Investigation of a large outbreak of Clostridium difficile PCR-ribotype 027 infections in northern France, 2006-2007 and associated clusters in 2008-2009

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In 2006 and 2007, a large outbreak of *Clostridium difficile* infections (CDIs) with PCR-ribotype 027 was identified in northern France. Overall, 38 healthcare facilities notified 529 CDIs over a 22-month period, including 281 laboratory-confirmed CDI 027 and 248 non-confirmed CDI 027 cases (incidence rate per 10,000 elective bed days: 1.63, range: 0.07 to 7.94). The cases occurred mainly in long-term care hospital facilities and nursing homes, near the border between France and Belgium. An active surveillance and prevention campaign was launched at the first epidemic peak including hygiene precautions for healthcare professionals, which supported healthcare facilities to improve care organisation. The outbreak was controlled at the end of 2007, but sporadic cases were identified until the end of 2009. A bundle of appropriate control measures may halt the spread of such outbreaks, provided that substantial human resources and financial support are available.

Background

Clostridium difficile is an anaerobic Gram-positive, spore-forming bacterium, which is responsible for 15–25% of antibiotic-associated diarrhoea and virtually all cases of pseudomembranous colitis [1]. Since 2003, outbreaks of severe *C. difficile*-infection (CDI) have been increasingly reported in Canada and the United States (US) [2,3]. These outbreaks were associated with the emergence and rapid spread of a specific strain of *C. difficile* belonging to PCR-ribotype 027 or pulsotype NAP1 (North American Pulsotype 1). Some of the characteristics of this strain are higher *in vitro* production of toxins A and B and presence of a third toxin named binary toxin [2,4]. The epidemic strain has begun to spread for the last five years in northern Europe (United Kingdom (UK), Belgium and the Netherlands) [5-7].

The first cases of the PCR-ribotype 027 epidemic strain in France were reported by a healthcare facility through the national mandatory notification system for nosocomial infections to the regional infection control coordinating centre (CCLIN) on 2 February 2006 [8,9]. All healthcare facilities in the region were alerted and urged to send *C. difficile* strains to the national reference centre to confirm whether they belonged to the 027 epidemic strain. An epidemiological investigation was then launched to evaluate the magnitude of the outbreak. In addition, a nationwide prevention and information campaign was implemented by the national institute for health surveillance (Institut de Veille Sanitaire, InVS) and the Ministry of Health to identify and control the potential spread of the outbreak.

Methods

C. difficile toxins were detected from stools using enzyme immunoassays or by cytotoxicity assay according to each local standard procedure. Culture of *C. difficile* was performed on selective media (cefoxitin-cycloserine fructose agar plates). After incubation at 35 °C for 48 hours under anaerobic conditions, suspected colonies (based on Gram staining, typical odour and chartreuse fluorescence under ultraviolet light) were confirmed using biochemical gallery (RapID 32A, Biomérieux). *C. difficile* isolates were then sent to the national reference laboratory for typing. Strains were characterised by PCR-ribotyping by previously described techniques [12].

The study area included two administrative regions (Nord Pas-de-Calais and Picardie) with 26,800 hospital beds in 145 healthcare facilities and with approximately 450 nursing homes. The study covered the period from the beginning of 2006 to the end of 2009. Among healthcare facilities, 55% were acute care hospitals and 27% were long-term care hospitals or rehabilitation centres. The term ‘outbreak’ is used here to

denominate the overall epidemic situation and a group of affected healthcare facilities. The term 'cluster of cases' is used here to denominate a local epidemic situation in one healthcare facility after the outbreak period. CDI was suspected in all patients presenting with unexplained diarrhoea and were tested for *C. difficile* toxin A and B using standard technique. Diarrhoea was defined as three or more liquid stools per day and pseudomembranous colitis was diagnosed based on colon videoscopy. A CDI was considered as severe if a patient presented with at least one of the following criteria: CDI requiring hospitalisation in intensive care, white cell count higher than 20,000/mm^3, need for digestive surgery, or fatal outcome within 30 days after CDI diagnosis.

To describe the outbreak, the case definition was based on standard clinical and microbiological criteria given in the guidelines from the European Centre for Disease Prevention and Control [10]. Confirmed cases were CDI cases PCR-positive for ribotype 027. Non-confirmed CDI 027 cases were CDI cases with a positive toxin assay and one of the following criteria: (i) a nosocomial case acquired in a healthcare facility where at least one confirmed case was staying at the time, or (ii) a case imported from a healthcare facility where at least one confirmed case was identified, or (iii) a recurrence in a patient from whom a 027 strain had been isolated in the past. All healthcare facilities having reported at least one confirmed or non-confirmed CDI 027 case were included in the study. Criteria for hospital-acquired infections were those established by the US Centers for Disease Control and Prevention [11].

