WETENSCHAPPELIJK INSTITUUT
VOLKSGEZONDHEID

INSTITUT SCIENTIFIQUE
DE SANTÉ PUBLIQUE

Trends in mortality and morbidity related to *Clostridium difficile* infections, Belgium 1998-2007

Operational Direction
Surveillance and Public Health
Rue Juliette Wytsmanstraat 14 |
1050 Brussel
T 02 642 57 33 | F 02 642 54 1
Scientific Institute of Public Health
Belgium

www.iph.fgov.be

Operational Direction Surveillance and Public Health
| April 2010 | Brussels, Belgium
N° de référence interne : 012
N° de dépôt ou ISSN : **D/2010/2505/18**

Gutiérrez I.[1,2]

Lambert ML.[1]

1. **Scientific Institute of Public Health, Brussels, Belgium.**
2. **European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, Stockholm, Sweden.**

Correspondence:

Lambert ML. (Marie-Laurence.Lambert@wiv-isp.fgov.be)

Executive summary:

Background

Clostridium difficile infection (CDI) incidence and mortality increased in North America and Europe over the last decade. Emerging hypervirulent, fluoroquinolone-resistant strains might have contributed to this. We measured CDI-related mortality, incidence and number of diagnostic tests performed for the period 1998-2007, to assess the epidemiology of CDI in Belgium.

Methods

We selected available data from: (1) mortality registries from Brussels, Flanders and Wallonia regions, (1998-2007)-records with ICD-10 code for *Clostridium difficile* enterocolitis. (2) from the Belgian hospital discharges database (1999-2007)-records with ICD-9-CM code for intestinal CDI. (3) from the Belgian social security database (1998-2007)-the number of CDI-related tests billed-. We calculated rates for mortality, hospital discharges and tests performed. We standardized mortality and hospital discharge data by age, using Belgian 2000 midyear population and European Standard population for international comparisons. We compared hospital discharge and diagnostic tests rate ratios.

Results

CDI-related crude mortality rate increased steadily since 1998 (0.1/100,000 inhabitants) in Brussels and Flanders, to its peak in Brussels in 2004 (5.7/100,000 inhabitants) , and its peak in Flanders in 2005 (1.3/100,000 inhabitants), and decreased in 2006 and 2007.The oldest age-group (>=80years) was most affected. After standardization for age, rates appear similar for men and women. Age-standardized rates of hospital discharge with a diagnosis of CDI increased from 17.1 per 100,000 inhabitants in 1999, to 41.7 in 2007. Between 2000 and 2007 hospital discharges with CDI diagnosis increased by 240%, whereas diagnostic tests performed in hospitals increased by 160%.Belgian standardized CDI-related mortality rates were lower than those from other European countries and the US.

Conclusion

Both CDI-related mortality and morbidity have dramatically increased in Belgium between 1998 and 2007, especially in Brussels region. Mortality, but not morbidity, seems to be decreasing in the last years studied.

Introduction

Clostridium difficile infection (CDI) is regarded as the main cause of nosocomial diarrhoea in western countries. (1). Prior use of antibiotics (2,3), previous hospitalization (4), advanced age and length of hospital stay(3) are considered as risk factors for CDI. Symptoms range from carrier status to diarrhoea with complications such as life-threatening enterocolitis (5).

CDI-related hospital discharges doubled between 1996 and 2004 in north America and Europe (6,7) and associated mortality also increased steeply (7,8,9). A decrease in mortality has only been reported in 2008 in England (10).
The mortality increase has been related to the larger number of hospitalizations(11) and to the emergence of a new *Clostridium difficile* epidemic strain: pulsed-field gel electrophoresis (PFGE) North American type 1(NAP1), restriction endonuclease analysis group BI and PCR ribotype 027.This strain was first isolated in North America in 2002; It caused healthcare-associated outbreaks, affecting more than 14,000 hospitalized patients in Quebec between 2003-2004 (12) and spread rapidly to many European countries (13). The virulence of this and other strains(14,15) is related to toxin A and B hyper production (12); NAP1, ribotype 027 : produces a third toxin (binary toxin), has deletions in the regulatory gene *tcd*C that allow increased toxin A and B production and is resistant to third generation fluoroquinolones (16).
In Belgium moxifloxacin was introduced in 2002. Shortly after, in 2003 and 2004 important outbreaks caused by *Clostridium difficile* occurred (17); PCR ribotype 027 was subsequently identified in isolates from those outbreaks - (18) Prospective surveillance was introduced in 2006(19) CDI-related mortality data and burden of disease in Belgium before the introduction of surveillance have not yet been described.

This study aimed at measuring CDI-related mortality, hospital discharges and number of diagnostic procedures performed in Belgium, between 1998 and 2007.

Methods

We conducted a descriptive study documenting trends in CDI epidemiology in Belgium, from 1998-2007.

Definitions

ICD: International Classification of Diseases is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States. We used ICD 9-CM (clinical modification) and ICD 10. The 10th revision was conducted in 1992. (20)

Death registry:

In Belgium death certificates for persons older than one year contain the causes of death. They are divided as follows:

-Immediate cause of death: disease or condition having directly caused the death.

-Underlying cause of death: disease in the origin of the chain of diseases or conditions that lead to the immediate cause of death.

-**Intermediate causes of death**: other causes in the chain of diseases or events that have finally led to death. Intermediate causes of death lead from the underlying cause of death to the immediate cause of death.

-Contributing causes of death: other important diseases or conditions that have contributed to death but without relationship with the disease or condition that caused it.

For the purpose of this study we often took into account the underlying cause of death as well as the addition of the underlying cause plus all other causes of death mentioned in the file, calling this category as **"total mentions"**.

It is important to know that in Belgium, death certificates are processed by the regions (Brussels, Flanders and Wallonia) according to the place of residence (not place of death)
Data are coded using ICD-10

Hospital discharge data:

RCM (Résumé Clinique Minimal) /**MKG** (Minimale Klinische Gegevens)
These data contain the ICD-9-CM diagnostic codes given to the patient at discharge from hospital. We use these codes in two ways:

"main diagnose" : diagnose contributing most to the hospitalisation (often, but not always, admission diagnosis)

"any diagnose", either main diagnose, or secondary diagnose (equivalent to "total mentions").

