WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID
INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE

Epidemiology of *Clostridium difficile* infection in Belgium

Report 2015

Hospital surveillance data 2007 - 2014

Hospital stay and CDI testing data 1999 - 2012

Death registrations 1998 - 2012

Fiona Neely, Marie-Laurence Lambert

Section : Public Health and Surveillance

Contact : mllambert@wiv-isp.be

Rue Juliette Wytsman 14

1050 Bruxelles | Belgique

www.wiv-isp.be

For the National Reference Laboratory:

M. Delmée, V. Avesani, E. Ngyuvula, L. Muytjens, J. Van Broeck.

Cliniques Universitaires Saint Luc

1200 Bruxelles | Belgique

Date of report: June 2015

Edited by: Boudewijn Catry

Public Health & Surveillance | Brussels | Belgium

Internal reference number: PHS-2015-028

Depot number: D/2015/2505/42

N° ISSN –online version : 2034-4562

Executive Summary

Clostridium difficile infection (CDI) is a major cause of diarrhoea and pseudomembranous colitis in both acute and chronic healthcare institutions. An increase in incidence has been reported in many countries across the world over the last decade. This increase has been attributed to a number of factors: the rising use of certain antibiotics, an increase in the population at risk (older people) and the emergence of hypervirulent strains of CDI.

This report summarizes the different sources of available data concerning the epidemiology of CDI in Belgium: national hospital surveillance (mandatory until 2014), including reference laboratory data (2008-2014), hospital stay (RHM/MZG 1999-2012) and billing data for CDI testing (INAMI/RIZIG) (2000-2012) and death registration data (1998-2011).

Surveillance data

Hospital participation is high and the majority of hospitals participate for the whole year exceeding the legal obligation (until 2014) to participate only for one semester (6 months) per year. The severity of infection has declined markedly from 10% in 2008 to 3% in 2014.

Epidemiological surveillance of *Clostridium difficile* infection: hospital participation, episodes characteristics and mortality, Belgium 2008-2014

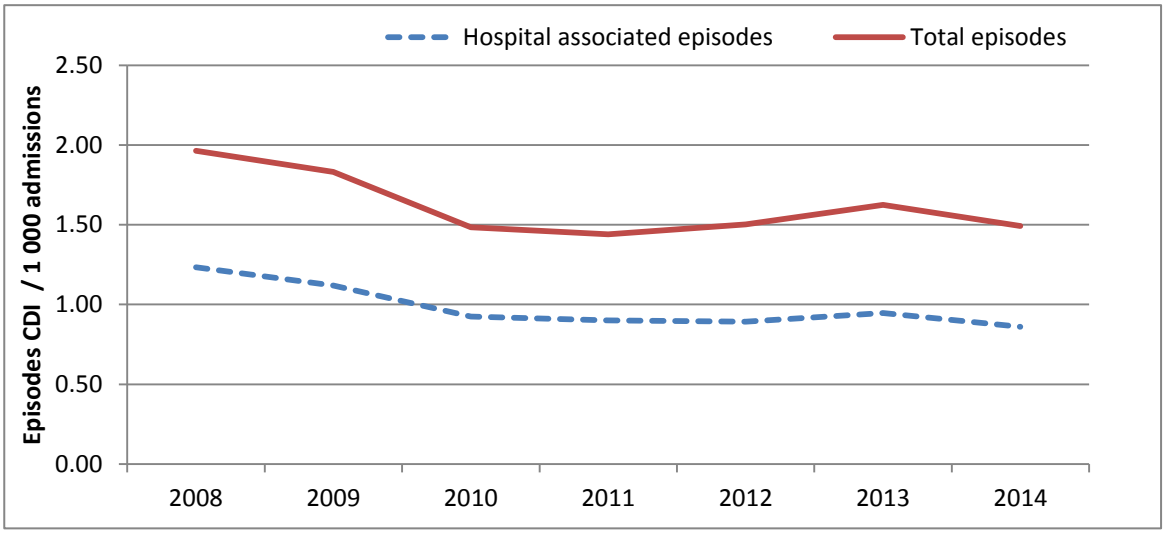
Year	2008	2009	2010	2011	2012	2013	2014
N hospitals participating at least one semester per year	148	149	147	145	144	141	141
Number of reported episodes	2,981	2,948	2,465	2,517	2,507	2,712	2,431
Hospital associated CDI*(%)	64%	61%	62%	63%	61%	59%	59%
Recurrent episodes CDI** (%)	11%	10%	9%	8%	9%	9%	9%
Death within 30 days – direct or indirect result of CDI (% of patients)	10%	5%	4%	3%	3%	4%	3%

**Definition: onset of symptoms >= 2 days after admission in the declaring hospital*
***Proportion of episodes which are recurrent*

In 2014, 54% of patients were female; the median age for patients with hospital associated CDI (HA-CDI) was 79 and 72 for non-HA CDI; 2% of patients were 2 years or less. Episodes of HA-CDI were principally diagnosed when patients were in the geriatrics department (31%), onco-haematology (9%) or the intensive care unit (7%).

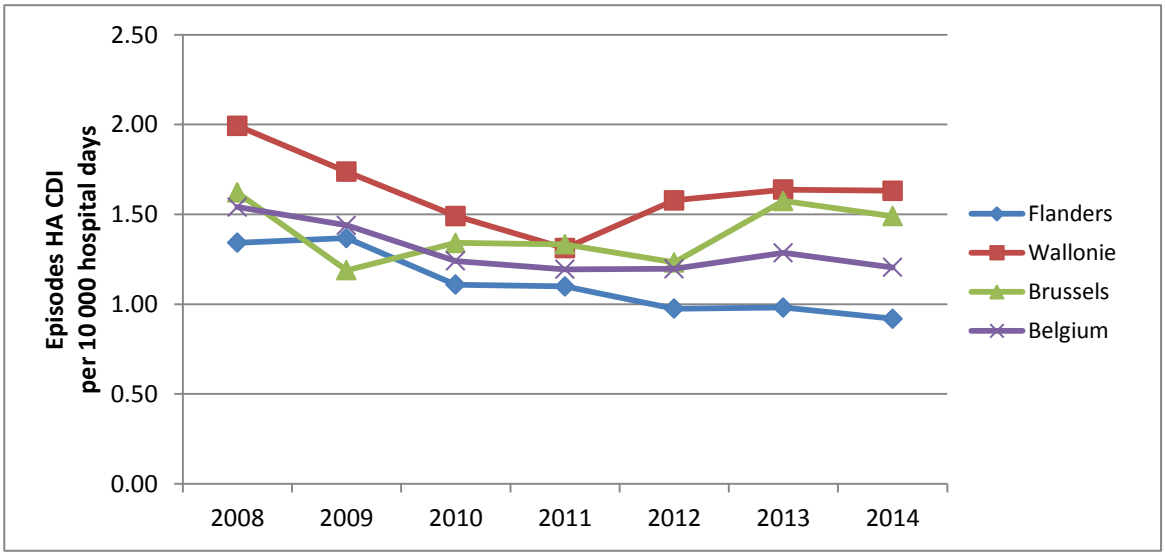
The mean incidence of CDI in 2013 was higher in 2013 than in the three previous years but diminished again in 2014 (1.49/1000 admissions).

Mean incidence of *Clostridium difficile* infection (CDI) in Belgian hospitals 2008-2014



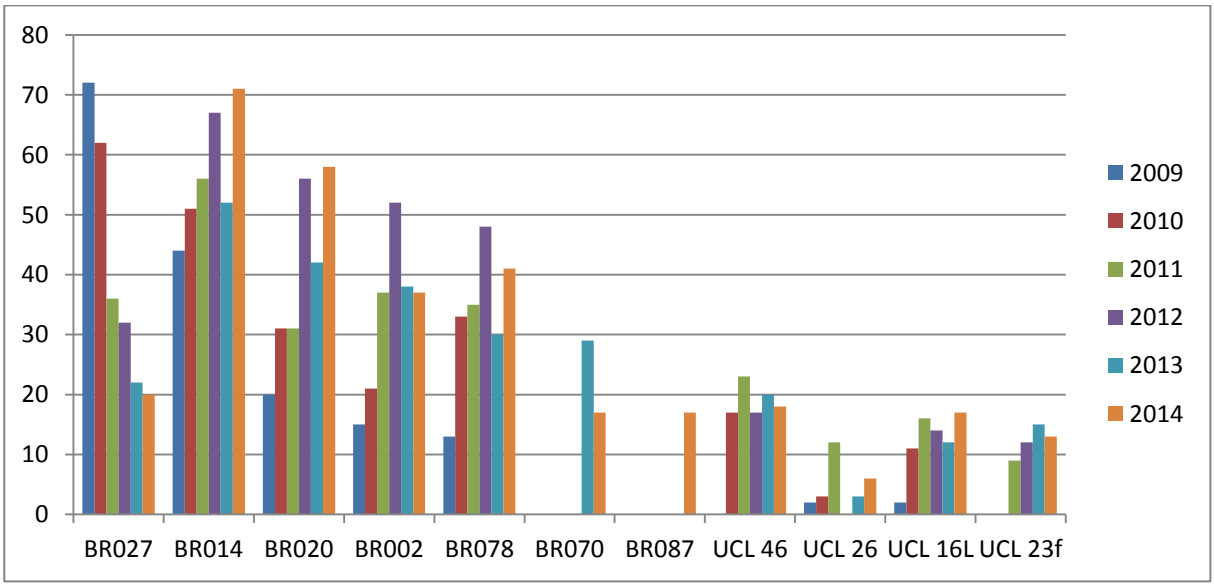
There is a large variability in incidence between hospitals. Flanders has the lowest incidence and Wallonia the highest. To enable easier comparison, the following figure shows incidence of episodes of HA-CDI for acute hospitals only, and as a function of hospital days, by region.

Mean incidence of hospital associated *Clostridium difficile* infection (HA-CDI) in acute hospitals, by region, Belgium 2008-2014



In 2014, 112 hospitals sent 740 isolates to the reference laboratory; 37 (5%) were not confirmed as *Clostridium difficile* (other species or culture impossible). 616 typed samples fulfilling the surveillance protocol criteria (5 consecutive specimens per hospital per semester), allowed identification of 121 different ribotypes, of which 66 were only isolated once. This illustrates the large variety of sources of infection. The most marked trend is the decline of the hypervirulent ribotype 027 (isolated in 34% of hospitals in 2009 and 12% in 2014). The most common ribotypes in 2014 were ribotype 014 (UCL16) and 020 (UCL16a), isolated in 38% and 37% of hospitals respectively.

Number of isolates for the most common strains in Belgium 2009-2014



Since 2011, it is possible to link the reference laboratory data with the epidemiological surveillance data. Among those patients infected by ribotype 027, 66% were 80 years or older (48% for patients infected by other ribotypes, p=0.00) ; 54% of episodes were associated with the declaring hospital (64% for other ribotypes, p=0.03) and 14% had complications of CDI (7% for other ribotypes, p=0.04).

Hospital stay and diagnostic testing data

Hospital stay data demonstrate a marked increase in the number of cases of CDI in the 2000s, with a peak in 2007-2008, the time of implementation of the surveillance programme. For the years when comparison is possible (2008-2012), the incidence of CDI calculated using hospital stay data is higher by about 30% than the incidence calculated using the surveillance data, but the trends observed are similar.

Between 2000 and 2012, the number of hospital stays with a diagnostic code of CDI has increased by 113% and the number of diagnostic tests billed for hospitalised patients has increased by 57%. The ratio of the number of tests to the number of cases of CDI declined from 29 in 2000 to 21 tests per case in 2012. Despite their limitations, these data suggest that the increase in number of tests and the improvement in diagnostic performance can only partially explain the increase in the number of cases diagnosed.

Death registration data

In 2011 and 2012 (latest years available), 86 and 88 deaths respectively could be attributed to CDI (crude mortality due to CDI 7.8 and 8.0 deaths per million inhabitants). These figures are lower than the peak in 2006 (156 deaths).

Discussion and key points

Belgium is one of the few countries that has implemented a mandatory surveillance system (2007-2014) for CDI. This has provided the country with data of high quality. International comparisons are difficult, in that data collection methods are different, but it seems that the incidence of CDI in Belgian hospitals is situated in the mid to lower range among other European countries.

The key points from data available in 2015 are:

- After a peak in 2008, the incidence of CDI in the last few years is relatively stable (despite a slight increase in 2013). The incidence is lowest in Flanders and highest in Wallonia.
- There is a decline in the severity of CDI and in the number of deaths attributed to CDI
- There is a large variation in the incidence of CDI between hospitals, which may indicate an important potential for prevention
- There is a large diversity of ribotypes identified by the reference laboratory, which illustrates the diversity of sources of transmission. The most notable trend is the decline in the hypervirulent ribotype 027.

