



National European guidelines for the prevention of *Clostridium difficile* infection: a systematic qualitative review

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SUMMARY

Background: *Clostridium difficile* is the most frequent infectious cause of nosocomial diarrhoea and a major topic in infection prevention.

Aim: To overview current national European guidelines for *C. difficile* infection (CDI) prevention and review the recommendations in respect of their evidence base and conformity to each other and the European Centre for Disease Control and Prevention (ECDC) guidance.

Methods: In 34 European countries, the ECDC healthcare-associated infection (HCAI) surveillance National Contact Points and other HCAI experts (NCPs) were invited to complete an online questionnaire and to supply their guidelines. Guidelines not available in English, French or German were translated into English. For the qualitative analysis, a matrix with key measures based on the 2008 ECDC guidance was established. The review process was conducted independently by two reviewers.

Results: All 34 NCPs responded to the questionnaire and supplied 15 guidelines in total. Six of 34 (18%) countries reported having used the ECDC guidance as a basis for the development or revision of their national guideline. There was wide variation in the scope and detailing. Only six of the documents and the ECDC guidance supplied a rating for the strength of recommendations. The rating systems varied in how the categories were defined. Furthermore, the stated strength for similar measures varied across different guidelines.

Conclusion: The ECDC guidance has not yet had a strong influence on the development or revision of national CDI prevention guidelines. One possible explanation for the variations is the necessity to adapt recommendations to national conditions. The use of internationally recognized instruments for the development of guidelines could help to improve their quality. Recommendations about monitoring or auditing the implementation would make them more useful.

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Introduction

In the last decade, large outbreaks with *Clostridium difficile* occurred in Canada and the USA with an increasing incidence of severe *Clostridium difficile* infection (CDI).^{1–3} *C. difficile* was soon recognized as an emerging pathogen in other regions of the world, particularly in Europe.^{4–8} *C. difficile* is now the most frequent infectious cause of nosocomial diarrhoea and a major topic in infection prevention and control (IPC).

The increased prevalence of *C. difficile* promoted the development of new national infection prevention programmes. The UK initiated public reporting of CDI cases by individual hospitals. In Germany, reporting severe cases to healthcare authorities has been mandatory. Many countries developed or revised their national guidelines for the prevention of CDI and in 2008 the European Centre for Disease Control and Prevention (ECDC) initiated the release of a European guidance to limit the spread of *C. difficile*.⁹ This guidance was based on a systematic review, an assessment of the quality of evidence using the Oxford Center for Evidence Based Medicine criteria, and reported the strength of recommendation using the Healthcare Infection Control Practices Advisory Committee (HICPAC) categories. Although the evidence supporting the IPC measures was generally poor, the authors of the guidance identified approximately 40 recommendations on different aspects of CDI prevention. The ECDC recommended using the guidance as a reference either to revise existing documents or to develop new national guidelines for CDI prevention.⁹

Our study aimed: (i) to provide an overview of national and subnational CDI guidelines in Europe; (ii) to assess the effect of the ECDC guidance on national guidelines; and (iii) to compare a number of core recommendations in terms of content, evidence, and strength of recommendation. The study was conducted by the Prevention of Hospital Infection by Intervention and Training (PROHIBIT) consortium, a framework 7 project (FP7) funded by the European Commission (Grant agreement no.: 241928).

Methods

The design was a systematic structured and qualitative review of national guidelines on prevention of nosocomial CDI. The ECDC Healthcare-Associated Infections (HCAI) surveillance National Contact Points and other HCAI experts (NCPs) from a total of 34 European countries (27 EU member states, with the UK comprising four countries, plus Switzerland, Norway, Croatia and Iceland) were invited to complete an online questionnaire about available national or subnational CDI prevention guidelines. The NCPs were also asked whether or not the documents were based on the ECDC guidance, and to send documents in print or, if available, provide the link to the web page for accessing the documents electronically.