Data sources and data requested.

We used yearly aggregated data from the following sources:

1) **Death Registries** from:
The Flemish Agency for Care and Health, Flemish Ministry for Welfare, Public Health and Family, Brussels, Belgium;
The Health and Social Observatory, Brussels region, Brussels, Belgium;
The French Community, Brussels, Belgium.
- Where we asked for aggregated data with ICD-10 A04.7 code for enterocolitis due to *Clostridium difficile* (1998-2007).

2) **Social security** (INAMI-RIZIV)
-Where we asked for the number of CDI-related diagnostic tests billed (codes 549850-for ambulatory patients- and 549861-for hospitalized patients) by year of performance (1998-2007).

3) **Belgian Hospitals Database**, Department of Health Care Facilities Organization (DG1), Federal Public Service (FPS) Health, Food Chain Safety and Environment, Brussels, Belgium.
-Where we asked for aggregated data with ICD-9-CM 008.45 code (intestinal infections due to *Clostridium difficile*) 1999-2007.

4) **National Institute for Statistics**.
- Population data (21).

Validation

We assessed reporting bias for CDI-related mortality by analyzing trends for other possibly CDI-related ICD-10 codes along the period 1998-2007 in Brussels and Flanders. We analyzed code A04.7 (Enterocolitis due to *Clostridium difficile*), A00-A09 (Intestinal Infections excluding records with code A04.7) and K52.9 ("Non infective gastroenteritis and colitis, unspecified").
Regarding death certificates records, ICD-10 codes were introduced in 1998 in Belgium.
Two updates in 2006 changed the meaning of A04.7 from "Enterocolitis due to *Clostridium difficile*" (until 2005) to "Enterocolitis due to Clostridium difficile, foodborne intoxication by *Clostridium difficile*, pseudomembranous colitis". Before 2006 "food borne intoxication by *Clostridium difficile*" was coded A05 and "pseudomembranous colitis without mention of Clostridium" was mostly coded K52.9.

Data analysis

We present crude numbers and proportions of underlying causes out of total mentions.
We calculated crude rates for CDI-related mortality, hospital discharges and number of diagnostic tests performed. We calculated age- and sex-specific rates for mortality and hospital discharges for 1998-2007. We performed direct standardization for mortality and hospital discharge data by age, using Belgian 2000 midyear population. We took year 2000 as a reference and calculated rate ratios for hospital discharge and diagnostic test rates comparing every year in the study period to the reference year.
We used Excel© and Stata v.10 (StataCorp, College Station,TX,USA).

Human subject protection

We used aggregated data, not allowing identification of the study subjects.

Results

CDI-related mortality

During the 10 year-period, 1067 CDI-related deaths were registered in Brussels and Flanders; for 540 (50,6%) CDI was the underlying cause of death; 943 deaths (88.4%) occurred between 2003 and 2007.The peak in the amount of cases happened in 2004 in Brussels and 2006 in Flanders. See Table 1.

Table 1	Number of deaths associated with *Clostridium difficile* enterocolitis, by region, Belgium 1998-2007									
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Belgium										
C.diff enterocolitis as "underlying" cause of death	N.A	N.A	N.A	N.A	N.A	N.A	146	150	N.A	N.A
C.diff enterocolitis as "total mentions"	N.A	N.A	N.A	N.A	N.A	N.A	273	258	N.A	N.A
percentage of "underlying" over "total mentions"	N.A	N.A	N.A	N.A	N.A	N.A	53.5%	58.1%	N.A	N.A
Brussels										
C.diff enterocolitis as "underlying" cause of death	1	0	2	1	7	20	57	39	33	20
C.diff enterocolitis as "total mentions"	2	3	5	3	19	45	108	78	74	37
percentage of "underlying" over "total mentions"	50.0%	0.0%	40.0%	33.3%	36.8%	44.4%	52.8%	50.0%	44.6%	54.1%
Flanders										
C.diff enterocolitis as "underlying" cause of death	5	7	7	11	17	32	64	78	82	57
C.diff enterocolitis as "total mentions"	8	15	19	16	34	60	124	134	158	125
percentage of "underlying" over "total mentions"	62.5%	46.7%	36.8%	68.8%	50.0%	53.3%	51.6%	58.2%	51.9%	45.6%
Wallonia										
C.diff enterocolitis as "underlying" cause of death	N.A	N.A	N.A	N.A	N.A	N.A	25	33	N.A	N.A
C.diff enterocolitis as "total mentions"	N.A	N.A	N.A	N.A	N.A	N.A	41	46	N.A	N.A
percentage of "underlying" over "total mentions"	N.A	N.A	N.A	N.A	N.A	N.A	61.0%	71.7%	N.A	N.A

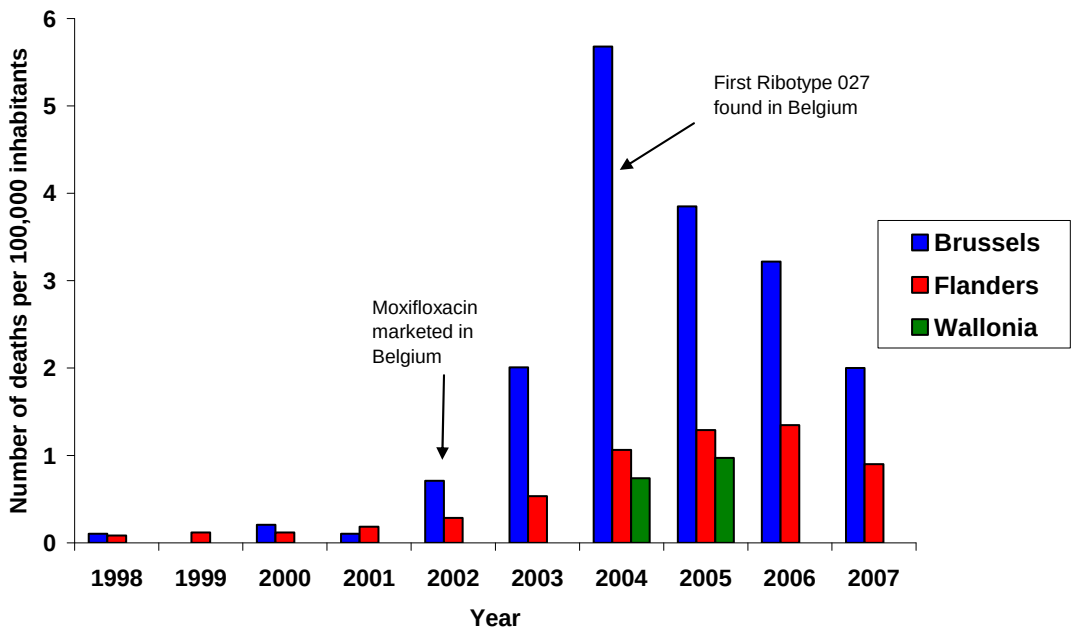
From 1998 to 2004 there was a 57 fold-increase in Brussels and an 11 fold-increase in Flanders in crude mortality attributed to CDI (underlying cause). See table 2.
From 1998 to 2004 there was a 54 fold-increase in Brussels and a 15.5 fold-increase in Flanders for CDI-related crude mortality (“total mentions”).

