AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

TRIM: D17-30545

March 2018

Clostridium difficile infection

Monitoring the national burden of *Clostridium difficile*

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ISBN: 978-1-925665-38-3

The Commission's preference is that you attribute this publication (and any material sourced from it) using the following citation:

> Australian Commission on Safety and Quality in Health Care. *Clostridium difficile* infection. Monitoring the national burden of *Clostridium difficile*. Sydney: ACSQHC; 2018

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Contents

Summary

Clostridium difficile[*] is an anaerobic, spore-forming, gram-positive bacillus typically associated with gastrointestinal disease. The spectrum of disease associated with *C. difficile* is wide, ranging from asymptomatic colonisation through to fulminant colitis and peritonitis. *C. difficile* is ubiquitous in the natural environment as well as in healthcare environments where there is potential for the bacterium to be spread between individuals via the faecal-oral transmission route, either directly or indirectly. The establishment of a *C. difficile* infection (CDI) is often linked to prolonged and unnecessary use of antimicrobial therapies.[1]

In 2015 the Australian Commission on Safety and Quality in Health Care produced a discussion paper - *Consultation on surveillance and monitoring of Clostridium difficile infection in Australia.*[23] This paper identified a lack of data and an understanding of the incidence and distribution of CDI as barriers to developing a national approach to the prevention and control of CDI.

This paper examines whether patient administrative data can be used as a means to monitor the prevalence of CDI in Australia in the absence of a national CDI surveillance system. Data related to the ICD-10 diagnosis code A04.7 (Gastroenterocolitis caused by *Clostridium difficile*) from 2011 to 2016 in the Admitted Patient Care National Minimum Data Set (APC-NMDS) was analysed and used to develop a mechanism to determine and monitor the national prevalence of CDI. Administrative data was compared against clinico-epidemiological (traditional) infection surveillance data provided by the individual states to determine the level of comparability between the two data sources.

Key findings from this work were:

- Between 2011 and 2016, the average prevalence of CDI diagnoses was 4.0 per 10,000 patient days. There were two major peaks observed in this period where the diagnosis rate was over 4.5 diagnoses per 10,000 patient days
- Patients with a CDI diagnosis have an average length of stay of 17.7 days. A patient with a principal CDI diagnosis has an average length of stay of 7.9 days. A patient whose primary reason for hospitalisation is not CDI but also has a CDI diagnosis assigned during their hospital stay has an average length of stay of 21.6 days
- It is estimated that severe CDI represents 2.2% of all CDI cases seen in Australian hospitals. The rate of severe disease has been increasing since 2012. The proportion of CDI cases where severe disease has resulted in death is 0.7%.
- Acquisition of CDI was directly attributable to the hospital care in 24.9% of separations assigned with a CDI diagnosis.

This is the first study to report on the burden of CDI diagnoses across Australia.

This study has also demonstrated the usefulness of administrative data for establishing the prevalence of CDI nationally.

[*] Now renamed as *Clostridioides difficile* (see: Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of *Clostridium difficile* as *Clostridioides difficile* (Hall and O'Toole 1935) Prévot 1938. Anaerobe. 2016;40:95-9)

Future directions
The Inter Jurisdictional Committee has indicated support for the Commission to use this approach to annually monitor the prevalence of CDI diagnosis rates.

Health services should, however, continue to use existing laboratory-based surveillance and exposure classification processes[2] to monitor local CDI trends in order to inform timely local infection prevention and control responses.

Background

Clinical overview

Pathogenicity and transmission

Clostridium difficile[*] is an anaerobic, spore-forming, gram-positive bacillus typically associated with gastrointestinal disease. The bacteria is ubiquitous in its spore form in the natural environment, persisting in soil and waterways[3], as well as in built environments where there is potential for the bacteria to be spread from humans and other animals carriers to environmental surfaces. Transmission of *C. difficile* occurs by ingestion of spores either through person-to-person contact, animal-to-person contact or environment-to-person contact. [3]

After transmission, colonisation of the gut will occur.[4] The gut's oxygen poor environment is ideal for supporting the sporulation and proliferation of the bacteria.[4, 5] Commensal bacteria usually control the extent of *C. difficile* colonisation in the gut and in turn, colonisation often is associated with an asymptomatic clinical presentation. Disruption of commensal bacteria can lead to a gross proliferation of *C. difficile* and the onset of symptomatic illness.[5] The most common cause of disruption to the interaction between commensal bacteria and *C. difficile* is the usage of antimicrobial agents.[1]

Clinical disease

Symptomatic *C. difficile* disease, also known as *C. difficile* infection (CDI), is mediated through toxin production by the bacteria. Non-toxigenic strains of *C. difficile* are rarely associated with symptomatic illness.[6] Production of toxin A and toxin B results in hyper-inflammation and necrosis of the gut lining. Some *C. difficile* strains also produce a third toxin, known as the binary toxin. The role of the binary toxin in disease manifestation is poorly understood[4, 7, 8], despite attempts to find associations between toxin production and disease duration, recurrence, severity[9], and strain virulence.[10]

The spectrum of disease associated with *C. difficile* is wide, ranging from asymptomatic colonisation through to fulminant colitis and peritonitis.[11] Table 1 describes the common disease states associated with CDI. In addition to intracolonic symptoms, severe CDI is characterised by the following systemic markers[12, 13]:

- Fever (>38.5°C)
- Haemodynamic instability
- Elevated lactate
- Elevated creatinine
- Rigors
- Leucocytosis (>15 x 10^9/L , <20% neutrophils)
- Lowered albumin levels

Approximately 20% of patients with an initial infection will have at least a second episode, with symptoms usually re-emerging within 21 days of the initial episode.[14]

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Table 1. Spectrum of disease associated with CDI[11, 14]

←Increasing disease severity	Disease state	Clinical presentation
	Asymptomatic colonisation	None
	C. difficile diarrhoea	Mild to moderate diarrhoea Lower abdominal cramps Abdominal pain
	C. difficile colitis	High-volume watery diarrhoea Mild to moderate abdominal pain Nausea Anorexia
	Pseudomembranous colitis	Possible diarrhoea Intense abdominal pain and tenderness in the left or right lower quadrant
	Fulminant colitis	Diarrhoea (in the absence of ileus) Severe lower quadrant or diffuse abdominal pain Distension Ileus Toxic megacolon Colonic perforation Mortality

Treatment and management

Given the relationship between antibiotic exposure and disease onset, the inciting antibiotic should be discontinued as soon as possible.[12, 14, 15] The initial treatment of CDI requires narrow-spectrum, specific antibiotic therapy, the discontinuation of all other non-essential antibiotic therapy, and fluid replacement to restore electrolyte balance.[12, 14, 16] Therapeutic Guidelines: Antibiotic provides for further advice on the appropriate antimicrobial therapy for initial or subsequent infection.[17] A faecal microbiota transplant may also be considered if recurrent disease is present.[12]

Prevention

Antimicrobial stewardship

It is critical that strategies are in place to ensure appropriate antimicrobial use given the possible link between hospital antibiotic exposure and CDI.[18, 19] Appropriate antimicrobial usage refers to appropriate clinical indication, dosage, duration and route of administration.[20]

Hand hygiene

Hand hygiene should always be performed regularly during the delivery of patient care. Healthcare workers should perform hand hygiene with soap and water when caring for patients with known or suspected CDI as alcohol-based hand rub alone may not be sufficient in reducing the risk of transmission associated with *C. difficile* spores.[18, 21]

Contact precautions and enhanced environmental cleaning

Contact precautions, in addition to standard precautions, should be employed when caring for patients with known or suspected CDI in order to minimise the risk of contact transmission.[15, 18, 21] These precautions include placement of the patient in a single room with dedicated bathroom facilities (where possible), the use of disposable or dedicated patient equipment and enhanced environmental cleaning.

Surveillance

Laboratory-based surveillance activities should be undertaken by individual healthcare facilities in order to monitor the prevalence of CDI and the effectiveness of the local measures employed to prevent CDI.[18]

The outbreak potential associated with CDI is high, given its mode of transmission and clinical presentation. Active surveillance of CDI at the local level is imperative for the early detection and control of CDI outbreaks.[15]

CDI surveillance

Current CDI surveillance in Australia

Traditional healthcare associated infection (HAI) surveillance, using clinico-epidemiological methods, are currently used in most states and territories to monitor cases of hospital identified CDI.[22] Table 2 summarises the scope of the various state and territory-based surveillance programs operating in public hospitals.