Guideline selection

National guidelines were defined as documents published by a nationally recognized committee such as the Working Party on Infection Prevention (WIP) in The Netherlands or by a public institution such as the Robert Koch Institute (RKI) in Germany or the US Centers for Disease Control and Prevention (CDC). All

guidelines published before 31 March 2011 were eligible for inclusion and the most recent version was analysed. The sections with the specific recommendations, the definitions used for the quality of evidence, and the definitions for strength of recommendation were translated into English if the documents were written in a language other than English, French, or German. Translations were sent to the NCPs for revision and approval.

Qualitative analysis of recommendations

To identify similarities, differences, and potential conflicts among the national CDI prevention guidelines, full text was analysed using NVivo, a qualitative research software programme (Version 8, QSR International Pty Ltd, Doncaster, Victoria, Australia). Using the ECDC guidance as a reference, this software allowed the production of a matrix of over-arching topics, including surveillance, use of medical devices, environmental cleaning, education and feedback, diagnostics, hand hygiene issues, isolation precautions, and the role of antibiotic stewardship.⁹ Recommendations were grouped by topic. If new topics were identified during the review process, the matrix was adapted accordingly. The reviews were done by a trained reviewer (E.K.) and validated by independent cross-checking by a second reviewer (M.M.). Consensus was obtained by discussion or, in case of disagreement, with the help of a third expert (M.D.).

Results

The response rate from the NCPs was 100% with reports from 18 countries of having issued a national guideline for CDI prevention: Austria (AT, 2007), Belgium (BE, 2008), Denmark (DK, 2011), Finland (FI, 2009), France (FR, 2010), Germany (DE, 2009), Ireland (IE, 2008), Italy (IT, 2009), Latvia (LV, 2007), Luxembourg (LU, 2007), Malta (MT, 2008), The Netherlands (NL, 2006), Sweden (SE, 2006), Switzerland (CH, 1995), UK England (UK-E, 2008), UK Northern Ireland (UK-NI), UK Wales (UK-W), and UK Scotland (UK-Sc, 2009).^{10–25} One statement was withdrawn by an expert after the survey had been completed. Six guidelines were based on the ECDC guidance according to the NCP for the respective countries.

All guidelines were web-based and potentially accessible by Internet. However, extensive search was needed to obtain some of the documents due to language barriers and because some websites were difficult to navigate. All guidelines were published exclusively in their countries' language, except the document from The Netherlands, which was also available in English. Five guidelines had to be translated from the original language into English (DK, FI, IT, LV, SE) in order to be reviewed. The study team was skilled in all of the languages used in the other documents.

Guideline descriptions

Northern Ireland and Wales followed the English guideline, which was an update of a previous guideline dating from 1994. These three countries were combined and designated 'UK'. Scotland published its own guideline in 2009 as a revision of a document from 2008. Malta did not have a national guideline but reported following US guidelines such as the Society for Healthcare Epidemiology of America/Infectious Diseases Society

Table 1

Concordance of recommendations in national European guidelines with IA-ranked recommendations in the ECDC guidance (PROHIBIT study group)

Country (publication year)	No 'test of cure'	Education of staff	Information for visitors	Do not share thermometers (medical devices in general)	Avoid electronic thermometers with disposable sheaths	Stop AB treatment as soon as possible
ECDC (2008)	Rec. (IA; 1a)	Rec. (IA; 1a, 2b, 4, 5)	Rec. (IA; 1a, 2b, 4, 5)	Rec. (IA; 1b, 2b); (pat. specific IB)	Rec. (IA; 1b, 2b)	Rec. (IA; 1a)
Austria (2007)	Rec. (IA)	Rec. (IA)	Education in outbreaks	Rec. IA [pat. specific (IB)]	Not explicitly mentioned	Rec. (IA)
Belgium (2008)			Rec.	Rec.	Not explicitly mentioned	Rec.
Denmark (2011)			Rec.	Avoid rectal thermometer (pat. specific)	Not explicitly mentioned	
Finland (2009)	Rec.	Rec.		Rec. (pat. specific)	Not explicitly mentioned	Rec.
France (2010)	Rec.		Rec.	Rec. (pat. specific)	Not explicitly mentioned	
Germany (2009)	Rec.	Rec.		Rec. (pat. specific)	Not explicitly mentioned	Rec.
Ireland (2008)	Rec.	Rec.	Rec.	Rec. (pat. specific)	Not explicitly mentioned	Rec.
Italy (2009)	Rec. (IA)	Rec. (IA)	Rec. (IA)	Rec. (IA) (pat. specific)	Rec. (IA)	Rec. (IA)
Latvia (2007)			Rec.	Rec. (pat. specific)	Not explicitly mentioned	
Luxembourg (2007)				(Pat. specific)	Not explicitly mentioned	Rec.
Malta (SHEA 2008)	Rec. (B-III)	Rec. (B-III)	Rec. (B-III)	Rec. (B-III) (pat. specific)	Not explicitly mentioned	
Netherlands (2006)				(Pat. specific)		
Sweden (2006)				(Pat. specific)		Rec.
Switzerland (1995)				(Pat. specific) (B)		Rec. (B)
UK – England (2008)		Rec. (B)	Rec. (A)			
UK – Scotland (2009)	Rec. (IA)	Rec. (IA)	Rec. (IA)	Rec. (IA) [single use (IB)]	Rec. (IA)	Rec. (IA)