Glossary

CDI	*Clostridium difficile* infection
CI	Confidence interval
HA-CDI	Hospital-associated *Clostridium difficile* infection (onset of diarrhoea 2 days or more after admission in declaring hospital)
CA-CDI	Community associated *Clostridium difficile* infection (onset of diarrhoea less than two days after admission to hospital with no previous admission to any hospital or long term care facility in previous 12 weeks)
LTCF	Long term care facility
ICD-10	International Classification of Diseases, 10th Revision
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICU	Intensive care unit
INAMI/RIZIV	Institut national d'assurance maladie-invalidité / Rijksinstituut voor ziekte- en invaliditeitsverzekering
LoS	Length of stay
LTCF	Long term care facility
MRSA	Methicillin resistant *Staphylococcus aureus*
MLVA	Multi Locus Variable number tandem repeat Analysis
N or n	Number
NRC-CD	National reference centre (laboratory) – *Clostridium difficile*
PCR	Polymerase chain reaction
Popn	Population
Pts	Patients
RHM/MZG	Résumés hospitaliers minima/ Minimale ziekenhuis gegevens (minimum hospital data set)
RNA	Ribonucleic acid
RR	Relative risk or risk ratio
UE	European Union
UK	United Kingdom
US	United States

Tables

Figures

1 Introduction

1.1 General background

Clostridium difficile infection (CDI) is one of the top 10 healthcare-associated infections in European hospitals, including Belgium[1] and has surpassed methicillin resistant *Staphylococcus aureus* (MRSA) as a leading cause of healthcare-associated infection in some European countries[2,3]. Patients with CDI are likely to spend an extra 1-3 weeks in hospital when compared to those without CDI, at an estimated additional cost of 14 000 euros[4].

In Europe as a whole, infection rates increased substantially between 2008-2013 from 4.1 to 7.9 cases per 10, 000 hospital bed days[4]. An event hosted by the European Parliament in December 2014 highlighted that urgent action was needed to address current issues relating to CDI.[5]

A multicentre point prevalence survey of CDI in hospitalised patients with diarrhoea (EUCLID)[6] found that both under-diagnosis and mis-diagnosis were commonplace in Europe between 2011-2013. Overall, 23% of 641 diarrhoea samples from 20 countries were found positive for *Clostridium difficile* as determined by the national laboratory but were not diagnosed by participating hospitals because of an absence of clinical suspicion. There was a 40 fold variation in testing frequency for CDI between countries. A previous European point prevalence survey suggested that testing rate might be associated with incidence rate between countries[7]. However this latest study could only find a correlation between testing rate and incidence of ribotype 027,[4] but not overall incidence of CDI.[6] In addition, not even 50% of hospitals reported using the currently optimal methods for testing (a two stage laboratory diagnosis including a sensitive *C.difficile* screening test followed by a *C.difficile* toxin assay). Encouragingly though, out of the 10 participating Belgian hospitals, no under-diagnosis was detected among the 156 submitted samples (i.e. sample not tested locally but tested positive at the national laboratory) and only 3% of total samples collected were false positives (positive detection of toxin at local laboratory but negative at national laboratory) and 1% were false negatives at the participating hospitals. Six of the ten Belgian hospitals used optimised diagnostic tests in the sampling periods of September 2012 & August 2013.

It is therefore pertinent that, Belgium is currently updating its own national recommendations for the prevention and control of *C. difficile* in acute hospitals and long term care facilities,[8] and ECDC has just published new recommendations for surveillance of CDI across Europe[9].

Looking at ribotypes, the 2011-13 EUCLID study[6] demonstrated a more diverse range of ribotypes across Europe when compared to a previous European study in 2008[7], and with no single strain dominating in any one country. In the EUCLID study, ribotype 027 was the most prevalent amongst typed isolates (18% of total), although around 88% of occurrences of this ribotype were recorded in only four countries – Germany, Hungary, Poland and Romania. Although ribotype 027 is not the most prevalent in the Netherlands, there have been an increasing number of outbreaks with this ribotype since 2013, regularly involving nursing homes as well as hospitals[10]. The second most prevalent ribotypes across Europe were 001/072 (11%), 014 (7%) and 002 (4%).

As typing techniques have become more sophisticated and more readily available, interest has developed in monitoring transmission patterns between hospital patients. It has been demonstrated by whole genome sequencing that nearly half of all cases in a hospital setting with good infection

control procedures are genetically distinct i.e. not resulting from in-hospital transmission.[11] This has sparked interest in other possible sources of infection, including animal reservoirs such as pigs and / or cattle in whom ribotypes 078 and 014/020 are prevalent.[12]

1.2 Objectives of this report

The objective of this report is to describe the epidemiology of *Clostridium difficile* infection in Belgium. For this 2015 report, we have analysed the latest data available:

- Hospital surveillance data (including reference laboratory data) for the years 2008 – 2014
- Hospital stay and CDI testing data for the years 1999 à 2012
- Death registration data for the years 1998 à 2012

2 Methodology

2.1 Hospital epidemiological surveillance programme co-ordinated by the Scientific Institute of Public Health (WIV-ISP)

Between July 2007 and 30 June 2014, it was obligatory for all acute hospitals to participate in this surveillance programme for at least one semester (6 months – Jan-June or Jul-Dec) each year (Arrêté Royal du 26-06-2007).

Since 1 July 2014, participation in the surveillance programme for *C.difficile* is no longer obligatory (Arrêté Royal du 08-01-2015[13]). However, there is an obligation for hospitals to participate in at least one of four of the following surveillance programmes:

i) Infections with *Clostridium difficile*
ii) Infections with vancomycin resistant enterococci
iii) Pneumoniae and septicaemiae in intensive care units or
iv) Surgical site infections

An electronic information portal collects the surveillance data for cases of *C. difficile* (NSIH Web 1).

The methods are described in detail in the protocol, available online in French and Dutch:
https://www.wiv-isp.be/nsih/surv_cdif/download_fr.asp
https://www.wiv-isp.be/nsih/surv_cdif/download_nl.asp

The data analysed for this report are for the period 1st January 2008 - 31 December 2014

An episode of *Clostridium difficile* infection (CDI) is defined a case which fulfils one or more of the following criteria:

1. Diarrhoea* or toxic megacolon, *and* a laboratory confirmed *C. difficile* toxin A and/or B in the stool or a strain producing toxins identified in the stools, by culture or another method
2. Pseudomembranous colitis observed by proctocolonoscopy of the lower gastro-intestinal tract
3. Histopathology characteristic of *C. difficile* in the colon (with or without diarrhoea) obtained by biopsy during endoscopy, colectomy or autopsy

*At least three liquid or non-formed stools (the stools take the form of the container) during 24 hours or less.

Hospital-associated CDI (HA-CDI) is defined in this report as CDI with an onset of diarrhoea 2 days or more after admission in the declaring hospital (onset date – admission date $\geq$2). Because of information collection issues, it does not include those cases which arise after but within 4 weeks of discharge from hospital and that would be included in the definition of "healthcare-associated infection" according to the surveillance protocol.

Those episodes that do not fulfil the report definition of hospital associated CDI have been categorised into the following groups by the clinician entering the data into NSIHweb1 according to the probable origin of infection: 1) home/community, 2) declaring hospital, 3) other hospital, 4) long term care facility or 5) unknown. The surveillance protocol gives the definition of community associated infection

(onset of diarrhoea less than two days after admission to hospital with no previous admission to hospital or long term care facility in previous 12 weeks), which should be used in allocating a case to "home/community". The category "declaring hospital" should pick up those infections with onset after but within four weeks of discharge from the declaring hospital, but undoubtedly also picks up some cases which are subjectively thought to be associated with the declaring hospital but do not fulfil the report definition given above.

2.2 Hospital stay data and CDI testing data

In Belgium, each hospital stay gives rise to a registration (RHM/MZG – minimum hospital data set). Diagnoses are coded using ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification).[14] We have analysed the hospital stays with a code 008.45 (Intestinal infections due to *C.difficile*) from 1999 to 2012 (latest available year). The diagnoses are classified as "primary diagnosis" – the pathology considered to explain the majority of the hospital stay (most commonly, but not necessarily, the reason for admission), and "secondary diagnosis".

The data provided in this report are provided by the Federal Public Health Service (Service Fédéral Santé Publique / Federale Overheidsdienst) and cover all hospital stays in Belgium, with the exception of psychiatric stays, and day cases. In previous reports, day cases have been included in the calculations. From last year's report in 2014, the analyses have been re-run for all years excluding day cases to allow better comparison with the mandatory hospital surveillance data.

The CDI testing data come from hospital billing information INAMI (Institut national d'assurance maladie-invalidité) / RIZIV (Rijksinstituut voor ziekte- en invaliditeitsverzekering). All tests for CDI on hospitalised patients (code 549861: tests for *C. difficile* toxin in the stools) were counted.

2.3 Death Registration Data

Death certificates in Belgium are coded according to ICD-10[14] system. We counted deaths with code A04.7 as underlying cause of death : "death due to a *Clostridium difficile* related enterocolitis" for the years 1998 – 2012 (latest available data). The underlying cause of death is the original disease causing the chain of events immediately leading to death.

Death registrations data have been extracted from the database of causes of death in Belgium, provided by DGSIE ("Statistics Belgium").[15]

The age standardised mortality rate is based on direct standardisation using the mid-year population figures for 2005,[16] divided into three age groups: 0-64, 65-79, $\geq$ 80 years.

Deaths are counted according to region of death, not according to region of residence of the deceased. The denominator for each region remains as the resident population of the region.

2.4 Reference Laboratory data

The *C. difficile* National laboratory Reference Centre for *Clostridium difficile* (NRC-CD) was officially established in 2011 but has been actively involved in the national surveillance since 2006. It is hosted at the Catholic University of Louvain on the site of Woluwe-St-Lambert, Brussels.

Since 2007, the surveillance program has included a mandatory bacteriological component for every participating Belgian hospital clinical laboratory. It requires each hospital laboratory to send five *C. difficile* strains isolated consecutively during one semester of the year, with additional accompanying information as listed on the website of the WIV-ISP (available in French and Dutch)
https://www.wiv-isp.be/nsih/surv_cdif/download_fr.asp
and https://www.wiv-isp.be/nsih/surv_cdif/download_nl.asp

In addition, a hospital may send locally isolated strains to the reference laboratory for typing in order to support the investigation of local increases in the number of cases or suspected outbreaks.

Each received sample is confirmed and typed. The currently applied method of ribotyping is that which is used in the majority of European reference centres. The details of the typing techniques are presented in the Annex.

2.5 Linkage of patient episode information and ribotyping data

Linkage is established between the epidemiological data from the hospital surveillance programme (NISHweb1 case based reporting) and the reference laboratory ribotyping data through the automatic code generated on printing the encoded case from NSIHweb1. This code is then sent (as part of the patient information) by the hospital laboratory, together with the patient sample to the NRC-CD for ribotyping.

3 Results

3.1 Hospital surveillance data

3.1.1 Hospital participation, characteristics of episodes and patients

The data analysed was last updated on 4 May 2015.

The participation of hospitals is important and the majority of hospitals participate in the surveillance for the entire year, despite the legal obligation (until mid-2014) being participation for only one semester.

Table 1 : Epidemiological surveillance of *Clostridium difficile* infection *(CDI)*: hospital participation and episodes reported, Belgium 2008-2014

Year	2008	2009	2010	2011	2012	2013	2014
N hospitals participating at least 1 semester/year	148	149	147	145	144	141	141
N hospitals participating 2 semesters/year	110	113	117	117	108	114	108
Total hospital-semesters	258	262	264	262	252	255	249
% hospital-semesters reporting no cases	11%	10%	8%	8%	10%	11%	10%
Episodes reported by hospital-semester							
P25	3	3	3	3	3	3	3
P50	8	8	7	7	7	7	6
P75	16	15	13	12	14	15	13
max	89	108	67	94	96	83	114

Table 2 describes episodes of CDI in hospitalised patients in Belgium for the period 2008-2014. It shows that there continues to be an increase in the proportion of community associated cases (CA-CDI) between 2008-2014, matched by a decreasing proportion of hospital associated cases (HA-CDIs).

The median age of patients with HA-CDI remains higher than that of other CDI patients. The proportion of recurrent cases has remained stable (Table 2).

Table 2 : Epidemiological surveillance of *Clostridium difficile* infection (CDI): characteristics of cases in Belgian hospitals 2008-2014

Year	2008	2009	2010	2011	2012	2013	2014
Episodes							
Total episodes reported	2 981	2 948	2 465	2 517	2 507	2 712	2 431
Episodes with hospital-associated (HA) CDI* (%)	64%	61%	62%	63%	61%	59%	59%
For episodes other than HA-CDI – Suspected origin of infection							
Community	56%	57%	59%	60%	63%	62%	64%
Declaring hospital**	12%	11%	11%	11%	9%	11%	10%
Other hospital	6%	6%	6%	6%	6%	4%	7%
Long Term Care Facility	16%	14%	12%	10%	10%	10%	9%
Unknown/missing	10%	12%	11%	12%	12%	12%	11%
Recurrent episodes*** (%)							
No	71%	72%	74%	76%	74%	73%	74%
Yes	11%	10%	9%	8%	9%	9%	9%
Unknown	17%	18%	17%	16%	18/%	17%	17%
Patients							
Total patients reported with CDI	2 820	2 789	2 348	2 417	2 402	2 576	2 325
Sex: female (%)	59%	59%	60%	59%	57%	57%	54%
Median age (years)							
Hospital associated case	80	80	79	80	80	80	79
Other cases	75	74	74	74	74	74	72

**Defined as onset of diarrhoea 2 days or more after admission in the declaring hospital (onset date – admission date >2)*
***Declaring hospital – excluding "Hospital-associated CDI (HA-CDI)" but including those cases still subjectively thought to have their origin in the declaring hospital and those with onset within 4 weeks after discharge*
****Defined as the proportion of episodes which are recurrent, and not the incidence of recurrences in patients presenting with a new episode of CDI*

3.1.2 Complications

The proportion of patients dying (either as a direct or indirect result of their CDI) within 30 days of onset of their infection decreased substantially between 2008-2014 (see Table 3). A smaller proportionate decrease is seen for other complications – pseudomembranous colitis, admission to the intensive care unit (ICU) or the need for surgery as a result of their CDI.