Table 2 Crude mortality rates (number of deaths per 100,000 inhabitants) for *Clostridium difficile* enterocolitis, by region, Belgium 1998-2007

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
C.diff enterocolitis as "Underlying" cause of death										
Brussels	0.1	0	0.2	0.1	0.7	2	5.7	3.9	3.2	2
Flanders	0.1	0.1	0.1	0.2	0.3	0.5	1.1	1.3	1.3	0.9
Wallonia	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	0.7	1	N.A.	N.A.
C.diff enterocolitis as "Total mentions"										
Brussels	0.2	0.3	0.5	0.3	1.9	4.5	10.8	7.7	7.2	3.6
Flanders	0.1	0.3	0.3	0.3	0.6	1	2.1	2.2	2.6	2
Wallonia	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	1.1	1.4	N.A.	N.A.

Age-standardized mortality rates for CDI as the “underlying cause” are shown in graph 1.

Graph 1 Age-standardized mortality rates for *Clostridium difficile* enterocolitis, as the "underlying" cause of death, by region, Belgium 1998-2007



*** Standardized with the Belgian 2000 midyear population**

In Brussels, age-standardized CDI mortality rates (underlying cause) varied between 0 and 5.5 deaths per 100,000 inhabitants for men, and between 0 and 4.7 deaths per 100,000 for women during the study period. In Flanders these rates ranged from 0.1 to 1.2 for men and women.

Elderly people of age over 79 years presented the highest mortality rates ranging from 0 to 87.8 deaths per 100,000 inhabitants in Brussels and between 0.5 and 23.9 in Flanders. See table 3

Table 3	Age-standardized* mortality rates by sex and age-specific mortality rates (number of deaths per 100,000 inhabitants) by *Clostridium difficile* enterocolitis, as "underlyig cause", by region, Belgium 1998-2007									
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Brussels										
Males*	0.0	0.0	0.6	0.0	0.0	1.4	5.5	3.7	2.6	2.2
Females*	0.1	0.0	0.0	0.2	1.0	2.1	4.7	3.1	2.6	1.4
0-64 years	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.2	0.1
65-79 years	0.0	0.0	0.0	0.9	1.8	4.5	14.6	5.6	2.8	3.9
>=80 years	2.4	0.0	4.8	0.0	11.2	30.6	87.8	67.3	58.1	30.7
Flanders										
Males*	0.1	0.1	0.2	0.2	0.2	0.6	0.8	1.1	1.2	0.3
Females*	0.1	0.1	0.1	0.2	0.3	0.5	1.1	1.1	1.1	1.2
0-64 years	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.2
65-79 years	0.4	0.4	0.4	0.5	0.7	1.0	2.6	1.5	2.1	2.2
>=80 years	0.5	1.5	1.5	3.3	4.0	9.4	17.3	23.9	22.9	11.2
Wallonia										
Males*	N.A	N.A	N.A	N.A	N.A	N.A	0.8	N.A	N.A	N.A
Females*	N.A	N.A	N.A	N.A	N.A	N.A	0.8	N.A	N.A	N.A
0-64 years	N.A	N.A	N.A	N.A	N.A	N.A	0.1	0.1	N.A	N.A
65-79 years	N.A	N.A	N.A	N.A	N.A	N.A	2.8	1.4	N.A	N.A
>=80 years	N.A	N.A	N.A	N.A	N.A	N.A	7.0	17.2	N.A	N.A

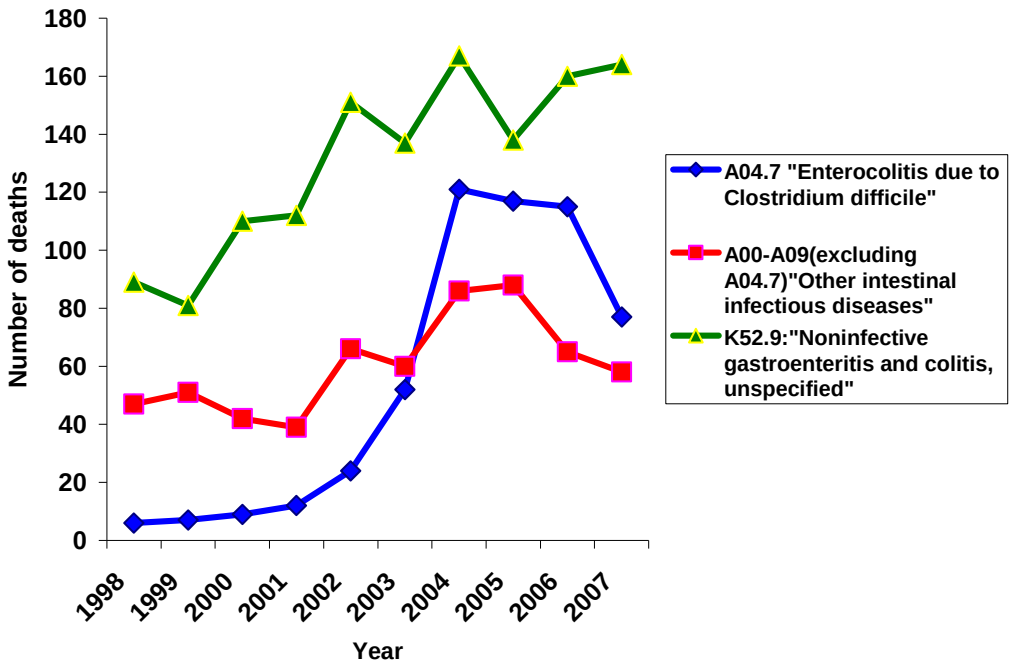
*** Standardized with the Belgian 2000 midyear population**