ECDC, European Centre for Disease Control and Prevention; PROHIBIT, Prevention of Hospital Infection by Intervention and Training; Rec., recommended; Pat., patient; AB, antibiotic; blank box, no statement identified for this measure.

Strength of recommendation indicated in parentheses. For the ECDC guidance, the strength of recommendation and the quality of underlying evidence are indicated.

Table II
Concordance of recommendations in national European guidelines for a selection of measures (PROHIBIT study group)

Country (publication year)	Placing of patients		Environmental disinfecting agent	Hand hygiene		Surveillance
	Single room isolation	Cohorting		Wearing of gloves	Washing or disinfecting	
ECDC (2008)	Rec. (IB; 1b, 2b)	Possible (IB; 1b, 4)	Chlorine-based (IB; 2b, 2c, 4)	Rec. (IB; 2a, 2b, 2c)	Washing (IB; 2a, 2b, 2c)	Rec. (IB; 2b, 3b, 4, 5)
Austria (2007)	Rec. (IB)	Possible (IB)	Sporicidal (IA)	Rec. (IB)	Disinfecting then washing (IB)	Rec. (IB)
Belgium (2008)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	Rec. (mandatory)
Denmark (2011)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	
Finland (2009)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	Rec.
France (2010)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	Rec.
Germany (2009)	Rec.	Possible	H ₂ O ₂ or chlorine	Rec.	Disinfecting then washing	Rec.
Ireland (2008)	Rec.	Possible	Chlorine-based	Rec.	Only washing	Rec. (mandatory)
Italy (2009)	Rec. (IB)	Possible (IB)	Chlorine-based (IB)	Rec. (IB)	Only washing (IB)	Rec. (IB)
Latvia (2007)	Rec.	Possible	Chlorine-based	Rec.	Washing or disinfecting with chlorhexidine	
Luxembourg (2007)			Chlorine-based	Rec.	Only washing	Rec.
Malta (SHEA 2008)	Rec. (B-III)	Possible	Chlorine-based (B-II)	Rec. (A-I)	Only washing (B-III)	Rec. B-III
Netherlands (2006)	Rec.	Possible	Not specified	Rec.	Only washing	
Sweden (2006)	Rec. (I)	Possible	Peracetic acid	Rec.	Washing then disinfecting (I)	
Switzerland (1995)	Rec.		Mechanics of cleaning more important	Rec.	Disinfecting or washing with antiseptic soap	
UK – England (2008)	Rec. (B)	Possible	Chlorine-based (B)	Rec. (B)	Washing then disinfecting (B)	Rec. (B) (mandatory)
UK – Scotland (2009)	Rec. (IB)	Possible (IB)	Chlorine-based (IB)	Rec. (IB)	Only washing (IB)	Rec. (IB) (mandatory)

PROHIBIT, Prevention of Hospital Infection by Intervention and Training; ECDC, European Centre for Disease Control and Prevention; SHEA, Society for Healthcare Epidemiology of America; Rec., recommended; blank box, no statement identified for this measure.

Strength of recommendation indicated in parentheses. For the ECDC guidance, the strength of recommendation and the quality of underlying evidence are indicated.