Table 3 : Complications in patients with *Clostridium difficile* infection (CDI) in Belgian hospitals, 2008-2014

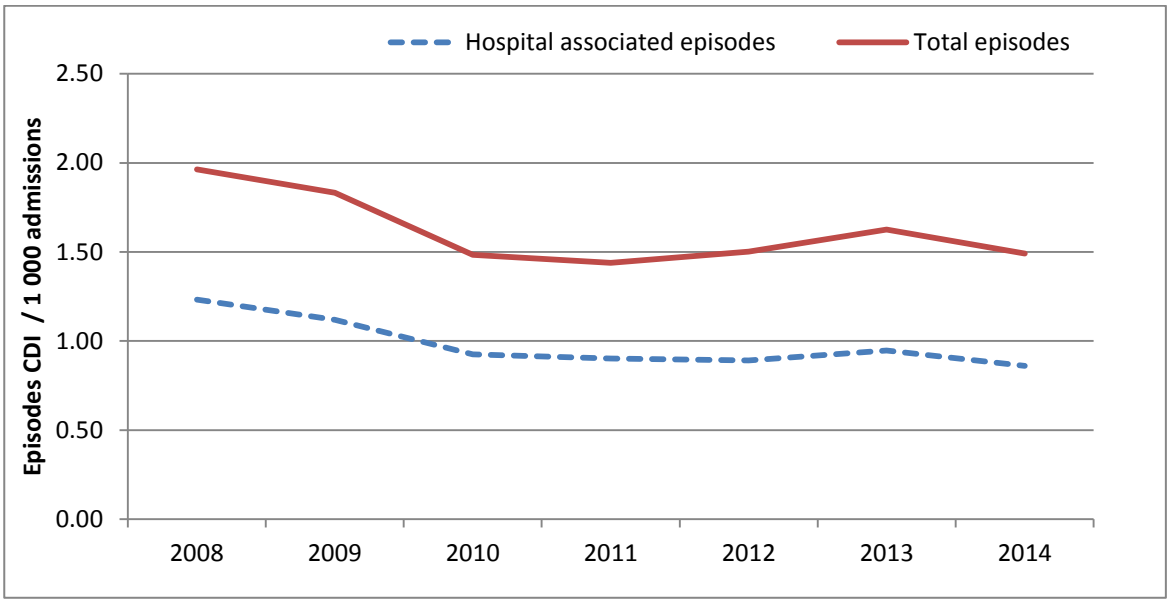
Year	2008	2009	2010	2011	2012	2013	2014
N Patients	2 820	2 789	2 348	2 417	2 402	2 576	2 325
Death within 30 days of onset – CDI indirect or direct cause (%)	10	5	4	3	3	4	3
Pseudomembranous colitis, ICU or surgical admission (%)	5	4	4	4	3	3	3
No complications (%)	71	69	69	69	70	70	69
Unknown/missing (%)	16	22	24	25	24	24	26

ICU – intensive care unit

3.1.3 Annual incidence

The overall incidence of CDI has declined between 2008-2014. From Table 4 and Figure 1 it can be seen that after a slight increase between 2011-2013, incidence has again decreased between 2013-2014, for both hospital-associated and non-hospital associated cases.

Figure 1 : Mean annual incidence of infection with *Clostridium difficile* (CDI) – total cases and hospital associated cases /1000 admissions, Belgian hospitals, 2008-2014



The Annex shows two further tables (Table 24 and Table 25) giving incidence of CDI separately for acute and chronic participating hospitals (mean length of stay <14 days or ≥ 14 days respectively).

From these tables, it can clearly be seen that incidence of HA-CDI calculated using the number of admissions as the denominator is higher in chronic hospitals than in acute hospitals and has decreased more sharply during the period 2008-2014 than has incidence in acute hospitals. Incidence of HA-CDI calculated using the number of hospital days as the denominator is comparable between acute and chronic hospitals (taking account of natural fluctuations in calculated incidence due to the small number of chronic hospitals).

Table 4 : Incidence of infection with *Clostridium difficile* (CDI) in Belgian hospitals, 2008-2014: surveillance data

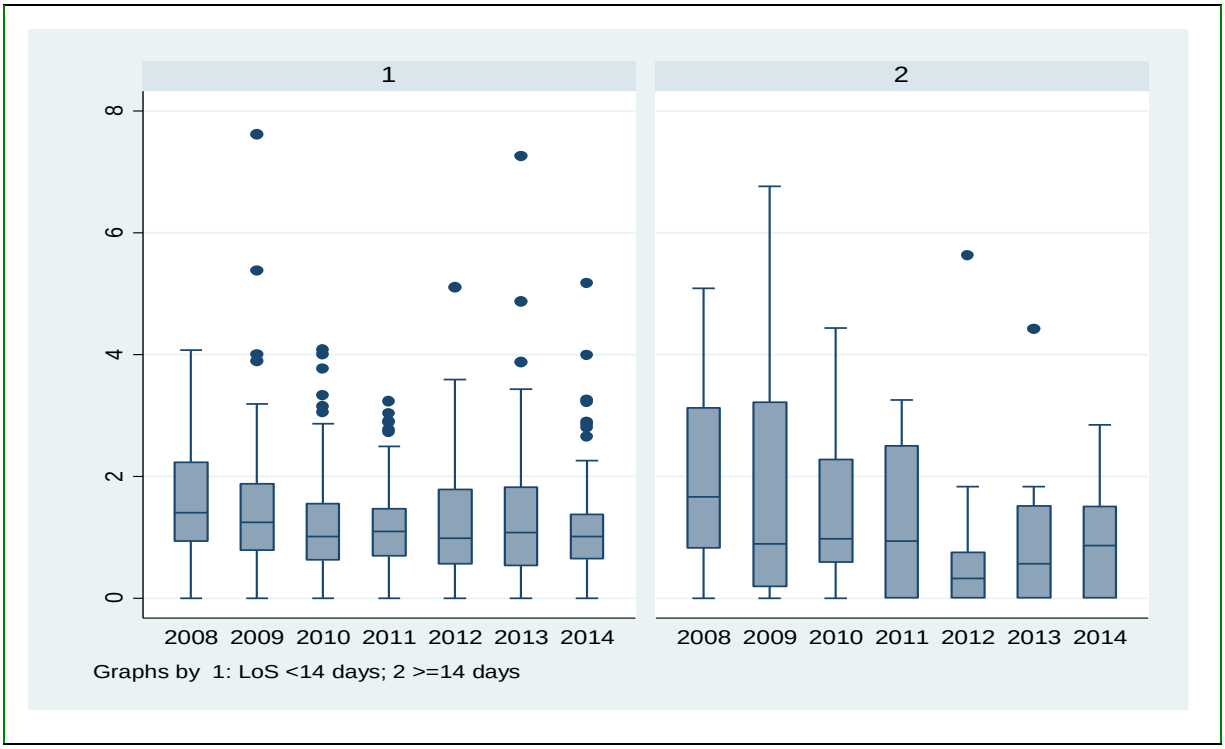
Year	2008	2009	2010	2011	2012	2013	2014
Denominators							
N hospitals included in the calculation of incidence (hospitals participating for whole year only)	103	108	111	113	104	112	99
Hospital associated episodes (HA-CDI)*							
N	1460	1385	1265	1218	1157	1326	1081
/ 10,000 days of hospitalisation :							
Mean Incidence*	1.55	1.44	1.23	1.20	1.18	1.28	1.19
Median	1.42	1.09	1.00	1.09	0.95	1.07	1.01
/ 1000 admissions							
Mean incidence **	1.23	1.12	0.93	0.90	0.89	0.95	0.86
Median	1.14	1.01	0.81	0.78	0.76	0.84	0.73
Other episodes							
N	865	883	764	728	793	953	794
/ 1000 admissions							
Mean Incidence **	0.73	0.71	0.56	0.54	0.61	0.68	0.63
Median	0.69	0.58	0.55	0.51	0.52	0.56	0.52
Total episodes							
N	2325	2268	2029	1946	1950	2279	1875
/1000 admissions							
Mean Incidence**	1.96	1.83	1.48	1.44	1.50	1.63	1.49
Median	1.90	1.63	1.32	1.41	1.31	1.50	1.31

**Defined as onset of diarrhoea 2 days or more after admission in the declaring hospital (onset date – admission date >2)*
*** Mean Incidence : total episodes/total denominator, LOS: length of stay*

For comparison, the mean incidence of hospital acquired methicillin resistant *Staphylococcus aureus* (MRSA) infections (samples from symptomatic patients) was 1.1/1000 admissions and 1.6/10 000 days of hospitalisation in acute hospitals in 2013.[17]

There is a large variability between hospitals in both the total number of cases recorded (illustrated in Table 1) and the incidence of hospital associated cases (Figure 2).

Figure 2 : Distribution of incidence of hospital associated *Clostridium difficile* infections (CDI) in Belgium, per 10 000 hospital days – comparison of acute and chronic hospitals, 2008-2014



Only hospitals providing data for the whole year are included:
LOS: length of stay in acute hospitals defined by mean length of stay <14 days, chronic >= 14 days

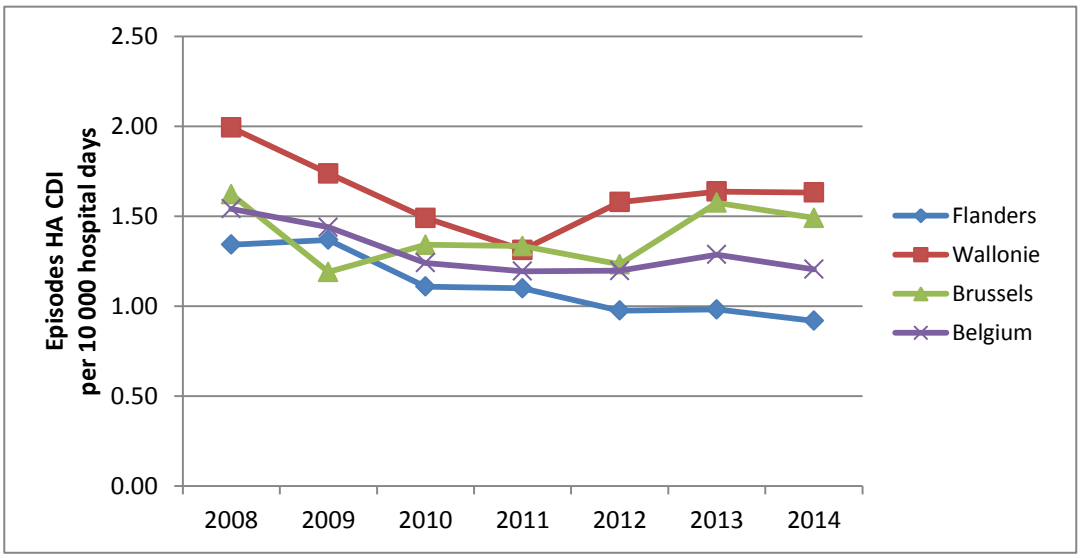
Table 5 shows the mean incidence of HA-CDI in acute hospitals, comparing the three regions of Belgium from 2008-2014. These incidences are depicted in Figure 3. Since 2010, mean incidence has consistently been lowest in Flanders and highest in Wallonia.

Table 5 : Hospital associated *Clostridium difficile* infections (CDI) per 10 000 hospital days in acute hospitals, by region - Belgium, 2008-2014

Year	2008	2009	2010	2011	2012	2013	2014
Flanders							
N hospitals	52	54	56	54	43	47	46
Mean incidence	1.34	1.37	1.11	1.10	0.98	0.98	0.92
Wallonia							
N hospitals	28	28	30	32	34	37	31
Mean incidence	1.99	1.74	1.49	1.31	1.58	1.64	1.63
Brussels							
N hospitals	14	14	16	16	17	15	13
Mean incidence	1.62	1.19	1.34	1.33	1.23	1.57	1.49

Acute hospitals: defined on the basis of mean length of stay <14 days
Only hospitals providing data for the whole year are included.
Mean incidence: total episodes/total denominators.