In Belgium more than 80% of CDI-related deaths took place in hospitals and more than 10% in nursing homes. See table 4.

Table 4	Place of death associated with *Clostridium difficile* enterocolitis, mentioned in the death certificate record, Belgium 2004-2005		
Place of death		**2004**	**2005**
Hospital	**N**	**230**	**223**
	%	**84.2%**	**86.4%**
Nursing home	**N**	**37**	**28**
	%	**13.6%**	**10.9%**
Home	**N**	**5**	**7**
	%	**1.8%**	**2.7%**
Others/Unknown	**N**	**1**	**0**
	%	**0.4%**	**0.0%**
Total	**N**	**273**	**258**

CDI-related deaths, (A04.7) and all other intestinal infections (A00 to A09, excluding A04.7) show an increasing trend until 2004 and 2005 decreasing since then whereas unspecified non infective gastroenteritis and colitis (K52.9) has increased for the whole period. Graph 2 shows the evolution of mortality attributed to *Clostridium difficile* enterocolitis and mortality attributed to other related ICD-10 codes, as the underlying cause of death, in Brussels and Flanders.

Graph 2 ***Clostridium difficile*** **enterocolitis- associated mortality and other ICD-10 codes used to assess reporting bias, Brussels and Flanders 1998-2007**



International comparisons for mortality

An increase of CDI-related deaths has been observed in England and Wales, Northern Ireland and Finland between 1998 and 2007 ; although data seem comparable because they have been standardized using the European Standard population, the way in which deaths due to *C.difficile* enterocolitis were ascertained differed among countries.

A sharp decrease took place in England and Wales in 2008. Moxifloxacin was marketed in the UK in March 2003.

Table 5	Standardized mortality rates for Clostridium difficile enterocolitis, as total mentions in the death certificate record, per 1,000,000 inhabitants. European Standard Population taken as standard.										
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008***
Brussels and Flanders*	1.0	1.7	2.2	1.7	4.4	8.7	18.6	16.2	17.7	14.0	
Males	0.8	1.3	4.1	2.1	4.5	8.5	17.5	17.6	20.0	7.4	
Females	1.0	2.1	1.0	1.4	4.3	8.8	19.3	15.3	15.9	19.7	
England and Wales**											
Males		11.4		13.3	15.2	18.8	23.7	37.0	65.5	84.7	61.9
Females		10.7		12.7	15.0	19.0	23.1	38.6	64.2	80.6	56.1
Northern Ireland**				6.4	11.0	13.9	18.8	14.5	24.3	28.8	
Finland *	10	9	10	12	15	17	16				

*** ICD-10 A04.7**
**** Besides code ICD-10 A04.7 codes A.41.4 A.49.8 were assessed for deaths corresponding to C.difficile.**
*****Data for England and Wales for 2008 are provisional**

Table 6	Standardized mortality rates for Clostridium difficile enterocolitis, as "underlying cause" in the death certificate record, per 1,000,000 inhabitants. American year 2000 population taken as standard.									
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Belgium (Brussels and Flanders)	0.7	0.9	1.1	1.4	2.9	6.1	13.4	13.0	12.3	8.3
Males	0.5	0.5	2.0	1.3	1.6	6.1	11.5	12.8	12.6	5.1
Females	0.8	1.1	0.7	1.5	3.5	6.2	14.1	13.0	11.8	10.9
US		2.9	3.9	4.7	7.7					
Males		2.3	3.1	3.5	6.0					
Females		3.5	4.7	5.8	9.2					

In the US the increase in mortality also took place.
Moxifloxacin was marketed in the US in December 1999.

CDI-related hospital discharges

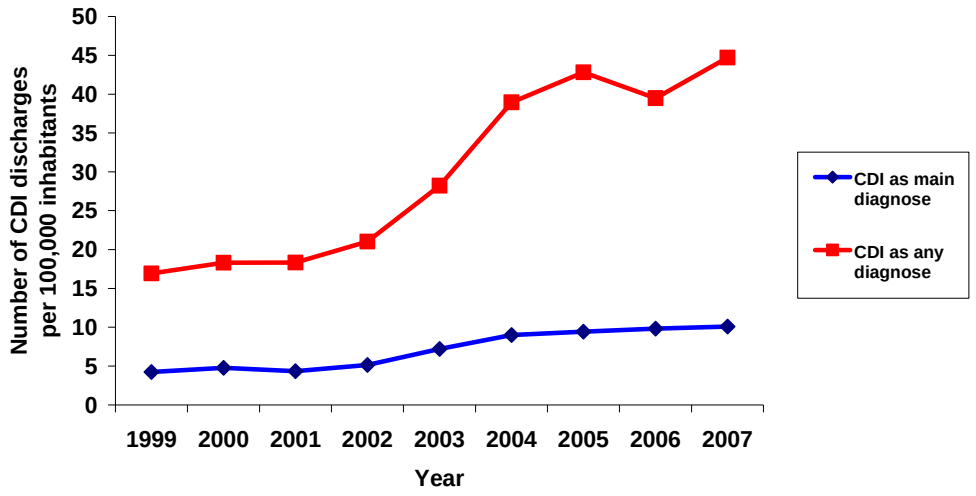
Hospital discharges with a CDI diagnosis (any diagnose), more than doubled from 1999 to 2004 and increased until 2007 (last year available). Age groups were affected in a different way. In 1999, less than 65 years old presented 6.8 discharges per 100,000 inhabitants whereas 65-79 years olds presented 43.4 and those over 79 years old presented 161.1 discharges per 100,000 inhabitants. The eldest age group had its highest discharge rate in 2005, while the discharge rate continued to raise in the others groups until 2007. See table 7.