Table 2. Summary of state and territory-based CDI surveillance programs

State or Territory	Year that jurisdictional surveillance program commenced	Surveillance elements			
		Hospital-identified	Exposure classification	Severity	Recurrence
ACT	There is no jurisdictional CDI surveillance				
NSW	2010	YES	NO	NO	NO
NT	There is no jurisdictional CDI surveillance				
Qld	2008§	YES	YES	NO	NO
SA	2006†	YES	YES*	NO	NO
Tas	2008†	YES	YES	NO	NO
Vic	2010§	YES	YES	YES	YES
WA	2010§	YES	NO	NO	NO

*Only collects healthcare-associated, health facility onset

† The national surveillance definition for CDI has been used since 2009

§The national surveillance definition for CDI has been used since the beginning of the jurisdictional surveillance program

In 2015 the Commission produced a consultation paper on the surveillance and monitoring of CDI in Australia.[23] This paper identified that a lack of data and understanding around the epidemiology and severity of CDI in the Australia is a key gap in the national approach to CDI surveillance and control.[24] In order to address this knowledge gap, it was advised to the Inter Jurisdictional Committee that a mechanism be established to undertake surveillance, monitor national incidence and severity trends and manage outbreaks (Meeting 39, 31 March 2016). Specifically, the Commission proposed to provide recommendations on[25]:

a) Public and private hospitals to continue to collect data on hospital-identified CDI
b) Public and private hospitals to undertake Healthcare Associated-Infection-Facility-Onset CDI surveillance, where possible
c) Jurisdictional rates of CDI will be monitored and considered biannually at the Commission's HAI Technical Working Group, and key advice will be provided to the IJC
d) A mechanism for monitoring severe cases of CDI will be developed through the Commission's HAI Technical Working Group
e) The Commission's HAI Advisory Committee will develop definitions for CDI severity.

This paper discusses actions to address Recommendations (a) to (d). Recommendation (e) has already been addressed as part of the *Implementation Guide for Surveillance of Clostridium difficile infection* (2013).[26]

National surveillance resources

The Commission produced *Implementation Guide for Surveillance of Clostridium difficile Infection* (the Implementation Guide) [26] in 2013 in an effort to standardise the surveillance approaches used by the individual states and territories. This guide provides detail on:

- The case definition for hospital identified CDI
- The calculation and interpretation of hospital identified CDI rates
- The definition and calculation of severe CDI
- The definitions for CDI exposure classifications.

Hospital-identified CDI refers to a case of CDI that is diagnosed in a patient attending a hospital, a hospital emergency department or an outpatient department.[26] A classification of hospital-identified CDI does not provide any insight into whether with CDI is acquired in the hospital or community. Hospital-identified CDI is centrally monitored in all states but is not centrally monitored in the Australian Capital Territory or the Northern Territory.

Severe disease surveillance

According to the Implementation Guide[26], a severe case is defined as a CDI patient who meets any of the following criteria within 30 days of symptom onset:

- History of admission to an intensive care unit for complications associated with CDI
- History of surgery for toxic megacolon, perforation or refractory colitis
- Death caused by CDI within 30 days after symptom onset

The incidence of severe disease is calculated as a proportion of the total number of hospital-identified CDI cases.

Understanding the prevalence of severe CDI in Australia is useful for informing resource allocation required for clinical care. Currently, statewide monitoring of severe CDI only occurs in Victoria.

Exposure surveillance

Hospital-identified CDI cases can be further classified by exposure [26]:

- Healthcare associated, community-onset
- Healthcare associated, health facility-onset
- Community onset
- Indeterminate
- Unknown.

Exposure surveillance provides useful information on the likely location of infection acquisition and disease onset. Location of disease onset provides hospitals with an indirect measure of the effectiveness of local infection prevention and control measures. Tasmania and Victoria are the only states that currently perform full exposure surveillance for all hospital-identified CDI cases. South Australia performs limited exposure surveillance to identify health facility onset cases. The other five states and territories do not perform any exposure surveillance.

National regulatory instruments

In 2011, the National Health Reform Agreement was signed off by the Council of Australian Governments (COAG). The objective of this agreement is to “improve health outcomes for all Australians and the sustainability of the Australian health system”.[27] The national Performance and Accountability Framework (PAF)[28] was then established as a reporting instrument for the implementation of the National Health Reform Agreement. Based on an earlier recommendation from the Australian Health Ministers Advisory Council in 2008[29], the healthcare associated CDI was included in the PAF included as an effectiveness (safety and quality) indicator for all Australian hospitals.

Local surveillance of healthcare associated infections is also a key requirement of the Preventing and Controlling Healthcare Associated Infections standard of the National Safety and Quality Health Service standards.[30]

Global disease trends

Many countries have established surveillance programs in place to monitor the prevalence of CDI in their health systems. Despite the existence of regional and national CDI surveillance programs, there is limited publicly available on national annual incidence rates. In the few countries where longitudinal data is publicly available, the overall incidence for CDI appears to be on the decline (Appendix 1).

Circulation of ribotype 027 in Europe and North America increased markedly in the early 2000s.[31, 32] Ribotype 027 infection is often associated with severe disease, higher rates of mortality and disease outbreak.[32] In the United Kingdom (UK), subsequent adoption of strict infection control measures, including mandatory reporting in 2004 and enhanced surveillance and routine ribotyping in 2007, was required to contain this particular strain.[33, 34] Prolonged adherence to these measures had a significant effect on the CDI rate in the UK: the CDI rate dropped from 14.9 cases per 10,000 patient days in 2007-08 to 3.67 cases per 10,000 patient days in 2016-17.[35] The effect of ribotype 027 has been largely limited to the northern hemisphere as little circulation of this strain has been observed in Australia to date.[36, 37]

Introduction

The current state-based surveillance approach is limited in its ability to inform on the epidemiology and prevalence of CDI across the country. Without detailed epidemiological information about the spread and prevalence of CDI in the country, it is difficult to assess whether there is potential for CDI to become an organism of national significance and if there is a need to develop and implement additional infection prevention and control strategies to counter the virulence and spread of CDI at a national level.

The primary purpose of this paper is to examine the usefulness of patient administrative data as a means to monitor the prevalence of CDI nationally and inform on whether additional infection prevention and control strategies are needed to control the spread of the CDI in Australia.

This paper also will establish the current epidemiology of CDI in Australia using both patient administrative data and laboratory-based surveillance data.

Methods

Admitted Patient Care National Minimum Data Set

The purpose of the Admitted Patient Care National Minimum Data Set (APC-NMDS) is to collect information about care provided to admitted patients in Australian hospitals. Data is collected at each hospital from patient administrative and clinical record systems. Hospitals forward data to the relevant state or territory health authority on a regular basis (e.g. monthly). State and territory health authorities provide the data to the Australian Institute of Health and Welfare for national collation.[38] Data is also collected on a six-monthly basis by the Independent Hospital Pricing Authority (IHPA) for the purposes of determining activity based funding.[39]

APC-NMDS data parameters

This analysis refers to episodes of care for admitted patients in all Australian public hospitals only. The following data periods have been included in this analysis: 2011-12, 2012-13, 2013-14, 2014-15 and 2015-16. No exclusion or filtering criteria was applied to the APC-NMDS. Data was based on the state or territory of the hospital that collected the data, not the state or territory where the patient resides.

Diagnosis coding

For the purposes of this analysis, diagnosis code A04.7 *Gastroenterocolitis caused by Clostridium difficile* was used to identify separations affected by CDI.[40]

Coding filters

Data associated with the ICD-10 diagnosis code A04.7 *Gastroenterocolitis caused by Clostridium difficile* was extracted from the APC NMDS. Data was then filtered to identify whether A04.7 was assigned as a principal or an additional diagnosis code. Each separation has one principal diagnosis code which denotes the condition that is chiefly responsible for the hospital admission.[41] In addition, up to 99 additional diagnosis codes can be assigned to each separation to describe other conditions that either emerged during or have contributed to the separation.

Additional A04.7 diagnosis codes were further filtered by condition onset flags (COF). There are two COFs[42]:

- COF1: a condition that has arisen during the episode of admitted care that would not have been present or suspected on admission
- COF2: a condition previously existing or suspected on admission such as the presenting problem, a comorbidity or chronic disease.