Table III

Categories of strength of recommendation and underlying levels of evidence in national European *Clostridium difficile* infection prevention guidelines (PROHIBIT study group)^a

Level of evidence	Country and category of strength													
	Malta (SHEA/IDSA)			ECDC, Austria, Scotland, Italy					England			Sweden		
	A	B	C	IA	IB	IC	II	UI	A	B	C	I	II	III
Meta-analysis or systematic reviews									X					
Randomized controlled trials	X			X					X					
Well-designed studies	X	X		X						X		X		
Suggestive studies					X		X			X			X	
Case–control and cohort studies		X		X	X					X				
Case reports; descriptive studies			X										X	
Theoretical rationale					X		X				X			X
Expert consensus			X							X	X			
Legal regulations						X				X				
Unresolved question								X						

PROHIBIT, Prevention of Hospital Infection by Intervention and Training; SHEA/IDSA, Society for Healthcare Epidemiology of America/Infectious Diseases Society of America; ECDC, European Centre for Disease Control and Prevention; UI, unresolved issue.

^a Table adapted from Cookson et al.²⁶

of America (SHEA/IDSA) guideline 'Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals' published in October 2008.²⁰ For Germany, no official guideline was issued by the healthcare infection advisory board (KRINKO) until March 2011. The German document included in this analysis is a recommendation published by the Robert Koch Institute (RKI).¹⁵

In total, 17 guidelines were analysed: 15 national European guidelines, the SHEA/IDSA guideline, and the ECDC guidance. The scope and structure of guidelines varied, ranging from a synopsis covering a few web pages to book-like compendia more than 100 pages in length. Most of the guidelines were published or revised between 2005 and 2010. The oldest document (Switzerland) dated back to 1995, whereas 10 guidelines had been published in 2008 or later. Of these, five national CDI guidelines (BE, DK, FI, IT, UK-Sc) were reported to be based on the ECDC guidance, which was published in the journal *Clinical Microbiology and Infection* in May 2008. The Austrian guideline was claimed to have been based on the ECDC guideline, but was published in December 2007. The SHEA/IDSA guideline and four European guidelines (DE, FR, IE, UK) were issued in 2008 or later, but did not refer to the ECDC guidance.

Comparison of recommendations

Four ECDC recommendations were given the highest strength of recommendation 'IA': (1) 'Do not perform a "test of cure" after treatment'; (2) 'Everyone who enters a patient's room/environment, including healthcare workers and visitors, should be educated about the clinical features, transmission and epidemiology of CDAD [*C. difficile*-associated diarrhoea]'; (3) 'Thermometers should not be shared and use of electronic thermometers with disposable sheaths should be avoided'; and (4) 'Stop any (non-*Clostridium difficile*) antimicrobial treatment in a patient with CDAD as soon as possible'. Table I summarizes how these IA recommendations were addressed by the national European guidelines. Half of the guidelines discouraged a 'test of cure', which is stool sampling or a rectal swab at the conclusion of CDI treatment. Staff education is recommended in eight of the 16 European guidelines, and

providing information to visitors is recommended in 10. Almost all guidelines recommend that medical devices should be dedicated to a single CDI patient, with some documents explicitly mentioning thermometers in this context. However, only two guidelines specifically discourage electronic thermometers with disposable sheaths. Almost all guidelines discuss the issue of terminating antibiotics in CDI. Interestingly, only three of the four IA recommendations in the ECDC guidance are also mentioned in the SHEA/IDSA document, published in the same year as the ECDC guidance (2008), and all of the recommendations received the ranking of B-III. 'B' indicates the second strongest recommendation category and the roman numeral 'III' indicates that these recommendations are based on a low level of evidence. The UK guideline ranks all of the concordant recommendations as 'B'.

There was a high level of agreement for some of the recommendations across all analysed guidelines such as placing CDI patients in single rooms, and using gloves for patient care (Table II). The strength of these recommendations was predominantly intermediate across the different guidelines. Only minor variations were detected among the documents based on the ECDC guidance and those published after 2008 (Table II).

