EPIDEMIOLOGY OF *CLOSTRIDIOIDES DIFFICILE* INFECTIONS IN BELGIAN HOSPITALS

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Report 2020
Data up to and including 2019

LAURE MORTGAT • ELS DUYSBURGH

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

BR	Brazier (European ribotype classification)
CA-CDI	Community associated *Clostridioides (Clostridium) difficile* infection
CDI	*Clostridioides difficile (Clostridium)* infection
C. difficile	*Clostridioides (Clostridium) difficile*
CI	Confidence interval
ECDC	European centre for disease prevention and control
FMT	Faecal microbiota transplantation
FPS	Federal Public Service (SPF/FOD)
HA-CDI	Hospital associated *Clostridioides (Clostridium) difficile* infection
HAI	Healthcare-associated infections
ICD-9 (10)-CM	International classification of diseases, 9th (10th) version, clinical modification
IPC	Infection prevention and control
IQR	Interquartile range
NIHDI (INAMI/RIZIV)	National Institute for Health and Disability Insurance (Institut national d'assurance maladie-invalidité/ Rijksinstituut voor ziekte- en invaliditeitsverzekering)
LTCF	Long term care facility
N or n	Number
NRC	National Reference Centre (Laboratory)
NSIH	National surveillance of healthcare-associated infections and antimicrobial resistance
PCR	Polymerase chain reaction
RHM/MZG	Résumé hospitalier minimum/ Minimale ziekenhuis gegevens (Minimum hospital data set)
SPMA	Standardised procedures for Mortality Analysis
UCL	Université catholique de Louvain (Belgian ribotype classification)
UCLouvain	Université catholique de Louvain

GLOSSARY

Acute care hospital
An acute care hospital is a hospital that is defined as such by the National Institute for Health and Disability Insurance (NIHDI) (INAMI-RIZIV list updated April 2017[1]).

Chronic/Long-term care hospital
A chronic or long-term care hospital is a hospital that is defined as such by the National Institute for Health and Disability Insurance (NIHDI) (INAMI-RIZIV list updated April 2017[1]).

Community associated *Clostridioides difficile* infection (CA-CDI)
Onset of symptoms less than two days after admission in the reporting hospital with no previous admission in any healthcare facility in the previous 12 weeks.

Hospital-associated *Clostridioides difficile* infection (HA-CDI)
Onset of symptoms 2 days or more after admission in the reporting hospital, or within four weeks of discharge from a healthcare facility. In this report, it is calculated as: date of onset - date of admission ≥ 2.

Hospitalisation-days (or patient-days or hospital-days)
Number of invoiced days for every patient admitted in a hospital as defined by the Belgian minimal hospital data classification (*Résumé hospitalier minimal/minimale ziekenhuisgegevens*, RHM/MZG). Ambulatory patients, day hospitalisations, or emergency room stays without overnight stay are not included.

Mean incidence
Sum of cases reported by participating hospitals for a given period, divided by the sum of denominators (admissions or hospitalisation days) for that period and the concerned hospitals.

Mean of the incidences
Sum of the incidences of all included hospitals divided by the number of participating hospitals.

Number of admissions (or discharges)
Number of standard hospitalisations with overnight stay, as defined by the Belgian minimal hospital data classification (*Résumé hospitalier minimal/minimale ziekenhuisgegevens,* RHM/MZG). Ambulatory patients, day hospitalisations, or emergency room stays without overnight stay are not included.

Primary hospitals
Primary hospitals are hospitals that are defined as acute hospitals without university characteristics by the Belgian Ministry of health in a list dated April 2019[2]. (In this report, the hospital type is provided at INAMI/RIZIV code level, and not at campus level).

[1] NIHDI – list hospitals - April 2017: acute / chronic / psychiatric hospitals.
[2] List of hospitals provided by the Belgian Ministry of health (*Dienst Datamanagement - Directoraat- Generaal Gezondheidszorg*); List dated April 2019: *Adressenlijst ziekenhuizen 04/2019 - Liste d'adresses des hôpitaux 04/2019*.

Secondary hospitals
Secondary hospitals are hospitals that are defined as acute hospitals with university characteristics by the Belgian ministry of health in a list dated April 2019[2]. (In this report, the hospital type is provided at INAMI/RIZIV code level, and not at campus level).

Tertiary hospitals
Tertiary hospitals are hospitals that are defined as university hospitals by the Belgian ministry of health in a list dated April 2019[2]. (In this report, the hospital type is provided at INAMI/RIZIV code level, and not at campus level).

EXECUTIVE SUMMARY

Clostridioides difficile infection (CDI), previously known as "*Clostridium difficile*" infection, is a major cause of infectious diarrhoea and pseudomembranous colitis predominantly acquired during acute or long-term care. Its symptoms range from mild diarrhea to a severe life-threatening infection, resulting in a high clinical and economic burden. This report aims to describe the epidemiology of CDI in Belgian hospitals, focusing on the year 2019. It summarises the data from four different sources, namely: (1) the national surveillance of CDI in hospitals, including data from the national reference laboratory (NRC 2008 – 2019); (2) hospitals stays (RHM/MZG 2000 – 2018); (3) billing of diagnostic tests (INAMI/RIZIV 2000 – 2019), and (4) the death registry (2000 – 2017).

Participation in the national surveillance system slowly decreased since 2015, the year since when registration was no longer mandatory, but remained good. In 2019, 81 hospitals (76%) out of the 107 hospitals eligible for CDI surveillance provided both numerators (cases) and denominators (number of hospitalisation-days and number of admissions) for at least one semester, while 61 hospitals provided these data all year long. More than 2,400 CDI cases were recorded.

The proportion of "hospital-associated" cases (HA-CDI, with date of onset ≥ 2days after admission) was 56% in 2019, compared to 62% 10 years ago. During the same period, the number of cases reported with a presumed origin being the community increased from 22% to 29 %. As usual, around 11% of cases were recurrent and female were slightly more affected (55%) than male, as were elderly people (median age of 75 years old). Equally, geriatrics, gastroenterology and oncology departments remained among the most affected wards. Less than 2% of CDI patients died because of their infection, which is lower than ever. Similarly, since 2017 the proportion of cases reported as "complicated" was exceptionally low (9% while before 2017, this was usually around 20%), coinciding with a change in this variable description.

At national level, the mean CDI incidence in acute hospitals computed from surveillance data did not change substantially since 2015, approaching 2.5/10,000 hospitalisation-days for total CDI and 1.4/10,000 hospitalisation-days for HA-CDI in 2019. Incidence was higher in Wallonia than in Flanders (see figure 1). There was a large variability in the reported incidence of CDI and HA-CDI between provinces and hospitals.

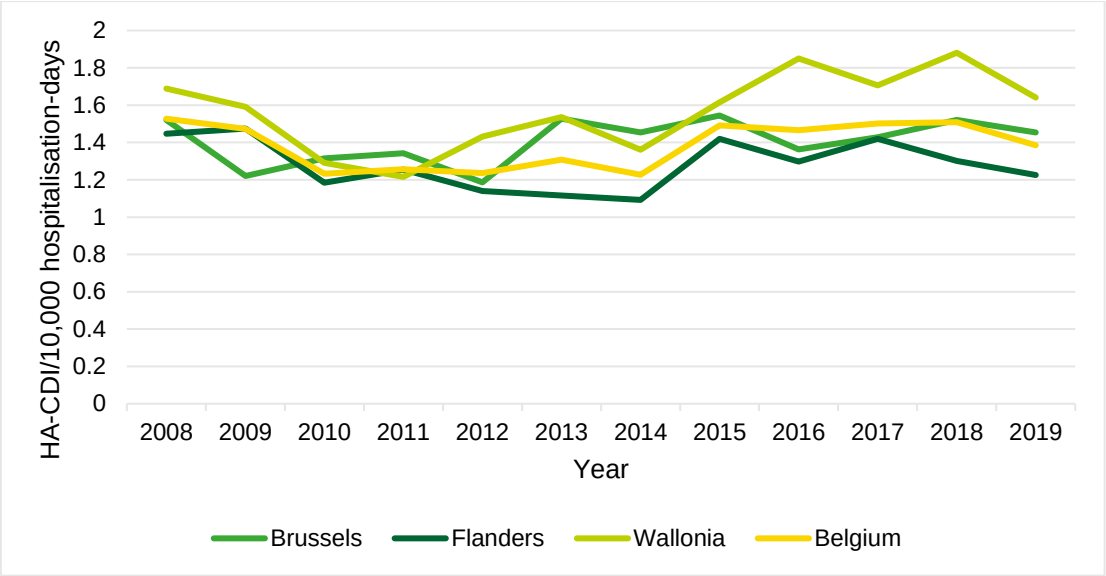


Figure 1: Mean incidence of HA-CDI/10,000 hospitalisation-days in acute care hospitals, per region, Belgium, 2008-2019 (HA-CDI: hospital-associated *Clostridioides difficile* infection; N: number)

*Note: Hospital-associated-*Clostridioides difficile *infection (HA-CDI): onset of symptoms ≥ 2 days after admission. Incidence calculation: inclusion of all acute care hospitals that provided complete data (numerators and denominators) for at least one semester/year.*

In 2019, 57 Belgian hospitals sent 698 toxigenic strains to the National Reference Centre (NRC Laboratory) for typing for surveillance purposes. Both the number of strains sent and the number of participating hospitals have been constantly decreasing since 2014. Ribotype BR[3]014 (UCL[4]16) remained the most prevalent and widespread strain type in Belgian hospitals in the three regions. The hypervirulent strain BR078 (UCL3) came second; while BR027 (UCL027) was less common in 2019 compared to previous years.

As shown in figure 2 and based upon latest available data from the dedicated federal public service (FOD/SPF), CDI incidence approached 3.2/10,000 hospitalisation-days in 2018, which is the highest number ever recorded. For this year 4,425 hospital stay records mentioned CDI as primary or secondary diagnosis. As this data are comprehensive, they are supposed to give a better estimate of CDI burden in Belgium. Trends were similar whether using hospital stay data or surveillance data.

[3] BR: European Brazier classification of ribotypes.
[4] UCL: Belgian classification of ribotypes.

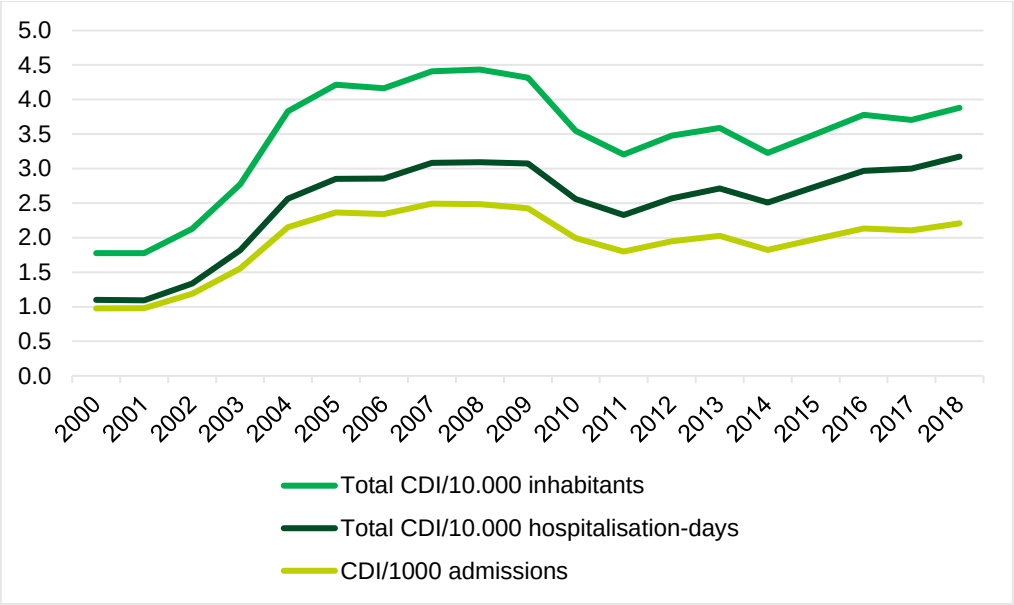


Figure 2: *Clostridioides (Clostridium) difficile* infection (CDI) incidence in Belgian hospitals, 2000-2018

Source: Federal Public Service of public health (SPF/FOD). Number of ICD-9-CM 008.45 (2000-2014) and ICD-10-CM A04.7 (2016-2018) codes (Enterocolitis due to Clostridioides *(*Clostridium*)* difficile*) included in the hospital stay database as primary or secondary diagnosis. Extrapolation made for 2015*[5]*.*

Around 167,000 tests applied for faecal toxin-producing *C. difficile* detection were billed in 2019, and nearly 15 tests were reimbursed per 1,000 insured inhabitants. These numbers are the highest ever recorded. This was essentially due to an increase in testing in ambulatory patients, while testing in hospitalised patients remained globally stable. As in previous years, around 19 tests were performed per CDI diagnosed in hospitals in 2018.

In 2015, mortality reached a peak, with 106 deaths recorded having as underlying cause « enterocolitis due to *C. difficile* ». This was probably due to unusually high prevalence of hypervirulent strains BR027 (UCL027) and BR078 (UCL3). In 2017 (most recent available mortality data), the number of deaths was 91, with an age-adjusted specific mortality rate of 0.73 deaths/100,000 inhabitants, slightly higher than in 2016. Mortality was higher in Brussels except for the last two available years. In 2017 the three regions exhibited similar mortality rates. Around 80% of deaths occurred in people aged 80 years or more.

In conclusion, the burden of CDI in Belgian hospitals did not change substantially during the last five years, and was slightly higher in 2018. Importantly, the fact that the incidence was lower during the period 2010 to 2014 as well as the variability between regions and hospitals suggests that there is still room for improvement. The role of the environment in CDI epidemiology as well as the impact of CDI in the community should be further investigated, Additionally, participation in the epidemiological surveillance, especially regarding the provision of denominators and the shipment of strains to the NRC, should be further encouraged given the decreasing participation rates. Currently, the best strategy to prevent and control CDI in Belgium remains good antimicrobial stewardship.

[5] Due to the transition from ICD-9 to ICD-10, 2015 data was unavailable and was calculated as being the average between 2014 and 2016 data.