Table 7	Trends for CDI-related hospital discharges, as "any diagnose", in Belgian population, Belgium 1998-2007								
	1999	2000	2001	2002	2003	2004	2005	2006	2007
CDI-associated total hospital discharges									
N	1730	1876	1886	2172	2928	4060	4487	4166	4751
CDI hospital discharge age-specific rates /100,000 inhabitants									
<65 years	6.8	7.2	7.5	7.8	9.6	10.4	12.1	13.4	15.9
65-79 years	43.4	48.3	48.0	51.8	69.1	102.5	106.3	106.4	110.2
>=80 years	161.1	165.6	155.7	198.7	277.6	406.5	438.5	331.5	384.8
CDI age-standardized* discharge rate/100,000 inhabitants									
	17.1	18.3	18.1	20.4	27.1	36.7	39.8	37.1	41.7

*Standardized with Belgian 2000 midyear population

CDI-related (ICD 9CM 008.45) crude hospital discharge rates almost tripled from 1999 to 2007 as any diagnose, going from 16.9 to 44.8 discharges per 100,000 inhabitants whereas CDI as main diagnose increased from 4.2 to 10.1 discharges per 100,000 inhabitants. See graph 3.

Graph 3 *Clostridium difficile*-associated disease (ICD 9-CM 008.45) hospital discharge rates in Belgian population, 1999-2007



International comparisons for CDI-related hospital discharges

Table 8 shows crude discharge rates (as “any diagnose”) in Belgium, the US and Finland.

Table 8 **Crude discharge rates for Clostridium difficile infection, as "any diagnose", per 100,000 inhabitants.**

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Belgium*				16.9	18.3	18.3	21	28.2	39	42.8	39.5	44.8
US*	31							61				
Finland**	16	19	20	21	20	25	29	27	34			

***ICD-9-CM code 008.45**
**** ICD-10 codes A.04.7 and K52.8**

CDI-related diagnostic procedures

The number of CDI-related diagnostic procedures performed in Belgium increased continuously. About one third of them where performed in ambulatory settings and two thirds in hospitals. See table 9.

Table 9 **Number of CDI diagnostic procedures billed, by place and year of performance, Belgium 1998-2007**

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Ambulatory (code 549850)										
N	24703	26984	28910	28952	32146	35644	37152	43389	47218	48844
%	33%	34%	35%	35%	36%	35%	33%	35%	36%	35%
Hospital (code 549861)										
N	50008	53062	52954	54553	57501	65589	75589	80031	83523	89534
%	67%	66%	65%	65%	64%	65%	67%	65%	64%	65%
Total										
N	74711	80046	81864	83505	89647	101233	112741	123420	130741	138378

Comparison between hospital discharges rates and the rate for number of diagnostic tests performed.

Table 10 shows rate ratios for diagnostic tests (performed in Belgian hospitals) and for hospital discharges taking as a reference the year 2000. The tests rates increased 1.6 times whereas the hospital discharges rates increased 2.4 times.

Table 10 **Trends for CDI-related diagnostic procedures and hospital discharges, Belgium 1998-2007**

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Diagnostic procedures*										
Rate per 100,000 population	**732.8**	**783.3**	**798.6**	**811.8**	**867.6**	**975.6**	**1081.8**	**1177.8**	**1239.5**	**1302.3**
Rate Ratio (ref 2000)	**0.9**	**1.0**	**Ref**	**1.0**	**1.1**	**1.2**	**1.4**	**1.5**	**1.6**	**1.6**
Hospital discharges										
Rate per 100,000 population	**N.A.**	**16.9**	**18.3**	**18.3**	**21.0**	**28.2**	**39.0**	**42.8**	**39.5**	**44.7**
Rate Ratio (ref 2000)	**N.A.**	**0.9**	**Ref**	**1.0**	**1.1**	**1.5**	**2.1**	**2.3**	**2.2**	**2.4**

* INAMI-RIZIV -social security- billing codes 549850 and 549861.

Discussion

CDI-related mortality increased steeply from 1998 in Brussels and in Flanders until 2004 and 2006 respectively, experiencing a remarkable decrease until 2007.
CDI-related hospital discharges increased in Belgium since 1998.

CDI-related mortality in Brussels and Flanders seems to be lower than the observed in other countries, particularly in England and Wales (7,9,22,23). Although rates are standardized with the European standard population, data are not really comparable because ascertainment of deaths due to *C.difficile* enterocolitis differed among countries.
CDI-related mortality in Brussels and Flanders followed the same increasing trend that was observed in different countries. The increase in mortality rates is Brussels and Flanders is the highest of the countries for which we found data. This could be real, but taking into account the rates from the first years (1998-2001) and comparing them to the rates of the other countries, a more likely explanation is that there was an under ascertainment of deaths due to *C. difficile* enterocolitis in Belgium during the first years of the study period.
Brussels, (where there are many tertiary teaching hospitals), suffered its highest CDI-related mortality rates during the same years (2002-2004) as the new epidemic strain Ribotype 027 stroke Canada and the US (24). In Flanders mortality peaked in 2006. Like elsewhere, in Belgium the most affected group was the eldest, although this group was the only one showing a decreasing trend since 2004 and 2005 in Brussels and Flanders respectively. The majority of the CDI-related deaths occurred in hospitals.

CDI-related hospital discharges maintained a slight increase for the period 1999-2007. Our data are consistent with CDI-related hospital discharges trends from the US and Finland for the period 1996 to 2003-4(6,7). The continuous increase in age-adjusted hospital discharge rates, might be due to increased awareness among clinicians, but a real increase in CDI transmission at hospital level seems to be occurring as showed by surveillance data: 66% of CDI Belgian cases were nosocomial in 2007-2008 (25). Unlike Methicillin resistant *Staphylococcus Aureus* (MRSA), whose incidence is decreasing in Belgium since 2003(26), *Clostridium difficile* incidence is not decreasing in Belgian hospitals.