In each participating healthcare facility, data were collected by the infection control team using a standardised questionnaire including information on age, sex, date of admission, CDI clinical characteristics (diarrhoea or colitis) and severity, date of CDI onset and outcome (death, hospital stay or not at the time of the study), date of the first positive toxin assay, and result of laboratory culture. Data were sent every week to the regional coordinating centre for nosocomial infection control for tracing the progression of the outbreak.

Data analysis was performed using Stata release 8.0 (Stata Corp LP). Incidence rates were the ratio of the number of cases per 10,000 bed days. Comparison of characteristics of confirmed versus non-confirmed cases was made using Student's t-test or Pearson's chi-square test. All tests were considered significant at $p<0.05$.

Table

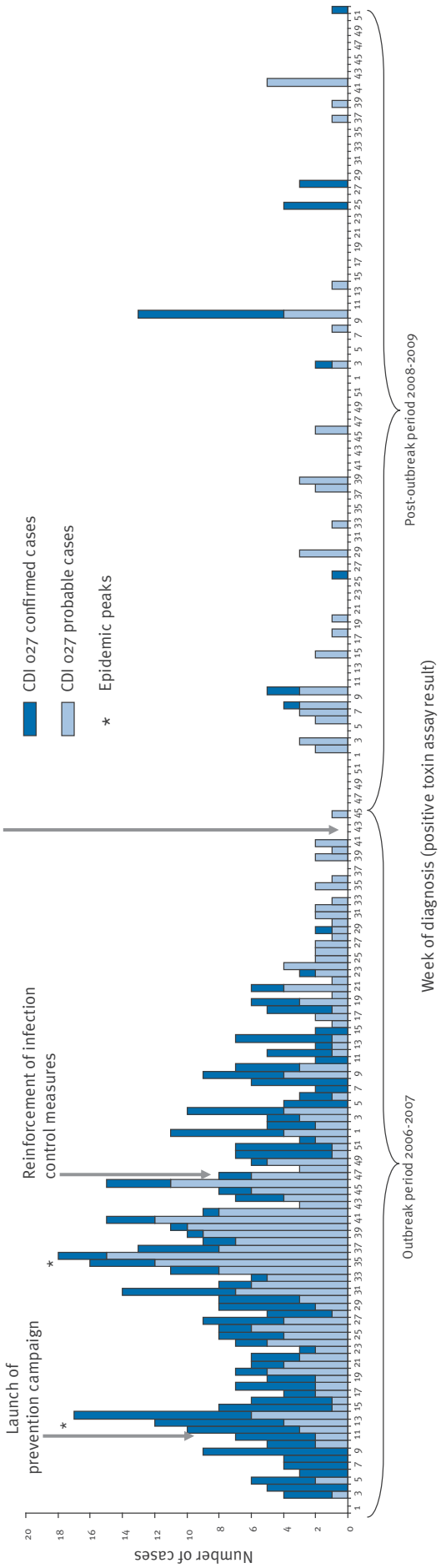
Characteristics of patients with *Clostridium difficile* 027 infection, northern France, outbreak period 2006-2007 (n=529)

Characteristics	Confirmed CDI 027 cases (n=281)	Non-confirmed CDI 027 cases (n=248)
Personal data		
Mean age (years)	79.8	77.6
Sex ratio male/female	0.53	0.48
Origin		
Acute care	68 (24.2%)	67 (27.0%)
Long-term care	130 (46.3%)	104 (41.9%)
Nursing home	25 (8.9%)	25 (10.1%)
Other hospital	21 (7.5%)	19 (7.7%)
Community-acquired	21 (7.5%)	14 (5.6%)
Unknown	16 (5.7%)	19 (7.7%)
Clinical data		
Diarrhoea	260 (92.5%)	233 (93.9%)
Pseudomembranous colitis	15 (5.3%)	14 (5.6%)
Unknown	6 (2.1%)	1 (0.4%)
Severity of CDI		
Severe	34 (12.1%)	33 (13.3%)
Mild	242 (86.1%)	214 (86.3%)
Unknown	5 (1.8%)	1 (0.4%)
Outcome		
Death	82 (29.2%)	82 (33.1%)
Hospital discharge	120 (42.7%)	91 (36.7%)
Transfer to another hospital	68 (24.2%)	54 (21.8%)
Unknown	11 (3.9%)	21 (8.5%)

CDI: *Clostridium difficile* infection.
No statistical significant difference between groups.