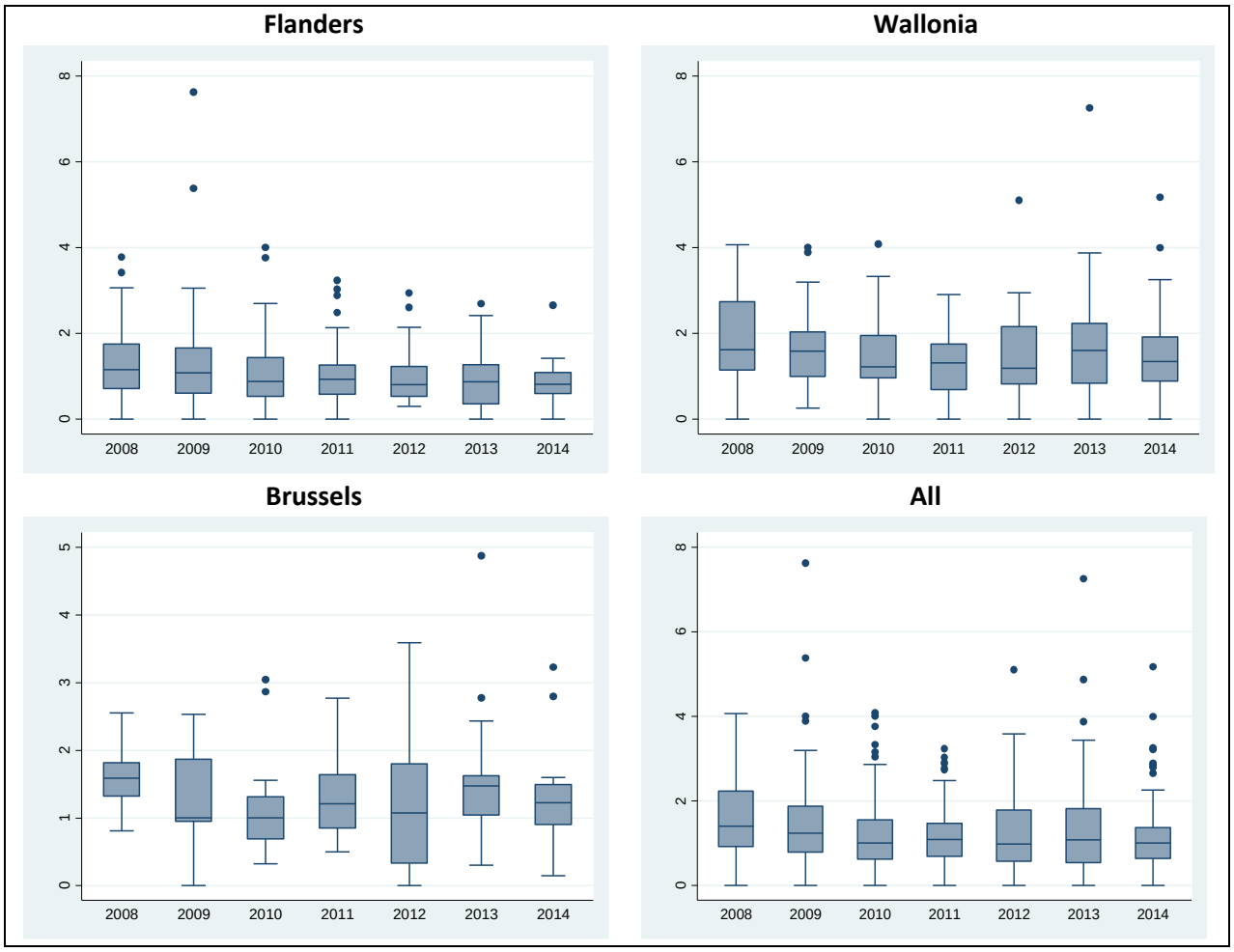
Figure 3 : Hospital associated *Clostridium difficile* infections (CDI) per 10 000 hospital days in acute hospitals, by region - Belgium, 2008-2014



Acute hospitals: defined on the basis of mean length of stay <14 days
Only hospitals providing data for the whole year are included.
Mean incidence: total episodes/total denominators.

Figure 4 shows the wide variation in incidence between hospitals in each of the three regions, with the lowest variation depicted in Flanders.

Figure 4 : Distribution of incidence of hospital associated *Clostridium difficile* infections (CDI) per 10 000 hospital days in acute hospitals, by region. Belgium, 2008-2014

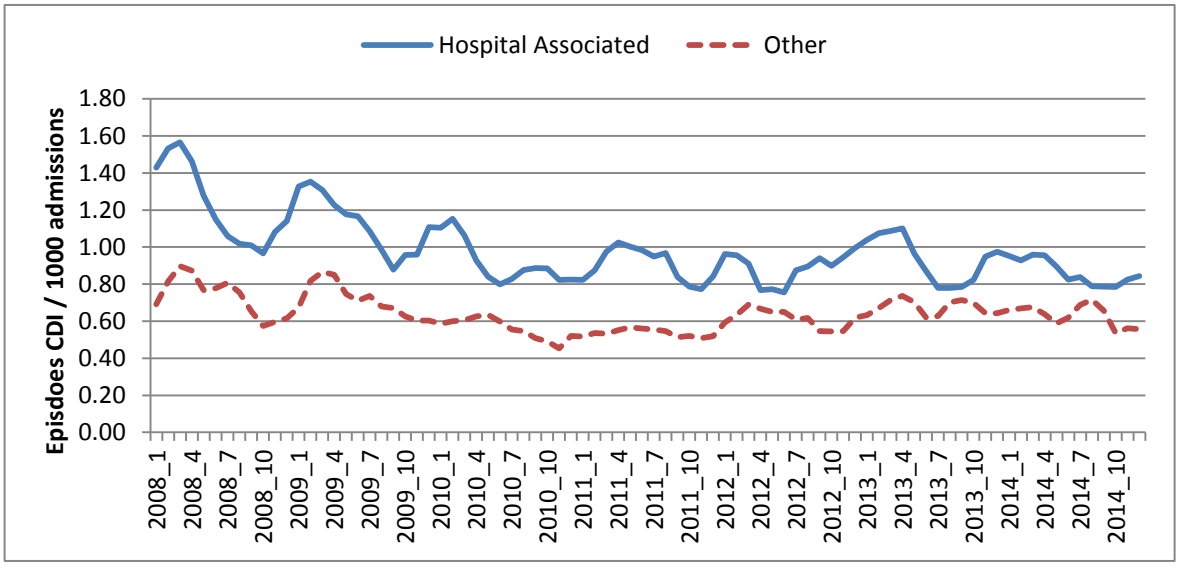


Acute hospitals: defined on the basis of mean length of stay <14 days
Only hospitals providing data for the whole year are included.

3.1.4 Seasonal variation

Figure 5 shows a seasonal peak of incidence during January to April. HA-CDI largely follows the same pattern as other cases, although for the year 2014, this pattern is not so clear.

Figure 5 : Monthly incidence (moving average*) of *Clostridium difficile* infections (CDI) in Belgian hospitals per 1000 admissions 2008-2014



Only hospitals providing data for the whole year are included.
**Moving average : each monthly incidence is the mean of the month, the preceding month and the following month.*

3.1.5 *Further descriptive epidemiology of cases 2014*

Approximately 70% of cases for whom department of diagnosis was recorded (55% of all cases) arise from four out of a total of 29 departments: geriatrics, gastroenterology, onco-haematology and general internal medicine.

For hospital associated infections, however, 40% of cases for whom department of diagnosis was recorded (31% of all hospital associated cases) arise in the geriatrics department (see Table 6).

Table 6 : Department of diagnosis for all hospital associated episodes of *Clostridium difficile* infection (CDI), 2014

Department	*Frequency*	*%*
Geriatrics	447	31
Haemato-oncology	128	9
Intensive care (ICU)	103	7
General Medicine	86	6
Gastro-enterology	81	6
Respiratory medicine	81	6
Cardiology	58	4
Nephrology/haemodialysis	58	4
Other	62	5
Departmentt unknown/missing	328	23
Total	1432	100

The age distribution of cases varied little between 2008 and 2014 and is consistent with that shown in Table 7 for the year 2014 below.

Table 7 : Age distribution of all patients, 2014

Age group	*No. of patients*	*%*
0-2	40	2
3-64	627	27
65-79	674	29
80-max	980	42
Age unknown	4	<1
Total	2325	100

3.3 Hospital stay and Clostridium difficile infection (CDI) testing data

Hospital stay records mentioning a primary or a secondary diagnostic code of "Intestinal infection due to *Clostridium difficile*" almost trebled from 1999, reaching a peak in 2008, subsided again between 2008-2011 but have risen again in the year 2012 (last available data), see Table 8 and Figure 6.

The proportion of stays with a primary diagnostic code of CDI – presumed in this case to be the reason for admission – remains stable. This acts as an approximation of cases associated in the community (serious enough to justify hospitalization) (CA-CDI), although for some of these patients, the origin of infection may have been a long term care facility or another hospital[1]. Patients with a secondary diagnostic code of CDI are assumed to be HA-CDI.

Table 8 : Hospital stays with an intestinal infection due to *Clostridium difficile (CDI)*, Belgium 2000-2012

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
CDI as primary diagnostic code (no.)	415	467	423	501	723	907	959	1007	1040	1116	1148	920	866	940
CDI as primary diagnostic code (% of total)	25%	26%	23%	23%	25%	23%	22%	23%	22%	23%	25%	24%	24%	24%
CDI as secondary diagnostic code* (no.)	1270	1356	1404	1698	2155	3086	3456	3383	3646	3633	3514	2947	2715	2939
Total no. cases CDI	1685	1823	1827	2199	2878	3993	4415	4390	4686	4749	4662	3867	3581	3879

**code ICD-9_CM 008.45*

[1] In a sub-analysis of 2011 hospital admissions (RHM/MZG data), 78% of those admitted with a primary diagnosis of CDI were admitted from home, 18% from LTCF, 2% from other hospitals and 2% from elsewhere (analysis by MLLambert, May 2015)

Table 9 : incidence of *Clostridium difficile* infection (CDI) per 100 000 Belgian population using hospital stay data, 2000-2012

Cases per 100 000 population	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
CA-CDI[a]	4.1	4.6	4.1	4.8	7.0	8.7	9.2	9.5	9.8	10.4	10.6	8.4	7.9	8.5
HA-CDI[b]	12.4	13.2	13.6	16.4	20.8	29.6	33.0	32.1	34.3	33.9	32.5	27.0	24.7	26.6
Total cases CDI	16.5	17.8	17.8	21.3	27.7	38.3	42.1	41.6	44.1	44.3	43.2	35.5	32.6	35.0

Population of Belgium[16]

[a] *assumed that those with primary diagnostic code of CDI are community associated (CA) infections*

[b] *assumed that those with secondary diagnostic code of CDI are hospital associated (HA) infections*

Table 10 shows the proportionate change in the number of tests for CDI in hospitalised patients compared to the number of cases discharged from hospital with a primary or secondary diagnosis of CDI, using the baseline year of 2000. The proportionate increase in the number of cases is far greater than the increase in testing. The number of tests per case has decreased from 29 in 2000 to 18-19 in the period of high incidence between 2004-2007 and has stabilised around 21 tests per case since then. This indicates that trends in the number of cases cannot wholly be attributed to trends in testing.

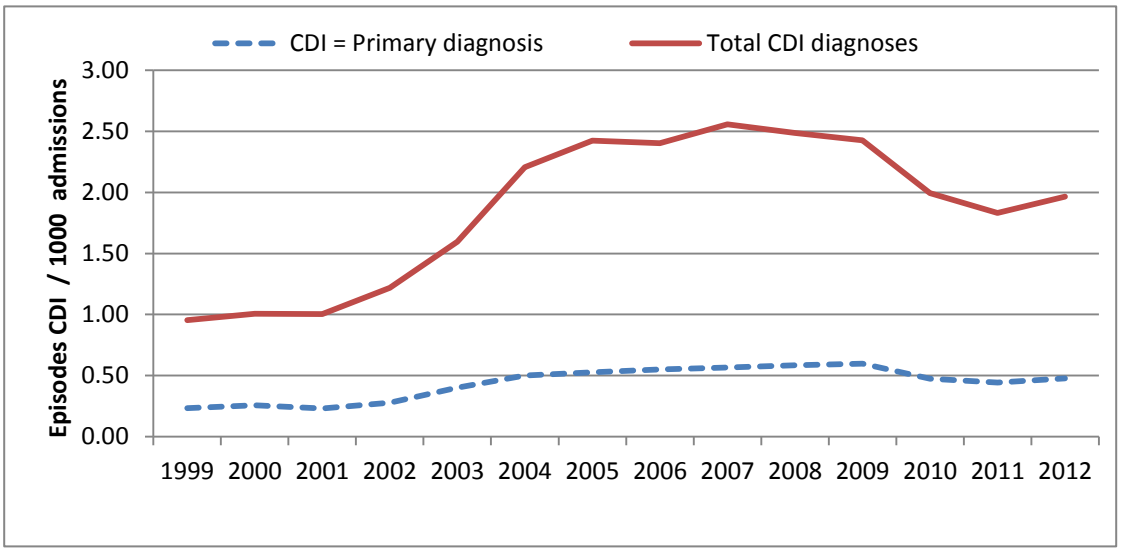
Table 10 : Relationship between number of tests[a] carried out in hospitalised patients for *Clostridium difficile infection* (CDI) and the number of cases discharged[b], 2000-2012

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total no. of CDI test[a]	52 107	56282	55 888	64 063	74 947	79 573	82 342	86 229	99 437	94 525	84 779	81 045	82 054
Total no. CDI cases[b]	1823	1827	2199	2878	3993	4415	4390	4686	4749	4662	3867	3581	3879
% increase in no. tests since year 2000		8	7	23	44	53	58	65	91	81	63	56	57
% increase in no.cases since year 2000		0	21	58	119	142	141	157	161	156	112	96	113
No. tests per case	29	31	25	22	19	18	19	18	21	20	22	23	21

[a] *Source: INAMI / RIZIV – CDI tests for hospitalised patients, February 2015*

[b] *Source: Hospital stay data- RHM/MZG, March 2015*

Figure 6 : Hospital stays with an intestinal infection due to *Clostridium difficile (CDI) Belgium 1999-2012**



** code ICD-9_CM 008.45*

Table 11 shows that the calculated incidence is elevated (25-35%) by measuring incidence using hospital stay data compared to when using the mandatory surveillance data. Differences could be due to the way CDI cases are identified but the reasons are not entirely clear. However, the key point is that the difference between the two measures remains approximately constant, indicating that the surveillance data provide a valid measure of incidence trends for CDI.