Additional diagnosis codes were filtered by COF1 qualification to identify the number of separations where CDI is likely to be attributable to the delivery of health care. Only hospitals where the coding of COF is highly reliable[43] were included in the sub-analysis (n= 511/708 hospitals) that is reported in Figures 4 and 5.

Data qualifications

All data collected in APC-NMDS are subject to the following qualifications:

1. Diagnosis codes can be attributed to either the month of admission or the month of discharge. In this analysis, diagnosis codes are attributed to the month of admission. If an admission is spread over more than one month, any diagnoses identified during the admission will be attributed to the month of admission, not the month of when the diagnosis was first made
2. For the purposes of this analysis, data from the APC-NMDS has been analysed by calendar year. Data in the APC-NMDS, however, is usually reported by financial year. Diagnosis rates when calculated by calendar year may slightly differ from diagnosis rates that are calculated by financial year
3. Each quarter, individual states and territories supply data to AIHW for inclusion in the APC-NMDS. Data for this analysis was retrieved in March 2017. Any *post hoc* adjustments that have subsequently been made to the data by individual states and territories may not be reflected in this analysis.

Rate calculations

Rate of CDI diagnosis

The monthly rate of CDI diagnosis was calculated using the following formula:

$$= \frac{\text{Number of A04.7 diagnoses}}{\text{Total patient days (including same day admissions)}} \times 10,000$$

Monthly counts of A04.7 diagnoses were obtained from the APC-NMDS for each state and nationally for the period between July 2011 and May 2016, inclusive.

Rate of hospital-identified CDI

The monthly rate of hospital-identified was calculated for each state using the national calculation for hospital identified *Clostridium difficile* infection:

$$= \frac{\text{Patient episodes of hospital-identified CDI (total hospital CDI cases)}}{\text{Total patient days (including same day admissions)}} \times 10,000$$

Individual state and territory health authorities provided the Commission with monthly counts of patient episodes of hospital-identified CDI[44] for the period between July 2011 and May 2016 inclusive. This data is collected from all hospitals in the jurisdiction by the relevant health authority.

Total patient days

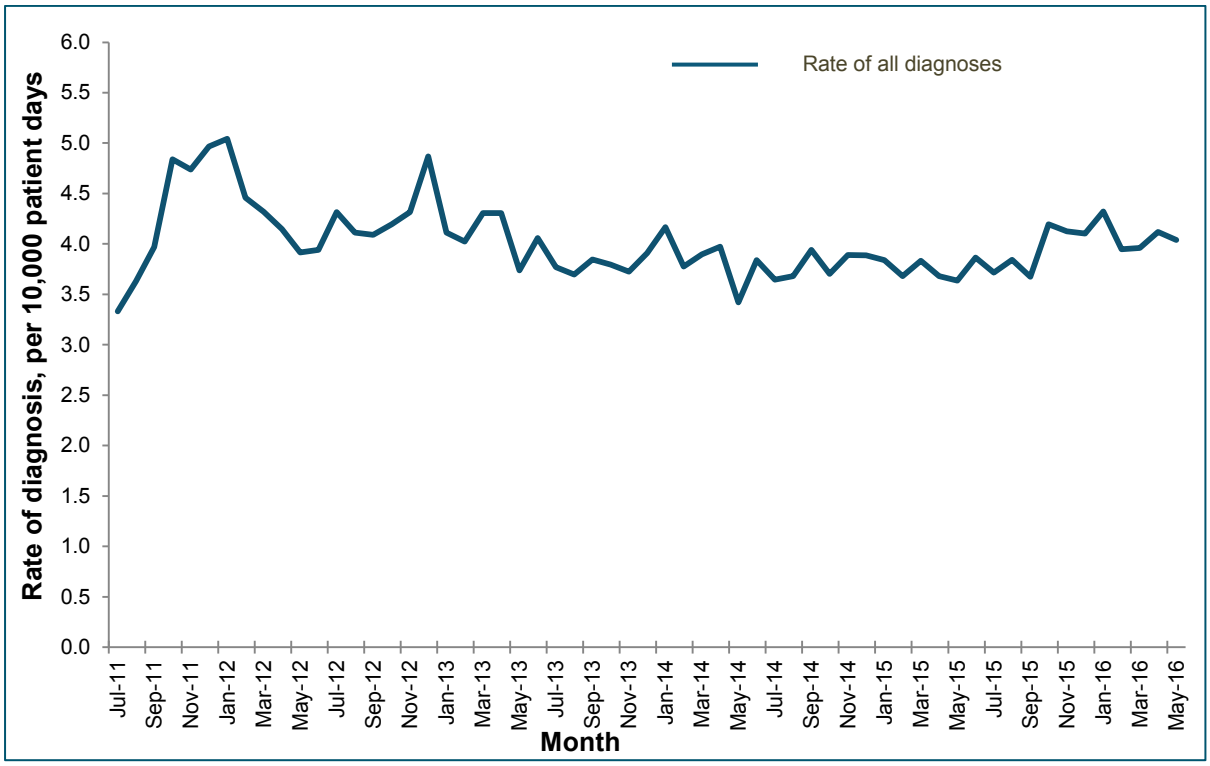
Total patient days for each month between July 2011 and May 2016 were extracted from the APC-NMDS for each state. Total patient days is defined in the national health data dictionary as the total number of days for all patients who were admitted for an episode of care and who separated during a specified reference period.[45]

Findings

National burden of CDI

Prevalence of CDI in Australia

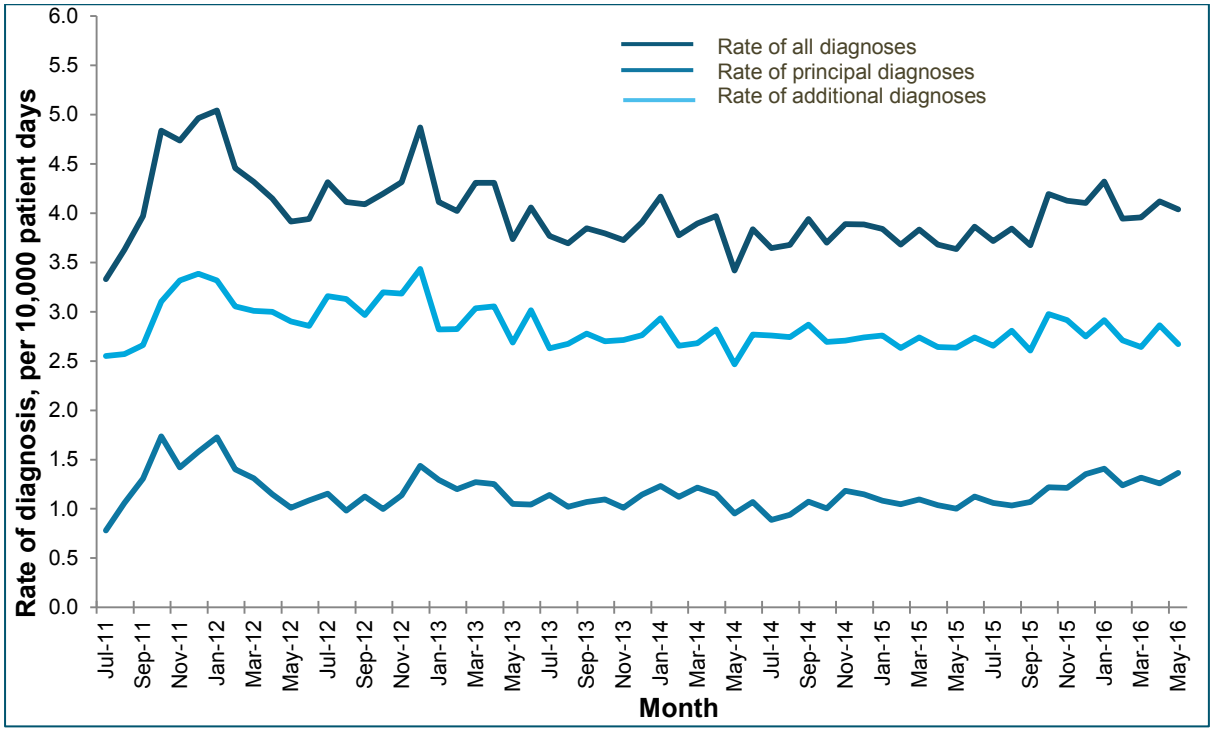
Figure 1. Monthly rate of A04.7 diagnoses in Australia, 2011-2016



Commentary

The rate of A04.7 diagnoses in Australia peaked twice in the data period. The first peak was in January-February 2012 and the second peak was in December 2012-January 2013. Both peaks resulted in a diagnosis rate of over 4.5 diagnoses per 10,000 patient days. After May 2013 peak, the diagnosis rate declined to around 4.0 diagnoses per 10,000 patient days. This lower rate was sustained until November 2015 when the diagnosis rate increased to above 4.0 diagnoses per 10,000 patient days. This higher diagnosis rate continued to be observed until the end of the data period in May 2016.