Figure 1

Confirmed and non-confirmed *Clostridium difficile* infection with ribotype 027 in northern France, 2006-2009 (n=602 cases)



Results

Outbreak period 2006-2007

From 1 January 2006 to 31 December 2007, 38 healthcare facilities (20% of healthcare facilities in the region) notified at least one confirmed or non-confirmed CDI 027 case, including 31 hospitals with more than one case. In addition, 27 (6% of nursing homes in the region) nursing homes reported community-acquired cases. Among 529 CDIs, 281 were confirmed cases and 248 non-confirmed. The number of confirmed and non-confirmed CDI 027 cases varied between the healthcare facilities, ranging from one to 126. The mean incidence rate of total CDIs per 10,000 hospitalised days was 1.63 (range: 0.07 to 7.94), with 1.19 cases per 10,000 days of hospitalisation in acute care facilities (range: 0.1 to 4.5) and 2.39 in long-term or rehabilitation facilities (range: 0.15 to 19.8).

Most cases were over 80 years-old (mean age: 79.8 years) and the male/female sex ratio was 0.53). Cases occurred more often in healthcare facilities, but a substantial number were detected in nursing homes. Diarrhoea was the main symptom (92.5%), whereas pseudo-membranous colitis was infrequent (5.3%). Comparison between confirmed and non-confirmed CDI 027 cases did not show any statistical differences (Table).

The epidemic curve is displayed in Figure 1, showing the timing of the prevention campaign. Overall, the outbreak developed over a period of 22 months. The index case was identified in week 4 in 2006. The epidemic curve presents two major peaks: the first from February to April 2006 with the highest number of cases in week 14 (17 cases), the second from September to December 2006 with the highest number of cases in week 36 (18 cases).

In April 2006, a prevention campaign was launched at the regional level in order to help infection control and medical staff to detect CDI cases early and promptly implement barrier precautions. Enhanced control measures and specific disinfection procedures against CDI were recommended including isolation precautions according to standards, reinforcement of hand hygiene using alcohol-based hand rub solutions following hand washing with liquid soap, wearing gloves, dedicating equipment, environmental cleaning with hypochlorite solutions (0.5%), and a specific process for waste management [13]. As cases were still occurring after the first bundle of measures, the campaign was reinforced with a focus on the implementation of cohorting units with isolation in private rooms and dedicated staff personnel. This second bundle of measures was maintained until the outbreak was considered to be under control at the end of 2007, when no healthcare facility had reported a new major cluster of cases in three months.

Spatial analysis of the reported cases highlighted two geographical outbreaks (Figure 2). During the epidemic

period 2006-2007, the main outbreak spread near the Belgian border, including 447 cases identified in 25 healthcare facilities (of which 56.1% were confirmed cases). Among them, 10 episodes included between six and 51 confirmed cases, 26 less than six confirmed cases and two clusters consisted only of non-confirmed CDI 027 cases. The index case of this outbreak was located in an area with a high density of hospital beds and frequent patient transfers among healthcare facilities. The second major outbreak spread near the Somme estuary, including 25 cases (of whom 21 were confirmed CDI 027 cases) identified in two healthcare facilities. A further 11 healthcare facilities with episodes of CDI 027 were distributed throughout the region and were not part of the two main geographical outbreak areas.

Post-outbreak period 2008-2009

After a two-month period with no cases, new cases were identified. Overall, 73 cases of CDI were notified in 2008 and 2009, 29 confirmed CDI 027 cases and 44 non-confirmed CDI 027 cases. These cases belonged to 15 notified clusters of CDI 027 with between two and 13 cases each, and to 22 sporadic cases in several healthcare facilities that had already been affected during the outbreak period. In 2009, 10 cases of CDI 027 occurred in the Paris area. The typing results showed that the patients were infected with the epidemic *C. difficile* 027 strain and were therefore considered as a consequence of the outbreak in northern France.