Table 11 : Mean incidence of *Clostridium difficile* infections (CDI) per 1000 hospital stays, Belgium, 2008-2012, according to data source

	2008	2009	2010	2011	2012
Hospital stay data (RHM/MZG)(a)	2.49	2.43	1.99	1.83	1.97
Mandatory hospital surveillance data (b)	1.96	1.83	1.48	1.44	1.50
a/b	127%	133%	134%	127%	131%

RHM/MZG: Résumés hospitaliers minima/ Minimale ziekenhuis gegevens (minimum hospital data set

3.4 Death registration data

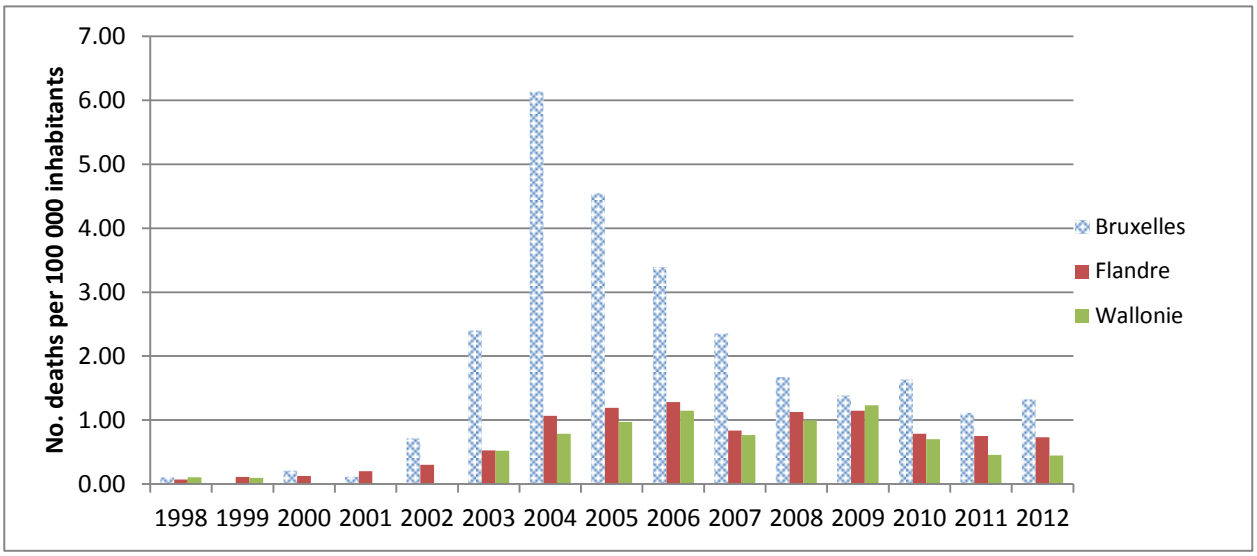
The following data are taken from death certificates recording underlying cause of death as enterocolitis due to *Clostridium difficile* (Code ICD-10 A04.7).

Table 12 : Deaths attributed to enterocolitis due to *Clostridium difficile by region, Belgium 1998-2012**

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Number of death certificates with ICD-10 code A04.7 as underlying cause of death															
Brussels	1	0	2	1	7	24	61	47	36	24	16	14	17	12	15
Flanders	4	6	7	11	17	30	63	72	80	54	75	76	55	56	55
Wallonia	3	3	NA	NA	NA	17	26	33	40	27	36	45	26	18	18
Belgium	8	9	NA	NA	NA	71	150	152	156	105	127	137	98	86	88
Crude specific mortality rate per 100 000 inhabitants															
Brussels	0.10	0.00	0.21	0.10	0.71	2.41	6.08	4.64	3.51	2.31	1.51	1.30	1.54	1.06	1.31
Flanders	0.07	0.10	0.12	0.18	0.28	0.50	1.04	1.19	1.31	0.88	1.21	1.25	0.88	0.88	0.86
Wallonia	0.09	0.09	NA	NA	NA	0.50	0.77	0.97	1.17	0.78	1.04	1.29	0.74	0.51	0.51
Belgium	0.08	0.09	NA	NA	NA	0.68	1.44	1.45	1.48	0.99	1.19	1.27	0.90	0.78	0.80

Mortality rates from enterocolitis due to *Clostridium difficile* increased rapidly from 1998 until 2004. Since 2006, one can see an large decline in deaths attributable to *Clostridium difficile*. Brussels has the highest standardised mortality rate, followed by Flanders and Wallonia, respectively (see Figure 7).

Figure 7 : *Clostridium difficile* infections (CDI): age-standardised mortality rate, by region Belgium 1998-2012



Enterocolitis due to Clostridium difficile as *underlying cause of death* (Code ICD-10 A04.7). *Direct standardisation using Belgian mid-year 2005 population as reference population, according to 3 age groups (0-64, 65-79, 80+).*

3.5 Microbiological surveillance – National Laboratory Reference Centre (NRC-CD) data

3.5.1 Participation

In 2014, 112 hospital sites participated in the annual surveillance programme – the greatest number of hospital sites since 2009. Eighty four laboratories sent cultures in the first semester, 73 in the second and 44 laboratories participated during both semesters. Since 2011, samples are counted according to the sample date and no longer according to the date of receipt in the NRC-CD.

Table 13 lists the distribution of laboratories as a function of the number of samples (1-10) sent as part of the annual surveillance. Twenty three labs participated in two semesters surveillance, with 22 of these sending at least 5 samples per semester.

Table 13 : Number of samples sent to NRC-CD by local laboratories in 2014

No. of samples sent to NRC-CD	No. of local laboratories
1	14
2	15
3	6
4	10
5	16
6	11
7	8
8	2
9	8
≥10	22
Total	**112**

In total, 740 isolates were received by the NRC-CD in 2014. Among these, 37 isolates were not confirmed as *Clostridium difficile* (other species identified or culture not possible). For those laboratories exceeding their quota of 5 isolates per semester, only the first five samples were entered into the calculation. In total 616 isolates were ribotyped as part of the surveillance programme. This number is higher than that of the preceding year (585) but less than the number ribotyped in the year 2012 (648) – see Table 15.

3.5.1 Ribotype distribution

Ribotyping of these 616 isolates in 2014 resulted in the identification of 121 different ribotypes of which 66 were only encountered a single time, 14 twice and 10 three times.

The most common ribotypes are found across most of the regions of the country (see Table 14).

Table 14 : Number of the most common *Clostridium difficile* ribotypes (BR) isolated in 2014 by province, Belgium

Ribotypes	BR014	BR020	BR078	BR002	BR106	BR027	BR070	BR087
Antwerpen	11	8	5	4	2	3	3	2
Vlaams-Brabant		7		2	1			
Brabant wallon	2	4		3				2
Bruxelles / Brussel	10	9	9	4	7	3	1	
West Vlaanderen	12	8	11	7	2	7	2	3
Oost-Vlaanderen	9	3	4	3		3	2	
Hainaut	9	8	3	4	4	1	6	2
Liège	6	4	6	4	2	3	1	3
Limburg	9	1	3	3	4			1
Luxembourg		1						
Namur	3	5		3			2	4

3.5.1 Trends in ribotype prevalence

Table 15 shows the most common ribotypes as a number and percentage of those typed as part of the surveillance programme. Table 16 shows how many hospitals (and the percentage of participating hospitals) where these ribotypes were isolated. These tables also show the change in prevalence of these ribotypes over time (2009-2014).

Table 15 : Number of *Clostridium difficile* isolates included in the surveillance programme and description of the most common ribotypes, Belgium 2009-2014

	2009	2010	2011	2012	2013	2014
N isolates received, typable & included in the surveillance programme	**389**	**505**	**462**	**648**	**585**	**616**
N isolates BR027 (UCL027)	72	62	36	32	22	20
%	18.5	12.3	7.8	4.9	3.8	3.2
N isolates BR014 (UCL 16)	44	51	56	67	50	71
%	11.3	10.1	12.1	10.3	8.6	11.5
N isolates BR078 (UCL3)	13	33	35	48	30	41
%	3.3	6.5	7.6	7.4	5.1	6.7
N isolates BR020 (UCL16a)	20	31	31	56	42	58
%	5.1	6.1	6.7	8.6	7.2	9.4
N isolates BR002(UCL32)	15	21	37	52	36	37
%	3.9	4.2	8.0	8.0	6.2	6
N isolates BR070 (UCL 47)				10	29	17
%				1.5	5.0	2.8
N isolates BR106 (UCL 48d)				7	18	22
%				1.1	3.1	3.6
N isolates BR087 (UCL 24)					7	17
%					1.2	2.8

As indicated in Table 15 and Table 16, ribotype BR027 as a proportion of all ribotypes isolated in 2014 continued to decline (3.2% in 2014 versus 3.8% in 2013) and the number of hospitals sending this ribotype (14 versus 15). However, there was an outbreak of this ribotype declared in West Flanders.

Ribotype BR014 (UCL16) remains, as in 2011, 2012 and 2013, the most commonly isolated ribotype, increasing in proportion to other ribotypes since last year (11.5% in 2014 versus 8.6% in 2013) and also in the number of hospital sites affected (42 versus 38).

Ribotypes BR020 (UCL 16a), BR002 (UCL32) and BR078 (UCL3) occupy positions 2 to 4 for the most commonly isolated ribotypes and all have increased since last year.

Ribotype BR070 (UCL47), which emerged last year, is in decline. It was isolated 17 times in 2014 (2.8% of all riboytpes) and 29 times in 2013 (4.9%) and was found in 14 different hospitals in 2014 (versus 24 in 2013).

The proportion of isolates that are typed as ribotype BR106 (UCL48d) is continuing to rise, after its emergence in 2012. Twenty two isolates were found in 18 different hospitals in 2014 (versus 7 isolates in 6 hospitals in 2012). The emergence of ribotype BR087 (UCL24) with 17 isolates in 13 different hospitals is also noted.

Table 16 : Participation in the surveillance programme (by hospital site) and evolution of the most common *Clostridium difficile* ribotypes, Belgium 2009-2014

	2009	2010	2011	2012	2013	2014
N hospitals (different sites) sending samples for typing	104	103	84	111	103	112
N hospitals isolating BR027 (UCL027)	35	34	17	19	15	14
%	33.6	33.0	20.2	17.1	14.6	12.5
N hospitals isolating BR014 (UCL 16)	35	34	32	45	38	42
%	33.6	33.0	38.0	40.5	36.9	37.5
N hospitals isolating BR078 (UCL3)	11	26	20	35	25	28
%	10.6	25.3	23.8	31.5	24.3	25.0
N hospitals isolating BR020 (UCL16a)				42	29	41
%				37.8	28.2	36.6
N hospitals isolating BR002(UCL32)				39	28	27
%				35.1	27.2	24.1
N hospitals isolating BR070 (UCL 47)				10	24	14
%				9.0	23.3	12.5
N hospitals isolating BR106 (UCL 48d)				6	13	18
%				5.4	12.6	16.0
N hospitals isolating BR087 (UCL 24)						13
%						11.6

Figure 8 and Figure 9 illustrate the evolution of the most common ribotypes in number and percentage.