Figure 2. Monthly rate of principal and additional A04.7 diagnoses in Australia, 2011-2016



Commentary

A04.7 additional diagnoses make up over two thirds of the total rate of A04.7 diagnoses in the data period. This finding indicates that the majority of CDI seen in hospitals is not the primary cause for hospitalisation. Troughs and peaks occur at the same time for principal and additional A04.7 diagnoses, suggesting that similar circulation patterns are in action.

Length of stay associated with CDI

Length of stay is a common measure of health system efficiency. Using the data available in the APC-NMDS (2011-12, 2012-13, 2013-14, 2014-15 and 2015-16) the average length of stay associated with the A04.7 diagnosis code was calculated using the following formula:

$$= \frac{\text{annual total patient days associated with the diagnosis code}}{\text{annual total patient days}}$$

The average length of stay was calculated for 2012, 2013, 2014 and 2015 as these were the only years where a complete dataset was available. The overall average length of stay for all separations in Australia was also calculated to provide a comparator for analysis. Table 3 tabulates average lengths of stay for any A04.7 diagnosis, for A04.7 as a principal diagnosis and A04.7 as an additional diagnosis.

Table 3. Average length of stay associated with the A04.7 diagnosis code, 2012-2015

Year	Average length of stay (patient days)		
	Any A04.7 diagnosis	Principal A04.7 diagnosis	Additional A04.7 diagnosis
2012	18.69	8.34	22.73
2013	17.17	7.91	20.91
2014	18.05	7.79	22.10
2015	16.91	7.60	20.68
Average	17.7	7.9	21.6

Commentary

The length of stay associated with an additional A04.7 diagnosis is almost three times longer than the length of stay associated with a principal A04.7 diagnosis.

The length of stay associated with an A04.7 diagnosis declined between 2012 and 2015. This decline was most pronounced for stays associated with an additional A04.7 diagnosis. The length of stay associated with a principal A04.7 diagnosis declined to lesser extent, with a 1.78 day reduction observed.

Prevalence of severe disease

There is substantial work and resource burden associated with the treatment and care of patients who have severe CDI. It is important to establish the proportion and nature of severe disease in Australia in order to ensure that there is adequate resource allocation to support patients with severe CDI.

There is no national dataset available that records severe CDI. It is possible however to estimate the national prevalence of severe CDI using state-based surveillance of severe CDI. Currently only Victoria collects surveillance data on severe CDI consistent with the *Implementation Guide for Surveillance of Clostridium difficile Infection*.[26, 46, 47] Surveillance data regarding severe CDI from 2011 to 2017 were provided by VICNISS. All data are collected by trained staff in hospitals, using laboratory data together with standardised clinico-epidemiological assessment of cases. These data were used to calculate the rate of severe disease and mortality due to severe disease (Table 4). Sub-analysis was also undertaken to determine the prevalence of the three severity markers described in the *Implementation Guide for Surveillance of Clostridium difficile Infection* (Table 5).[26]

Table 4. Rates of severe CDI and mortality due to severe CDI in Victoria, 2012-2015

Year	Total patient days	Number		
		CDI cases	Severe CDI cases (% of total CDI cases)	Death due to severe CDI (% of total CDI cases)
2012	5,868,315	1812	26 (1.43)	17 (0.94)
2013	4,696,220	1553	27 (1.74)	7 (0.45)
2014	4,859,297	1567	28 (1.79)	11 (0.70)
2015	4,960,991	1634	36 (2.20)	11 (0.67)
Overall	**20,384,823**	**6566**	**117 (1.78)**	**46 (0.70)**

Commentary

The rate of severe disease appears has remained constant over the data period and little change was observed in the mortality rate associated with severe CDI.

In 2015, a total of 19,616,532 patient days were recorded in Australia. Based on the average rates calculated for Victoria between 2012 and 2015, it is estimated that there would have been 113 cases of severe disease and 44 cases where severe CDI resulted in death in Australia in 2015.

Table 5. Prevalence of severity criteria among patients with severe CDI in Victoria, 2011-2017

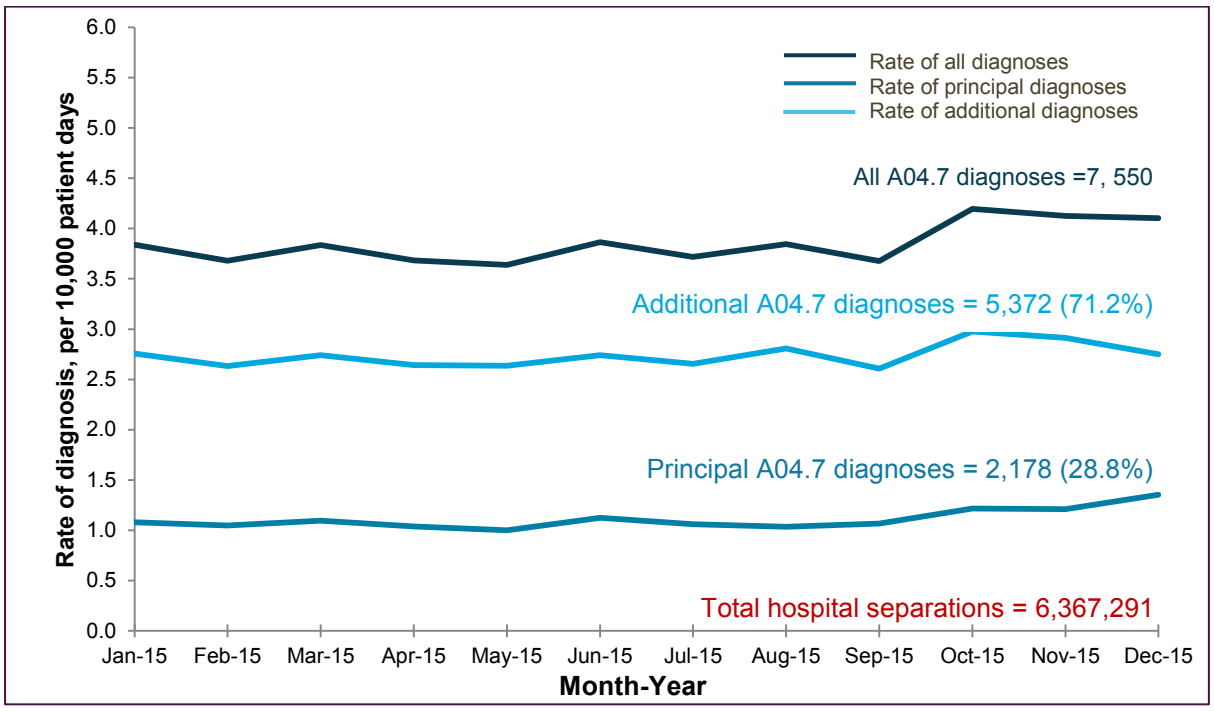
Severity Criteria 1 (ICU admission only)	Severity Criteria 2 (Surgery only)	Severity Criteria 3 (Death only)	Severity Criteria 1&2 (ICU + Surgery)	Severity Criteria 1&3 (ICU + Death)	Severity Criteria 2&3 (Surgery +Death)	All criteria (ICU+Surgery+ Death)
83 (45.9%)	11 (6.1%)	49 (27.1%)	17 (9.4%)	6 (3.3%)	4 (2.2%)	11 (6.1%)

Commentary

Between 2012 and 2016, severe CDI represented 1.8% (117/6566) of all CDI cases in Victoria. The most prevalent marker of severe CDI was admission to an intensive care unit due to CDI. Admission to an intensive care unit was associated with approximately 75% of all severe cases and on its own (i.e. not in combination with other markers) accounted for almost half of all severe cases. The least prevalent marker was surgery related to CDI complications, which accounted for only 6% of all severe cases.