Grading and strength of recommendation

The SHEA/IDSA document, the ECDC guidance and five of the 15 national European guidelines used a grading system for the strength of recommendation. Among the guidelines, there was variation in how 'strength of recommendation' was defined, and in how the quality of scientific evidence was appraised (Table III). The ECDC guidance not only indicates the strength of recommendation but also reports the quality of evidence of all individual publications, on which a recommendation is based (e.g. 'Do not perform a "test of cure" after treatment' indicated with IA [strength of recommendation], 1a [quality of evidence] and the citation number of the underlying publication). The quality of evidence is defined according to the Oxford Centre for Evidence-Based Medicine standards, which distinguishes 10 different levels [1a (highest quality) to 5 (lowest quality)] of

quality of evidence. The Austrian and the Italian guidelines follow this system, with national adaptations for some of the recommendations. For example, Austria recommends that a disinfecting agent must be sporicidal with a ranking of IA (Table II). The Scottish guideline uses the same system but only indicates the strength of recommendation. The Belgian, Danish, and Finnish documents, claiming to be based on the ECDC guidance, neither indicate the strength of the recommendation nor the quality of evidence. The SHEA/IDSA document stratifies both the quality of evidence and the strength of recommendation into three categories. Each recommendation is followed by a combination of strength of recommendation (A, B or C) and the underlying quality of evidence (I, II or III); for example: 'Do not repeat *C. difficile* testing at the end of successful therapy for a patient recently treated for CDI (B-III)'. The publications on which a recommendation is based are not always cited. Similar to the SHEA/IDSA document, the UK guideline divides the strength of recommendation into three categories (A, B and C). However, category B also includes national legislation. A similar tripartite system is used in the Swedish guideline, but categories are labelled with roman numerals (I, II or III) (Table III). In these systems, in contrast to the ECDC system, neither the underlying scientific literature nor the quality of evidence for a given recommendation can be evaluated.

Scientific basis for recommendations

The UK guideline and the ECDC guidance reference approximately three times more publications than the SHEA/IDSA document. However, the UK guideline includes many official regulations issued by the Department of Health (14), the Health Protection Agency and the Healthcare Commission (nine). None of the references cited by the ECDC guidance for some recommendations, for example, for dedicating medical devices/thermometers to CDI patients (seven references), staff education (six references), and CDI surveillance (five references), was identified in the SHEA/IDSA document. For the UK guideline, only four, two, and one of these references were identified, respectively.

Discussion

A total of 15 national European guidelines that had been published by the end of March 2011 were identified for this review of guidelines for nosocomial CDI prevention. These guidelines varied substantially in detailing, evidence base, and how the 'strength of recommendations' was applied. For example, the very explicit and strongly recommended measure 'avoid the use of electronic thermometers with disposable sheaths' (IA) in the ECDC guidance was not part of any other document. On the other hand, the ECDC guidance does not mention whether visitors should wear gloves and/or gowns, whereas the SHEA/IDSA and the French guideline consider this as an unresolved issue. In Belgium and Denmark such protective measures are recommended when visitors assist in patient care. This example raises the question of how single measures, found to be effective or non-effective in the literature, are incorporated into a national guideline or left out. Although the ECDC guidance, which served as the reference for this study, is based on a systematic review and provides information about the search strategy, it does not explain on what grounds one

recommendation was included while another was not.⁹ The same is true for the other guidelines: none clearly explains how the recommended measures were ultimately selected. According to AGREE (Appraisal of Guidelines for Research and Evaluation), and the World Health Organization handbook for guideline development, the questions addressed by guideline developers should be described specifically.^{27,28} Such explicit phrasing of questions is missing in all of the guidelines analysed. Although the overall research question may be implicitly contained within a given recommendation, the absence of such specification can be criticized as lacking in transparency and, in part, may explain the discrepancy in the documents.