Figure 8 : Evolution of number of isolates belonging to the most common ribotypes in Belgian hospitals 2009-2014

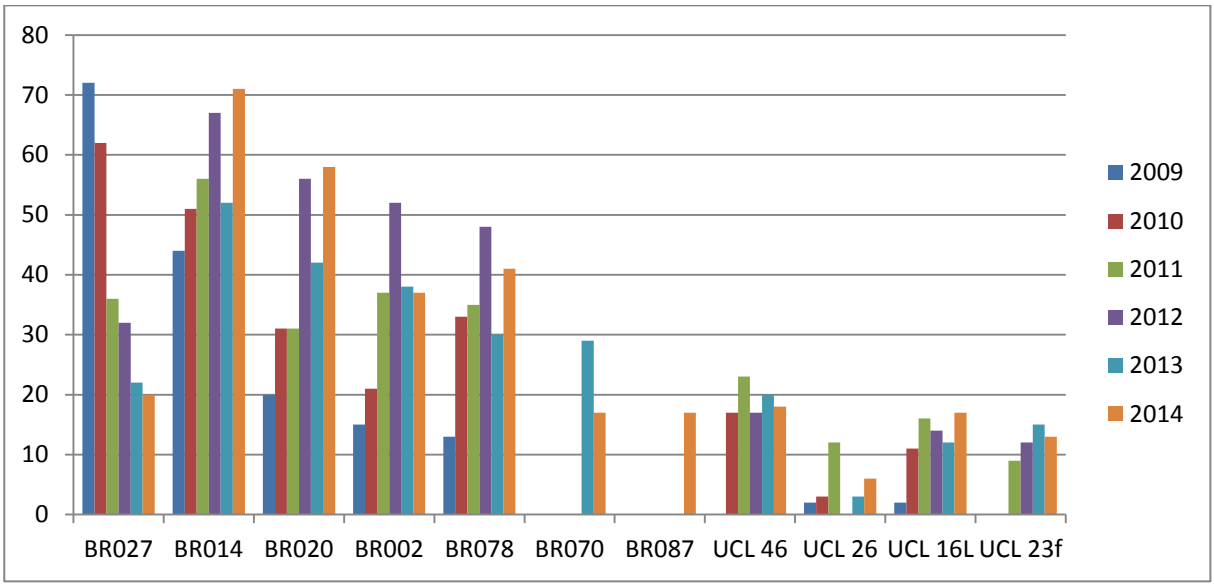


Figure 9 : Evolution of the percentage of ribotypes belonging to the most common ribotypes in Belgian hospitals 2009-2014

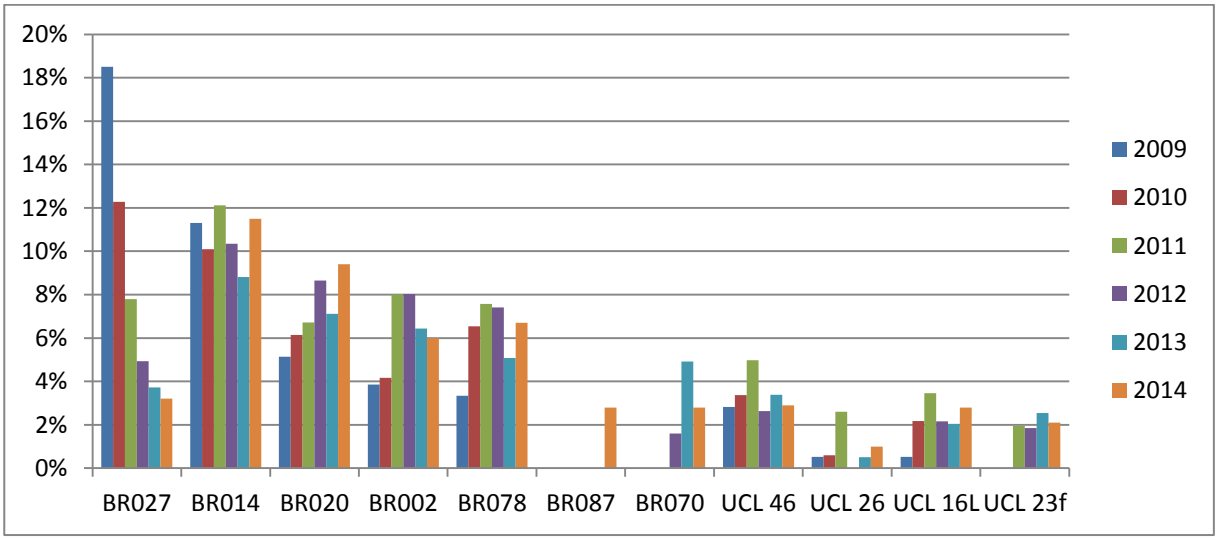
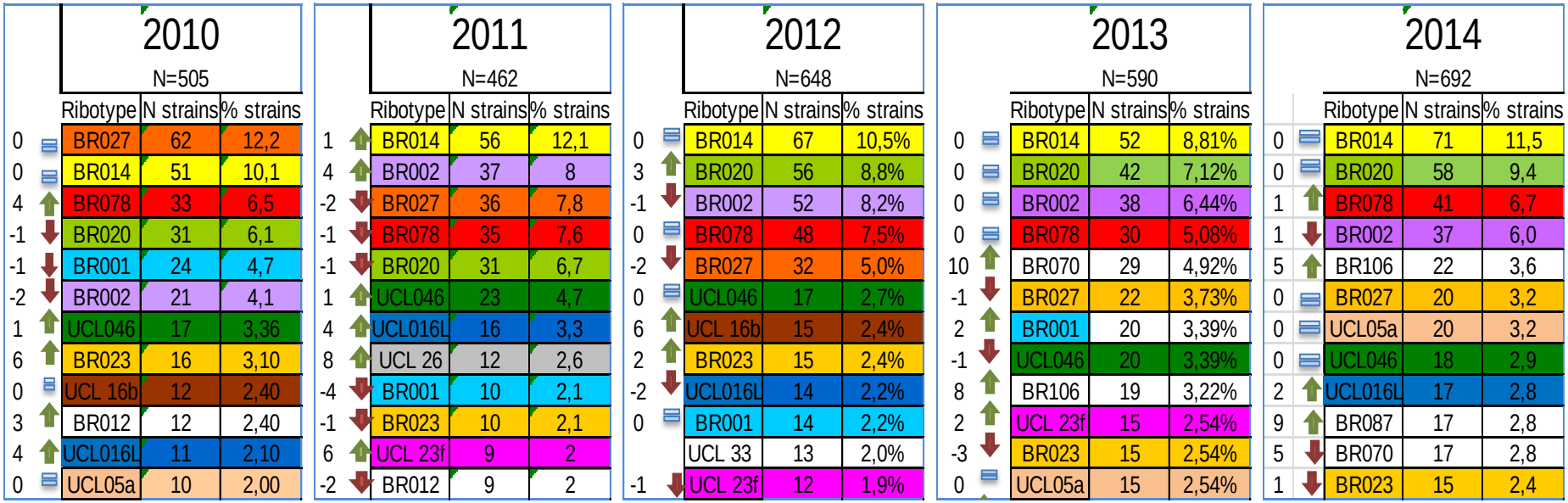


Figure 10 : Evolution of the frequency of the most commonly identified ribotypes in Belgian hospitals, 2010 - 2014



2010 N=505

	Ribotype	N strains	% strains
0	BR027	62	12,2
0	BR014	51	10,1
4	BR078	33	6,5
-1	BR020	31	6,1
-1	BR001	24	4,7
-2	BR002	21	4,1
1	UCL046	17	3,36
6	BR023	16	3,10
0	UCL 16b	12	2,40
3	BR012	12	2,40
4	UCL016L	11	2,10
0	UCL05a	10	2,00

2011 N=462

	Ribotype	N strains	% strains
1	BR014	56	12,1
4	BR002	37	8
-2	BR027	36	7,8
-1	BR078	35	7,6
-1	BR020	31	6,7
1	UCL046	23	4,7
4	UCL016L	16	3,3
8	UCL 26	12	2,6
-4	BR001	10	2,1
-1	BR023	10	2,1
6	UCL 23f	9	2
-2	BR012	9	2

2012 N=648

	Ribotype	N strains	% strains
0	BR014	67	10,5%
3	BR020	56	8,8%
-1	BR002	52	8,2%
0	BR078	48	7,5%
-2	BR027	32	5,0%
0	UCL046	17	2,7%
6	UCL 16b	15	2,4%
2	BR023	15	2,4%
-2	UCL016L	14	2,2%
0	BR001	14	2,2%
	UCL 33	13	2,0%
-1	UCL 23f	12	1,9%

2013 N=590

	Ribotype	N strains	% strains
0	BR014	52	8,81%
0	BR020	42	7,12%
0	BR002	38	6,44%
0	BR078	30	5,08%
10	BR070	29	4,92%
-1	BR027	22	3,73%
2	BR001	20	3,39%
-1	UCL046	20	3,39%
8	BR106	19	3,22%
2	UCL 23f	15	2,54%
-3	BR023	15	2,54%
0	UCL05a	15	2,54%

2014 N=692

	Ribotype	N strains	% strains
0	BR014	71	11,5
0	BR020	58	9,4
1	BR078	41	6,7
1	BR002	37	6,0
5	BR106	22	3,6
0	BR027	20	3,2
0	UCL05a	20	3,2
0	UCL046	18	2,9
2	UCL016L	17	2,8
9	BR087	17	2,8
5	BR070	17	2,8
1	BR023	15	2,4

In Figure 10, the arrows accompanying the number indicate the gain or loss of place for the different ribotypes in terms of frequency classification.

3.6 Linkage between laboratory and epidemiological surveillance data

Linkage has improved continuously between 2011-2014 (see Table 17). For the year 2014 we were able to match 96% of all[2] typed toxigenic *Clostridium difficile* reference laboratory specimens with hospital epidemiological records. Twenty seven percent of hospitalised CDI cases were ribotyped and matched.

Note that the total number of laboratory specimens included in this analysis includes all specimens typed by the NRC-CD, unlike the analyses in section 3.5 which include only the first 5 specimens per semester per hospital site that comprise the official surveillance programme.

Table 17 : Matching reference laboratory ribotyping with epidemiology surveillance data from Belgian hospitals, 2011-2014

	2011		2012		2013		2014	
	N	%	N	%	N	%	N	%
N records in epi database	2564		2565		2782		2470	
Epi records merged with reflab (by NSIHweb1 year*)	228	9%	627	24%	640	23%	678	27%
N records available for analyses in reflab database	203		633		699		709	
Lab records merged with epi (by reflab year*)	179	88%	588	93%	655	94%	679	96%
N hospitals with *C.diff* cases	137		136		134		134	
N hospitals with matched data	58		97		99		104	

**Reference laboratory (reflab) year is based on date of sampling whereas NSIHweb1 year is based on onset of symptoms of CDI*
Epi: case based database NSIHweb1 containing epidemiological information

[2] Excluding specimens with no patient details, no hospital details or no year for sample

Table 18 shows CDI episodes for all available years (Sep 2011- Apr 2015) and illustrates that when compared to the overall population of hospitalised CDI cases that were not ribotyped, those cases that were ribotyped and matched with their epidemiological data were older, more likely to have hospital associated- and less likely to have community associated- infection and were less likely to have recurrent infection.

Table 18 : Comparison of characteristics for ribotyped matched *Clostridium difficile* episodes and un-matched episodes in Belgian hospitals, 2011-2015

	Ribotyped & matched		Un-matched			
	N	%	N	%	Chi^2	p
All cases	2515		8687			
Male	1073	43	3702	43	0.19	0.67
Age 80+	1223	49	3762	43	18	0.00
Hospital associated CDI (HA-CDI)	1600	64	5118	59	13	0.00
Community associated CDI	536	21	2177	25	17	0.00
LTCF associated CDI	110	4	312	4	2.9	0.09
Complications and death due to CDI	140	6	490	6	0.04	0.85
Recurrent infection	185	7	778	9	6.2	0.01
Time to infection for HA-CDI episodes (days)	Mean 26	Median 16	Mean 24	Median 14		

LTCF: Long term care facility

Table 19, Table 20 and Table 21 show the top seven most common ribotypes in Belgium between 2011-2015 and illustrate the differences in population affected and resulting likely disease outcome for these ribotypes.

Hospital associated infection (HA-CDI) was defined as onset of symptoms $\geq$ 2 days after hospitalisation in the declaring hospital; Complications were defined as death (as a direct or indirect result of CDI) within 30 days of onset of infection, pseudomembranous colitis, or the need for admission to the intensive care unit or for surgery as a result of CDI.

Table 19 : *Clostridium difficile* ribotype characteristics with respect to patient age, episodes in hospitalised Belgian patients 2011-2015

Brazier classification Ribotype_X	With Ribotype_X Total no.	With Ribotype_X Proportion age 80+(%)	Without Ribotype_X Total no.	Without Ribotype_X Proportion age 80+(%)	Prevalence ratio (RR)	95%CI	p
Ribotype 014	281	50	2228	49	1.0	0.9-1.2	0.61
Ribotype 020	213	46	2296	49	0.9	0.8-1.1	0.40
Ribotype 002	194	55	2315	48	1.1	1.0-1.3	0.06
Ribotype 078	171	49	2338	49	1.0	0.9-1.2	0.92
Ribotype 027	102	66	2407	48	1.4	1.2-1.6	0.00
Ribotype 106	75	37	2434	49	0.8	0.6-1.0	0.05
Ribotype 001	76	53	2433	49	1.1	0.9-1.3	0.49
Other Ribos	1397	47	1112	51	0.9	0.9-1.0	0.07
All ribotypes	2509	49					

**Equivalent UCL classification (UCL ribotype 16=BR 014, UCL 16a=BR 020, UCL 32*=BR 002, UCL 3=BR 078, UCL 027= BR 027, UCL 48d=BR 106, UCL 23e=BR001)*

Those infected with ribotype 027 were more likely to be aged 80 or over than those affected by all other ribotypes (Relative risk [RR] 1.4, 95% confidence interval [CI] 1.2-1.6). Those infected with ribotype 106 were less likely to be aged 80 or over than those affected by all other ribotypes (RR 0.8; CI 0.6-1.0) (see Table 19).

Table 20 : *Clostridium difficile* ribotype characteristics with respect to origin of infection, episodes in hospitalised Belgian patients 2011-2015

Brazier classification Ribotype_X	With Ribotype_X		Without Ribotype_X				
	Total no.	Proportion HA-CDI(%)	Total no.	Proportion HA-CDI(%)	Prevalence ratio (RR)	95%CI	p
Ribotype 014	280	65	2228	64	1.0	0.9-1.1	0.66
Ribotype 020	212	68	2296	63	1.1	0.1-1.2	0.19
Ribotype 002	193	64	2315	64	1.0	0.9-1.1	0.98
Ribotype 078	171	61	2337	64	1.0	0.8-1.1	0.40
Ribotype 027	102	54	2406	64	0.8	0.7-1.0	0.03
Ribotype 106	76	63	2432	64	1.0	0.8-1.2	0.91
Ribotype 001	76	70	2432	64	1.1	0.9-1.3	0.27
Other Ribos	1398	64	1110	64	1.0	0.9-1.1	0.94
All ribotypes	2508	64					

**Equivalent UCL classification (UCL ribotype 16=BR 014, UCL 16a=BR 020, UCL 32*=BR 002, UCL 3=BR 078, UCL 027= BR 027, UCL 48d=BR 106, UCL 23e=BR001)*

Those infected with ribotype 027 were less likely to have hospital associated infection than those affected by all other ribotypes (RR 0.8, CI 0.7-1.0) (see Table 20).