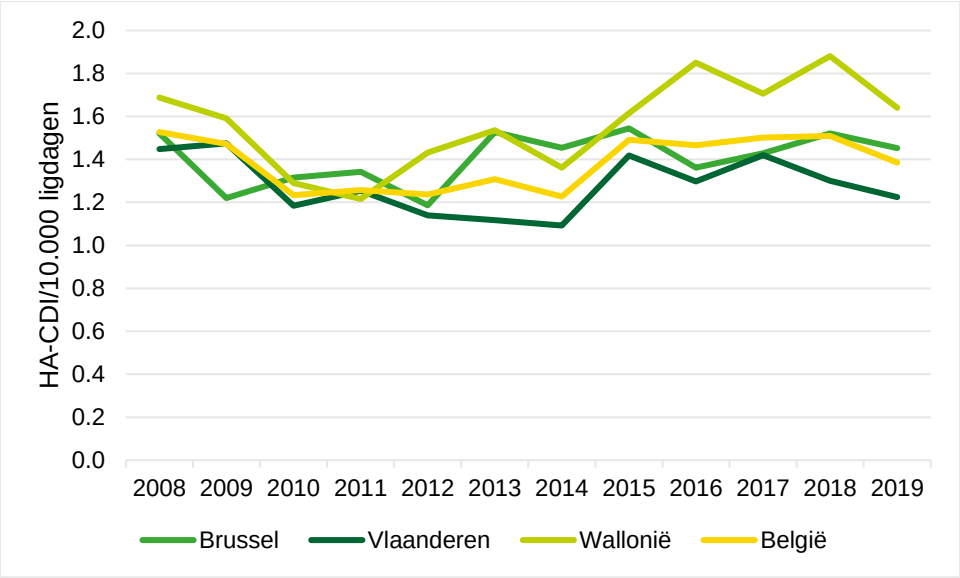
NEDERLANDSE SAMENVATTING

Clostridioides difficile infectie (CDI), voorheen bekend als '*Clostridium difficile*' infectie, is een belangrijke oorzaak van infectieuze diarree en pseudomembraneuze colitis voornamelijk verworven tijdens acute of chronische zorg. De symptomen variëren van milde diarree tot een ernstige levensbedreigende infectie, met als gevolg een hoge medische en economische belasting. Dit rapport heeft tot doel de epidemiologie van CDI in Belgische ziekenhuizen te beschrijven met de focus op het jaar 2019. Het rapport vat de gegevens uit vier verschillende bronnen samen, namelijk: (1) de nationale surveillance van CDI in ziekenhuizen, inclusief gegevens van het nationale referentielaboratorium (NRC 2008 – 2019); (2) minimale ziekenhuisgegevens (MZG 2000 – 2018); (3) facturatie van diagnostische tests (RIZIV 2000 – 2019); en (4) het overlijdensregister (2000 – 2017).

Deelname aan de nationale surveillance nam sinds 2015, het jaar waarin verplicht deelname stopte, langzaam af, maar bleef goed. In 2019 hebben ongeveer 81 (76%) van de 107 ziekenhuizen die voor de CDI surveillance in aanmerking komen gedurende ten minste één semester zowel tellers (gevallen) als noemers (ligdagen en aantal opnames) geregistreerd, terwijl 61 ziekenhuizen deze gegevens het hele jaar door leverden. Er werden in totaal meer dan 2.400 CDI gevallen geregistreerd.

De proportie 'ziekenhuis-geassocieerde' gevallen (HA-CDI, met startdatum ≥ 2 dagen na opname) bedroeg 56% in 2019, vergeleken met 62% 10 jaar geleden. In dezelfde periode steeg het aantal gerapporteerde gevallen met de gemeenschap als vermoedelijke oorsprong van 22% tot 29%. Vergelijkbaar met vorige analyses, ging het in ongeveer 11% om wederkerend gevallen, waren er iets meer vrouwelijke patiënten (55%), en waren patiënten voornamelijk ouderen (mediaanleeftijd van 75 jaar). Geriatrie, gastro-enterologie en oncologie bleken nog steeds de meest getroffen afdelingen. Minder dan 2% van de CDI-patiënten stierf als gevolg van hun infectie, wat lager is dan ooit tevoren. Evenzo is sinds 2017 de proportie gevallen dat met 'complicaties' werd gerapporteerd uitzonderlijk laag (9% in 2019, terwijl dit vóór 2017 meestal rond 20% was). Dit kan te wijten zijn aan een recente wijziging in de definitie van deze variabele.

Sinds 2015 is de gemiddelde CDI-incidentie in de acute ziekenhuizen, berekend op basis van de surveillancegegevens, op nationaal niveau niet wezenlijk veranderd. Deze bedroeg in 2019 voor het totaal aantal CDI gevallen 2,5/10.000 ligdagen en voor het aantal HA-CDI gevallen 1,4/10.000 ligdagen. In Wallonië was de incidentie hoger dan in Vlaanderen (zie figuur 1). Er blijft een grote variabiliteit tussen provincies en ziekenhuizen in de gerapporteerde incidentie van CDI en HA-CDI.



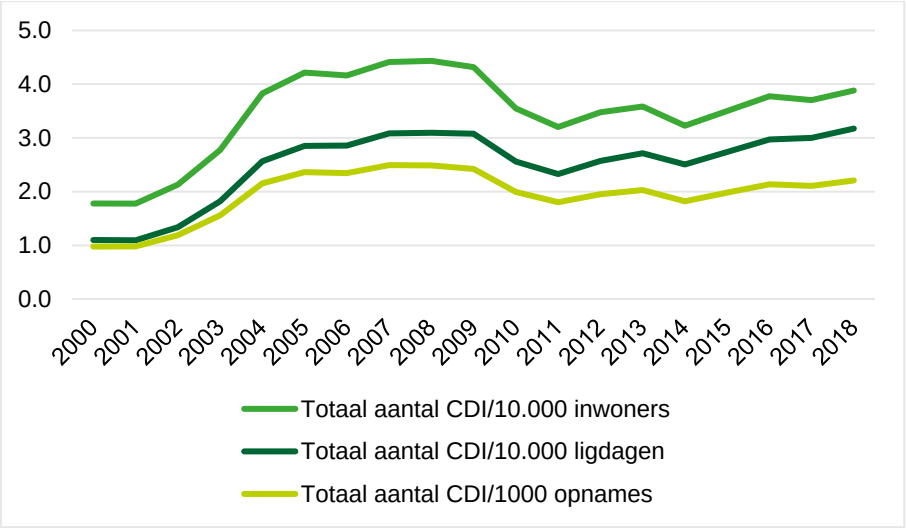
Figuur 1: Gemiddelde incidentie van HA-CDI/10.000 ligdagen in acute ziekenhuizen, per regio, België, 2008-2019

Opmerking: Ziekenhuis-geassocieerde Clostridioides difficile *infectie (HA-CDI): begin van de symptomen ≥ 2 dagen na opname. Incidentieberekening: omvat alle acute ziekenhuizen die volledige gegevens (tellers en noemers) verstrekten voor ten minste één semester/jaar.*

In 2019 hebben 57 Belgische ziekenhuizen 698 toxigene stammen naar het nationaal referentiecentrum (NRC laboratorium) gestuurd om ze voor surveillancedoeleinden te typeren. Zowel het aantal opgestuurde stammen als het aantal deelnemende ziekenhuizen is sinds 2014 voortdurend gedaald. Ribotype BR[6]014 (UCL[7]16) bleef het meest voorkomende en wijdverspreide stam-type in de Belgische ziekenhuizen in de drie gewesten. De hypervirulente stammen BR078 (UCL3) kwam op de tweede plaats; terwijl BR027 (UCL027) minder vaak voorkwam in 2019 in vergelijking met voorgaande jaren.

Zoals blijkt uit figuur 2 en op basis van de meest recent beschikbare gegevens van de federale overheidsdienst volksgezondheid (FOD) betrof in 2018 de CDI-incidentie 3,2/10.000 ligdagen, wat het hoogst geregistreerd aantal ooit is. Voor 2018 vermelden 4.425 ziekenhuisverblijven CDI als primaire of secundaire diagnose. Aangezien deze gegevens alle gevallen omvatten, worden ze verondersteld een betere schatting te geven van de CDI-belasting (burden) in België. CDI-trends waren vergelijkbaar, ongeacht of ziekenhuisverblijfsgegevens of surveillancegegevens werden gebruikt.

[6] BR: Europese Brazier classificatie voor ribotypes.
[7] UCL: Belgische classificatie voor ribotypes.



Figuur 2: *Clostridioides (Clostridium) difficile* infectie (CDI) incidentie in Belgische ziekenhuizen, 2000-2018

Bron: Federale Overheidsdienst Volksgezondheid (FOD). Aantal ICD-9-CM 008.45 (2000-2014) en ICD-10-CM A04.7 (2016-2018) codes (Enterocolitis als gevolg van Clostridioides *(*Clostridium*)* difficile*) opgenomen in de minimale ziekenhuisgegevens databank als primaire of secundaire diagnose. Extrapolatie gemaakt voor 2015*[8]*.*

In 2019 werden ongeveer 167.000 tests voor het opsporen van fecale toxine-producerende *C. difficile* gefactureerd, goed voor bijna 15 tests per 1.000 verzekerde inwoners die werden terugbetaald. Deze aantallen zijn de hoogste ooit geregistreerd. Dit was voornamelijk het gevolg van een toename in het testen van ambulante patiënten, terwijl het testen van gehospitaliseerde patiënten globaal stabiel bleef. Net als in voorgaande jaren werden in 2018 in ziekenhuizen gemiddeld ongeveer 19 tests uitgevoerd per gediagnosticeerde CDI.

In 2015 bereikte het sterftecijfer een piek met 106 geregistreerde sterfgevallen met onderliggende oorzaak 'enterocolitis als gevolg van *C. difficile*'. Dit was waarschijnlijk het gevolg van de ongewoon hoge prevalentie van de hypervirulente stammen BR027 (UCL027) en BR078 (UCL3). In 2017 (meest recente gegevens) was het aantal sterfgevallen 91, met een '*age-adjusted specific mortality rate'* van 0,73 sterfgevallen/100.000 inwoners. Dit is iets hoger dan in 2016. Het sterftecijfer was hoger in Brussel, behalve gedurende de laatste twee jaren met beschikbare gegevens. In 2017 vertoonden de drie gewesten vergelijkbare sterftecijfers. Ongeveer 80% van de sterfgevallen deed zich voor bij mensen ouder dan 80 jaar.

Samengevat kan worden gesteld dat de CDI-belasting (burden) in de Belgische ziekenhuizen de afgelopen vijf jaar niet wezenlijk veranderde maar dat deze in 2018 zelfs iets hoger was. Belangrijk is te zien dat de incidentie in de periode 2010-2014 lager was dan nu, evenals de variabiliteit tussen provincies en ziekenhuizen. Dit suggereert ruimte voor verbetering. De invloed van omgevingsfactoren op de CDI-epidemiologie en de impact van CDI in de gemeenschap moeten verder worden onderzocht. Bovendien moet de deelname aan de epidemiologische surveillance, met name wat betreft het verstrekken van noemergegevens en het verzenden van stammen naar de NRC, verder worden aangemoedigd gezien de

[8] Als gevolg van de overgang van ICD-9 naar ICD-10 waren gegevens voor 2015 niet beschikbaar en werden deze berekend als het gemiddelde tussen 2014 en 2016.

dalende deelnamepercentages. Momenteel blijft de beste strategie om in België CDI te voorkomen en te controleren een goed antimicrobiële beleid en stewardship.

RÉSUMÉ EN FRANÇAIS

L'infection à *Clostridioides difficile* (ICD), auparavant appelée infection à "*Clostridium difficile*", est une cause importante de diarrhée infectieuse et de colite pseudo-membraneuse principalement acquises lors des soins aigus et chroniques. Ses symptômes peuvent varier d'une diarrhée légère à une infection sévère voire mortelle, ce qui entraîne une charge clinique et économique élevé. Ce rapport vise à décrire l'épidémiologie des ICD dans les hôpitaux belges, avec un focus sur l'année 2019. Il résume les données provenant de quatre sources différentes, à savoir (1) la surveillance nationale des ICD dans les hôpitaux, y compris les données du laboratoire national de référence (CNR 2008 - 2019) ; (2) les séjours hospitaliers (RHM/MZG 2000 - 2018) ; (3) la facturation des tests diagnostiques (INAMI/RIZIV 2000 - 2019) et (4) le registre des décès (2000 - 2017).

La participation au système national de surveillance est en léger déclin depuis 2015, l'année depuis laquelle l'enregistrement n'était plus obligatoire, mais reste correcte. En 2019, 81 hôpitaux (76%) sur les 107 hôpitaux éligibles à la surveillance des CDI ont fourni à la fois des numérateurs (cas) et des dénominateurs (nombre de journées d'hospitalisation et nombre d'admissions) pendant au moins un semestre, tandis que seuls 61 hôpitaux ont fourni ces données tout au long de l'année. Plus de 2.400 cas des CDI ont été enregistrés en 2019.

La proportion d'ICD " associées à l'hôpital " (avec début des symptômes ≥ 2 jours après l'admission) était de 56% en 2019, contre 62% il y a 10 ans. Au cours de la même période, le nombre de cas dont l'origine présumée était « la communauté » est passé de 22% à 29%. Comme pour les années précédentes, environ 11% des cas étaient récurrents et les femmes étaient légèrement plus touchées (55%) que les hommes, tout comme les personnes âgées (âge médian de 75 ans). De même, les services de gériatrie, de gastroentérologie et d'oncologie sont restés parmi les services les plus affectés. Moins de 2% des patients avec une ICD sont décédés à cause de leur infection. Ce chiffre est plus bas que jamais, probablement grâce au développement de l'arsenal thérapeutique disponible contre cette infection ces dernières années. De même, la proportion de cas déclarés comme "compliqués" est exceptionnellement faible depuis 2017 (9% en 2019 alors qu'elle se situe habituellement autour de 20%), coïncidant avec un changement dans la description de cette variable.

Au niveau national, l'incidence moyenne des ICD dans les hôpitaux aigus calculée à partir des données de surveillance n'a pas beaucoup changé depuis 2015, approchant 2,5/10.000 journées d'hospitalisation pour les ICD totales et 1,4/10.000 journées d'hospitalisation pour les ICD associées à l'hôpital en 2019. L'incidence était plus élevée en Wallonie qu'en Flandre (voir figure 1). L'incidence des ICD et des ICD associées à l'hôpital variait considérablement d'une province à l'autre et d'un hôpital à l'autre.