CDI-related diagnostic tests increased significantly although at a lower rate than CDI-related hospital discharges, especially since the year 2004. Although billing codes for tests did not change along the period, we did not account for changes in CDI-related diagnostic procedures; thus if tests with higher specificity and sensitivity were adopted from 2004 onwards, this might explain why the increase in testing was not so steep as the increase of hospital discharges.

Our study has some limitations. First, the coding of the information contained in the death certificate could result in classification bias: in this sense we rely on the trend because the coding team is the same for Brussels and Flanders and has not changed during the study period. Thus, we dealt with the different causes of death (”underlying cause” and “contributing cause”) analyzing “underlying” on the one side and “total mentions” (which groups the “underlying” and the “contributing” causes of death) on the other. For comparisons, we used “total mentions” as a better proxy for the burden of disease.
We looked at trends for other ICD codes to detect changes in coding practices during the study period, particularly deaths records coded as related to “other intestinal infections” (ICD-10 A.00-09) and “non infective gastroenteritis and colitis” (ICD-10 K.52.9). Deaths under these codes also increased until 2004 in Brussels and Flanders thus it is unlikely that a shifting in codes occurred towards “enterocolitis due to *clostridium difficile*” (A0.4.7). An update in ICD 10 codes in 2006, (after CDI-related mortality had already increased steeply) might have led to mortality overestimation because it gathered more diagnoses under code A04.7 than it did before, but we observed a decrease for this code instead.

In conclusion, as documented in other Western countries, CDI-related mortality has dramatically increased in Belgium between 2000 and 2007, with sharp differences between regions. Brussels region has the highest mortality rate, but overall mortality seems to be decreasing. By contrast, the continuous increase in morbidity since 1998 showed no sign in abating in 2007. *Clostridium difficile* remains an important source of mortality and morbidity in Belgium.

Reference List

(1) Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J, Jr. Clostridium difficile-associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995; 16(8):459-477.

(2) Bartlett JG. Clostridium difficile: Old and New Observations. Journal of Clinical Gastroenterology 2007; 41.

(3) Debast SB, Vaessen N, Choudry A, Wiegers-Ligtvoet EA, van den Berg RJ, Kuijper EJ. Successful combat of an outbreak due to Clostridium difficile PCR ribotype 027 and recognition of specific risk factors. Clin Microbiol Infect 2009; 15(5):427-434.

(4) Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated Clostridium difficile infection. J Antimicrob Chemother 2008; 62(2):388-396.

(5) Bartlett JG. Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. Ann Intern Med 2006; 145(10):758-764.

(6) McDonald LC, Owings M, Jernigan DB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996-2003. Emerg Infect Dis 2006; 12(3):409-415.

(7) Lyytikainen O, Turunen H, Sund R, Rasinpera M, Kononen E, Ruutu P et al. Hospitalizations and deaths associated with Clostridium difficile infection, Finland, 1996-2004. Emerg Infect Dis 2009; 15(5):761-765.

(8) Redelings MD, Sorvillo F, Mascola L. Increase in Clostridium difficile-related mortality rates, United States, 1999-2004. Emerg Infect Dis 2007; 13(9):1417-1419.

(9) Anonym. Deaths involving Clostridium difficile: England and Wales, 2001-2005. Health Stat Q 2007;(33):71-75.

(10) Carter J. Deaths involving Clostridium difficile: England and Wales, 2008. Health Stat Q 2009;(43):43-47.

(11) Zilberberg MD, Shorr AF, Kollef MH. Increase in adult Clostridium difficile-related hospitalizations and case-fatality rate, United States, 2000-2005. Emerg Infect Dis 2008; 14(6):929-931.

(12) Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet 2005; 366(9491):1079-1084.

(13) Kuijper EJ, Barbut F, Brazier JS, Kleinkauf N, Eckmanns T, Lambert ML et al. Update of Clostridium difficile infection due to PCR ribotype 027 in Europe, 2008. Euro Surveill 2008; 13(31).

(14) Arvand M, Hauri AM, Zaiss NH, Witte W, Bettge-Weller G. Clostridium difficile ribotypes 001, 017, and 027 are associated with lethal C. difficile infection in Hesse, Germany. Euro Surveill 2009; 14(45).

(15) Borgmann S, Kist M, Jakobiak T, Reil M, Scholz E, Eichel-Streiber C et al. Increased number of Clostridium difficile infections and prevalence of Clostridium difficile PCR ribotype 001 in southern Germany. Euro Surveill 2008; 13(49).

(16) Razavi B, Apisarnthanarak A, Mundy LM. Clostridium difficile: emergence of hypervirulence and fluoroquinolone resistance. Infection 2007; 35(5):300-307.

(17) Cherifi S, Delmee M, Van Broeck J, Beyer I, Byl B, Mascart G. Management of an outbreak of Clostridium difficile-associated disease among geriatric patients. Infect Control Hosp Epidemiol 2006; 27(11):1200-1205.

(18) Kuijper EJ, Coignard B, Tull P. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect 2006; 12 Suppl 6:2-18.

(19) Delmee M, Ramboer I, Van Broeck J, Suetens C. Epidemiology of Clostridium difficile toxinotype III, PCR-ribotype 027 associated disease in Belgium, 2006. Euro Surveill 2006; 11(9):E060914.

(20) International classification of diseases (ICD). World Health Organization. Available from http://www.who.int/classifications/icd/en/ [consulted on 23/02/2010](21)

(21) Standardized Procedures for Mortality Analysis. The Centre for Operational Research in Public Health, Scientific Institute of Public Health, Brussels, Belgium .Available from http://www.iph.fgov.be/epidemio/spma/ [consulted on 16/03/2009]

(22) Anonym. Deaths registered in Northern Ireland with Clostridium difficile mentioned on the death certificate (2001-2008). Northern Ireland Statistics Research Agency. Available from http://www.nisra.gov.uk/archive/demography/publications/mrsa_papers/CDiff_2008.pdf [consulted on 16/03/2010]

(23) Wysowski DK. Increase in deaths related to enterocolitis due to Clostridium difficile in the United States, 1999-2002. Public Health Rep 2006; 121(4):361-362.