Only seven of the 17 analysed guidelines provided information on the strength of recommendations. The ECDC guidance ranked four of its recommendations with the strongest category 'IA'. The three guidelines claiming to follow the ECDC guidance and to report a category of 'strength of recommendation' (AT, IT, UK-Sc) provide the same category of strength. Interestingly, the two guidelines using another grading system (SHEA/IDSA and UK) assigned only the second strongest category to the same recommendations. Additionally, the SHEA/IDSA document scored the same recommendations with the lowest level of evidence (III). As all three guidelines (ECDC, SHEA/IDSA, UK) were published in 2008, we can assume that all guideline-developing groups had access to the same scientific evidence. What then is the source of these differences in categorization of strength and rating of evidence? In 2008, the ECDC guidance group recognized that the studies about CDI prevention were of limited quality and suggested that more well-designed studies were needed. Thus, it is interesting that four of approximately 40 recommendations were graded as 'IA' and only two are rated as 'unresolved issue'. The majority of the remaining recommendations are graded as 'IB', defined as: 'strongly recommended for implementation and strongly supported by some experimental, clinical or epidemiological studies and a strong theoretical rationale.'

A possible explanation is that recommendations from expert groups are driven by other factors in addition to the underlying evidence. In fact, the assessment of the quality of evidence and the rating of strength of recommendation are two distinct steps in a guideline development process. When rating the strength of a recommendation, guideline developers should also weigh aspects other than evidence base, such as positive and negative effects of a recommendation, and resource allocation. These aspects should be integrated into the rating system and reported transparently.^{29,30} Following this logic, weak evidence may result in a strong recommendation and good evidence may result in a weak recommendation.³¹ An example from the ECDC guidance might be the issue 'to stop all antibiotic treatment as soon as possible if CDI is diagnosed', ranked with 'IA'. The cited Cochrane review (level of evidence 1a), claims that, based on the identified studies alone, the authors are not able to make any statement about the efficacy of terminating an antibiotic therapy.³² Thus, the empirical evidence for this recommendation is weak despite having a strong theoretical rationale.

Another source of variation is the way that evidence is identified. This depends on the databases and search terms that are used for the systematic reviews.^{33–35} These in turn depend on the defined questions intended to be addressed by a guideline. Neither the ECDC guidance nor the SHEA/IDSA guideline or the UK guideline explicitly explains the study questions used for data retrieval. Only the ECDC guidance

includes information about the specific search terms and the databases that were searched. The number of referenced publications in these documents differs substantially, with about three times as many references listed in the ECDC guidance and the UK guideline compared to the SHEA/IDSA document. In addition, there is only a low level of agreement about the cited literature for the following recommendations: dedicated medical devices/thermometers, education of staff, and surveillance, to name only a few examples.

As the number of published studies dealing with *C. difficile* is expanding, an updated search could substantially change the grading of some of the recommendations or even bring up new aspects for prevention. Unfortunately, a statement about a scheduled revision of the documents is generally missing in the guidelines.

In the past 10 years, a growing body of literature has emerged on the implementation of IPC measures. Although such publications rarely suggest new procedures, they add strength to the evidence that supports established procedures. Some of the papers have defined 'bundles' of measures and followed a rigorous implementation approach.^{36–39} Whereas many studies addressing behavioural change successfully reduced a range of HCAs, guidelines rarely comment on the effectiveness of such interventions, nor mention the role of specific implementation strategies. Organizational and individual factors that serve as barriers and facilitators to applying the guideline should be described as well as resources to be committed as specified by AGREE.⁴⁰ The SHEA/IDSA document provides practical process indicators to be used in monitoring the implementation process.²⁰ A minority of the other CDI guidelines supply instruments or criteria for implementation success monitoring. The absence of implementation tools is a shortcoming in many clinical practice guidelines. This problem may only be overcome if relevant expertise on implementation is represented on guideline development teams.^{41,42}

This study had some limitations. First, translation from the original languages was required for a number of guidelines and there may have been misunderstandings or misinterpretation of terminology. However, all translations were reviewed by the NCP of each country for verification, which should have minimized the risk of misinterpretation. Second, we were not able to translate documents in their entirety, some of which were over 100 pages in length, and we were not able to review background documents. These references may have provided additional information about the methodology used for guideline development. However, a major strength of the study is its completeness. Given a response rate of 100% by the contacted experts, this review provides a complete set of published and valid national CDI guidelines across Europe.