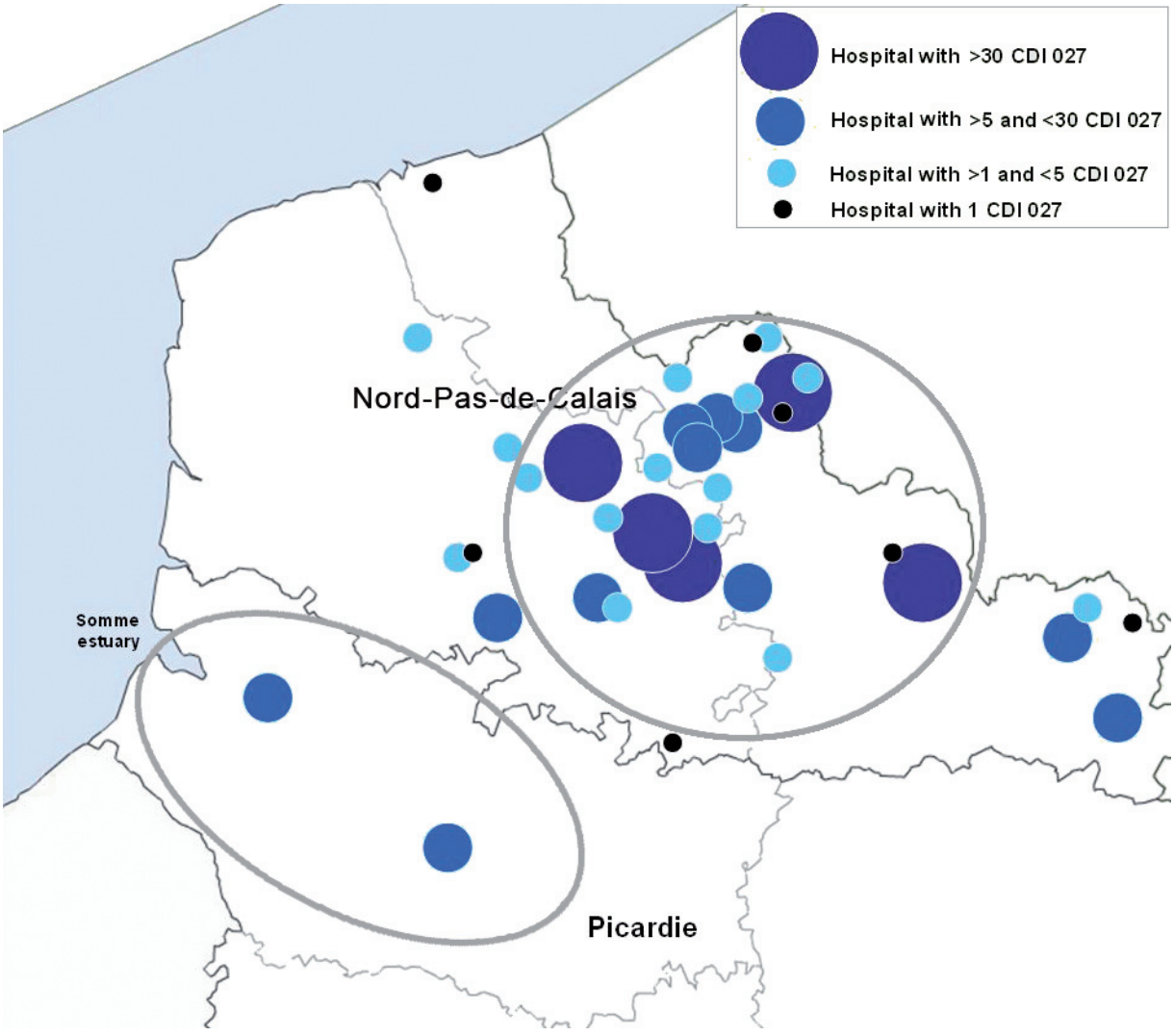
The proportion of confirmed cases was higher in the period 2008-2009 (83.3%) than in the period 2006-2007 (35.3%). The ratio confirmed/non-confirmed cases varied from 0 to 10 according to week of diagnosis.

Discussion

Since the emergence of the *C. difficile* 027 epidemic in North America and Europe, this is the first time that a large outbreak of CDI with PCR-ribotype 027 is described in France. This outbreak seems to be under control now in this country, although sporadic cases

Figure 2

Spatial distribution of healthcare settings with clusters of cases of *Clostridium difficile*-027 associated disease in northern France, 2006-2007 (n=38 healthcare facilities)



Grey circles indicate two geographically separate outbreaks.

are still occurring. Accordingly, surveillance data in Canada and the US show a similar increasing incidence of CDI directly associated with the emergence of *C. difficile* PCR-ribotype 027. In 2005, this organism represented 80% and 50%, respectively, of strains isolated in Canada and the US [14,15]. This strain then spread through northern Europe, especially the UK and the Netherlands, and in Belgium bordering the epidemic area in northern France with higher than usual incidence rates [6,10,16,17].

