

# CLOSTRIDIUM DIFFICILE: SUMMARY OF ACTIONS IN THE EUROPEAN UNION

C Suetens (carl.suetens@ecdc.europa.eu)<sup>1</sup>

1. European Centre for Disease Prevention and Control, Stockholm, Sweden

This week's issue of Eurosurveillance includes two papers on *Clostridium difficile* infection (CDI), also referred to as *C. difficile*-associated disease (CDAD). The term CDI is increasingly being preferred in recent international literature [1-4], mainly because CDAD is regularly used for *C. difficile*-associated "diarrhoea" as well [5-7], an entity that does not cover the entire clinical spectrum of the disease.

*C. difficile* is an anaerobic bacterium that was identified as part of the normal flora of neonates in 1935 and can be isolated from the stool of 3% of healthy adults and in at least 10% of asymptomatic hospitalised patients [7,8]. It was identified as the cause of antibiotic-associated pseudomembranous colitis in 1974 and has since been recognised as the most common cause of healthcare-associated diarrhoea, often, but not always, in association with previous antibiotic use. The clinical spectrum of CDI ranges from mild diarrhoea to potentially life-threatening colitis that may result in toxic megacolon, colon perforation and multiorgan failure. The pathogenesis is mediated through the production of toxins, toxin-negative strains do not cause disease [8-10].

In recent years outbreaks of CDI and an increase in the incidence of healthcare-associated CDI have been described in the United States (US), Canada and several European countries, mostly associated with a new virulent strain characterised as toxinotype III, North American pulse-field type 1 (NAP1) and PCR ribotype O27 (Type O27) [9]. In the Euroroundup article published in this issue, E Kuijper et al. report that Type O27 has now been isolated in 16 European countries, and has been associated with outbreaks in nine of them. However, it has become clear that also other PCR ribotypes are associated with the increase of CDI, such as the new emerging Type O78 strain which has similar mechanisms for hyper-production of toxins as Type O27 and has been reported in Belgium, The Netherlands, Northern Ireland, Scotland, and possibly Spain.

The paper from Spain by A. Asensio et al. unfortunately lacks microbiological typing data, but it provides an interesting approach for a retrospective analysis of the increase of CDI at the national level using data from the EPINE study (Estudio de prevalencia de las infecciones nosocomiales en los hospitales españoles) a national prevalence survey of nosocomial infections performed repeatedly every year since 1990. Assuming a constant methodology over time, the study clearly shows an increase in the prevalence of nosocomial CDI from 0.039% in 1999 to 0.122% in 2007.

This latter figure is still 10 times lower than the 1.21% hospital-associated CDI prevalence reported in 270 hospitals across the United Kingdom (UK) and the Republic of Ireland in 2006 [11]. However, differences in case-finding methods for CDI between the two surveys certainly account for a part of this difference.

Since 2006, the European Centre for Disease Prevention and Control (ECDC) has been addressing the new CDI situation. Considering the worrying evolution of CDI in Northern America [6,12,13], reports of Type O27 CDI outbreaks in Belgium [14], The Netherlands [15] and the UK [16] in 2005, and the preliminary results of an EU-wide study conducted in 2005 by the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for *C. difficile* (ESGCD) [17], ECDC convened a group of experts consisting of members of ESGCD, epidemiologists from healthcare-associated surveillance networks from the European Union (EU) and from the US Centers for Disease Control and Prevention (CDC).

This ECDC working group recognised the emergence of a new CDI problem in some EU Member States and the potential for spread to other countries and decided to act by:

- informing Member States and the scientific community;
- fostering the coordination of national surveillance activities and exploring the need for additional studies to assess the spread of Type O27 in Europe;
- exploring ways to improve microbiological standardisation, in particular typing methods, common typing nomenclature and sharing of reference strains; and
- developing best practice guidance to Member States.

Follow-up meetings were held at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Nice (2006) and Munich (2007), at ECDC in January 2007 and at the Second International *C. difficile* Symposium in Maribor, Slovenia in June 2007. The ECDC working group produced the first background paper on the emergence of CDI in Europe that included interim case definitions for CDI as well as other recommendations for surveillance [9]. Similar, interim recommendations for surveillance were later published by a CDC working group [18], but their appropriateness in long-term care facilities (LTCF), in particular the attribution of cases to either the hospital or the LTCF in delayed-onset cases was recently discussed in the context of public reporting of CDI rates in the US [5].

Members of the ECDC working group also communicated regular updates on the epidemiological situation in Europe at scientific conferences and in scientific journals [19]. Finally, the working group recently published a systematic review of infection control measures to limit the spread of *C. difficile* that can be used for the elaboration of evidence-based guidelines in Member States [20]. These should combine early diagnosis, surveillance, education of staff, appropriate isolation precautions, adapted hand hygiene and use of protective clothing before and after contact with symptomatic cases, environmental cleaning and cleaning of medical equipment, good antibiotic stewardship, and specific measures during outbreaks. The paper underlines the specific difficulties to prevent *C. difficile* transmission linked to the capacity of *C. difficile* to form spores that survive for months in the environment, may be excreted in large numbers by affected patients, cannot be destroyed by standard alcohol-based hand disinfection and persist despite usual environmental cleaning agents.