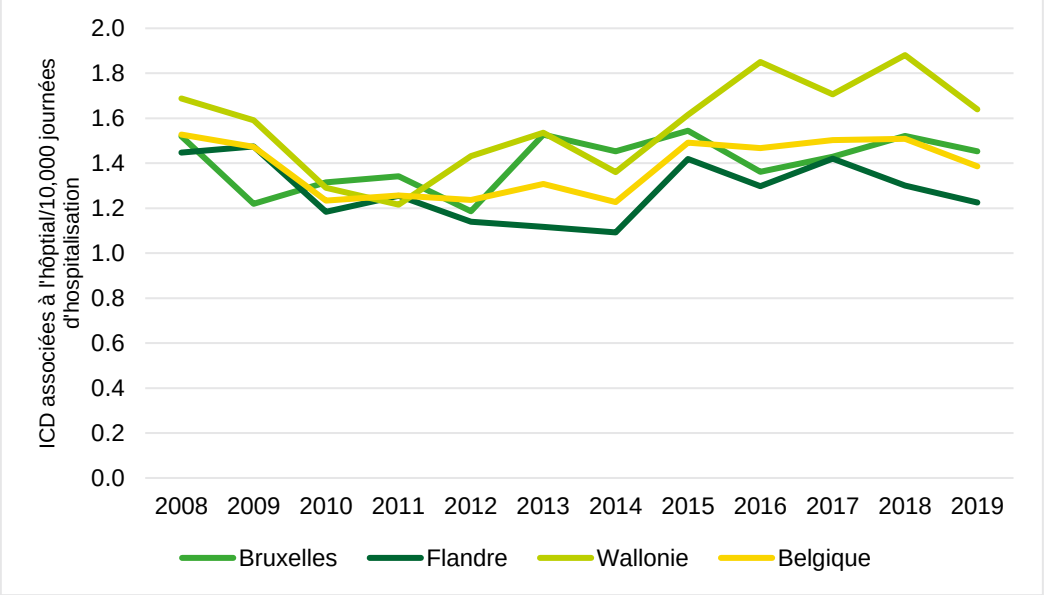


Figure 1: Incidence moyenne des ICD associées à l'hôpital, par 10.000 journées d'hospitalisation dans les hôpitaux aigus, par région, Belgique, 2008-2019

Remarque : ICD associées à l'hôpital : début des symptômes ≥ 2 jours après l'admission. Calcul de l'incidence : inclusion de tous les hôpitaux aigus ayant fourni des données complètes (numérateurs et dénominateurs) pendant au moins un semestre/année.

En 2019, 57 hôpitaux belges ont envoyé 698 souches toxinogènes au Centre national de référence (laboratoire CNR) pour un typage à des fins de surveillance. Tant le nombre de souches envoyées que le nombre d'hôpitaux envoyant des souches étaient en constante diminution depuis 2014. Le ribotype BR[9]014 (UCL[10]16) était le plus fréquent et le plus répandu dans les hôpitaux belges, et ce dans les trois régions. La souche hypervirulente BR078 (UCL3) s'est retrouvée en deuxième position tandis que BR027 (UCL027) était moins fréquente en 2019 par rapport aux années précédentes.

Comme le montre la figure 2 et sur la base des dernières données disponibles du service public fédéral (SPF) santé publique, l'incidence des ICD approchait 3,2/10.000 journées d'hospitalisation en 2018, ce qui est le nombre le plus élevé jamais enregistré. Pour cette même année, 4.425 séjours hospitaliers mentionnaient l'ICD comme diagnostic primaire ou secondaire. Comme ces données sont exhaustives, elles sont censées donner une meilleure estimation de la charge que représentent les ICD en Belgique. Les tendances temporelles restent similaire, que l'on utilise les données relatives aux séjours hospitaliers ou les données de surveillance.

[9] Classification européenne des ribotypes (Brazier).
[10] Classification belge des ribotypes.

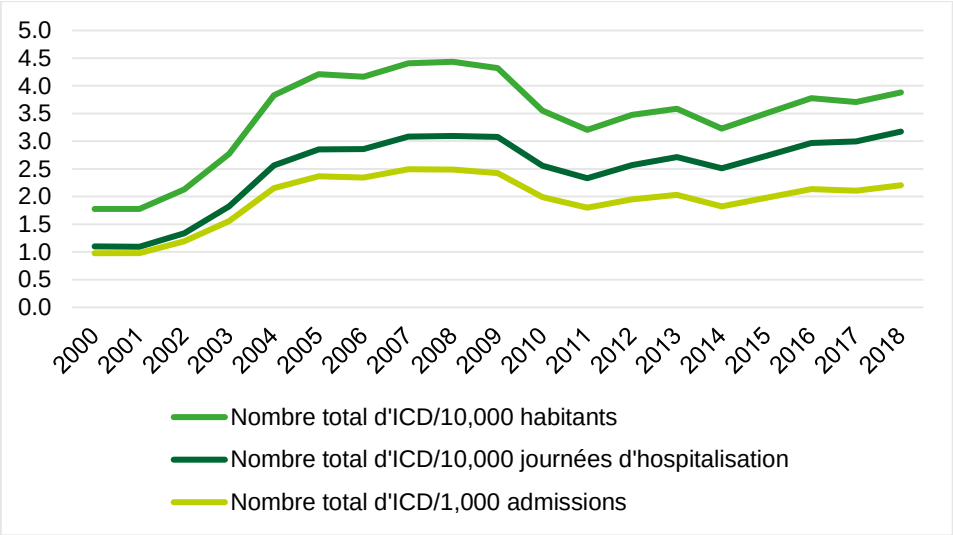


Figure 2: Incidence des infections à *Clostridioides (Clostridium*) dans les hôpitaux belges, 2000-2018

Source : Service public fédéral (SPF) santé publique. Nombre de codes ICD-9-CM 008.45 (2000-2014) et ICD-10-CM A04.7 (2016-2018) (entérocolite à Clostridioides *(*Clostridium*)* difficile*) repris dans la base de données des séjours hospitaliers comme diagnostic primaire ou secondaire. Extrapolation faite pour 2015*[11]*.*

Environ 167.000 tests pour la « recherche de *C. difficile* toxinogène dans les selles » ont été facturés en 2019, et près de 15 tests ont été remboursés pour 1.000 habitant assurés. Ces chiffres sont les plus élevés jamais enregistrés. Cela s'explique essentiellement par une augmentation des tests chez les patients ambulants, alors que les tests chez les patients hospitalisés sont restés globalement stables. Comme les années précédentes, environ 19 tests ont été réalisés par ICD diagnostiquée dans les hôpitaux en 2018.

En 2015, la mortalité a atteint un pic, avec 106 décès enregistrés ayant comme cause sous-jacente une " entérocolite due à *C. difficile* ". Cela était probablement dû à une prévalence exceptionnellement élevée de souches hypervirulentes BR027 (UCL027) et BR078 (UCL3). En 2017 (données disponibles les plus récentes), le nombre de décès était de 91, avec un taux de mortalité spécifique standardisé pour l'âge de 0,73 décès/100.000 habitants. La mortalité est plus élevée à Bruxelles, à l'exception des deux dernières années disponibles. En 2017 en effet, les trois régions ont présenté des taux de mortalité similaires. Environ 80% des décès sont survenus chez des personnes âgées de 80 ans ou plus.

En conclusion, la charge des ICD dans les hôpitaux belges n'a pas changé de manière substantielle au cours des cinq dernières années, avec une légère augmentation en 2018. Toutefois, le fait que l'incidence ait été plus faible au cours de la période de 2010 à 2014, ainsi que la variabilité entre les provinces et les hôpitaux suggère qu'il y a encore une marge d'amélioration possible. Le rôle de l'environnement dans l'épidémiologie des ICD ainsi que l'impact des ICD dans la communauté devraient être étudiés plus en détail. De plus, la participation à la surveillance épidémiologique, notamment en ce qui concerne l'envoi des dénominateurs et des souches au CNR, devrait être davantage encouragée étant donné la diminution des taux de participation. Actuellement, la meilleure stratégie pour prévenir et contrôler les ICD en Belgique reste la bonne gestion des antimicrobiens.

[11] En raison du passage de l'ICD-9 à l'ICD-10, les données de 2015 n'étaient pas disponibles et ont été calculées comme étant la moyenne des données de 2014 et de 2016.

INTRODUCTION

1. Background

Clostridioides difficile (C. difficile, previously known *as Clostridium difficile*) is an anaerobic, Gram-positive, spore-forming bacterium often found in the intestinal tract of healthy individuals and different animals. It can become harmful once the normal balance of the gut microbiota (flora) is disturbed, a phenomenon known as “dysbiosis”. The intestinal microbiota can be impacted by various environmental or individual factors, such as genetics, immune defence system, diet, stress, and medication, in particular antibiotic agents (1). Pathogenic *C. difficile* strains produce toxins (toxin A and/or B, and/or binary toxin) responsible for symptoms ranging from mild diarrhoea to a severe life-threatening infection, depending on host susceptibility and the virulence of the infecting strain. Antibiotic exposure, being the main trigger for dysbiosis, is therefore the major risk factor for the development of *Clostridioides difficile* infection (CDI), together with advanced age, presence of co-morbidities and increased length of hospitalisation (2). *C. difficile* can survive for long periods in the environment and its potential for spreading and generating outbreaks in healthcare facilities is particularly high. Treatment usually involves a long course of antibiotics and can be challenging, furthermore it has been documented that the infection is recurrent in around 20% of the cases who initially respond to treatment, and this risk further increases with the number of previous recurrences (3). CDI therefore results in a high clinical and economic burden due to increased duration of hospitalisation, re-admission, and management of complications.

CDI is the most important cause of infectious diarrhoea acquired in healthcare institutions and is responsible for around 3.6% of healthcare-associated infections (HAI) in European hospitals (4). In the last decades, various countries around the world reported an increase in incidence of CDI, with, however, wide variations between countries (5–7). This increase has been attributed to different factors such as changes in the prevailing ribotypes and emergence of hypervirulent strains like BR027[12]/NAP1[13], the ageing of the population, and the increase in antibiotic consumption.

As a result of this increasing incidence of CDI and the emergence of hypervirulent strains and outbreaks, surveillance of CDI in Belgian hospitals was implemented in 2007. The objectives of the surveillance are to:

- Monitor CDI incidence, burden and trends at hospital and national level;
- Identify and monitor the microbiological characteristics of strains isolated in Belgian hospitals through collaboration with the National Reference Laboratory (NRC).

Data used in this report comes from four sources, being: (1) the national surveillance of CDI in hospitals, including data from the national reference laboratory (NRC 2008 – 2019); (2) hospital stays (RHM/MZG 2000 – 2018); (3) billing of diagnostic tests (INAMI/RIZIV 2000 – 2019) and (4) the death registry (2000 – 2017). Main results are presented in the body of the report while more detailed data are included in the annex.

[12] European Brazier classification of *C.difficile* ribotypes based on polymerase chain reaction.
[13] North American classification of *C.difficile* strains based on pulsed-field gel electrophoresis.

2. Objectives

The objective of this report is to describe the epidemiology of CDI in Belgium, with a focus on year 2019. It aims to present an estimate of CDI incidence in Belgium acute care hospitals and its trends during the last years, to assess the burden and adverse outcomes of CDI, and to describe its microbiological characteristics.

METHODS

1. National surveillance of CDI in hospitals

HOSPITAL DATA

Participation in the CDI surveillance was mandatory until 2014 for all general hospitals, except specialised or geriatric hospitals with less than 150 beds, palliative hospitals and burn units. Since 2015, participation in the CDI surveillance is no longer mandatory, but acute care hospitals have to participate in at least one out of the four following surveillance program: CDI, surgical site infections, vancomycin-resistant enterococci, and ventilation-associated pneumonia and bloodstream infections in intensive care units. The hospital wide surveillances of blood stream infections, methicillin resistant *Staphylococcoccus aureus*, and multiresistant Gram negative bacteria remain by default mandatory for all general hospitals (RD 22/06/2017).

Participation in the CDI surveillance involves the registration of all cases identified in hospitalised patients in the facility for a minimum of 6 months as well as the shipment of five consecutive strains per surveillance period to the NRC for further typing. Hospital data and NRC data are related via a unique code that is generated automatically for each individual hospital record and sent to the NRC with the corresponding strain.

Denominators, being the monthly number of admission and number of hospitalisation-days must also be provided by each participating hospital. One-day admissions are excluded. The methodology used for data collection is given in detail in the surveillance protocol, available at our website in Dutch (http://www.nsih.be/surv_cdif/deelname_nl.asp) and French (http://www.nsih.be/surv_cdif/deelname_fr.asp). This protocol is regularly updated, and streamlining with the European surveillance protocol of CDI is encouraged (enhanced option).(8)

Data on CDI occurring before the 1st of July 2017 was entered and reported on the online tool NSIHweb1. Hospitals were then identified by a specific “NSIH code”, only used for the surveillance coordinated by the “National surveillance of HAI and antimicrobial resistance” (NSIH) unit of Sciensano. Since mid-2017, all data have been collected via Healthdata (https://healthdata.sciensano.be/en/home, https://www.healthdata.be/dcd/#/collection/NSIH-CDIF/version/6). This new platform enables data collection, storage, and analysis, while reporting is done via their data visualisation platform “Healthstat” (https://www.healthstat.be/). In the Healthdata application hospitals are identified by their hospital and campus number defined by the “National Institute for Health and Disability Insurance” (NIHDI), allowing for a better standardisation.

To be considered for registration, a CDI case must fulfil at least one of the following criteria:

1. Diarrhoea or toxic megacolon, and a positive laboratory test for *C. difficile* toxin A and/or B in the stools or a toxin-producing strain identified in the stools, by culture or another method;

2. Pseudomembranous colitis identified by endoscopy of the lower gastro-intestinal tract;
3. Histopathology characteristic of *C. difficile* in the colon (with or without diarrhoea) on a biopsy obtained during endoscopy, colectomy or autopsy.

NATIONAL REFERENCE LABORATORY DATA

Every participating hospital is required to send maximum five consecutively isolated strain to the NRC, managed by the “Institut de Recherche Expérimentale et Clinique” of the Université catholique de Louvain (UCLouvain). Each strain must be accompanied by a minimal set of case information, including the automatically generated code, that links hospital and NRC data. In addition, an hospital may send locally isolated strains to the NRC for typing in order to support the investigation of a local increase in the number of cases or a suspected outbreak. These strains are not considered in this report.

Each received sample is confirmed and typed. The currently applied method of ribotyping is capillary-based polymerase chain reaction (PCR). In Belgium, the NRC has developed an in-house ribotype classification (UCL), which was readapted in 2019. This report will use the new UCL nomenclature, whose correspondence with the previous UCL nomenclature as well as with the European Brazier classification (BR) –when available – can be found in Annex 3 (table 8).

Data is currently transmitted to Sciensano via an Excel sheet but Healthdata onboarding is in progress and almost ready to become operational.

