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Chapter 2

Decrease of hypervirulent *Clostridium difficile*

PCR ribotype 027 in the Netherlands

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Abstract

After the first outbreaks of *Clostridium difficile* PCR ribotype 027 (North American pulsed-field type 1, restriction endonuclease analysis group BI) in the Netherlands in 2005, a national surveillance programme for *C. difficile* infection (CDI) was started. Furthermore, national guidelines were developed to rapidly recognise type 027 infections and prevent further spread. The mean incidence of CDI, measured in 14 hospitals, remained stable throughout the years: an incidence of 18 per 10,000 admissions was seen in 2007 and 2008. Between April 2005 and June 2009 a total of 2,788 samples were available for PCR ribotyping. A decrease was seen in the number and incidence of type 027 after the second half of 2006. In the first half of 2009, the percentage of type 027 isolates among all CDI decreased to 3.0%, whereas type 001 increased to 27.5%. Type 014 was present in 9.3% of the isolates and *C. difficile* type 078 slightly increased to 9.1%. We conclude that currently there is a significant decrease in type 027-associated CDI in the Netherlands.

Since the new hypervirulent strain of *Clostridium difficile*, PCR ribotype 027, North American pulsed-field type 1 (NAP1), restriction endonuclease analysis (REA) group BI, was found in the United States and Canada in 2001, a large number of countries worldwide reported *C. difficile* infections (CDI) due to this type^{1,2}. Several reports indicated that CDI due to type 027 is associated with a higher morbidity and mortality and also has the tendency to relapse more frequently³⁻⁶. An overview published in July 2008 revealed that type 027 was detected in 16 European countries and was associated with outbreaks in Belgium, Finland, France, Germany, Ireland, Luxembourg, the Netherlands, Switzerland and the United Kingdom⁷. As of July 2008, outbreaks have also been reported in Austria⁸ and Denmark⁹.

Soon after the first outbreaks in the Netherlands in 2005, a national surveillance programme for *C. difficile* was initiated by the Leiden University Medical Centre (LUMC) and the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment. All medical microbiologists in the Netherlands were requested to send *C. difficile* isolates to the Dutch national reference laboratory at the LUMC for rapid PCR ribotyping and characterisation in case of an outbreak (more than two CDI cases within one week in one department) or when a patient suffered from severe CDI. In addition, a prospective, three year-long surveillance study of the incidence of CDI and the distribution of the *C. difficile* PCR ribotypes was started in 14 Dutch hospitals in June 2006.

In the period between April 2005 and June 2009, a total of 3,137 samples were submitted to the reference laboratory, of which 89% (n=2,788) were available for PCR ribotyping. Of those 2,788 samples, 51% had been submitted by medical microbiologists because of either severe disease or a CDI outbreak, whereas the remaining 49% were part of the national surveillance study. Since no difference in the distribution of various PCR ribotypes was found between the two surveillance systems, we represent the data combined. The reason for this equal distribution is that most hospitals that encountered an outbreak or a case of severe CDI, continued to submit samples on a regular basis thereafter.

Figure 1 depicts the distribution of the five most common PCR ribotypes in the Netherlands between April 2005 and June 2009. Although the total number of submitted samples increased from 35 in the second quarter of 2005 to a steady number between 150 and 250 after the first quarter of 2006, a decrease in the number of type 027 isolates has been observed since the second half of 2006. In the 14 hospitals participating in the continuous surveillance, a decrease in the quarterly incidence of type 027 (number of isolates per number of admissions) was seen.

This decrease was confirmed in linear regression and remained significant after adjustment for the number of samples that we received ($p=0.03$).

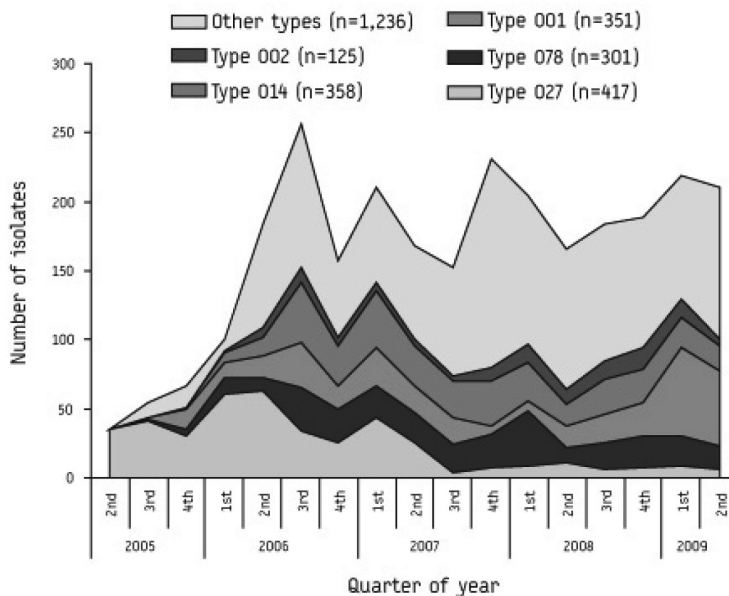


Figure 1. *C. difficile* PCR ribotypes in the Netherlands, April 2005 – June 2009 (n=2,788)