In conclusion, about half of the 34 European countries included in this study have a guideline for CDI prevention. The scope and amount of detail provided by these guidelines vary widely. Despite the publication of the evidence-based and well-structured ECDC guidance, some of the national guidelines issued subsequently did not incorporate much of this information in their documents. One possible reason for such selective adoption of information may be that national experts adapted the guidance to fit their national context, e.g. if financial restrictions would preclude the use of single-use thermometers, this recommendation is not made. Unfortunately, the ECDC guidance has not yet inspired the development or revision of national guidelines in many European

countries. In addition, very few of the guidelines were fully transparent about the scope and the methodology used to define recommendations. Internationally recognized instruments for guideline development such as GRADE or AGREE would improve quality if applied consequently.^{27,29,31} The inclusion of advice and tools for monitoring successful implementation of preventive measures would add value and increase the applicability of guidelines.

Guidelines are indispensable for HCAI prevention and this also applies to the problem of CDI. The development of a transparent state-of-the-art guideline is time- and resource-consuming and it cannot be expected that every country in Europe or elsewhere would invest such effort. On the other hand, comprehensive reference guidelines such as the ECDC guidance or SHEA/IDSA guidelines do not provide a 'one size fits all' solution. Instead, they must be adapted to national/local circumstances of culture and healthcare. Reference guidelines, however, may serve as state-of-the-art documents providing the results of systematic reviews, assessing the quality of evidence and suggesting recommendations. National guidelines may take up the scientific work of the reference guidelines and adapt recommendations to the local context – without changing or selecting evidence and quality assessment but with full transparency as to why some evidence is taken up for recommendation whereas other evidence is not. For these reasons, we believe that the development of European reference guidelines would support the implementation of a series of useful evidence-based national guidelines.

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Conflict of interest statement

All authors had salary support from the European Community for the submitted work. None of the authors reported a financial relationship with any organization that might have an interest in the submitted work in the previous three years or any other relationships or activities that could appear to have influenced the submitted work.