DATA ANALYSIS

Data validation was performed using SAS Entreprise guide 7.1, and confirmed manually. Only validated records were included in the analysis. Merging of hospital and NRC data and the descriptive analysis presented in this report were done using STATA 16.1. For the calculation of CDI incidence per admission or per hospitalisation-days, every acute hospital that provided complete data, including numerators and denominators, for at least one semester was included. For the description of the characteristics of CDI, all valid CDI cases were considered, irrespective of whether the corresponding hospital provided denominators. Results are presented at the level of hospital group (RIZIV/INAMI number), and not at campus level.

Concerning the NRC microbiological data, analysis was performed using the first five consecutive strains sent by the participating hospitals and for which a corresponding CDI case was identified in the hospital CDI surveillance database.

2. Hospital stays

In Belgium, each hospital stay has to be registered in a “minimum hospital data set” (RHM/MZG). Since 2016, diagnoses are registered using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM). The transition from ICD-9-CM to ICD-10-CM was done in 2015 for which no data is available. The code used to identify a

"Enterocolitis due to *Clostridium difficile*" is the code A04.7, regrouping "recurrent" (A04.71) and "not specified recurrent" (A04.72) cases, that are not yet available separately.

We analysed the hospital stays with code A04.7 from 2000 to 2018 (most recent available year) included in the RHM/MZG dataset. This data was provided to us by the Belgian Federal Public Service (FPS) of Public Health. For each hospital stay, the RHM/MZG dataset reports both a "primary diagnosis", that is the condition considered to be the primary reason for the patient's admission, and "secondary diagnosis", that are the conditions present at admission or that developed thereafter and influenced patient care during the current hospitalisation. Information on whether these diagnosis (either primary, either secondary) were made at hospital admission or during hospitalisation was also provided when available.

Additionally, RHM/MZG provided us with denominators, being the total yearly number of admissions and of hospitalisation-days, excluding day-care and ambulatory care provided in the emergency room. To calculate incidence per 10,000 inhabitants, we used the mid-year Belgian population, obtained on SPMA (Standardized Procedures for Mortality Analysis), a software application developed by Sciensano to facilitate the analysis of vital statistics for Belgium by year, and crossed checked on Statbel, the Belgian statistical office.

The RHM/MGZ data are exhaustive as they include all hospital stays in Belgium and should therefore provide an accurate view on the total number of CDI in Belgian hospitals as well as CDI trends over the years. They allow the validation of surveillance data.

Analysis was done in Excel, and data for year 2015 was extrapolated by calculating the average between results for year 2014 and 2016.

3. Billing of diagnostic tests

The NIHDI (INAMI/RIZIV) is the Belgian public social security institution that manages and supervises the Belgian health care insurance system[14]. Reimbursement of healthcare services is obtained via nomenclature codes for each service provided.

We analysed the billing codes for "faecal toxin-producing *C. difficile* testing" for ambulatory and hospitalised patients, that are codes "549850" and 549861" respectively. Data from year 2000 to 2019 (most recent available year) was analysed using Excel. NIHDI also provided denominators, being: the yearly number of patient admissions[15](available until year 2018) and the yearly number of persons insured in Belgium. We used these data, along with the mid-year Belgian population obtained on SPMA to compute specific incidences.

It should be noted that billing data are only provided for health services covered by the Belgian healthcare insurance system (e.g. costs of health services linked to a work-related accident are covered by another insurance system).

[14] Every inhabitant of Belgium is enrolled in the healthcare insurance system.
[15] Admissions relate to "classical hospitalisations", excluding day-care, emergency room, long stay and rehabilitation.

4. Death registry

Mortality data was obtained via SPMA, that receives their data from the FPS Economy. FPS Economy centralises mortality information from the Belgian communities. The mortality cause is coded according to the ICD-10 classification.

We analysed deaths with code A04.7 as underlying cause of death, representing “deaths due to a *Clostridium difficile* related enterocolitis” for the years 2000 – 2017 (latest available data,) in Excel. The underlying cause of death is considered to be the original disease causing the chain of events immediately leading to death.

Deaths were analysed according to region of death, and not to region of residence of the deceased. The age standardised mortality rate was based on direct standardisation using the Belgian mid-year 2010 population as reference population and three age groups (0-64, 65-79, > 80).

The population data for each region and for the whole country was obtained on SPMA and validated on Statbel.

RESULTS

1. National surveillance of CDI in hospitals

HOSPITAL DATA

Participation

Participation of Belgian hospitals in the national CDI surveillance decreased slowly since 2015, the year in which the surveillance became no longer mandatory. The introduction, in July 2017, of a new data collection system (Healthdata) probably also contributed in this decrease. Out of 107 hospitals eligible for participation (101 acute and 6 long-term care, based on the last version of the list provided by the NIHDI in April 2017), 69 hospitals (67 acute and 2 long-term care hospitals) registered their cases all year long for 2019, compared to 75 in the previous two years. Among these hospitals, 61 also provided denominator data (including 1 long-term care hospital). At semester level, 81 hospitals (including 2 long-term care hospitals) provided both numerator and denominator data for at least one semester in 2019, which represents around 76% of the eligible hospitals. This is less than previous years.

In 2019, 87 hospitals registered 2.403 CDI cases (after data cleaning and validation), belonging to 2.216 patients. The maximum number of registered cases per hospital per semester was 84, with a median of 12, which is comparable to previous years. In 2019, less than 3% of participating hospitals-semesters reported zero case. These data are detailed in Annex 1 (table 3).

Characteristics of CDI, 2019

Fifty-six% of the CDI patients had symptoms occurring 2 days or more after admission in the reporting hospital, and were therefore considered “hospital-associated” (HA-CDI). Half of these episodes occurred 12 days or later after admission. This proportion is stable since three years, but has been slowly decreasing over the past 10 years (in 2009, it involved 62% of the cases). Similarly, the proportion of CDI with a presumed origin defined as “acute hospital” decreased from 68% in 2009 to 57% in 2019, and is associated with an increase in cases from the “community” (22% in 2009 to 29% in 2019).The number of cases with a reported origin being a “long-term care facility” (LTCF) did not change substantially across the years, and accounted for 5% of the cases in 2019.

In 2019, as in previous years, the majority of cases were females (55%).Half of the patients were older than 75 years of age. Patients with HA-CDI had a median age of 78, six years more than the median age of patients with an infection non considered as “hospital-associated” (median age of 72).

Similar to previous years, around 11% of the reported CDI were labelled as “recurrent”, on a total including 10% of cases with an unknown recurrence status. The most affected wards were as usual geriatrics (28%) and gastroenterology (11%), followed by oncology (7%), pneumology (4%) and general medicine (4%). Since 2018, we recorded an important drop in

episodes labelled as “complicated”, which accounted for only 7% of CDI in 2019 compared to >20% before 2017. This is probably due to the use of a new registration system since 2017, in which this variable is categorised differently.

In 2019, 17.1% (381) of patients with a CDI died, with 10.2% (39) of these deaths being related to CDI, which is less than previous years. That means 1.8% of patients affected by CDI died possibly or definitely because of their infection. This percentage is lower than ever.

CDI trends and incidences per admissions and hospitalisation-days

At national level, the mean CDI incidence per 1,000 admissions or 10,000 hospitalisation-days did not change substantially since 2015 and even decreased slightly compared to previous years. In 2019, CDI incidence was 1.6 CDI cases per 1,000 admissions (figure 1) and 2.5 CDI cases per 10,000 hospitalisation-days. For HA-CDI, these numbers were respectively 0.9 per 1,000 admissions and 1.4 per 10,000 hospitalisation-days (figure 1 and 2).

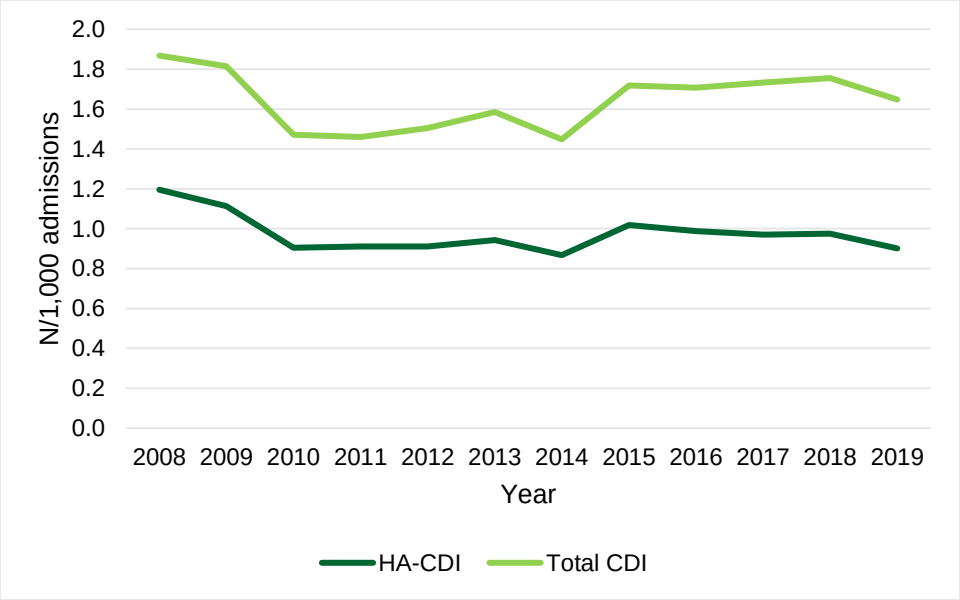


Figure 1: Mean incidence of CDI in acute care hospitals per 1,000 admissions, Belgium 2008-2019 (CDI: *Clostridioides difficile* infection; HA-CDI: hospital-associated-CDI; N: number)

Note: Hospital-associated-CDI (HA-CDI): onset of symptoms ≥ 2 days after admission. Incidence calculation: inclusion of episodes reported by all acute care hospitals that provided complete data (numerators and denominators) for at least one semester/year.

Since 2015, the incidence of CDI per 10,000 hospitalisation-days was highest in Wallonia and lowest in Flanders (figure 2).

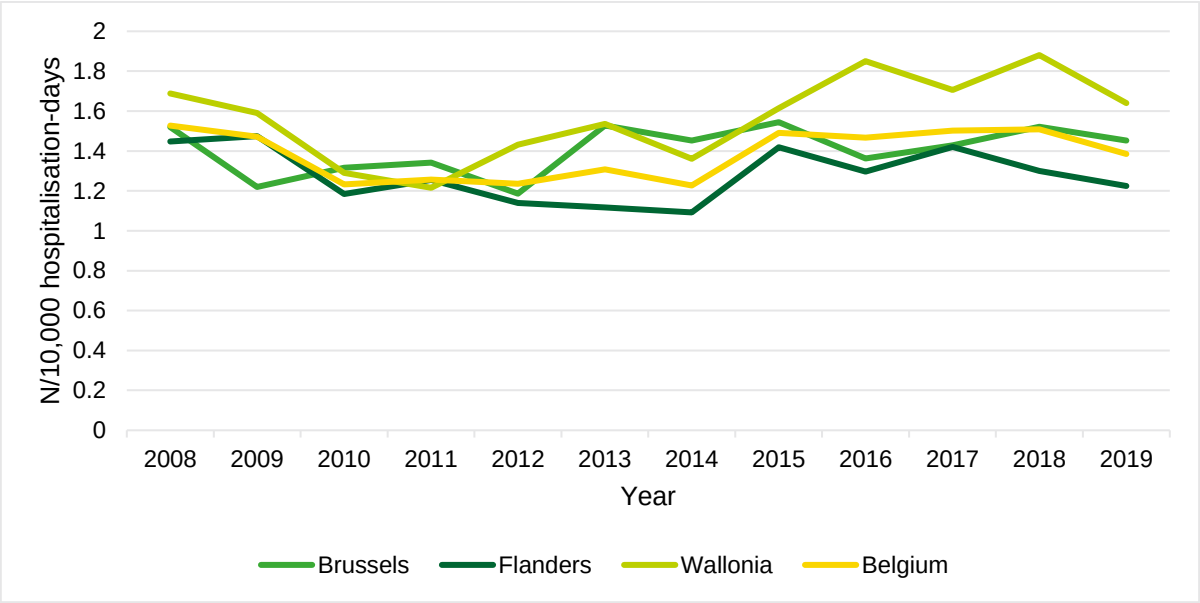


Figure 2: Mean incidence of HA-CDI/10,000 hospitalisation-days in acute care hospitals, per region, Belgium, 2008-2019 (HA-CDI: hospital-associated *Clostridioides difficile* infection; N: number)

Note: Hospital-associated-CDI (HA-CDI): onset of symptoms ≥ 2 days after admission. Incidence calculation: inclusion of episodes reported by all acute care hospitals that provided complete data (numerators and denominators) for at least one semester/year.

Figure 3 shows a large variability in reported incidence of HA-CDI between provinces. Incidence was highest in the provinces of Hainaut, Namur and Limburg (descending order) and lowest in the provinces of Luxembourg (but only two hospital-semesters participated), Flemish Brabant, and Liège (ascending order). Categories are based on the distribution of data in Belgium (quartiles) to allow for benchmarking between provinces. Details on incidences are presented in Annex 2 (tables 4 and 5).

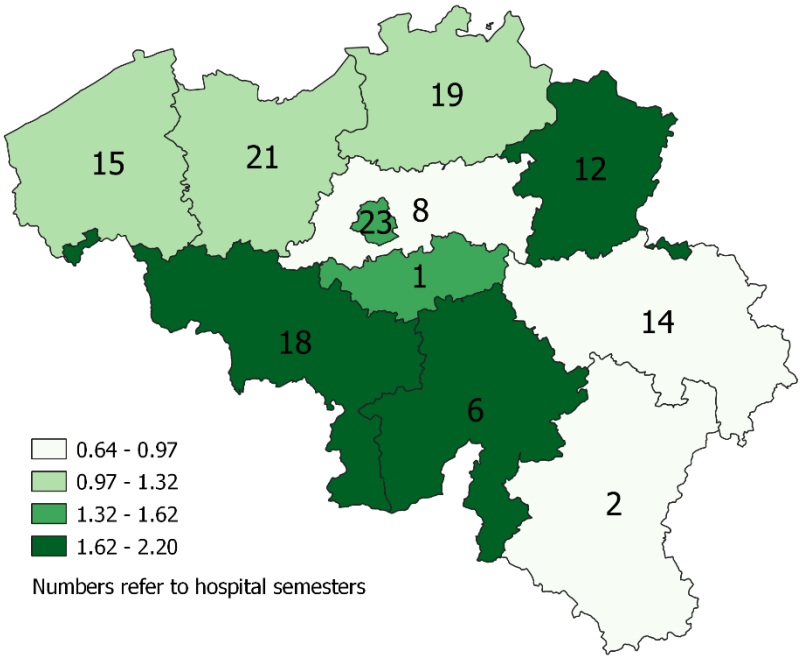


Figure 3: Mean incidence of HA-CDI/10,000 hospitalisation-days in acute care hospitals, per province, Belgium, 2019 (HA-CDI, hospital-associated *Clostridioides difficile* infection)

Note: Mean incidence of episodes reported by all acute care hospitals that provided complete data (numerators and denominators) for at least one semester. The number given in each province indicates the number of contributing hospital-semesters. Categories are based on distribution quartiles.

