitioner with diarrhoea and who have had recent antibiotic exposure, or are aged over 65 years, or have negative tests for other types of bowel infection. Further efforts are required to educate laboratories and to promote standardised testing according to guidelines.*

*Improved co-operation between hospitals, nursing homes and community healthcare providers is necessary in laboratory testing and in the interpretation and use of the results.*

*The impact of improved *C. difficile* testing on overall healthcare costs needs to be assessed. Managers should take into account potential savings, as well as benefits for patients, resulting from improved CDI management and avoidance of costly outbreaks.*

*The approval of new laboratory tests for *C. difficile* should be supported by robust evidence of their accuracy, clinical validity and cost-effectiveness compared with existing tests.*

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### Treatment

*Awareness of, and compliance with, CDI treatment guidelines needs to be improved among healthcare professionals, in conjunction with education on diagnosis.*

*Further research is required to answer outstanding questions about optimal CDI treatment, in particular to establish the relative benefit of treatment options on mortality in CDI patients and to support improved guidance in special clinical cases where data are presently limited.*

*Existing guidelines should be updated when necessary in order to take account of new published data. Future guidelines should better define 'severe' CDI in order to guide therapy.*

*As new treatment options become available there is an increasing need for ways of identifying in clinical practice which patients will benefit from the available therapies.*

*The role of the microbiota in defending against CDI should be further explored with specific attention directed to new therapeutic interventions to prevent CDI or its recurrences.*

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**Infection control and prevention**

*Improvements in CDI diagnosis and treatment are vital to infection control and prevention, as well as to optimise the standard of care for individual patients.*

*Policymakers need to support and communicate the need for CDI-specific interventions and guidance to be integrated within policies and initiatives on patient safety and HAI prevention and control.*

*Infection control should be a priority in all relevant aspects of healthcare management, including facility design and planning.*

*Improving compliance with infection control measures for all HAIs, among all healthcare staff, is crucial. Routine infection control should be encouraged through high-profile education and communications directed to all staff throughout institutions. Compliance should be audited regularly.*

*CDI-specific performance indicators should be assessed and used to help drive up patient safety and quality of care. Infection control data should ideally be publicly available. Sharing best practice internationally may help improve standards.*

*Specific protocols for cleaning and disinfection against *C. difficile* should be developed and implemented.*

*Infection control procedures in nursing homes need to be assessed and improved where necessary.*

*New, user-friendly disinfectants active against *C. difficile* are required. To help the development and evaluation of new agents, policymakers at European and national levels should support the introduction of standardised tests and laboratory services.*

*Further research is required to address outstanding questions regarding the sources of *C. difficile* contamination, modes of transmission, and the optimal, cost-effective means of infection prevention and control.*

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**Surveillance**

*CDI must be considered a 'targeted infection type' for which healthcare institution surveillance should be supported at the European and national levels.*

*All European countries should institute national-level surveillance systems for hospital-acquired CDI. These should utilise standardised case definitions and laboratory tests according to current recommendations. Ribotyping services should be available, as strain typing is important for outbreak investigations. However, surveillance should not focus on certain so-called 'hypervirulent' types. Data reporting should ideally be mandatory and public. Countries setting up such systems may benefit from the experience of others that have successfully implemented and evaluated such systems.*

*Surveillance systems should be developed for community and nursing home CDI. The application of clear, standardised definitions of CDI in each setting will be important in order to provide comparable data across studies.*

*The European Commission should provide ongoing support for the European CDI Surveillance Network (ECDIS-Net) in order to facilitate European-level surveillance and national and international capacity building and education for *C. difficile* testing services.*

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**Patient empowerment**

*Measures to help improve education and awareness of CDI among the general public need to be included within public health education programmes.*

*Educational collaboration between CDI experts and patient organisations representing groups at risk of CDI should be supported at European and national levels to improve CDI awareness and encourage better communication with healthcare professionals.*

*Patients and visitors should be encouraged to comply with infection prevention precautions within hospitals and nursing homes, especially concerning patient isolation and hand hygiene.*

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