Table 21 : *Clostridium difficile* ribotype characteristics with respect to complications, episodes in hospitalised Belgian patients 2011-2015

Brazier classification Ribotype_X	With Ribotype_X		Without Ribotype_X				
	Total no.	Proportion with complic(%)	Total no.	Proportion with complic(%)	Prevalence ratio (RR)	95%CI	p
Ribotype 014	209	9	1613	8	1.2	0.8-2.0	0.42
Ribotype 020	170	6	1652	8	0.8	0.4-1.4	0.35
Ribotype 002	141	8	1681	8	1.0	0.6-1.8	0.96
Ribotype 078	119	10	1703	8	1.3	0.8-2.4	0.31
Ribotype 027	71	14	1751	7	1.9	1.0-3.5	0.04
Ribotype 106	46	11	1776	8	1.4	0.6-3.3	0.41
Ribotype 001	66	3	1756	8	0.4	0.1-1.5	0.15
Other Ribos	1000	7	822	8	0.9	0.6-1.2	0.30
All ribotypes	1822	8					

**Equivalent UCL classification (UCL ribotype 16=BR 014, UCL 16a=BR 020, UCL 32*=BR 002, UCL 3=BR 078, UCL 027= BR 027, UCL 48d=BR 106, UCL 23e=BR001)*

Those infected with ribotype 027 were more likely to have complications than those affected by all other ribotypes (RR 1.9, CI 1.0-3.5). The relative risk of complications in those with ribotypes 078 and 106 were also raised and that of ribotype 001 lowered but did not reach statistical significance. However, overall numbers suffering from complications were small (see Table 21).

3.7 International comparisons

Table 22: International comparison of incidence of *Clostridium difficile* infection – for hospital patients only

	N. Ireland[18]	Australia[19]	Germany[20]	Netherlands[21]	Italy[4]	Belgium	Belgium
Year & duration of study	2014 continuous	2011-2012 1 year	2013 continuous	2012-13 continuous	2012-13 1 year	2014 continuous	2012 continuous
Data source	Mandatory surveillance	Voluntary surveillance	Voluntary surveillance	Sentinel surveillance	Survey	Mandatory surveillance	Hospital discharge data
Hospital population	Age 2+ In-pts	Age 2+ In-pts & clinic pts	All ages In-pts	All ages In-pts	All ages In-pts	All ages In-pts	All ages In-pts
N hospitals	All	450	275	20		108	All
Trend of incidence	Stable 2011-14	↑ 2011-12	Stable 2007-12 ↑ 2013	Stable 2010-13	↑ since previous survey in 2008	↓ 2008-2014	↓ 2008-11 ↑ 2011-12
total cases /							
10 000 hosp days	2.4	3.7	7.2	2.9	8.3	1.34	2.6
1 000 admissions			2.1	1.6		0.97	2.0
Hospital associated cases /							
10 000 hosp days		3.0	4.4			0.73	2.0
1 000 admissions						0.32	1.5
% Hospital associated							
	62[ac]		58[b]			59[b]	

[a]all episodes – in-patient and out-patient, [b]in-patient episodes only, [c]65 years and over, popn: population (inhabitants)
Pts= patients

Table 23: International comparison of incidence of *Clostridium difficile* infection – for hospital and community patients

	US[22]	England[23,24]	Scotland[25]	Belgium
Year & duration of study	2011 1 year	2013-14 continuous	2013 continuous	2012 continuous
Data source	Survey	Mandatory surveillance	Mandatory surveillance	Hospital discharge data
Population	Age ≥1 Hosp & community pts	Age 2+ Hosp & community pts	Age 15+ Hosp & community pts	All ages Hosp In-pts
N hospitals	*	All	All	All
Trend of incidence	↑ 2011-2012	↓ 2007-2014	↓ 2007-2013	↓ 2008-11 ↑ 2011-12
total cases /				
10 000 hosp days		3.9	3.5	
1 000 admissions				
100 000 popn	147.2	25.0		35.0
Hospital associated cases /				
10 000 hosp days		1.47		
1 000 admissions				
100 000 popn	95.3			26.6
Community associated cases /				
100 000 popn	51.9			8.5
% Hospital associated				
	65[a]	38[a] 58[b]		

**Reference[22] –total population, approximately 11.2 million, 34 counties. Reference[26] - 10 % decrease in hospital-associated C. difficile infections between 2011 and 2013 in survey of 3500 US hospitals [a]all episodes – in-patient and out-patient, [b]in-patient episodes only, popn: population (inhabitants), hosp=hospital*

In Europe as a whole, infection rates increased substantially between 2008-2013 from 4.1 to 7.9 cases per 10, 000 hospital bed days[4]. However, some European countries within this grouping have succeeded in decreasing their incidence during this time, notably the UK and Belgium.

Direct comparisons between countries are difficult. Completeness of surveillance varies widely – with only Belgium and UK using mandatory surveillance. Other countries use continuous voluntary surveillance and others undertake surveys to quantify infection in a subset of hospitals over a short period. The frequency of testing varies between countries; testing algorithms vary, with a variety of different sensitivity tests used. Definitions of infection, such as hospital-acquired/ hospital-associated/ hospital-onset cases which can be defined as onset of symptoms anywhere between ≥2 days to 4 days after admission. Post-discharge infections which can be attributed to hospital care may be more completely included in some countries and denominators also vary between countries.

Table 22 shows that the reported national incidence of CDI in hospitalised patients in Belgium is less than that of Germany and Italy and on a par with the Netherlands and N. Ireland (for the respective years given in the table). However, the incidence of total cases / 100 000 national population is calculated as greater in Belgium than in England, despite the fact that the English data include hospitalised and non-hospitalised CDI patients and Belgium includes only hospitalised patients (Table 23).

On the basis of these data, even given the caveats in making comparisons, we believe it can be said that Belgium has an incidence of CDI in the mid to lower range of other European countries, and certainly somewhat lower than the United States.

The proportion of hospitalised patients who have hospital associated CDI is remarkably consistent at 58-59% in Belgium, Germany and England.

The European prevalence studies noted an increase in the prevalence of ribotype 027 across Europe as a whole[4], in marked contrast to the declining trend in UK[27] and Belgium (see NRC laboratory report in section 3.5).

4 Discussion and conclusions

4.1 Discussion

This report summarises the different sources of available data on the epidemiology of *Clostridium difficile* infection (CDI) in Belgium. A large number of hospitals have participated in the surveillance programme whilst it has been mandatory between 2007-2014. The majority of them have provided data for the whole year, despite the legal obligation being to provide data for only six months. It remains to be seen how the change in legal obligation, effective from the end of 2014, will affect future participation and thus our ability to monitor the epidemiology of *Clostridium difficile* in Belgium.

Incidence of CDI in hospitalised patients has declined almost continuously between 2008-2014. In 2014 (latest data), the mean incidence of all CDI from all participating hospitals was 1.49 per 1 000 admissions (1.46 episodes for acute hospitals and 4.91 episodes for chronic hospitals per 1000 admissions), less than the preceding year. The mean incidence of hospital-associated CDI was higher in chronic hospitals when measured in episodes per 1000 admissions but higher in acute hospitals when measured per 10 000 hospital days (0.84 episodes for acute and 3.30 episodes for chronic hospitals per 1000 admissions; and 1.20 episodes for acute and 0.93 episodes for chronic hospitals per 10 000 hospital days). Incidence has consistently been lowest in the northern part of the country (Flanders).

Changes in testing rates cannot fully explain the national trends in incidence of CDI.

The proportion of hospital associated cases has decreased from 64% to 59% of total cases between 2008-2014 with a reflected increase in community associated cases (from 56% to 64% of all other cases) during the same time period.

Mortality and hospital stay data highlighted an important increase in incidence in CDI and CDI deaths from the early 2000s reaching a peak between 2007-2008. Mortality rates for CDI decreased markedly after the peak in 2005-2006 and now are either stable or decreasing in all regions. The CDI mortality rate for Belgium was 0.80 deaths per 100 000 inhabitants in 2012 (the latest year with available data). Mortality rates (crude or age standardized) are highest in Brussels and for most years since the peak, have been lowest in Wallonia. The high rate in Brussels probably reflects the high number of secondary and tertiary referral hospitals in the region. Surveillance data indicates that the proportion of patients suffering complications of CDI (pseudomembranous colitis, admission to the intensive care unit or the need for surgery as a result of CDI) have also decreased between 2008-2014.

There is a seasonal variation in incidence of CDI with a peak during January-April months each year. Hospital associated cases follow the same seasonal pattern as other cases. Research could examine a possible association with antibiotic therapy for seasonal respiratory tract.

There exists a large variability in the incidence of hospital associated CDI between hospitals and between regions. Even with the usual precautions of interpretation applied (different populations of patients, case-mix, different diagnostic tests with different sensitivity), there may, nevertheless, remain an important potential for prevention of CDI such as in infection prevention and control or antibiotic stewardship.

The incidence of CDI calculated when using hospital stay data was greater than that calculated when using hospital surveillance data (mandatory hospital programme), but the difference between the two measures remains constant (2008-2012), indicating the validity of the surveillance data.

Other countries use different definitions and include different cases within their surveillance. As far as possible we have tried to be consistent with common practice and guidelines throughout the EU and the world. Examples of differences are the inclusion of 0-2 year olds in the Belgian surveillance system and a difference in the definition of healthcare-associated, hospital associated or hospital acquired cases. We have shown that only 40 (1.7%) of all cases in 2014 were 0-2 years old, and the exclusion of them made little difference to the results of our analyses. There was also very little difference in the results when we re-defined hospital-associated cases as those with onset $\geq$3 days after admission instead of $\geq$ 2 days after admission.

International comparisons indicate that Belgium has incidence rates of CDI in the mid- to lower range of other European countries and lower than that in the United States.

The process of sending *Clostridium difficile* samples by the local laboratories to the NRC-CD for ribotyping has now stabilised and participating laboratories are to be congratulated. There is a great variety of ribotypes circulating in Belgium, which indicates that transmission is not caused by one particular strain and that there are multiple pathways of transmission. The different ribotypes are generally spread throughout the whole country without localisation within certain towns or regions.

The prevalence of ribotype 027 continues to diminish (now 3% of all ribotyped samples). There was an initial rise in the prevalence of ribotype 078 in 2010 but this levelled off quickly to around 7%. The predominant strain is now 014 (12% of ribotyped samples).

Ribotype BR106, for which the prevalence is rising in Belgium is a ribotype that was second in frequency in UK in 2007-2008 but which has decline there since then.[28]

Linkage of patient information with their laboratory ribotyping information is continuing to improve. We have shown that those patients whose samples are sent to the reference laboratory for ribotyping and are matched with their epidemiological data from NSIHweb1 are older and ;ore likely to have HA-CDI or recurrent CDI than the overall population of CDI patients. For the first time, we have described certain epidemiological characteristics of patients and their CDI with the infecting ribotypes.

Our data show that those hospitalised patients with ribotype 027 are more likely to be aged 80 and over than those infected with other ribotypes and their infection is less likely to be hospital associated than those with other ribotypes. Patients with ribotype 027 are more likely to suffer complications. This is consistent with other studies.[29] In addition, other studies have indicated that riobtypes 078[30] and 014[30] may have more severe outcomes and that ribotype 001[31] less severe outcomes. Our data point in the direction to confirm these findings although overall numbers of patients with complications are low.

4.2 Conclusions and key points

- There was a peak in incidence in 2008. Incidence has declined in acute and chronic hospitals and in most years up until and including 2014.
- Of the three regions, Flanders has had the lowest incidence of CDI since 2010
- Mortality rates continue to decrease after their peak in 2004-2005, and there is no further sign of increasing severity of cases in recent years.
- Mortality rates have consistently been highest in Brussels out of the three regions
- The incidence of hospital associated infection is very variable between hospitals and regions and indicates a potentially important area for prevention
- The incidence of infection is seasonal
- There has been an increase in the proportion of community associated cases and a decrease in the proportion that have hospital associated infection between the years 2008-2014
- Reference laboratory data provide evidence of a large variety of strains. The most notable trend is the decline since 2009 of ribotype 027. The predominant strains in Belgium are now 014 and 020. Ribotype 078 is now the third most common ribotype in Belgium. Ribotype 106 has emerged in the last two years.