Similarly, we observed a large variability in HA-CDI incidence across the different Belgian hospitals, represented in the funnel plot[16] below (figure 4), allowing the identification of outliers. Unlike the previous year, the incidence seems to increase according to the hospital type (higher in tertiary hospitals), but not in a statistically significant way. (box-plot[17], figure 5).

[16] Funnel plots are a graphical aid for hospital comparisons. An estimate of the parameter (here HA-CDI incidence/10,000 hospitalisation-days) is plotted against a measure of its precision (here number of hospitalisation-days). It is a useful display method when denominator sizes vary, indeed, in small hospitals, chances of variation are bigger. Funnel plots also give a visual identification of statistically significant outliers (those falling above or below the 95% and 99.8% confidence intervals), enabling further investigation and data validation.

[17] The boxplot displays the median incidence (blue line in the box) of HA-CDI per 10,000 hospitalisation-days of all hospital semester, per type of hospitals. The box limits represent the P25 and P75 values, the whiskers mark the lower and upper adjusted values (respectively P25 - 1.5 interquartile range (IQR) and P75 + 1.5 IQR) and the dots represent the outliers (outside values). The diamond shape indicates the mean incidence density.

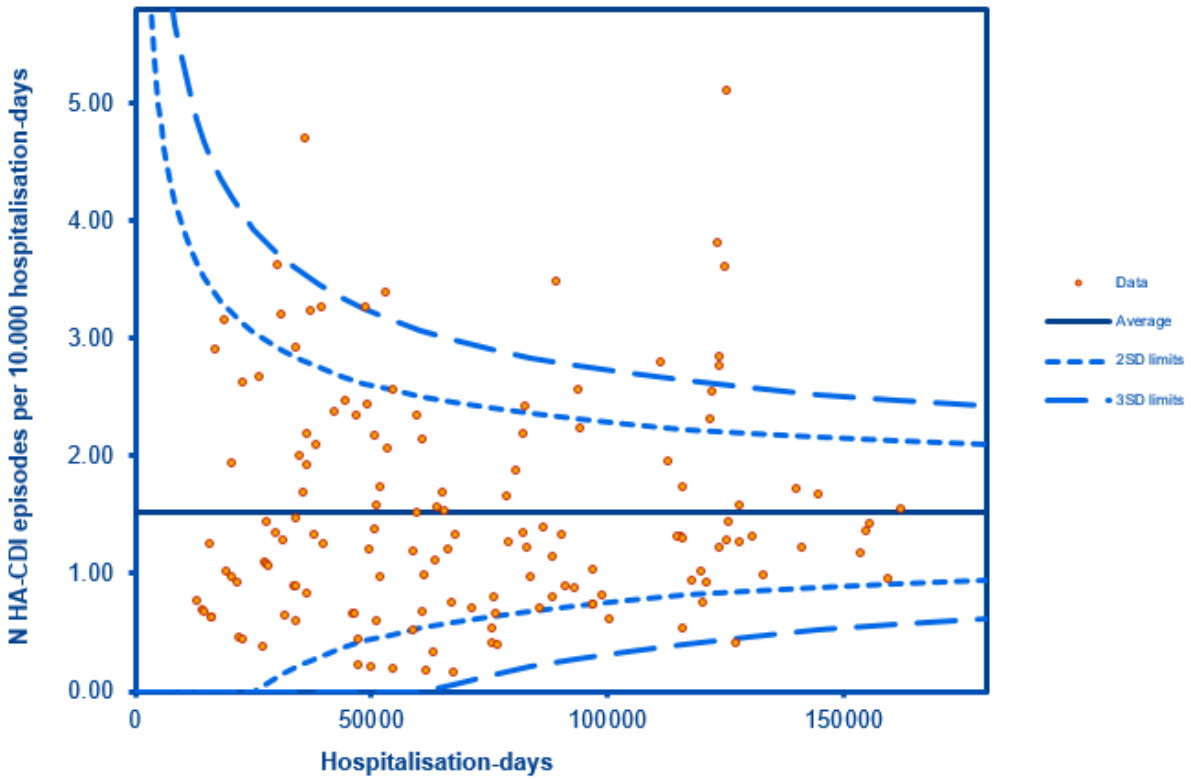


Figure 4: Incidence of HA-CDI per 10,000 hospitalisation-days per hospital-semester, Belgium, 2019 (HA-CDI: hospital-associated *Clostridioides difficile* infection; N: number)

Note: Each dot is the incidence for one hospital/semester plotted against the number of hospitalisation-days in that hospital during the semester. « Average » = mean of all incidences. Dots outside confidence intervals (95% and 99.8%, Poisson distribution) are statistical outliers. SD: standard deviation.

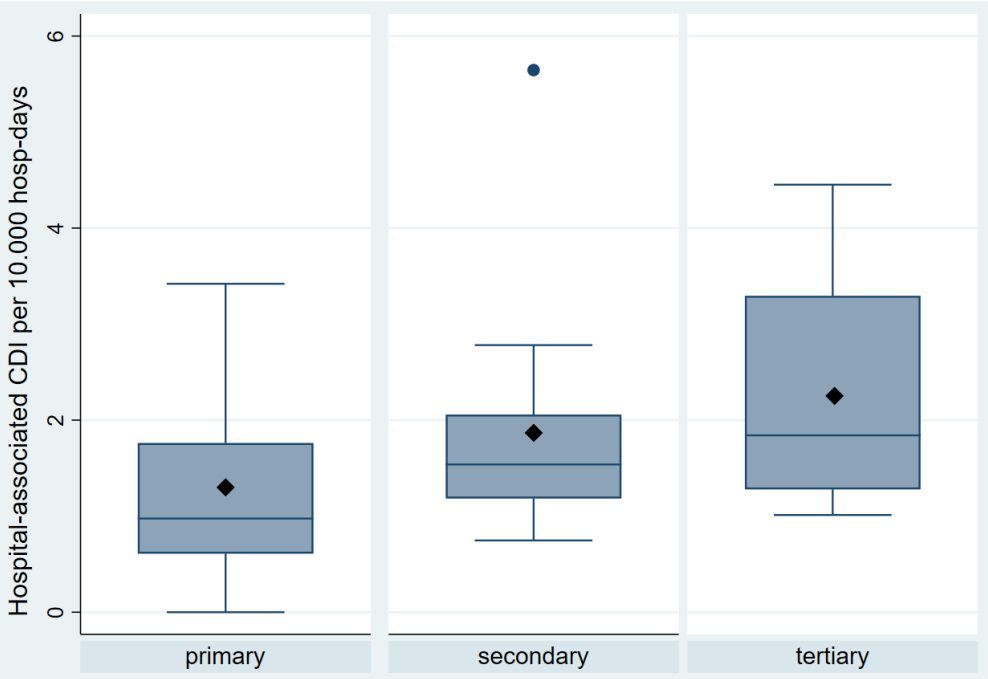


Figure 5: Distribution of HA-CDI per 10,000 hospitalisation-days by hospital type, Belgium 2019 (HA-CDI: hospital-associated *Clostridioides difficile* infection; N: number)

Note: Are included in the analysis 61 primary hospitals, 13 secondary hospitals and 4 tertiary hospitals, according to the classification provided by the Belgian ministry of health (list dated April 2019). The two long-term care hospital and one specialised hospital were excluded. The black diamond represents the mean of the incidences.

NATIONAL REFERENCE LABORATORY DATA

Despite the protocol requirement to send maximum five strains per semester per hospital to the NRC, Belgian hospitals tend to send more strains. In 2019, a total of 757 strains were sampled and sent to the NRC in the context of surveillance, coming from 57 hospitals (median: 7.5 strains/hospital/year). Culture did not identified *C. difficile* in 41 (5.4%) of these strains, and a cytopathogenic effect was detected in 698 (97.5%) of the 716 remaining strains. Both the number of strains sent and the number of participating hospitals have been constantly decreasing since 2014. Indeed, 30 hospitals that participated in the surveillance and entered cases in Healthdata for 2019 did not send strains to the NRC.

When considering only the first five strains per hospital per semester, the most frequently isolated and widespread strain in 2019 remained, as in previous years, BR014 (table 1 and 2). It represented 14.2% of the total samples and was found in 50.9% of the participating hospitals. The hypervirulent strain BR078 comes second, accounting for 7.8% of the samples and found in 35.1% of participating hospitals (table 1 and 2). On the contrary, BR027 was distributed less widely than previous years (in 10.5% of the participating hospitals), and accounted for 2.2% of the samples, mainly reported in the provinces of East Flanders and Antwerp. The hypervirulent ribotype identified in 2018 labelled “585” in the UCL classification (corresponding to BR181*) was not identified anymore in 2019.

Table 1: Distribution of the five most frequently isolated ribotypes (number and %) among total samples of *Clostridioides difficile* typed in 2019 as part of the national surveillance, Belgium 2013-2019 (Brazier classification).

Year	2013		2014		2015		2016		2017		2018		2019	
Total samples	461	*100 %*	496	*100 %*	545	*100%*	470	*100%*	427	*100%*	415	*100%*	358	*100%*
BR014	54	*11.7 %*	71	*14.3 %*	66	*12.1 %*	62	*13.2 %*	62	*14.5 %*	52	*12.5 %*	51	*14.2 %*
BR078	26	*5.6 %*	36	*7.3 %*	49	*9.0 %*	28	*6.0 %*	33	*7.7 %*	38	*9.2 %*	28	*7.8 %*
BR020	41	*8.9 %*	56	*11.3 %*	47	*8.6 %*	26	*5.5 %*	39	*9.1 %*	37	*8.9 %*	23	*6.4 %*
BR002	26	*5.6 %*	33	*6.7 %*	45	*8.3 %*	39	*8.3 %*	29	*6.8 %*	30	*7.2 %*	22	*6.1 %*
BR106	12	*2.6 %*	15	*3.0 %*	19	*3.5 %*	21	*4.5 %*	21	*4.9 %*	20	*4.8 %*	21	*5.9 %*

Source: National reference center (NRC). BR: Brazier classification
Note: Are only considered the first five consecutive samples sent by hospital, by semester.

Table 2: Distribution of the five most frequently isolated *Clostridioides difficile* ribotypes (number and %) among hospitals participating in the 2019 national surveillance, Belgium 2013-2019 (Brazier classification)

Year	2013		2014		2015		2016		2017		2018		2019	
Total Hospitals	83	*100%*	87	*100%*	81	*100%*	70	*100%*	72	*100%*	64	*100%*	57	*100%*
BR014	37	*44.6%*	41	*47.1%*	43	*53.1%*	39	*55.7%*	36	*50.0%*	34	*53.1%*	29	*50.9%*
BR078	22	*26.5%*	23	*26.4%*	35	*43.2%*	21	*30.0%*	26	*36.1%*	31	*48.4%*	20	*35.1%*
BR106	9	*10.8%*	13	*14.9%*	16	*19.8%*	14	*20.0%*	15	*20.8%*	17	*26.6%*	18	*31.6%*
BR020	28	*33.7%*	39	*44.8%*	34	*42.0%*	21	*30.0%*	26	*36.1%*	26	*40.6%*	17	*29.8%*
BR002	22	*26.5%*	23	*26.4%*	31	*38.3%*	26	*37.1%*	25	*34.7%*	23	*35.9%*	16	*28.1%*

Source: National reference center (NRC). BR: Brazier classification.
Note: Are only considered the first five consecutive samples sent by hospital, by semester.

The distribution of the five most frequently isolated ribotypes differed in the three geographical regions as illustrated in figure 6. BR005 was almost exclusively found in Flanders while BR017 and BR020 were most frequent in Brussels and Wallonia respectively. A comprehensive list with the number of strains per ribotype, and the number of hospitals in which each ribotype was isolated in 2019 can be found in Annex 3 (table 7).

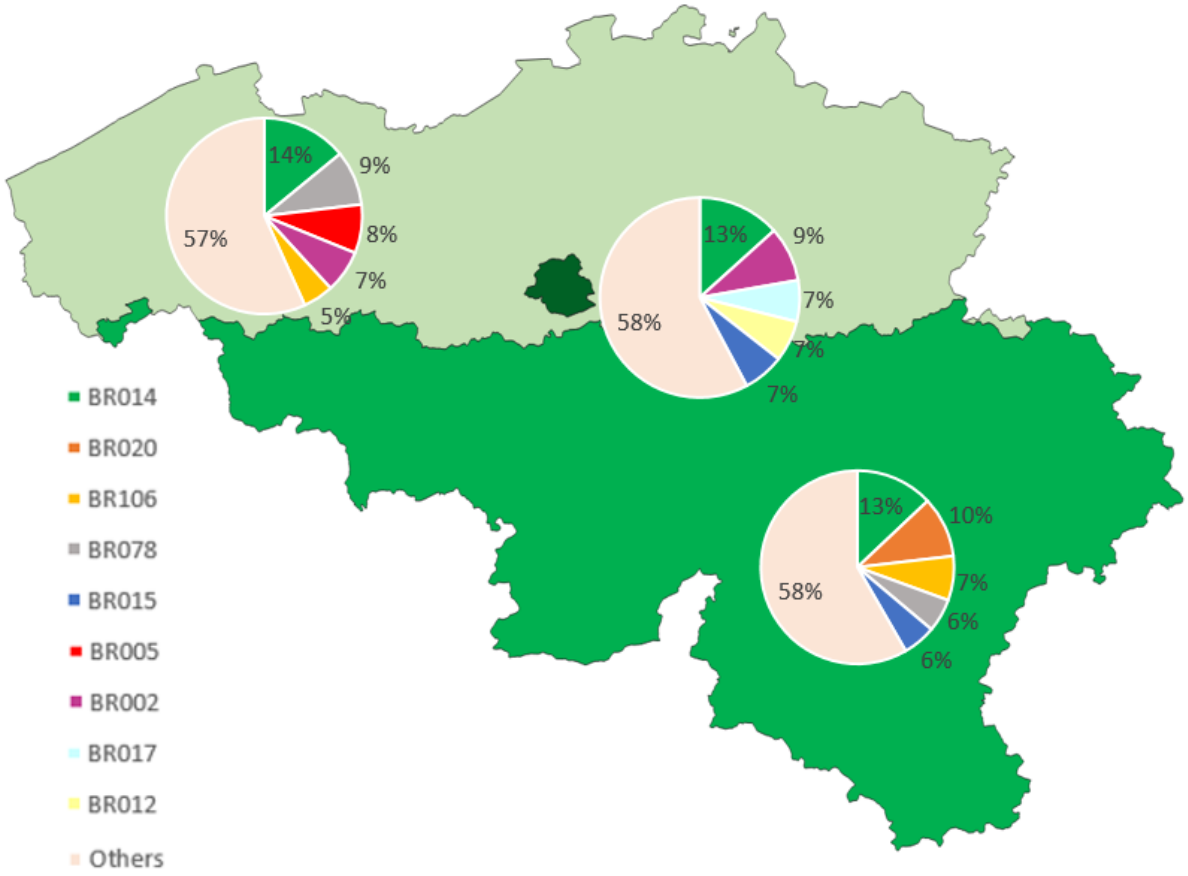


Figure 6: Distribution (%) of the five most frequently isolated ribotypes per region, Belgium 2019.