In the first half of 2009, type 027 was found in 3.3% of the 430 submitted samples. Type 001 (n=118; 27.4%) was the most common type, followed by type 014 (n=40; 9.3%), 078 (n=39; 9.1%) and 002 (n=19; 4.4%). We also encountered a number of isolates that did not match a PCR ribotype in our database and belonged to different, yet unknown types (n=49; 11.4%). These are currently subject of further investigation. Finally, of all isolates in the first two quarters of 2009, 35.1% belonged to 41 different PCR ribotypes, which were present in small numbers. Types 015 (n=15; 3.5%), 056 and 087 (both 2.6%), 017 and 046 (both 1.9%) were the five most frequently found types among those. The types that could not be matched in our database and the 41 less common types were combined in the group ‘other types’, as displayed in figure 1.

To determine the incidence of CDI in the Netherlands, we used the continuous surveillance data only. From the beginning of 2007 to the end of 2008, the mean incidence was 18 per 10,000 hospital admissions, ranging from 8 to 35 per 10,000 admissions among the 14 hospitals. These numbers are in line with a previous study performed in the Netherlands, which showed an incidence of 16

per 10,000 admissions¹⁰. A nationwide incidence study in neighbouring Belgium revealed a similar (median) incidence of 15 per 10,000 admissions¹¹.

Discussion and conclusions

To our knowledge, the Netherlands are the first European country with a documented decrease of the hypervirulent type 027. The detection of type 027 in 2005 resulted in a number of measurements taken on a national level. Most hospitals which experienced CDI due to type 027 followed the principles of the infection control guideline supported by the European Centre for Disease Prevention and Control (ECDC) to limit the spread of *C. difficile*, emphasising the importance of responsible use of antimicrobial drugs in conjunction with proper environmental disinfection, compliance with hand hygiene, protective clothing, education of staff and single-room isolation or cohorting of CDI patients^{12,13}. Although the role of fluoroquinolones as an important predisposing factor for CDI due to type 027 has been recognised in several outbreaks^{13, 14}, the observed decrease in incidence of type 027 in the Netherlands is not related to a change of nationwide use of fluoroquinolones since this remained stable in hospitals¹⁵.

The relatively high frequency of type 001 in Dutch hospitals is not exceptional and has recently also been reported in southern Germany, Ireland, Luxembourg and the United Kingdom^{7, 16}. Type 014 is also frequently found in other European countries: it is the most common strain found in Hungary (2002-2004), Norway and Sweden (2008), and the second most common strain in Austria (2006) and Poland (2002-2003)^{7, 8, 17, 18}. An increase of type 078 had been noticed previously in the Netherlands¹⁹. In the quarterly data presented here, the increase is also seen: in the first trimester of 2008 19% of all samples consisted of type 078. After this peak, however, the contribution of type 078 decreased and it became the third most common strain in the Netherlands. Also in several other European countries type 078 is increasingly observed⁷. This type is a predominant strain in some farm animals (especially in pigs and dairy calves) and has recently been found in retail meat in North America²⁰. The genetic similarity between animal and human type 078 strains as demonstrated by the highly discriminatory multilocus variable number of tandem repeats analysis (MLVA), also suggests a possible common source of animal and human type 078 strains. Type 078 and type 027 have similar virulence factors (positive for toxin A, B and binary toxin, and a dysfunctional toxin regulator gene). Furthermore, they resemble CDI in their clinical presentation: both cause severe

diarrhoea in 40% of cases. A complicated course is seen less often in CDI caused by type 078, possibly because type 078 is observed in a younger population, with a higher frequency of community-associated CDI¹⁹.

In conclusion, CDI caused by the hypervirulent 027 strain is now observed less frequently in the Netherlands, while the 'common' types 001 and 014 remain prominently present in the Dutch hospitals. Type 078 is currently the third most common PCR ribotype in the Netherlands and other European countries, whereas its occurrence before 2005 was very rare. More research is needed on the source of this strain and a possible exchange between animals and humans.

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