The time period between the occurrence of the first case and the first notification to health authorities which launched the prevention campaign was about three months. This raises the question of why there was such a delay although an effective mandatory notification system was in place in France for early detection of outbreaks in general or unusual healthcare-associated infections. According to national guidelines promoted by the Ministry of Health, the notification should be made by a hospital infection control practitioner according to defined criteria. During the outbreak, a large information campaign on CDI 027 was held in northern France. This campaign has increased the awareness among medical and paramedical teams of the notification and of why, when and how to notify a case of CDI. Furthermore, microbiologists have been informed on and trained in methods of toxin assay and stool culture for isolation of *C. difficile*. In consequence, the number and the quality of microbiological analyses and notifications have increased following the outbreak period.

However, most epidemic cases of CDI in our study could not be notified promptly because they occurred in long-term care facilities or nursing homes that had few healthcare personnel and often no infection control specialist. In addition, there are no defined criteria for diarrhoea or associated gastroenteric diseases in the current mandatory notification system for nosocomial diseases. Extended notification criteria or a new targeted surveillance system focused on acute enteric diseases in healthcare facilities should further improve the effectiveness of outbreak detection.

As already demonstrated, isolation of symptomatic patients with CDI is a key measure to control *C. difficile* outbreaks [18-20]. Indeed, environmental contamination occurs as a result of CDI, especially when patients have large amounts of liquid stool or stool incontinence. Our study suggests that the incidence of CDI decreases if a bundle of measures such as strict enteric contact precautions, double hand hygiene washing off spores with soap before using alcohol-based hand rub, and appropriate cleaning of the environment surrounding cases are performed. Better hygiene practices should be combined with a better organisation of care including cohort nursing, i.e. gathering cases in a designated ward, movement restrictions on staff and patients, and intensive education of staff. Whether *C. difficile* PCR-ribotype 027 is more easily cross-transmissible than non-027 strains remains questionable. Akerlund *et al*. demonstrated that the epidemic (027/NAP1) strain in Sweden sporulated more effectively (60%, $p<0.001$) than others. They conclude that this contributes to its survival and facilitates cross-transmission and spread despite standard hygiene precautions [21]. Antibiotics treatments and particularly the use of fluoroquinolones have certainly had an influence in the occurrence of this outbreak [22].

Detection of asymptomatic *C. difficile* carriers is an additional possible control measure, although it remains controversial. Riggs *et al*. demonstrated that more than half of the patients surrounding epidemic cases were asymptomatic carriers and should be actively screened [23]. Additionally, colonisation of the skin and airborne transmission may play an important role in the epidemiology of CDI [23]. The isolation of asymptomatic carriers may contribute to combatting outbreaks. On the other hand, systematic screening of patients (on admission and weekly or monthly), especially in nursing homes or long-term care is costly and hard to implement. In an epidemic context, the screening would be more cost-effective when focussed on newly admitted patients. In our study, only a small proportion (10%) of cases came from other care facilities, suggesting that systematic screening would have been feasible.

The outbreak mostly affected elderly patients and was therefore characterised by significant mortality and severe disease. The mortality rate given in the Table is a crude rate and does not consider comorbidity, medical history or exposure to antibiotics of the patients, which can be confounding factors. The mortality rate would need to be adjusted for these confounding factors to avoid potential bias. The high severity of CDI 027 is assumed to be associated with higher amounts of toxin production of this strain [2,24]. However, implementation of control measures was highly time-consuming with heavy financial consequences for the healthcare system. Strong efforts were required from both personnel working in healthcare facilities and the infection control specialists who help implement control measures with the support of the public health authorities. Based on a subset of healthcare facilities, we estimated the extra-cost of such an outbreak including only charges due to additional personnel, material and products to be about EUR 31,000 per patient-case and EUR 1,000 per day. This estimate is consistent with those previously reported [25].

The CDI 027 notified in 2008 and 2009 were mostly sporadic cases or part of small clusters. This observation could be explained by the spread of the epidemic strain in the community. A recent article has estimated the proportion of community-acquired CDI in North Carolina, US, at 20% [26]. Elderly patients (the main population affected during the outbreak period was over 80-years-old) are sometimes transferred to nursing homes after their hospitalisation. As a step between the hospital

and the patient's home, nursing homes could facilitate the spread of *C.difficile* strains from hospitals to the community. Transmission of the epidemic strain from an infected patient to other people living in the same nursing home could create human reservoirs of *C. difficile* in this population. Conversely, the life of people in nursing homes often being disrupted by hospital stays, the hospitalisation of a patient coming from home or nursing home and infected or colonised with *C. difficile* 027 could provoke an outbreak in the hospital, if the infection control precautions are not quickly implemented, even more so if this happens in a region never affected by the epidemic strain before. To prevent such a scenario, sustained efforts of detection and control are warranted to prevent the re-emergence of a new epidemic wave. A crucial point is informing healthcare workers about the infection control measures against *C. difficile* transmission.

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