(24) Pepin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004; 171(5):466-472.

(25) Lambert ML, Mertens K, Ramboer I, Delmee M, Suetens C. Nation-wide prospective surveillance of Clostridium difficile infections in hospitals in Belgium, July 2007-June 2008. Euro Surveill 2009; 14(14):2-4.

(26) Jans B. Surveillance Nationale de Staphylococcus aureus Multi-Résistant (MRSA).National Surveillance of Infections in Hospitals. Scientific institute of Public Health. Available from http://www.nsih.be/surv_mrsa/inleiding_fr.asp [consulted on 23/02/2010]

Acknowledgements

K. Bollaerts, S. Drieskens, B. Jans, E. Leens, H. Van Oyen, Operational Direction Surveillance and Public Health, Scientific Institute of Public Health, Brussels.

A. Kongs, E. Hendrickx, H. Cloots, Flemish Agency for Care and Health, Flemish Ministry for Welfare, Public Health and Family, Brussels.

M. de Spiegelaere, D. Mazina, M. A. Luque, Health and Social Observatory, Brussels region, Brussels.

J. Henkinbrant, V. Charlier, French Community, Brussels.

N. Baldo-Vink, F. Windey. Department of Health Care Facilities Organization (DG1), Federal Public Service (FPS) Health, Food Chain Safety and Environment, Brussels.

M. Dehnert, Department of Infectious Disease Epidemiology Robert Koch Institute, Berlin, Germany.

E. Kissling, F. Luquero, EPIET graduates.

M. Delmée, J. Van Broeck, Microniology unit, Saint Luc Hospital, Catholic University of Leuven, Brussels.

O. Lyytikäinen, S. Guedes, E. Sarvikivi, R. Rimhanen-Finne, National Institute for Health and Welfare, Helsinki, Finland.

Annexes

Graph 1 Crude mortality rates for *Clostridium difficile* enterocolitis, as the underlying cause of death, by region, Belgium 1998-2007

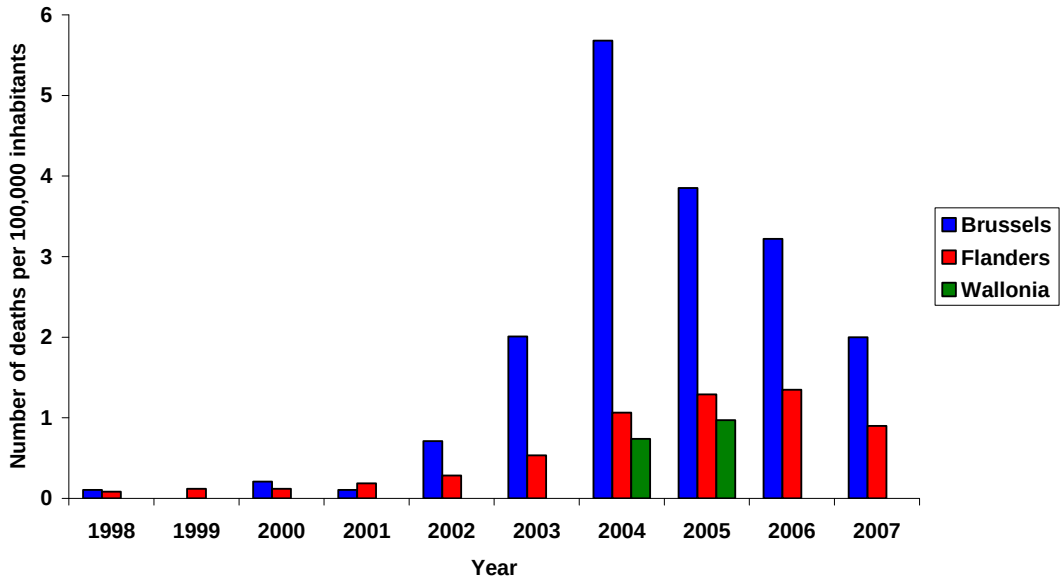
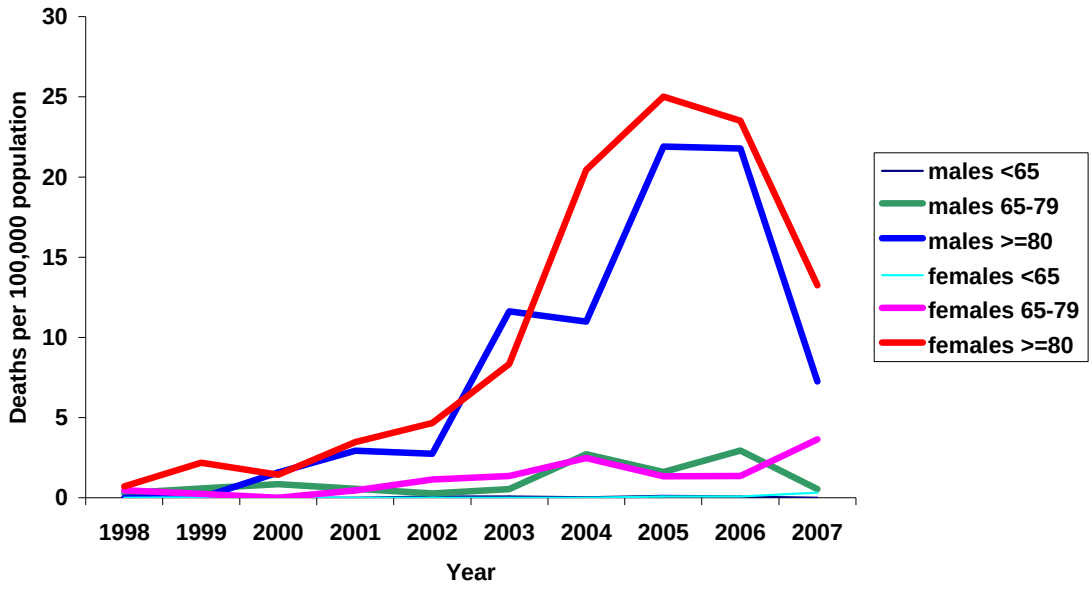