Source: National reference center (NRC). BR: Brazier classification.
Note: Are only considered the first five consecutive samples sent by hospital, by semester.

To monitor antimicrobial susceptibility, 73 isolates (a representative sample of strains sent in 2019 to the NRC in the context of surveillance), were tested by disk diffusion for moxifloxacin, tetracycline, erythromycin, clindamycin, chloramphenicol and rifampicin (CA-SFM 2020 guidelines), and by E-test for metronidazole and vancomycin (EUCAST V10 guidelines). All isolates were susceptible to vancomycin (MIC ≤2 mg/L) and metronidazole (MIC ≤2 mg/L). As shown in figure 7, erythromycin, moxifloxacin, and clindamycin resistance (20.5%, 26.0%, and 97.3% of the total isolates, respectively) were evident in multiple ribotypes. Resistance to tetracycline, rifampicin and chloramphenicol were observed in 6.8%, 4.1% and 4.1% of isolates respectively. BR027, BR012 and BR017 and BR078 were associated with multiple antimicrobial resistance.(9,10)

Percentage resistance of *Clostridioides difficile* isolates (N=73, 2019)

Antibiotics	% R
Chloramphenicol	4.11
Clindamycin	97.26
Erythomycin	20.55
Moxifloxacin	26.03
Rifampicin	4.11
Tetracycline	6.85
Metronidazole	0.00
Vancomycin	0.00

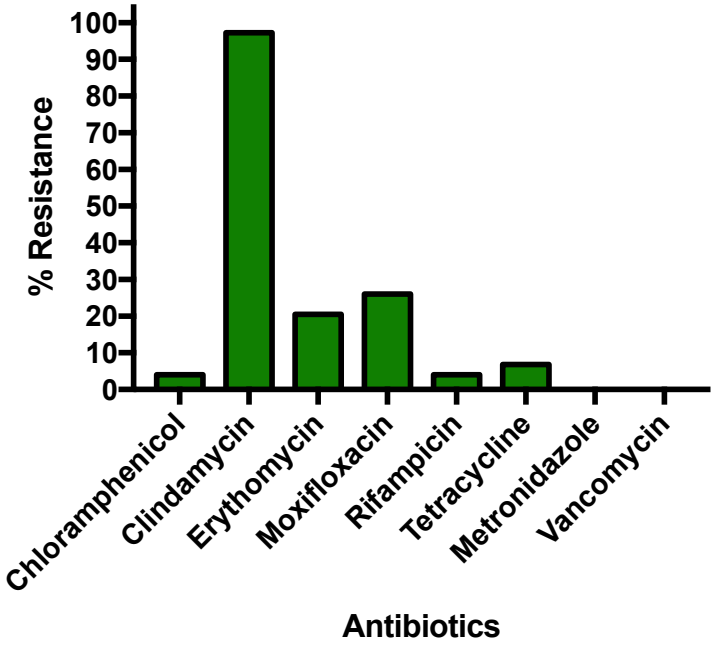


Figure 7: Rates (%) of *Clostridioides difficile* isolates resistant to antibiotics, Belgium 2019.

Source: National reference center (NRC)

2. Hospital stays

In 2018 (most recent available data), 4,425 hospital stay records mentioned CDI as primary or secondary diagnostic code. The incidence of total CDI in the hospital was 2.2 per 1,000 admissions (highest number recorded since 2009) and 3.2 per 10,000 hospitalisation-days (highest number ever recorded). Trends since year 2000 are displayed in figures 8 and 9.

Comparing with data obtained from the national surveillance of CDI in hospitals, 61% of CDI cases identified via hospital stay records in 2018 were reported in the surveillance. For the same year, the incidence of CDI per 10,000 hospitalisation-days found in the national surveillance was 14% lower than the incidence found using the hospital stay data, and this difference reached 20% when using admissions as denominator. However, CDI trends seemed similar throughout both sources, as shown in figure 9. Further details are given in Annex 4.

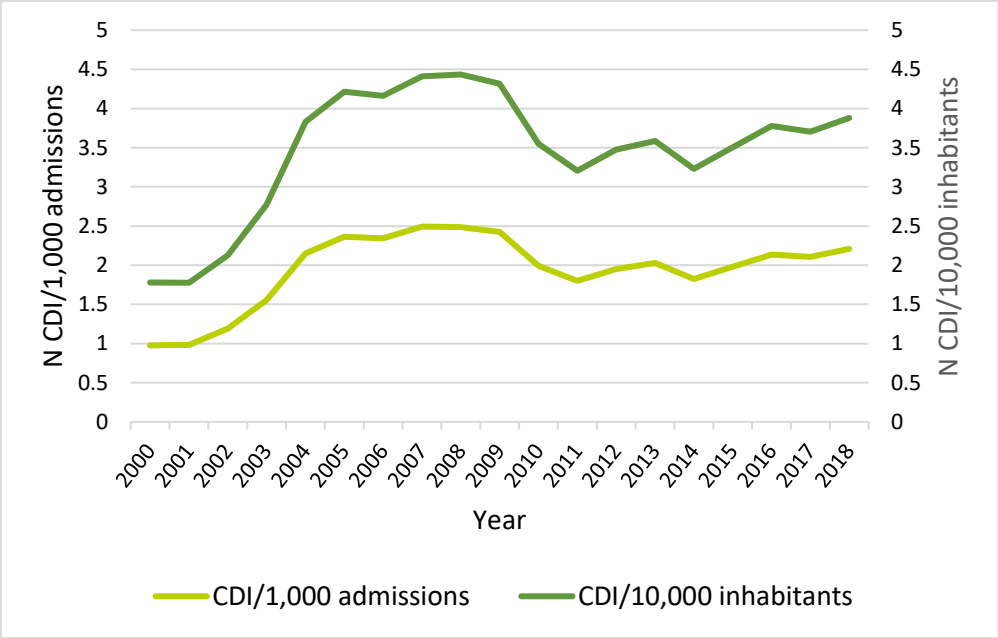


Figure 8: CDI incidence in Belgian hospitals, 2000-2018 (CDI: *Clostridioides difficile* infections; N: Number)

Source: Federal Public Service of public health (SPF/FOD). Number of ICD-9-CM 008.45 (2000-2014) and ICD-10-CM A04.7 (2016-2018) codes (Enterocolitis due to Clostridium difficile*) included in the hospital stay database as primary or secondary diagnosis. Extrapolation made for 2015.*

The percentage of stays with a primary diagnostic code of CDI – presumed in this case to be the reason for admission – remained stable across the years, approaching in 2018 24.5% of the total stays with a diagnostic code of CDI (figure 8). Among the total number of CDI cases, the percentage of cases “not present at admission” approached 32%. It should be noted here that this figure, which we would tend to associate with hospital-associated cases, should be interpreted with caution, partly because there might have been cases for which the presence or absence of the CDI diagnosis at admission was difficult to establish or uncertain.

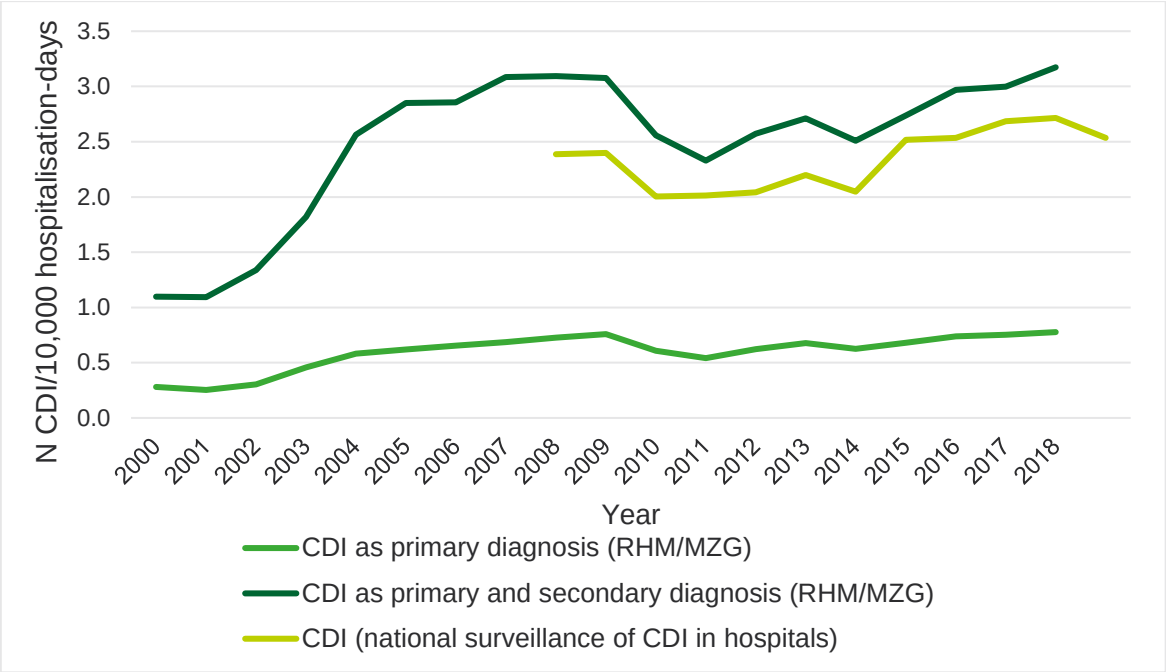


Figure 9: CDI incidence in Belgian hospitals, per 10,000 hospitalisation-days, 2000-2018 (CDI: *Clostridioides difficile* infections; N: Number)

Source: Federal Public Service of public health (SPF/FOD): Number of ICD-9-CM 008.45 (2000-2014) and ICD-10-CM A04.7 (2016-2018) codes (Enterocolitis due to Clostridium difficile*) included in the hospital stay database as primary or secondary diagnosis. Extrapolation made for year 2015. Surveillance data: incidence calculation by including CDI episodes reported by all acute care hospitals that provided complete data (numerators and denominators) for at least one semester/year.*

3. Billing of diagnostic tests

In 2019, there were around 86,000 tests billed for hospitalised patients and around 81,000 tests billed for ambulatory patients in Belgium. The total number of tests searching for faecal toxin-producing *C. difficile* billed in Belgium is the highest ever recorded and reflects the steady increase in testing in ambulatory patients since year 2000 (figure 10). Equally, we observed an increase in the number of tests reimbursed per 1,000 insured Belgian inhabitants, which reached 14.8 in 2019.

In 2018, there were around 19 tests billed for hospitalised patients per CDI diagnosed in hospitals, which is comparable to the previous years. So is the number of tests per 1,000 admissions, approaching 46 for that year (figure 11). Detailed data are presented in Annex 5.

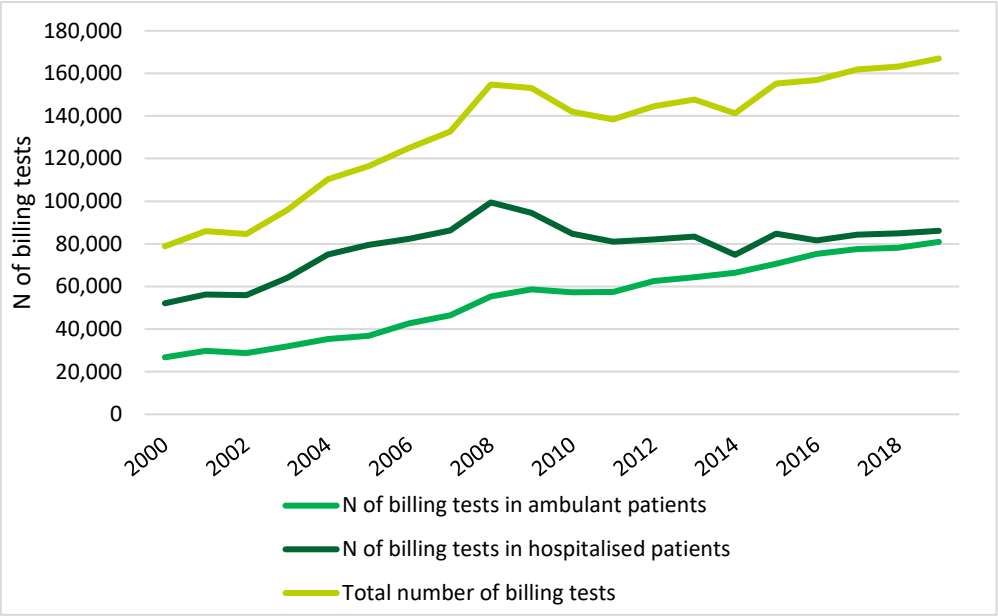


Figure 10: Number of tests billed for *C. difficile* testing in ambulatory and hospitalised patients. Belgium, 2000-2019 (N: Number)

Source: NIHDI (INAMI/RIZIV) for the number of billing tests for CDI.