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References

1. Anonymous. Severe *Clostridium difficile*-associated disease in populations previously at low risk – four states, 2005. *Morb Mortal Wkly Rep* 2005;54:1201–1205.
2. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353:2442–2449.
3. Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *Can Med Assoc J* 2004;171:466–472.
4. Kuijper EJ, Coignard B, Tull P. Emergence of *Clostridium difficile*-associated disease in North America and Europe. *Clin Microbiol Infect* 2006;12(Suppl. 6):2–18.
5. Soes L, Molbak K, Strobaek S, et al. The emergence of *Clostridium difficile* PCR ribotype 027 in Denmark – a possible link with the increased consumption of fluoroquinolones and cephalosporins? *Euro Surveill* 2009;14:19176.
6. Birgand G, Blanckaert K, Carbonne A, et al. Investigation of a large outbreak of *Clostridium difficile* PCR-ribotype 027 infections in northern France, 2006–2007 and associated clusters in 2008–2009. *Euro Surveill* 2010;15:19597.
7. Kotila SM, Virolainen A, Snellman M, Ibrahim S, Jalava J, Lyytikäinen O. Incidence, case fatality and genotypes causing *Clostridium difficile* infections, Finland, 2008. *Clin Microbiol Infect* 2010;17:888–893.
8. Bauer MP, Notermans DW, van Benthem BH, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. *Lancet* 2011;377:63–73.
9. Vonberg RP, Kuijper EJ, Wilcox MH, et al. Infection control measures to limit the spread of *Clostridium difficile*. *Clin Microbiol Infect* 2008;14(Suppl. 5):2–20.
10. Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (AGES). *Prävention und Kontrolle von Clostridium difficile in Krankenhäusern und Einrichtungen der stationären Pflege*. Vienna, Austria, December, 2007.
11. Conseil Supérieur de la Santé. *Recommandations belges pour le contrôle et la prévention des infections à Clostridium difficile dans les hôpitaux aigus et dans les maisons de repos et de soins*. Brussels, Belgium, May 2008.
12. Statens Serum Institut. *National Infection Prevention and Control Guidelines for treatment of patients with communicable diseases, including isolation*. Copenhagen, Denmark, 2011.
13. National Institute for Health and Welfare (THL). *Clostridium difficile: toimenpideohjeet tartuntojen ehkäisemiseksi*. Helsinki, Finland, January 2011.
14. Société Française d'Hygiène Hospitalière. *Surveiller et prévenir les infections associées aux soins: Infection associées aux soins à transmission digestive*. Brest, France, 2010.
15. Robert Koch Institut. *Clostridium difficile – RKI Ratgeber Infektionskrankheiten – Merkblätter für Ärzte*. Berlin, Germany, 2009.
16. Health Protection Surveillance Centre. *Surveillance, Diagnosis and Management of Clostridium difficile-associated disease in Ireland*. Dublin, Ireland, 2008.
17. SIMPIOS. *Prevenzione e controllo delle infezioni da Clostridium difficile*. Milan, Italy, 2009.
18. Sabiedrības Veselības Agentūra. *Labas sabiedrības veselības prakses vadlīnijas rīcībai Clostridium Difficile apstiprināšanas adījumā ārstniecības iestādē*. Riga, Latvia, 2007.
19. Conseil Supérieur d'Hygiène. *Emergence des Infections à Clostridium difficile 027 au Luxembourg*. Luxembourg, 2007.
20. Dubberke ER, Gerding DN, Classen D, et al. Strategies to prevent *Clostridium difficile* infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008;29(Suppl. 1):S81–S92.
21. Dutch Working Party on Infection Prevention. *Infection prevention measures for Clostridium difficile infection*. Leiden, The Netherlands, 2006.
22. Socialstyrelsen. *Att förebygga vårdrelaterade infektioner, Ett kunskapsunderlag*. Stockholm, Sweden, 2006.
23. SwissNoso. *Clostridium difficile: Epidemiologie und präventive Maßnahmen*. Lausanne, Switzerland, 1995.
24. Department of Health and Health Protection Agency. *Clostridium difficile infection: how to deal with the problem*. London, UK (England) December, 2008.
25. Health Protection Network. *Guidance on prevention and control of Clostridium difficile infection (CDI) in healthcare settings in Scotland*. Glasgow, UK (Scotland, 2009).
26. Cookson B, Mathai E, Allegranzi B, et al. Comparison of national and subnational guidelines for hand hygiene. *J Hosp Infect* 2009;72:202–210.
27. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;12:18–23.
28. World Health Organization. *WHO Handbook for guideline development*. Geneva: WHO; 2010.
29. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ* 2008;336:1049–1051.
30. Terracciano L, Brozek J, Compalati E, Schunemann H. GRADE system: new paradigm. *Curr Opin Allergy Clin Immunol* 2010;10:377–383.
31. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–926.
32. Bricker E, Garg R, Nelson R, Loza A, Novak T, Hansen J. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database Syst Rev* 2005;(1):CD004610.
33. Suarez-Almazor ME, Belseck E, Homik J, Dorgan M, Ramos-Remus C. Identifying clinical trials in the medical literature with electronic databases: Medline alone is not enough. *Control Clin Trials* 2000;21:476–487.
34. Sampson M, Barrowman NJ, Moher D, et al. Should meta-analysts search Embase in addition to Medline? *J Clin Epidemiol* 2003;56:943–955.
35. Wilkins T, Gillies RA, Davies K. Embase versus Medline for family medicine searches: can Medline searches find the forest or a tree? *Can Fam Physician* 2005;51:848–849.
36. Abbott SK, Yokoe DS, Lipsitz SR, et al. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 2009;30:1062–1069.
37. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725–2732.
38. Bouadma L, Mourvillier B, Deiler V, et al. A multifaceted program to prevent ventilator-associated pneumonia: impact on compliance with preventive measures. *Crit Care Med* 2010;38:789–796.
39. Muto CA, Blank MK, Marsh JW, et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive “bundle” approach. *Clin Infect Dis* 2007;45:1266–1273.
40. AGREE Next Steps Consortium (2009). The AGREE II Instrument. Available at: www.agreetrust.org [accessed 09.01.12].
41. Alonso-Coello P, Irfan A, Sola I, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. *Qual Saf Health Care* 2010;19:e58.
42. Barajas-Nava L, Sola I, Delgado-Noguera M, et al. Quality assessment of clinical practice guidelines in perioperative care: a systematic appraisal. *Qual Saf Health Care* 2010;19:e50.