5 ANNEX

5.1 Comparison of incidence of Clostridium difficile infection between acute and chronic hospitals

Table 24 : Incidence of infection with *Clostridium difficile* (CDI), acute[$] hospitals, Belgium 2008-2014

Year	2008	2009	2010	2011	2012	2013	2014
Denominators							
N hospitals included in the calculation of incidence (hospitals which participate for the whole year and with mean LoS < 14 days)	94	96	102	102	94	99	90
Episodes of hospital associated CDI (HA-CDI)*							
N	1396	1308	1218	1146	1120	1258	1044
/ 10,000 hospital days :							
Mean Incidence**	1.54	1.44	1.24	1.19	1.20	1.29	1.20
Median	1.41	1.24	1.01	1.09	0.98	1.08	1.01
/ 1000 admissions							
Mean incidence **	1.19	1.07	0.90	0.86	0.87	0.91	0.84
Median	1.10	0.96	0.79	0.77	0.74	0.79	0.72
Other episodes							
N	850	864	762	706	784	929	776
/ 1000 admissions							
Mean Incidence **	0.72	0.71	0.56	0.53	0.61	0.67	0.62
Median	0.70	0.57	0.56	0.51	0.53	0.55	0.51
Total episodes							
N	2246	2172	1980	1852	1904	2187	1820
/1000 admissions							
Mean Incidence**	1.91	1.77	1.46	1.38	1.48	1.58	1.46
Median	1.82	1.55	1.28	1.34	1.31	1.41	1.26

**Defined as onset of diarrhoea 2 days or more after admission in the declaring hospital (onset date – admission date ≥2)*

*** Mean Incidence : total episodes/total denominator, LOS: length of stay*

[$]*Acute hospitals defined by mean length of stay <14 days, chronic >= 14 days*

Table 25 : Incidence of infection with *Clostridium difficile* (CDI), chronic[$] hospitals, Belgium 2008-14

Year	2008	2009	2010	2011	2012	2013	2014
Denominators							
N hospitals included in the calculation of incidence (hospitals which participate for the whole year and with mean LoS >= 14 days)	9	12	9	11	10	13	9
Episodes of hospital associated CDI (HA-CDI)*							
N	64	77	47	72	37	68	37
/ 10,000 hospital days :							
Mean Incidence**	1.92	1.50	1.06	1.33	0.91	1.09	0.93
Median	1.66	0.89	0.97	0.94	0.33	0.57	0.86
/ 1000 admissions							
Mean incidence **	6.62	5.66	4.55	5.54	3.64	3.75	3.30
Median	7.14	3.18	3.82	6.27	2.05	2.96	3.68
Other episodes							
N	15	19	2	22	9	24	18
/ 1000 admissions							
Mean Incidence **	1.55	1.40	0.19	1.69	0.89	1.32	1.61
Median	0.64	0.82	0	0	0	1.67	1.79
Total episodes							
N	79	96	49	94	46	92	55
/1000 admissions							
Mean Incidence**	8.18	7.06	4.74	7.24	4.53	5.08	4.91
Median	9.64	5.28	3.82	6.79	2.21	4.38	3.68

**Defined as onset of diarrhoea 2 days or more after admission in the declaring hospital (onset date – admission date ≥2)*

*** Mean Incidence : total episodes/total denominator, LoS: length of stay*

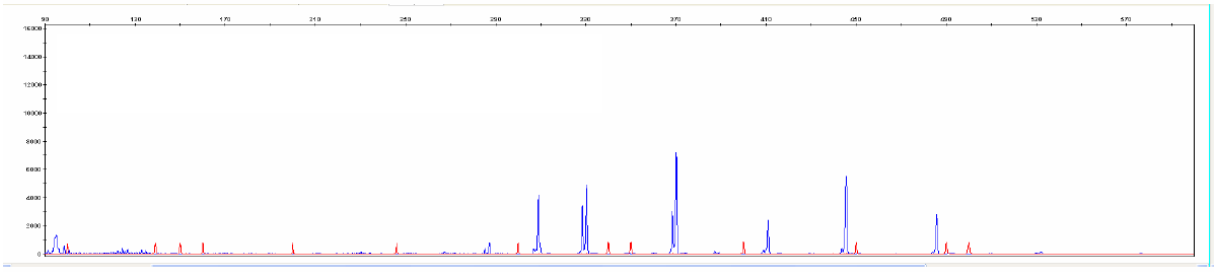
[$]*Acute hospitals defined by mean length of stay <14 days, chronic >= 14 days*

5.2 Reference laboratory (NRC-CD) methods

5.2.1 Ribotyping

The ribotyping technique is based on the existence of several ribosomal RNA loci within the bacterium which code for the genes 16S-23S-5S. The genes 16S and 23S are separated by a intergenic non-coding region of variable size. The ribotyping technique consists of amplification of these regions by PCR. The selected primers allow amplification from one segment of the 16S gene to another of the 23S gene. The resulting amplicons are analysed by capillary electrophoresis in a sequencer. Figure 11 shows an example of such a profile obtained. The strains are then analysed and interpreted by the software GeneMapper.

Figure 11 : Example of trace obtained by capillary electrophoresis for ribotyping



A European collection of reference strains allows classification of 21 ribotypes. Table 26 shows the how the 21 European reference ribotypes (Brazier classification) correspond to the internal nomenclature that is used within Belgium. In the Belgian NRC-CD, nearly 500 different profiles/ribotypes have so far been identified. The European ribotyping nomenclature is indicated by the prefix « BR » and the Belgian nomenclature by « UCL »

5.2.2 MLVA

The technique of MLVA typing (Multi-Locus Variable number tandem repeat Analysis) allows a different characterisation of strains which enables distinction of clones within the same ribotype. It is based on the existence within the *Clostridium difficile* chromosome of a series of tandem repeat sequences of DNA situated in a number of different loci within the bacterial genome. Several of these loci, chosen for their discriminatory power, are amplified and the size of these amplicons is measured by capillary electrophoresis.

Once the length of a repeat element is known, the number of repetitions can be calculated. This can be done with a software programme (BioNumerics) which also allows visual analysis by means of a dendrogram or a " Minimum Spanning Tree" (MST). This technique is used during hospital outbreaks or to follow up the more common ribotypes in Belgium

Table 26 : Equivalent European (Brazier- BR) and Belgian (UCL) classification of *Clostridium difficile* ribotypes

European Ribotype Nomenclature (Brazier)	Ribotype Nomenclature (UCL)
001	23e
002	32*
003	49
012	44
014	16
015	23
017	14
020	16a*
023	4
027	027
029	28
053	395
056	55a
070	47
075	141
078	3
081	33
087	24
095	21d
106	48d
131	48c

.

6 Reference List

(1) European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012. Stockholm: ECDC; 2013. http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=1155

(2) Health Protection Agency. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011: Preliminary data. London; 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/331871/English_National_Point_Prevalence_Survey_on_Healthcare_associated_Infections_and_Antimicrobial_Use_2011.pdf Date accessed 13-5-2015

(3) Meyer E, Gastmeier P, Weizel-Kage D, Schwab F. Associations between nosocomial meticillin-resistant Staphylococcus aureus and nosocomial Clostridium difficile-associated diarrhoea in 89 German hospitals. J Hosp Infect 2012 Nov;82(3):181-6.PM:23021304

(4) European Centre for Disease Control. EUCLID - European multi-centre prospective bi-annual point prevalence study of *Clostridium difficile* infection in hopsitalised patients with Diarrhoea: the fuller picture of the incidence of Clostridium difficile infection (CDI) across Europe . Job code FDX/14/0017/EUc. 2014. http://www.multivu.com/assets/71400524/documents/71400524-EUCLID-backgrounder-original.pdf

(5) Experts Attend European Parliament to Call for Urgent Action to Improve Clostridium Difficile Infection Management in Europe. http://www prnewswire co uk/news-releases/experts-attend-european-parliament-to-call-for-urgent-action-to-improve-clostridium-difficile-infection-management-in-europe-284435891 html 2014 December 2

(6) Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID). Lancet Infect Dis 2014 Dec;14(12):1208-19.PM:25455988

(7) Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, et al. Clostridium difficile infection in Europe: a hospital-based survey. Lancet 2011 Jan 1;377(9759):63-73.PM:21084111

(8) Conseil Supérieur de la Santé, Belgian Infection Control Society, Institut Scientifique de Santé Publique. 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. 2008 May. Report No.8365. http://www.gezondheid.belgie.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/14112500_fr.pdf

(9) European Center for Disease Prevention & Control. European Surveillance of *Clostridium difficile* infections: Surveillance protocol version 2.1. Stockholm: ECDC; 2015 May. Report No.: Technical document.http://ecdc.europa.eu/en/publications/Publications/Clostridium-difficile-infections-surveillance-protocol-version-2.1.pdf

(10) Outbreaks of Clostridium difficile-027 Netherlands. Wekelijks overzicht van infectieziektesignalen week 8, 3-4. 19-2-2015. Rijksinstituut voor Volksgezondheid en Milieu, Ministerie van Volksgezondheid, Welzijn en Sport.

(11) Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, et al. Diverse sources of C. difficile infection identified on whole-genome sequencing. N Engl J Med 2013 Sep 26;369(13):1195-205.PM:24066741

(12) Janezic S, Zidaric V, Pardon B, Indra A, Kokotovic B, Blanco JL, et al. International Clostridium difficile animal strain collection and large diversity of animal associated strains. BMC Microbiol 2014;14:173.PM:24972659

(13) Arrêté Royal, C-2015/24034, Moniteur Belge - Belgisch Staatsblad 27.01.2015, Arrêté Royal, (2015).http://www.nsih.be/download/CDIF/Arrete%20Royal%202015.xps

(14) World Health Organisation. International Classification of diseases (ICD). http://www who int/classifications/icd/en 2011

(15) Belgian Federal Government. Direction générale Statistique et Information économique (DGSIE). http://statbel fgov be/en/statistics/organisation/statistics_belgium/ 2013 Accessed 2014 Jun 12

(16) Institut Scientifique de Santé Publique. SPMA : Standardized Procedures for Mortality Analysis - Belgium/Population. https://www wiv-isp be/epidemio/spma/index htm 2014 https://www wiv-isp be/epidemio/spma/index htm Last update 2014

(17) Jans B, Glupczynsk Y, Denis O. Surveillance des bactéries résistantes aux antibiotiques dans les hôpitaux belges: Rapport annuel 2013. Institute Scientifique de Santé Publique, Bruxelles; 2014 Dec. Report No.: 2014- 046 http://www.nsih.be/download/MRSA/MRSA_RAP_2013/RAPPORT_COMPLET_Y2013_FR_final.pdf

(18) Public Health Agency NI. *C.difficile* surveillance: Quarterly report Oct-Dec 2014 (Q4 2014). 2015. http://www.publichealth.hscni.net/directorate-public-health/health-protection/healthcare-associated-infections

(19) Slimings C, Armstrong P, Beckingham WD, Bull AL, Hall L, Kennedy KJ, et al. Increasing incidence of Clostridium difficile infection, Australia, 2011-2012. Med J Aust 2014 Mar 17;200(5):272-6.PM:24641152

(20) Nationales Referenzzentrumfür Surveillancevon Nosokomialen Infektionen. KISS Krankenhaus-Infektions-Surveillance-System Modul CDAD-KISS Referenzdaten. 2013 Apr 16. Report No.: Berechnungszeitraum: 1 Januar 2012 bis 31 Dezember 2012.http://www.nrz-hygiene.de/surveillance/kiss/cdad-kiss/

(21) Leiden University Medical Center DoMM, Center for Infectious Diseases Control (CIb) RB. Seventh Annual Report of the National Reference Laboratory for Clostridium difficile and results of the national surveillance May 2012 to May 2013. 2013. http://www.rivm.nl/dsresource?objectid=rivmp:211067&type=org&disposition=inline&ns_nc=1

(22) Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med 2015 Feb 26;372(9):825-34.PM:25714160

(23) Public Health England. Annual epidemiological commentary: MRSA, MSSA and E. coli bacteraemia and C. difficile infection data up to and including financial year April 2013 to March 2014. 2014 Jul 10. Report No.: Publications gateway: 2014160. https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary

(24) Eyre DW, Walker AS, Griffiths D, Wilcox MH, Wyllie DH, Dingle KE, et al. Clostridium difficile mixed infection and reinfection. J Clin Microbiol 2012 Jan;50(1):142-4.PM:22075589

(25) Health Protection Scotland. Healthcare Associated Infection Annual Report 2013. 2014 May. http://www.hps.scot.nhs.uk/haiic/publicationsdetail.aspx?id=58412

(26) WHO Media Centre. WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health. http://www who int/mediacentre/news/releases/2014/amr-report/en/ 2014 April 30

(27) Public Health England. Clostridium difficile Ribotyping Network (CDRN) for England and Northern Ireland. 2014 Jan. Report No.: PHE publications gateway number: 2013396.http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317140658750

(28) Clostridium difficile Ribotyping Network: 2011-2013 report. Health Protection Report - Weekly Report 31-1-2014;8(4). http://www.hpa.org.uk/hpr/archives/2014/news0414.htm#snslnflnz

(29) Jones AM, Kuijper EJ, Wilcox MH. Clostridium difficile: a European perspective. J Infect 2013 Feb;66(2):115-28.PM:23103666

(30) Walker AS, Eyre DW, Wyllie DH, Dingle KE, Griffiths D, Shine B, et al. Relationship between bacterial strain type, host biomarkers, and mortality in Clostridium difficile infection. Clin Infect Dis 2013 Jun;56(11):1589-600.PM:23463640

(31) Patterson L, Wilcox MH, Fawley WN, Verlander NQ, Geoghegan L, Patel BC, et al. Morbidity and mortality associated with Clostridium difficile ribotype 078: a case-case study. J Hosp Infect 2012 Oct;82(2):125-8.PM:22947650