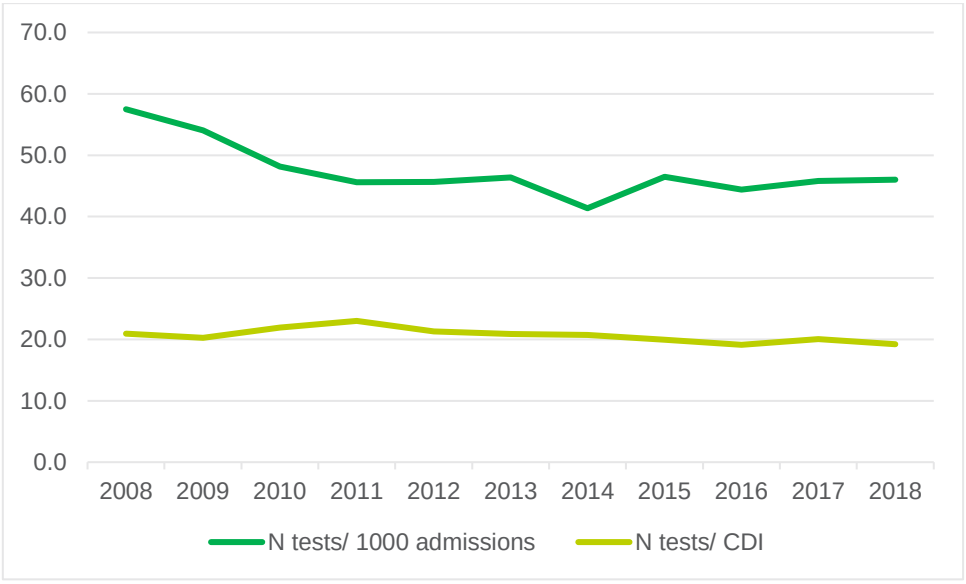


Figure 11: Number of tests billed for *C. difficile* testing in hospitalised patients, per 1,000 admissions and per CDI diagnosed in the hospital. Belgium, 2008-2018 (CDI: *Clostridioides difficile* infections; N: Number)

Source: NIHDI (INAMI/RIZIV) for the number of billing tests for C. difficile and the number of admissions, and Federal Public Service of public health (via RHM/MZG) for the total number of CDI diagnosed in the hospital.

4. Death registry

Mortality in Belgium with « enterocolitis due to *C. difficile* » as underlying cause decreased steadily from 2009 to 2014, but rose again in 2015, reaching 106 documented deaths. This was the highest number of deaths observed since 2009. Since then, mortality decreased and in 2017 (most recent available data), 91 deaths were recorded, slightly more than in 2016 (figure 12). As for the previous years, the majority of these deaths (80%) occurred in people aged 80 years or more. Crude and adjusted mortality rates were respectively 0.80 and 0.73 deaths/100,000 inhabitants in 2017, showing a small increase compared to 2016. If mortality used to be always higher in Brussels, this was not the case in the two last available years. Across the years, mortality in Flanders and Wallonia seems comparable. Detailed data by region are available in Annex 6.

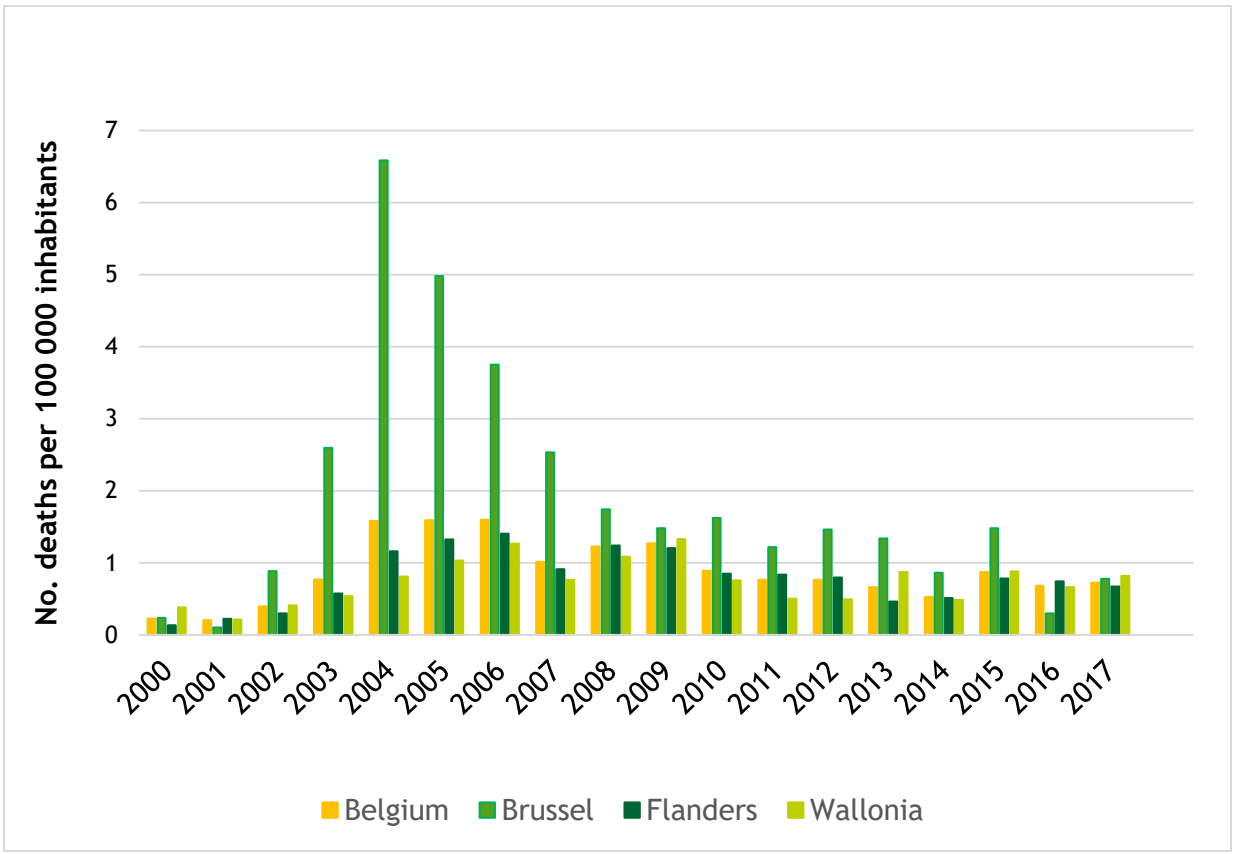


Figure 12: Age-standardised mortality rates, enterocolitis due to *Clostridioides difficile*, by region, Belgium, 2000-2017 (N: Number)

Source: Death registry, code ICD10 A047 as underlying cause of death. Direct standardisation using the Belgian mid-year 2010 population as reference population, according to 3 age groups (0-64, 65-79, 80+). Deaths are registered according to place of death and not place of residence.

DISCUSSION

This report draws its strength from the use of four different data sources, providing a solid and broad overview of the epidemiology of CDI in Belgium. This is further reinforced by the relatively high participation rate of hospitals to the national CDI surveillance program (76%), although this participation rate is slowly decreasing. This might be explained by the fact that since 2015 CDI surveillance is no longer mandatory, as well as by a switch to a new registration tool, Healthdata, during mid-2017. Similarly, and also of concern, the number of hospitals that sent their strains to the NRC decreased again in 2019. Hospitals are indeed performing less and less culture for *C. difficile*, especially since the introduction of new, easier diagnostic tests. This is why also fresh stools specimen can now be sent to the NRC instead of purified laboratory cultures.

In autumn 2019, a satisfaction survey regarding all the NSIH surveillance systems was organised by the NSIH unit. Out of the 120 responses, 36 (30%) related to the CDIF surveillance. Main reasons for participation cited included the fact that this surveillance was perceived as important, provided useful results and was mandatory. Two out of the 36 respondents did not participate because of limited time and resources and because they perceived the results as not useful. The national report was used by 75% of the respondents, and the individual hospital reports by 70%, essentially to discuss with the infection prevention and control (IPC) team, to present results to their direction, to compare with their own results or to investigate possible room for improvements. Those who did not use the national report mentioned the content was not useful for clinical practice, or preferred to use the results of their own surveillance system. Individual reports were not used mainly because of technical complications. In general, suggestions for improvement and increase participation related to the registration tool (HD4DP) and the reporting tool (Healthstat) and included amongst others a better layout, an easier access, the automatisation of imports and a timely feedback. These suggestions have and still are being discussed with the Healthdata team. Local training have already been organised for each hospital hygiene platform that wished so.

Characteristics of CDI cases did not change much in recent years. The increase in CDI originating in the community, as well as the increase in the number of CDI tests billed in ambulatory patients, should encourage us to explore more thoroughly CDI outside the hospital setting. Indeed, the prevalence of community-acquired CDI is on the rise worldwide.(11) The decreasing length of hospital stay might trigger a shift of CDI occurrence towards the community. This also goes well with the slow decrease in the proportion of HA-CDI, that remains lower than in other European countries.(12)

The decrease in cases labelled as “complicated” could possibly be explained by the recent change of variable description from a categorical variable (detailing the possible complications) to a dichotomous variable (complicated versus non complicated). The proportion of recurrent cases (11%) was stable, and remains lower than documented elsewhere.(3,11) As around 10% of cases in the national surveillance of CDI in hospitals had an unknown recurrent status, the proportion of recurrent cases might in fact be higher. For these cases, as well as for refractory or severe cases, faecal microbiota transplantation (FMT) appears to be a promising and efficient treatment modality.(15) The proportion of CDI patients dying from their infection is lower than ever (1.8%), possibly due to the improved

awareness, the extended diagnostic and therapeutic options available against this infection in recent years,(16) or a change in the virulence of circulating strains.

The hospital stay data are comprehensive and therefore allow for a better estimation of the real burden of CDI in Belgium. They can also be used to validate data collected through the national surveillance of CDI in hospitals. The difference found when comparing CDI incidence computed from these two sources calls for further investigation. However, incidence trends displayed by both hospital stay data and national surveillances followed the same pattern, and revealed a higher incidence in 2018 compared to previous years. The fact that incidence was lower during the period 2010 to 2014 suggests that the CDI burden in Belgium can still be reduced. The variability between provinces and hospitals leads us to the same conclusion.

The death registry data reported a peak in mortality in 2015, after a constant decline since 2009. This might be explained by the unusually high prevalence of hypervirulent strains BR027 (UCL027) and BR078 (UCL3) that year. Mortality decreased since then, but was slightly higher in 2017 than in 2016. Brussels usually exhibits the highest mortality rate in Belgium, possibly because three out of the four participating tertiary hospitals are located there, however in 2017, the three regions exhibited similar mortality rates.

Based on current evidence, one of the best strategies to prevent and control CDI today remains antimicrobial stewardship. Additionally, measures such as standard and contact precautions, healthcare facility cleaning and disinfection, and participation in a national surveillance program of CDI in hospitals remain at the cornerstone of CDI infection prevention and control.(17)

KEY FINDINGS

Participation rate of Belgian hospitals in the national surveillance of CDI in hospitals is slowly decreasing since 2015, year in which the surveillance became no longer mandatory. In 2019, 87 hospitals reported CDI cases for at least one semester, and 69 hospitals reported CDI cases all year long. However, around 10% of these hospitals did not enter corresponding denominator data, and only 57 hospitals sent their strains to the NRC.

At national level, HA-CDI incidence per 10,000 hospitalisation-days approached 1.4 and is globally stable since 2015, although it decreased slightly since 2018. Differences between regions, provinces and hospitals remained substantial. As in previous years, incidence was higher in Wallonia than in Flanders. Incidence seemed higher in tertiary hospitals, but this finding was not significant.

Ribotype BR014 remained the most prevalent and widespread strain in Belgian hospitals, this for the three regions. The hypervirulent strain BR078 came second, while BR027 seemed less and less common. The hypervirulent ribotype BR181* identified in 2018 was not identified anymore in 2019.

The proportion of HA-CDI decreased in the last ten years to reach 56% in 2019, and seemed partly related to an increase in CDI originating in the community. The proportion of patients suffering CDI complications decreased remarkably in the last two years. As for previous years, about 11% of CDI episodes were recurrent. Geriatric patients are, as usual, the most affected. Around 17% of patients affected by CDI died from various causes, while 2% died possibly or definitely because of their infection.

Hospital stay data recorded around 4,425 CDI cases in 2018, the highest number since 2009. The incidence of total CDI per 10,000 hospitalisation-days found in the national surveillance was 14% lower than the incidence found using the hospital stay data. However, the incidence trends followed the same pattern, whatever the data source, with a small increase in 2018.

The total number of tests billed for *C. difficile* was higher than ever in 2019. This seemed essentially due to an increase in tests prescribed in ambulatory care, while the number of tests in hospitalised patients did not change substantially in the last few years.

In 2015, mortality reached a peak after having declined constantly since 2009. Mortality decreased since then, but was however a bit higher in 2017 compared to 2016.

RECOMMENDATIONS

To researchers of Sciensano involved in the CDI national surveillance program, we recommend the following:

- Validate surveillance data, starting with an in-depth comparison with hospital stay data (RHM/MZG), and investigate why incidence computed from the national surveillance of CDI in hospitals is systematically lower.
- Promote participation in the surveillance, both in terms of hospital recruitment and in terms of data completeness. Participation requires not only the reporting of case-based data, but also the reporting of denominators and the shipment of corresponding stools/cultures to the NRC. More email reminders could be used for these purposes.
- Continue improving accessibility and usability of both the data collection and reporting tools, in collaboration with Healthdata.
- Investigate further CDI in the community, regional and inter-hospital differences in incidences and mortality, as well as the role of the environment and food producing animals in the disease (one-health approach).
- Ensure a yearly update of the surveillance protocol and publication of a national report.
- Consider extending the surveillance to related mitigation measures like faecal microbial transplantation.
- Assess the increase in CDI originating in the community, as well as the increase in the number of CDI tests billed in ambulatory patients and the possible roll of tests conducted by private laboratories in the increase of CDI tests billed in ambulatory patients.

To policy makers, we recommend the following:

- Continue support the national surveillance of CDI in Belgian hospitals, as a key element in CDI prevention and control. Especially the impact of the COVID-19 crisis on the occurrence of CDI should be assessed. To be able to do this, participation in this surveillance is crucial.
- Continue support researchers in their routine surveillance tasks as well as the tasks mentioned above.
- Consider extending the surveillance to related mitigation measures like faecal microbial transplantation.
- Ensure adequate support (structural, educational and financial) to infection prevention and control teams in Belgian hospitals.
- Continue promoting good quality of care practices, especially focused on infection prevention and control and antibiotic use, in Belgian hospitals.

To hospitals, we recommend the following:

- Assess if it still is possible to decrease CDI incidence in their hospital, and if so, implement or improve implementation of appropriate infection and prevention measures.
- Continue or resume registering CDI in the national surveillance program in order to monitor CDI incidence at hospital level as well as contribute to national and international CDI epidemiological surveillance. Especially the impact of the COVID-19

crisis on the occurrence of CDI should be assessed. To be able to do this, participation in this surveillance is crucial.

- Continue collaboration with the NRC, by ensuring the shipment of five CDI strains per semester for confirmation and typing, which is a key element of the CDI surveillance.