Snapshot: CDI in 2015

Figure 3. National rate of A04.7 diagnoses in Australia, 2015 (n = 708 hospitals)

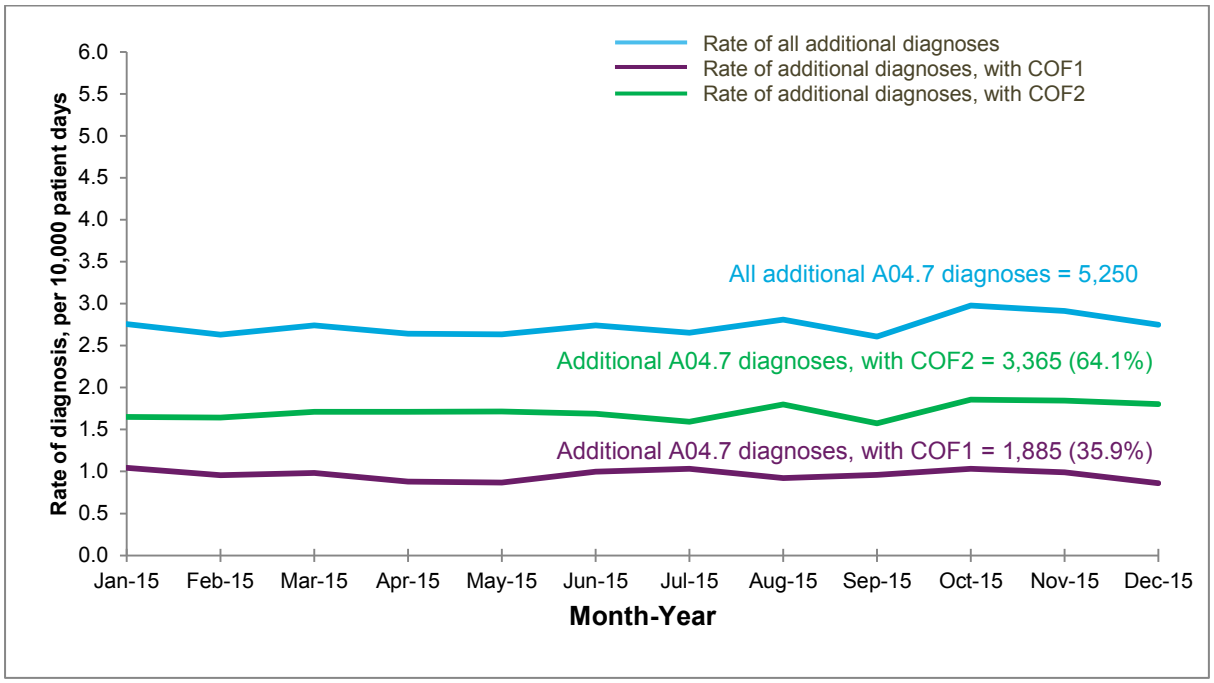


Commentary

Based on data collected from 708 hospitals across Australia, the monthly rate of A04.7 diagnoses was between 3.9 and 3.7 diagnoses per 10, 000 patient days between January and September 2015.

Additional A04.7 diagnoses accounted for over 70% of all A04.7 diagnoses in 2015. It is estimated that 0.11% of all hospital admissions in 2015 were affected by a CDI diagnosis. This is a crude estimation that assumes that each A04.7 diagnose is related to a new admission and does not factor in CDI diagnoses associated with re-admissions. The APC-NMDS does not enable analysis of the prevalence of CDI associated with hospital re-admissions.

Figure 4. Sub analysis of A04.7 additional diagnoses in Australia, 2015

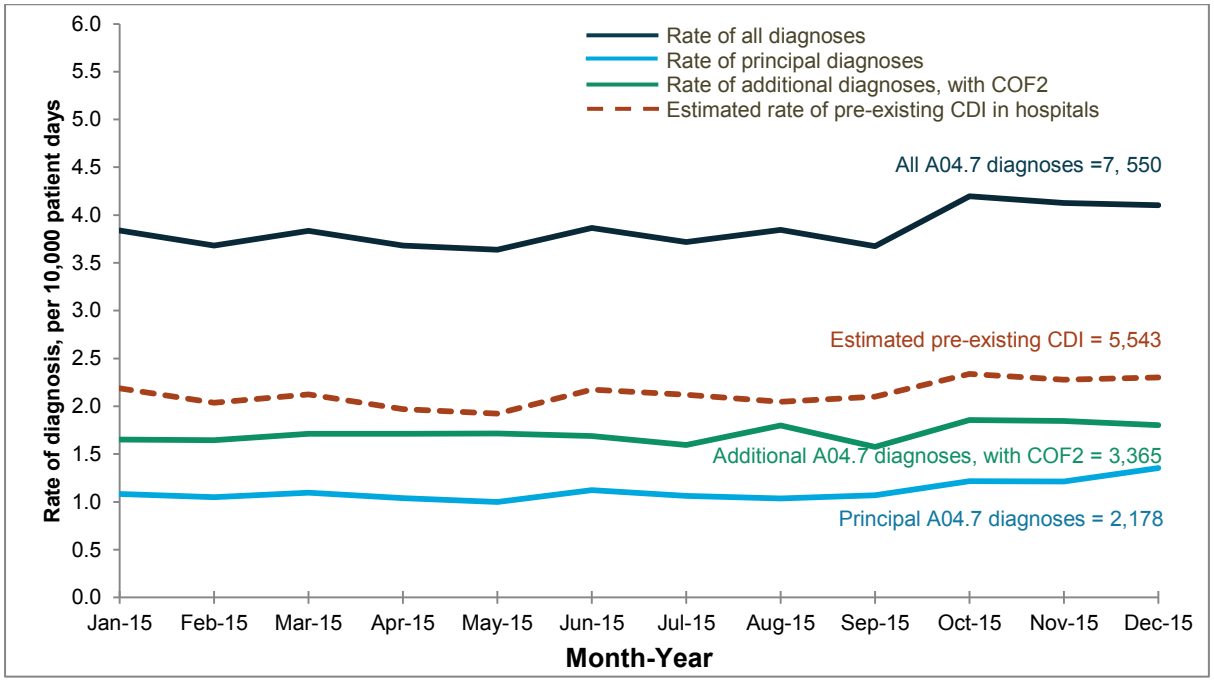


Commentary

Based on data provided from the 511 hospitals with highly reliable coding of COF, there were 5,250 A04.7 additional diagnoses in Australia. This represents 97.7% of all A04.7 additional diagnoses identified in Australian public hospitals (n=708).

Over 60% of additional A04.7 diagnoses were qualified as COF2, indicating that the majority of CDI acquisition is not related to the delivery of health care during that particular hospital admission. The rate of additional A04.7 diagnoses with a COF2 was slightly increased in August and October. After a rate increase in October, the rate remained slightly elevated for the rest of the year and did not return to the earlier lower rate. The rate of additional A04.7 diagnoses with COF1 (purple line) increased did not change very much during the year. This suggests that increases in additional A04.7 diagnoses with a COF2 (green line) and principal A04.7 diagnoses (Figure 3, bottom line) drove the overall increase in A04.7 diagnoses during the last quarter of 2015.

Figure 5. Estimated burden of pre-existing CDI presenting to hospitals, 2015



Commentary

The total burden of pre-existing CDI presenting to Australian hospitals was estimated by combining the number of principal A04.7 diagnoses (n=2,178) with the number of additional A04.7 diagnoses with a COF2 qualification (n=3,365). It estimated that 73.4% CDI diagnoses made in 2015 reflected pre-existing infections, indicating that the majority of CDI found in hospitals is not due to the delivery of health care during the separation for which the diagnosis was assigned.

Comparison of administrative data and traditional HAI surveillance data

In early 2017, the Commission requested traditional HAI surveillance data from the six states that centrally collate CDI surveillance data. These states provided datasets for 2011 to 2016 and state data was compared to relevant data from the APC-NMDS on a state by state basis.