The ECDC is currently financing a European prospective CDI incidence survey coordinated by the Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM). The study aims at assessing the baseline incidence of hospital-acquired and community-acquired *C. difficile* infections in a selected number of hospitals from all EU Member States using the interim case definitions and will collect information on the severity of disease, the complication rate and the mortality of CDI as well. One of the major objectives of the survey is to build a network of laboratories with links to national surveillance institutes in all MS capable of isolating and characterising *C. difficile* isolates. This objective is pursued through training in typing techniques and distribution of reference strains of the most frequently occurring strains in Europe. It is expected that the project will result in a better standardisation of *C. difficile* typing. The resulting network of national *C. difficile* laboratories will be instrumental in setting up a future continuous surveillance of CDI in Europe: by performing typing of strains according to a EU-agreed laboratory and surveillance protocol; by improving the capacity of peripheral laboratories in the individual countries to diagnose CDI on a routine basis using standardised methods [21] allowing to follow-up the baseline incidence in healthcare institutions and to timely detect CDI outbreaks; and by assisting hospital infection control staff and public health authorities in implementing appropriate control measures.

## References

- Gerding DN, Muto CA, Owens RC Jr. Measures to control and prevent Clostridium difficile infection. Clin Infect Dis. 2008;46 Suppl 1:S43-9.
- Labbé AC, Poirier L, Maccannell D, Louie T, Savoie M, Béliveau C, et al. Clostridium difficile infections (CDI) in a Canadian tertiary care hospital before and during a regional epidemic associated with the BI/NAP1/027 strain. Antimicrob Agents Chemother. 2008 Jun 23. [Epub ahead of print].
- Owens RC Jr, Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for Clostridium difficile infection. Clin Infect Dis. 2008;46 Suppl 1:S19-31.
- Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated Clostridium difficile infection. J Antimicrob Chemother. 2008;62:388-96.
- Mylotte JM. Surveillance for Clostridium difficile-associated diarrhea in long-term care facilities: what you get is not what you see. Infect Control Hosp Epidemiol. 2008 Aug;29 [Epub ahead of print].
- Pépin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171:466-72.
- Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P. Costs of nosocomial Clostridium difficile-associated diarrhoea. J Hosp Infect. 2008 Jul 2. [Epub ahead of print].
- Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. Lancet Infect Dis. 2005;5:549-57.
- Kuijper EJ, Coignard B, Tüll P. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006;12 Suppl 6:2-18.
- Kuipers EJ, Surawicz CM. Clostridium difficile infection. Lancet. 2008;371:1486-8.
- Smyth ET, McIlvenny G, Enstone JE, Emmerson AM, Humphreys H, Fitzpatrick F, et al. Four country healthcare associated infection prevalence survey 2006: overview of the results. J Hosp Infect. 2008;69(3):230-48.
- McDonald LC, Killgore GE, Thompson A, Owens RC Jr, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med. 2005;353:2433-41.
- McDonald LC. Clostridium difficile: responding to a new threat from an old enemy. Infect Control Hosp Epidemiol. 2005;26:672-5.
- Joseph R, Demeyer D, Vanrenterghem D, van den Berg R, Kuijper E, Delmée M. First isolation of Clostridium difficile PCR ribotype 027, toxinotype III in Belgium. Euro Surveill. 2005;10(42):pii=2815. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2815>
- Kuijper EJ, Debast SB, van Kregten E, Vaessen N, Notermans DW, van den Broek PJ. Clostridium difficile ribotype 027, toxinotype III in the Netherlands. Ned Tijdschr Geneesk. 2005;49:2087-9.
- Outbreak of Clostridium difficile in a hospital in south east England. CDR Weekly. 2005;15. Available from: <http://www.hpa.org.uk/cdr/archives/archive05/News/news2405.htm>
- Barbut F, Mastrantonio P, Delmée M, Brazier J, Kuijper E, Poxton I. Prospective study of Clostridium difficile infections in Europe with phenotypic and genotypic characterisation of the isolates. Clin Microbiol Infect. 2007;13:1048-57.
- McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK. Recommendations for surveillance of Clostridium difficile-associated disease. Infect Control Hosp Epidemiol. 2007;28:140-5.
- Kuijper EJ, Coignard B, Brazier JS, Suetens C, Drudy D, Wiuff C, et al. Update of Clostridium difficile-associated disease due to PCR ribotype 027 in Europe. Euro Surveill. 2007;12(6):pii=714. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=714>
- Vonberg RP, Kuijper EJ, Wilcox MH, Barbut F, Tüll P, Gastmeier P, et al. Infection control measures to limit the spread of Clostridium difficile. Clin Microbiol Infect. 2008;14 Suppl 5:2-20.
- Barbut F, Delmée M, Brazier JS, Petit JC, Poxton IR, Rupnik M, et al. A European survey of diagnostic methods and testing protocols for Clostridium difficile. Clin Microbiol Infect. 2003;9:989-96.

This article was published on 31 July 2008.

Citation style for this article: Suetens C. Clostridium difficile: summary of actions in the European Union. Euro Surveill. 2008;13(31):pii=18944. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18944>