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ANNEXES

1. Hospital contributing data to the national surveillance of CDI

Table 3: Participation of Belgian hospitals in the national surveillance of CDI in hospitals. Belgium, 2008-2019

2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
N hospitals providing cases for at least one semester											
102	104	103	103	104	105	104	104	100	99	91	87
N hospitals providing numerators and denominators for at least one semester											
100	101	101	101	102	103	103	101	98	91	89	81
N hospitals providing cases for the whole year											
76	84	81	80	82	84	82	88	83	75	75	69
N hospitals providing numerators and denominators for the whole year											
71	76	78	78	78	81	81	84	82	53	71	61
Total hospital-semesters providing numerators and denominators											
171	177	179	179	180	184	184	185	180	147	163	142
% hospital-semesters with zero case											
6	6	4	4	4	5	5	3	5	5	1	3
N cases per hospital per semester: median											
12	11	9	10	11	11	9.5	12	11	11	13.5	12
N cases per hospital per semester: maximum											
89	108	67	94	96	83	114	77	79	73	74	84
Total number of registered cases											
2,948	2,900	2,451	2,496	2,505	2,664	2,414	2,977	2,804	2,691	2,690	2,403

Source: surveillance data.

Note: Including long-term care hospitals.

2. CDI incidences in acute care hospitals, Belgium, 2008-2019

Table 4: Incidence of CDI in acute care hospitals, Belgium, 2008-2019

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Mean incidence, per 1,000 admissions												
Hospital-associated CDI	1.20	1.11	0.90	0.91	0.91	0.94	0.87	1.02	0.99	0.97	0.97	0.90
Total CDI	1.87	1.81	1.47	1.46	1.51	1.58	1.45	1.72	1.71	1.73	1.75	1.65
Mean incidence, per 10,000 hospitalisation-days												
Hospital-associated CDI	1.53	1.47	1.23	1.26	1.24	1.31	1.23	1.49	1.47	1.50	1.51	1.39
Total CDI	2.39	2.40	2.00	2.01	2.04	2.20	2.05	2.52	2.53	2.68	2.72	2.54
N acute care hospitals contributing data												
	95	96	95	96	97	98	98	95	92	88	86	79

Note: All acute care hospitals with complete numerator and denominator data for at least one semester are included in incidence computation. Mean incidence: total registered CDI or HA-CDI episodes for all hospitals and all semesters X 1,000 or 10,000/ total admissions or hospitalisation-days for all corresponding semesters.

Table 5: Mean incidence of HA-CDI/10,000 hospitalisation-days in acute hospitals, per region, Belgium, 2008-2019

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Mean incidence, HA-CDI per 10,000 hospitalisation-days												
Brussels	1.52	1.22	1.32	1.34	1.19	1.53	1.45	1.54	1.36	1.43	1.52	1.45
Flanders	1.45	1.47	1.18	1.25	1.14	1.12	1.09	1.42	1.30	1.42	1.30	1.23
Wallonia	1.69	1.59	1.29	1.22	1.43	1.54	1.36	1.62	1.85	1.71	1.88	1.64
Belgium	1.53	1.47	1.23	1.26	1.24	1.31	1.23	1.49	1.47	1.50	1.51	1.39
N acute care hospitals contributing data												
Brussels	11	11	11	11	11	11	11	12	11	10	12	12
Flanders	52	53	53	51	51	53	53	51	48	47	45	43
Wallonia	32	32	31	34	35	34	34	32	33	31	29	24
Belgium	95	96	95	96	97	98	98	95	92	88	86	79

Note: All acute care hospitals with complete numerator and denominator data for at least one semester are included in incidence computation. Mean incidence: total registered HA-CDI episodes for all hospitals and all semesters X 10,000/ total hospitalisation-days for all corresponding semesters.

Table 6: Incidence of HA-CDI in acute hospitals, per province, Belgium

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Mean incidence, HA-CDI per 10,000 hospitalisation-days												
Antwerp	1.08	0.99	0.85	1.21	0.88	1.03	0.93	1.50	1.41	1.27	1.01	1.02
Walloon Brabant	1.00	1.15	0.52	0.25	1.12	0.69	0.75	1.04	1.53	1.99	1.02	1.50
Brussels	1.52	1.22	1.32	1.34	1.19	1.53	1.45	1.54	1.36	1.43	1.52	1.45
Hainaut	1.44	1.33	1.18	1.26	1.49	1.76	1.61	1.67	1.91	1.86	2.18	2.20
Limburg	2.31	2.05	1.46	1.45	0.92	0.95	1.22	1.92	1.63	1.85	2.29	1.74
Liège	2.03	1.97	1.21	1.20	1.49	1.40	1.22	1.59	1.91	1.61	1.26	0.92
Luxembourg	1.92	2.08	1.32	1.29	1.10	1.74	0.72	0.89	1.30	1.76	0.93	0.64
Namur	1.87	1.69	2.02	1.43	1.27	1.28	1.29	1.93	1.73	0.88	2.91	1.94
Eastern Flanders	1.59	1.81	1.25	1.06	1.08	0.95	0.86	0.94	1.18	1.11	1.07	1.32
Flemish Brabant	1.65	1.59	1.09	1.39	1.37	1.13	1.64	0.52	0.75	1.13	0.77	0.80
Western Flanders	1.18	1.37	1.45	1.38	1.55	1.49	1.23	1.78	1.19	1.84	1.40	1.10

Note: All acute care hospitals with complete numerator and denominator data for at least one semester are included in incidence computation. Mean incidence: total registered HA-CDI episodes for all hospitals and all semesters X 10,000/ total hospitalisation-days for all corresponding semesters.

3. Ribotyping data

Table 7: Ribotypes isolated in Belgium in more than one hospital, 2019: number of isolates and number of hospitals (UCL classification)

Ribotype (UCL-new)	Isolates N=358	Hospitals N=57
16	37	24
3	28	20
362	21	18
306	22	17
46	19	15
32	20	14
340	11	10
344	10	9
316	11	9
44	8	8
4	8	7
27	8	6
594	6	6
47	10	6
33	6	6
313	6	5
23	6	5
14	6	5
601	5	5
49	5	5
161	5	5
118	3	3
349	3	3
26	3	3
588	4	3
343	3	3
28	3	3
48	3	3
22	4	3
630	3	2
307	2	2
595	2	2
308	2	2
35	2	2
598	2	2
589	2	2
333	2	2
24	2	2

Note: Are only considered the first five consecutive strains per hospital per surveillance period.
Source: NRC, new UCL classification.

Table 8: Mapping between the current (new) Belgian UCL classification, the previous (old) and the European (Brazier) classification of *Clostridioides difficile* ribotypes

New UCL classification (valid from 2019 onwards)	Old UCL classification (valid until 2018 included)	Corresponding BRAZIER classification	New UCL classification (valid from 2019 onwards)	Old UCL classification (valid until 2018 included)	Corresponding BRAZIER classification
541	541	001	15	15	054
343	23e	001	600	55a	056
32	32	002	86	86	057
283	283	002	56	56	062
598	32*	002	613	20*	064
49	49	003	232	232	067
493	493	004	47	47	070
46	46	005	340	23b	072
52	52	006	67	67	073
310	16e	007	141	141	075
122	122	009	592	16b*	076
36	36	010	307	16b	076
22	22	011	21	21	077
44	44	012	3	3	078
118	118	013	33	33	081
589	16*	014	548	548	083
591	16b(*)	014	110	110	085
316	16L	014	24	24	087
16	16	014	290	290	093
344	23f	015	334	21d	095
23	23	015	57	57	097
14	14	017	595	22a	103
82	82	019	362	48d	106
306	16a	020	64	64	107
590	16a*	020	446	446	118
4	4	023	601	5a	126
337	22c	024	304	12a	127
48	48	026	356	46d	128
027	027	027	361	48c	131
28	28	029	313	16i	154
95	95	031	363	84a	159
209	209	033	586	027*	176
9	9	039	104	104	181
431	431	042	5	5	193
63	63	043	308	16c	207
349	36a	046	20	20	216
35	35	050	593	16o**	220
165	165	050	594	20a	258
246	246	051	588	14a	265
26	26	052	137	137	276
395	395	053	303	11a	293
333	21c	296	333	21c	296

368	100b*	328	
302	9a	338	
161	161	430	
599	46**	570	
365	85a	668	
329	20b	864	
262	262	014*	
325	16u	014*	
342	23d	015*	
585	585	181*	
322	16r	220*	
299	299	284*	
65	65	414*	

4. Hospital stays data

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Table 9: Number and incidence of enterocolitis due to *C. difficile* in hospital stay data. Comparison with incidence obtained via surveillance data. Belgium 2000-2018

2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Number of hospital stays with code ICD-10-CM A04.7 (Enterocolitis due to* Clostridium difficile*) as primary or secondary diagnosis																		
1,823	1,827	2,199	2,878	3,993	4,415	4,390	4,686	4,749	4,662	3,867	3,522	3,848	3,990	3,609	NA	4,267	4,205	4,425
Incidence of total CDI per 10,000 inhabitants																		
1.78	1.78	2.13	2.77	3.83	4.21	4.16	4.41	4.43	4.32	3.55	3.20	3.48	3.59	3.23	NA	3.78	3.71	3.88
Incidence of total CDI per 1,000 admissions																		
0.98	0.98	1.19	1.56	2.15	2.36	2.34	2.49	2.49	2.42	1.99	1.80	1.95	2.03	1.82	NA	2.13	2.11	2.21
Incidence of total CDI per 10,000 hospitalisation-days																		
1.10	1.09	1.34	1.82	2.56	2.85	2.86	3.09	3.09	3.08	2.56	2.33	2.57	2.71	2.51	NA	2.97	3.00	3.17
Incidence of total CDI per 1,000 admissions from surveillance data (and % from incidence computed from hospital stay data)																		
								1.87 (75%)	1.81 (75%)	1.47 (74%)	1.46 (81%)	1.51 (77%)	1.58 (78%)	1.45 (79%)	1.72	1.71 (80%)	1.73 (82%)	1.75 (80%)
Incidence of total CDI per 10,000 hospitalisation-days from surveillance data (and % from incidence computed from hospital stay data)																		
								2.39 (77%)	2.40 (78%)	2.00 (78%)	2.01 (86%)	2.04 (79%)	2.20 (81%)	2.05 (82%)	2.52	2.53 (85%)	2.68 (90%)	2.72 (86%)
Total cases reported by surveillance (and % from cases reported in hospital stays data)																		
								2,948 (62%)	2,900 (62%)	2,451 (63%)	2,496 (71%)	2,505 (65%)	2,664 (67%)	2,414 (67%)	2,977	2,804 (66%)	2,691 (64%)	2,690 (61%)

Source: Hospital stay data (RHM/MZG). Federal Public Service of public health (SPF/FOD).

Source: Statbel for number of inhabitants.

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5. Billing of diagnostic tests

Table 10: Number of diagnostic tests for *C. difficile* in stool samples billed to social insurance, Belgium 2000-2019

2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
N tests in hospitalised patients																		
52,107	56,282	55,888	64,063	74,947	79,573	82,342	86,229	99,437	94,525	84,779	81,045	82,054	83,370	74,841	84,691	81,583	84,267	84,982
		• ***N tests per 1,000 admissions***																
NA	NA	33.33	38.37	44.67	47.08	48.65	50.71	57.49	54.05	48.16	45.61	45.65	46.37	41,37	46.47	44.38	45.82	46.02
		• ***N tests billed per CDI diagnosed in the hospital***																
28.58	30.81	25.42	22.26	18.77	18.02	18.76	18.40	20.94	20.28	21.92	23.01	21.32	20.89	20.74	NA	19.15	20.08	19.20
Total tests billed (hospitalised and ambulatory patients)																		
78,848	86,010	84,580	95,903	110,295	116,392	125,074	132,665	154,755	153,101	141,990	138,398	144,572	147,676	141,202	155,293	156,923	161,800	163,114
		• ***Total tests billed per 1,000 insured inhabitants***																
7.85	8.52	8.35	9.42	10.79	11.24	12.03	12.68	14.67	14.39	13.24	12.80	13.27	13.48	12.82	14.04	14.12	14.49	14.54

Source: INAMI-RIZIV for number of tests, number of admissions and number of insured persons. Nomenclature codes 549861 and 549850 are for hospitalised and ambulatory patients respectively.

Source: Hospital stay data (RHM/MZG), Federal Public Service of public health (SPF/FOD) for number of CDI diagnoses.

6. Death registry data per region.

Table 11: Specific mortality rates, enterocolitis due to *C. difficile*, per region. Belgium 2000-2017

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of death records with code ICD10 A047 « enterocolitis due to C. difficile » as underlying cause of death																		
Belgium	19	18	36	71	150	151	156	103	127	135	97	86	88	78	63	106	84	91
Brussels	2	1	8	24	61	47	36	24	16	14	16	12	15	13	8	15	3	8
Flanders	7	11	16	30	63	72	80	54	75	76	55	56	55	33	37	58	56	52
Wallonia	10	6	12	17	26	32	40	25	36	45	26	18	18	32	18	33	25	31
Crude specific mortality rate, per 100,000 inhabitants																		
Belgium	0.19	0.17	0.35	0.68	1.44	1.44	1.48	0.97	1.19	1.25	0.89	0.78	0.80	0.70	0.56	0.94	0.74	0.80
Brussels	0.21	0.10	0.81	2.41	6.08	4.64	3.51	2.31	1.51	1.30	1.45	1.06	1.31	1.12	0.68	1.27	0.25	0.67
Flanders	0.12	0.18	0.27	0.50	1.04	1.19	1.31	0.88	1.21	1.22	0.88	0.88	0.86	0.52	0.58	0.90	0.86	0.80
Wallonia	0.30	0.18	0.36	0.50	0.77	0.94	1.17	0.73	1.04	1.29	0.74	0.51	0.51	0.90	0.50	0.92	0.69	0.86
Age-standardised specific mortality rate*, per 100,000 inhabitants																		
Belgium	0.23	0.21	0.40	0.77	1.58	1.59	1.59	1.02	1.23	1.27	0.89	0.76	0.76	0.66	0.53	0.87	0.68	0.73
Brussels	0.24	0.11	0.88	2.60	6.59	4.98	3.75	2.53	1.74	1.48	1.62	1.22	1.46	1.34	0.86	1.48	0.30	0.78
Flanders	0.14	0.22	0.30	0.57	1.16	1.33	1.41	0.91	1.24	1.21	0.85	0.84	0.80	0.46	0.51	0.78	0.74	0.67
Wallonia	0.38	0.22	0.41	0.54	0.81	1.03	1.27	0.77	1.08	1.33	0.76	0.50	0.49	0.87	0.49	0.88	0.66	0.82

*Source : death registries. *Indirect standardisation, three age categories (0-64, 65-79, 80+), using 2010 Belgian population age structure as a standard.*

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