To enable comparison between administrative data and traditional HAI surveillance data, the following assumptions were made:

- A separation assigned with an A04.7 as a principal or additional diagnosis code is equivalent to a case classified as hospital-identified CDI
- A separation assigned with an A04.7 as a principal diagnosis code is equivalent to a case classified as community onset CDI
- A separation assigned with an A04.7 as an additional diagnosis code with a COF1 qualification is equivalent to a case classified as healthcare-associated CDI, health facility onset CDI
- A separation assigned with an A04.7 as an additional diagnosis code with no COF1 qualification is equivalent to a case classified as healthcare-associated CDI, community onset CDI.

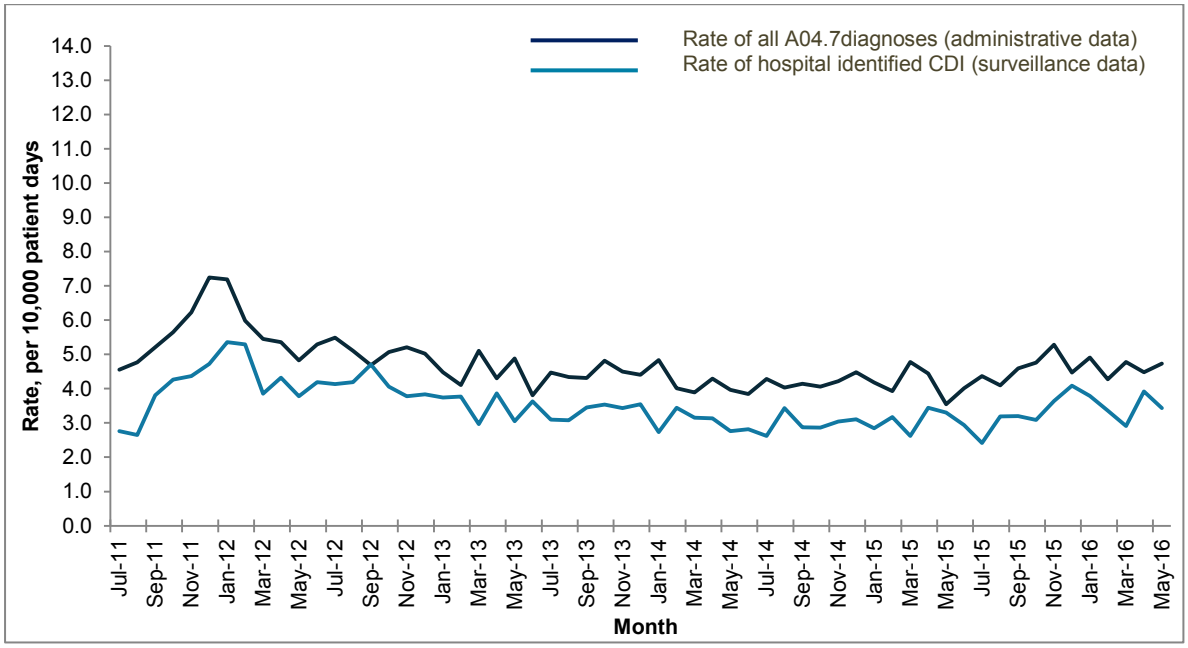
Simple analysis of state-level data was undertaken to assess the comparability of the administrative data in comparison to traditional HAI surveillance data. There were two aspects to this analysis:

- Visual analysis: Do the two datasets share common data landmarks? Do peaks and troughs occur at the same time?
- Statistical analysis: Is there a statistically significant difference between the two datasets?

Statistical analysis was carried out using a two-tailed paired t test. It was assumed that the two datasets has equal variances. Analysis was performed using the Data Analysis pack in Microsoft Excel (Version 14.0, Microsoft Office Standard 2010). The significance level was set at p=0.05.

New South Wales

Figure 6. Monthly rates of all A04.7 diagnoses and hospital identified CDI in New South Wales, 2011-2016



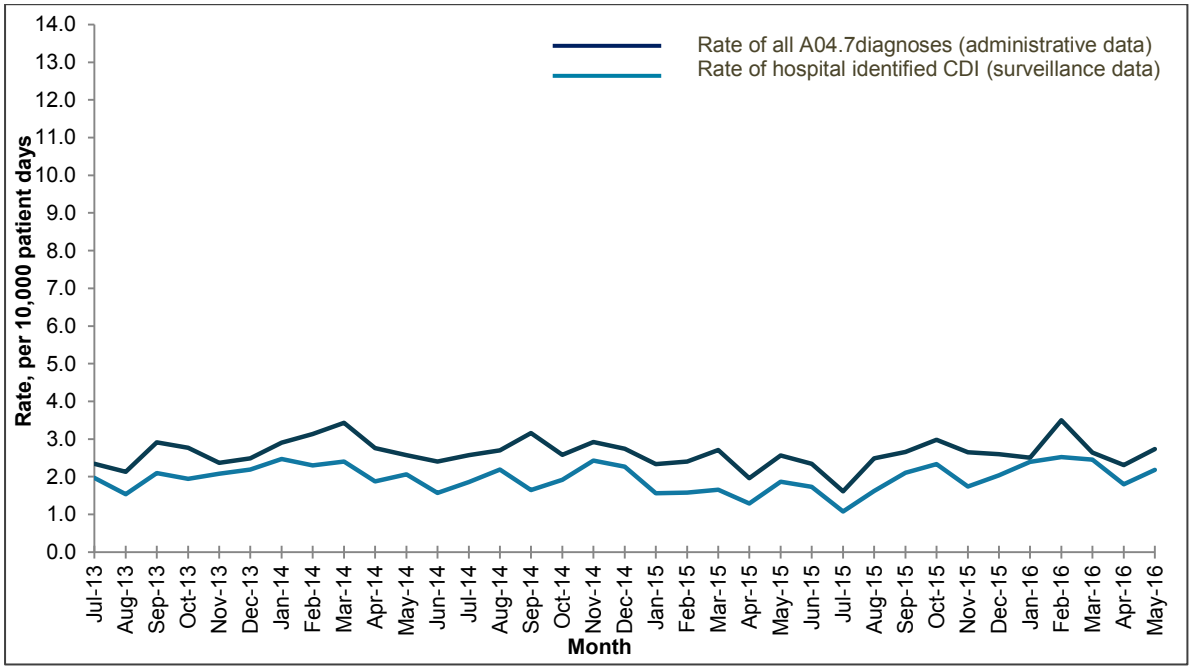
Commentary

The shape of the two datasets is visually comparable. Analysis of this data indicated one instance of convergence in October 2012, when the rate of diagnosis dropped and the rate of infection increased. Traditional HAI surveillance data lagged behind admissions data by up to two months between March 2013 and July 2013 and between May 2015 and early 2016. This is likely, in part, due to the difference in when the onset is attributed, i.e. at admission, or discharge as described earlier.

Note: In New South Wales, the CDI rate is usually reported as patient episodes of hospital identified CDI per 1,000 acute separations.

Queensland

Figure 7. Monthly rates of all A04.7 diagnoses and hospital identified CDI in Queensland, 2013-2016