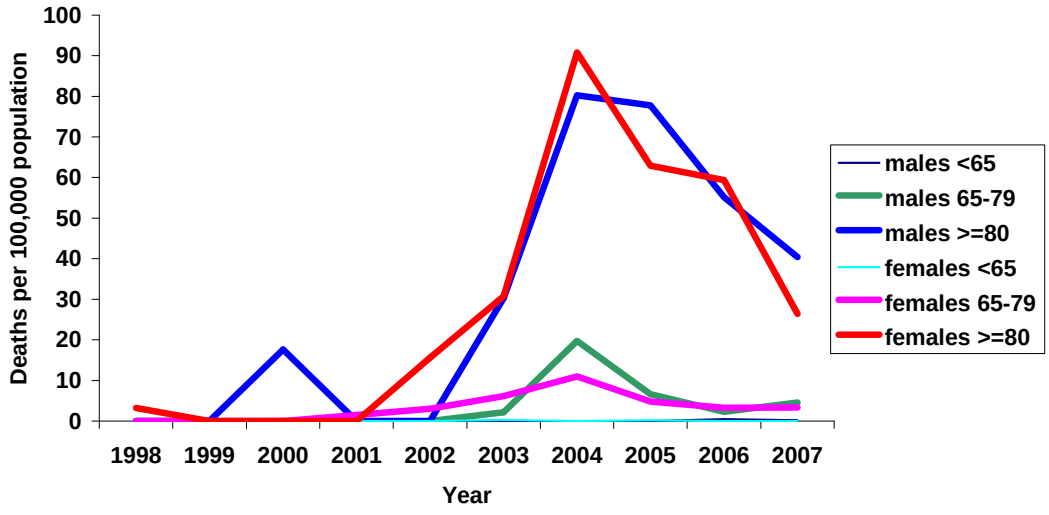
Table 1 Age-standardized mortality rates for *Clostridium difficile* enterocolitis, by region, Belgium 1998-2007

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
CDI as the "Underlying" cause of death										
Brussels	0.1	0,0	0.2	0.1	0.6	1.8	5.1	3.2	2.6	1.7
Flanders	0.08	0.12	0.12	0.19	0.28	0.51	0.98	1.16	1.18	0.8
Wallonia							0.7	0.9		

Graph 2 Age and sex-specific mortality rates due to *Clostridium difficile* enterocolitis as "underlying "cause of death, Flanders 1998-2007



Graph 3 Age and sex-specific mortality rates due to *Clostridium difficile* enterocolitis as "underlying "cause of death, Brussels 1998-2007



Graph 4 Age-specific mortality rates due to *Clostridium difficile* enterocolitis as "underlying" cause of death, Wallonia, 2004-2005

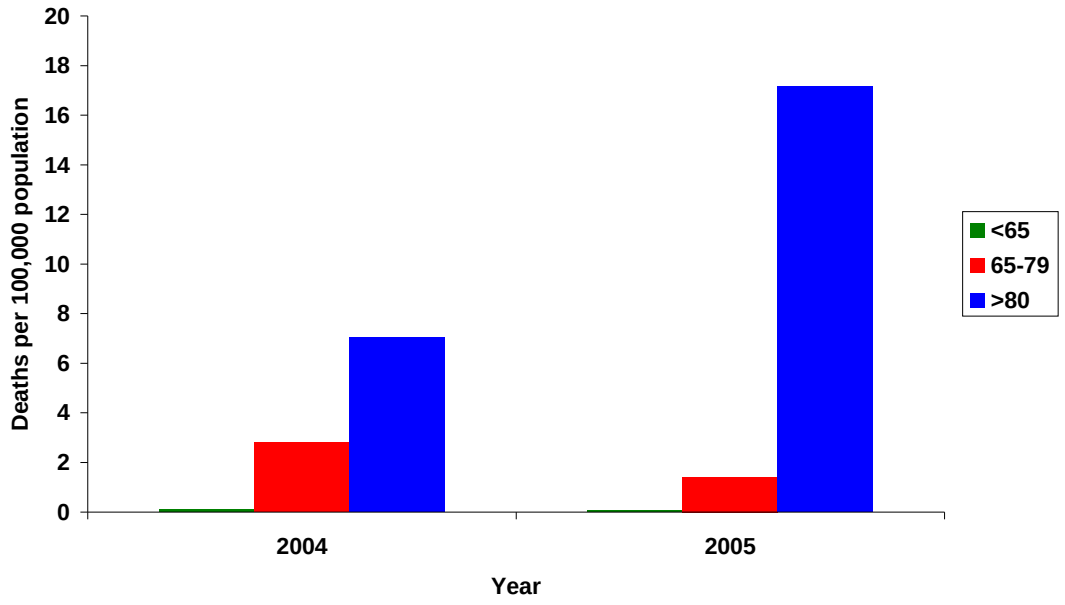


Table 2 Trends for CDI-related hospital discharges, Belgium 1998-2007

	1999	2000	2001	2002	2003	2004	2005	2006	2007
Age-and sex-specific CDI total discharge rates /1,000 hospital discharges									
Men									
<65 years	0.3	0.4	0.3	0.3	0.4	0.5	0.5	0.6	0.6
65-79 years	0.7	0.9	0.9	0.9	1.1	1.5	1.7	1.6	1.5
>=80 years	2.2	2.1	1.7	2.5	3.3	4.5	5.3	4.2	4.4
Women									
<65 years	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.6
65-79 years	1.1	1.1	1.0	1.0	1.4	2.0	2.0	2.0	2.0
>=80 years	2.8	2.8	2.7	3.2	4.4	6.7	6.8	5.0	5.8
CDI discharge rate/1,000 hospital discharges									
	0.7	0.7	0.7	0.7	1.0	1.3	1.4	1.3	1.4

Graph 5 **Age- and sex-specific hospital discharge rates for *Clostridium difficile* - associated infection, as "any diagnose", Belgium 1999-2007**