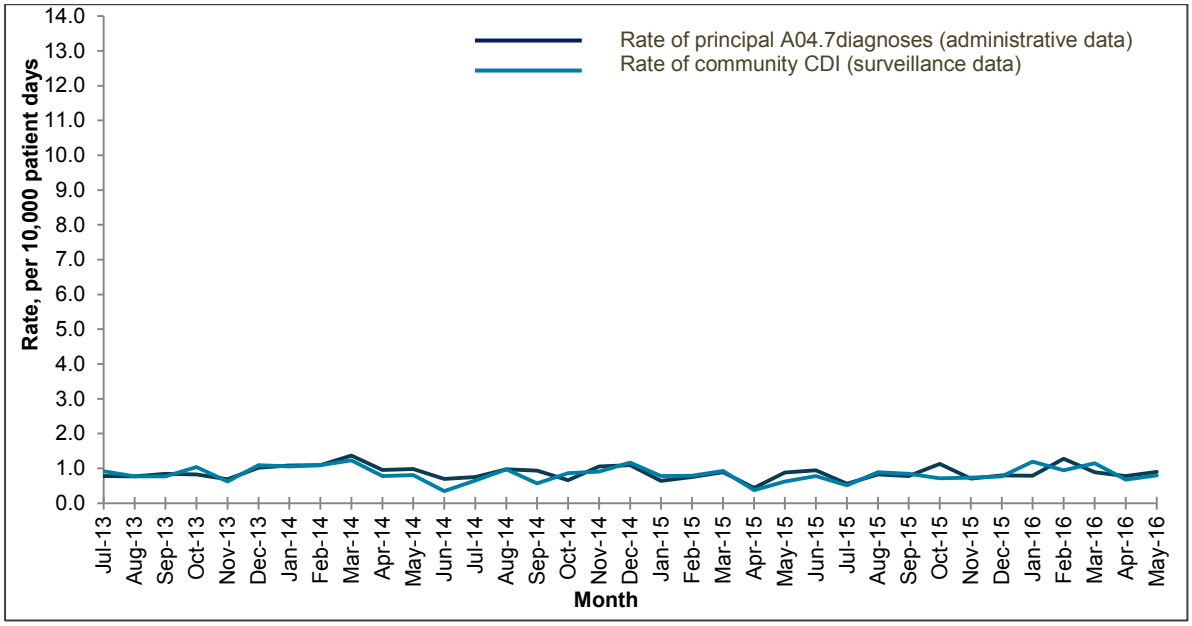


Commentary

The shape of the two datasets is visually comparable. There was regular commonality with regards to the timing of peaks and troughs, however the amplitude of peaks and troughs in the administrative dataset appears to be greater. No points of convergence were observed. There was one instance where administrative data lagged behind admissions data by up to two months; this occurred in between August 2014 and November 2014.

The rate of hospital identified CDI was always lower than the rate of all A04.7 diagnoses across the entire period. The gap between the two datasets is statistically significant ($p<0.05$).

Figure 8. Monthly rates of principal A04.7 diagnoses and community CDI in Queensland, 2013-2016

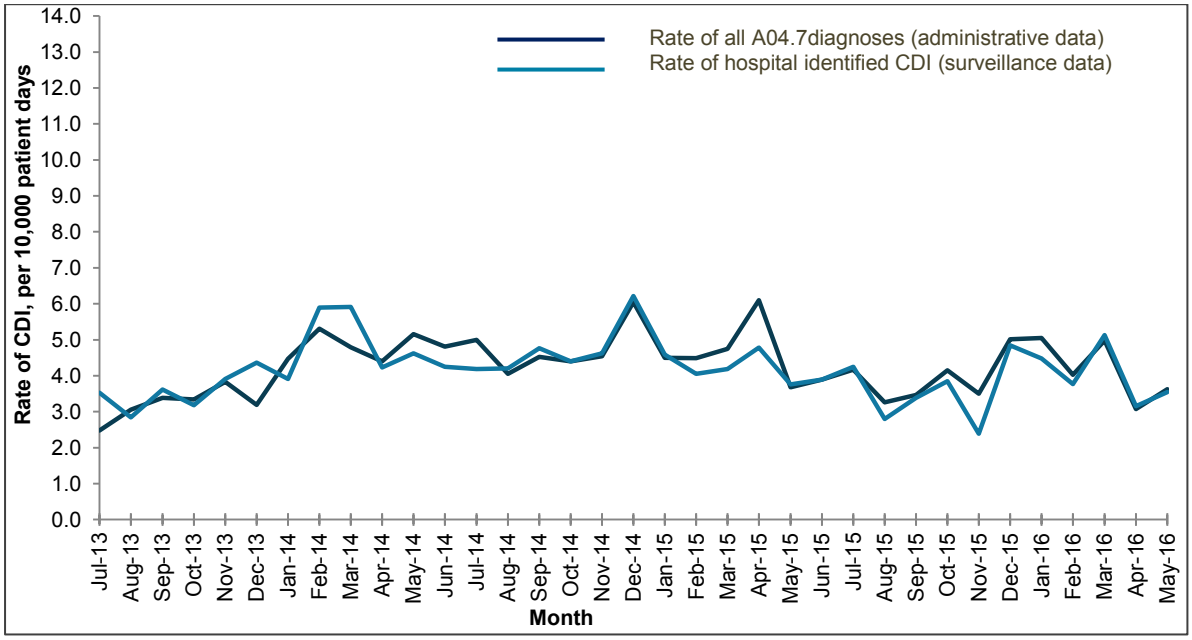


Commentary

Both datasets have relatively flat trends lines. The datasets converge at multiple points during the data period. Low rates are observed in both datasets, oscillating around 1.0 events per 10,000 patient days. There is a high level of similarity between the two datasets, with the difference is *not* statistically significant (p=0.38, p>0.05).

South Australia

Figure 9. Monthly rates of all A04.7 diagnoses and hospital-identified CDI in South Australia, 2013-2016



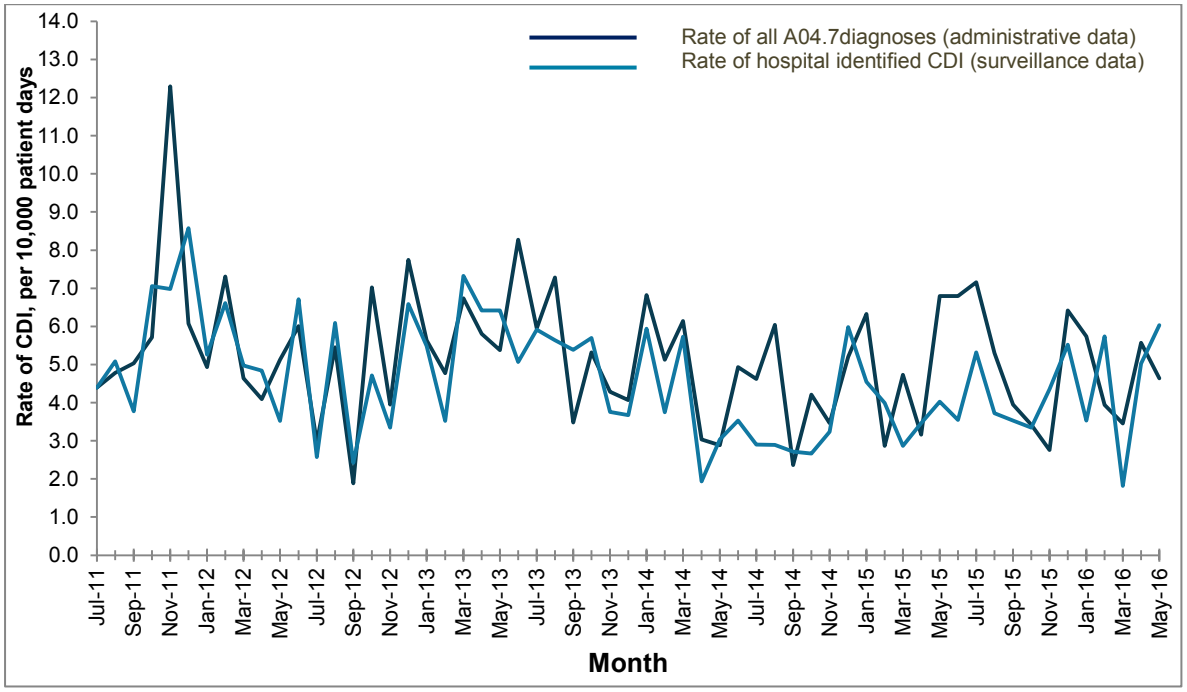
Commentary

The shape of the two datasets is visually comparable. Several points of convergence were observed, including two periods of sustained convergence (October 2014 to January 2015 and May 2015 to July 2015).There was regular commonality between the two data sets with regards to the timing of peaks and troughs.

Overall, the rate of hospital identified CDI is *not* significantly different to rate of all A04.7 diagnoses for this period (p=0.28, p>0.05).

Tasmania

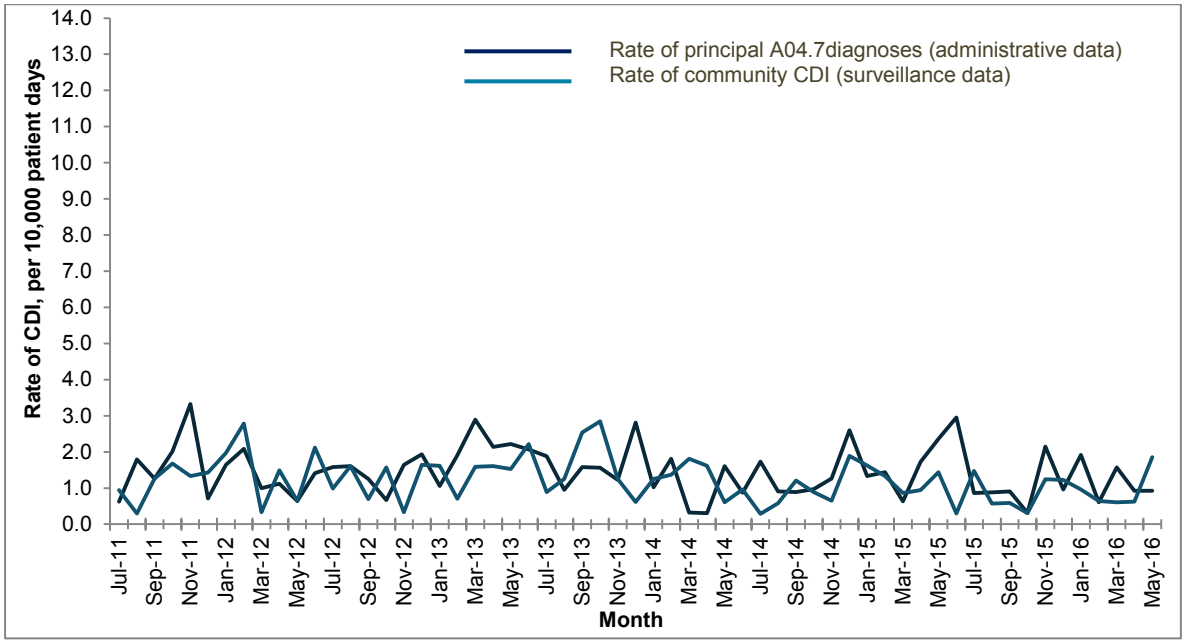
Figure 10. Monthly rates of all A04.7 diagnoses and hospital-identified CDI in Tasmania, 2011-2016



Commentary

There is similarity between the two datasets, characterised by several long periods where the timing of peaks and troughs is well matched (December 2011 to April 2013, October 2013 to April 2014). After May 2014 there appears to be some disparity between the two lines with regards to direction, timing and amplitude. The rate of hospital identified CDI is *not* significantly different to the rate of all A04.7 diagnoses for this period (p=0.06, p>0.05).

Figure 11. Monthly rates of principal A04.7 diagnoses and community CDI in Tasmania, 2011-2016

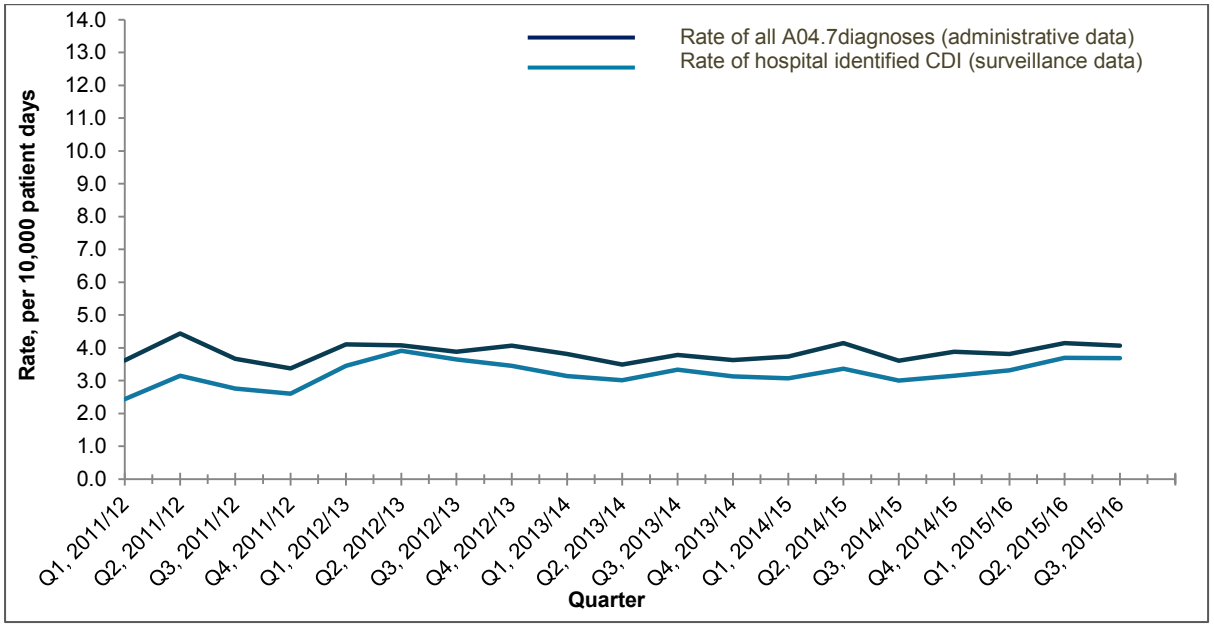


Commentary

The shape of the two datasets is comparable in terms of scale. The difference between the two datasets is significant ($p=0.04$, $p<0.05$) and is likely to be the result of signalling associated with small numbers.

Victoria

Figure 12. Quarterly rates of A04.7 diagnoses and hospital identified CDI in Victoria, 2011-2016

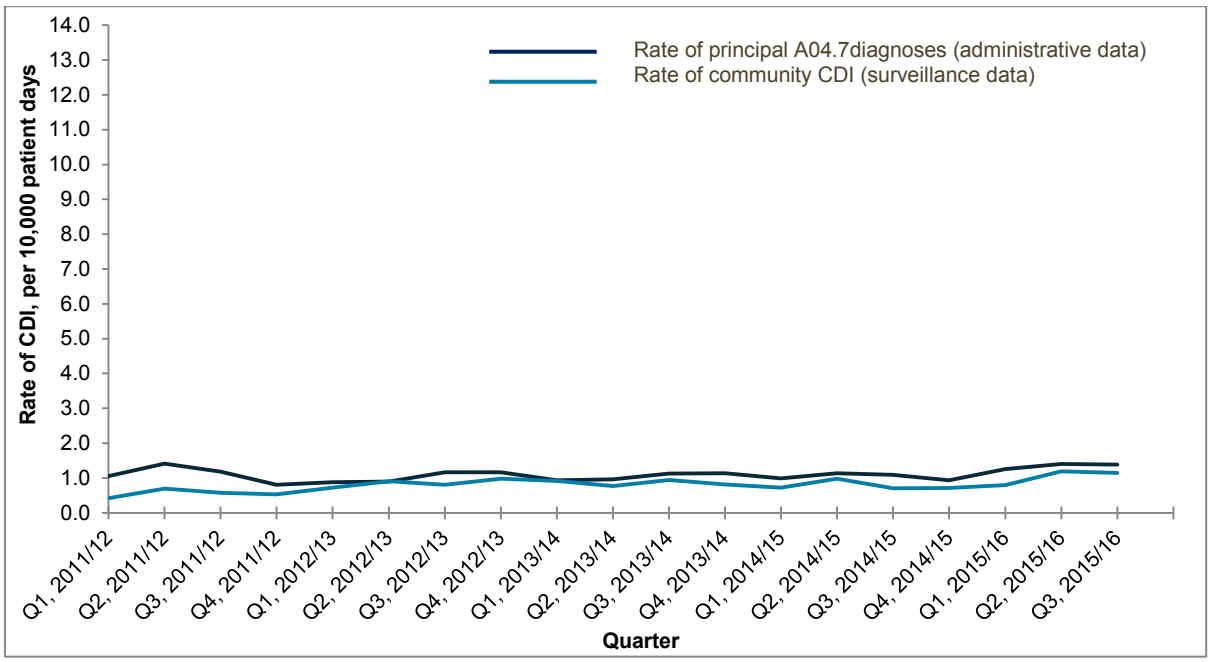


Commentary

Visually, the shape of the two datasets is comparable with regards to landmarks. This is particularly evident at Q2 2011/12, Q4 2011/12, Q2 2013/14, Q2 2014/15 and Q3 2014/15 where both trend lines changed direction at the same time. No points of convergence were observed.

There is some difference in scale, with the administrative data recording more events overall compared to the traditional HAI surveillance data. The gap between the two datasets during the entire data period is statistically significant ($p<0.05$).

Figure 13. Quarterly rates of principal A04.7 diagnoses and community CDI in Victoria, 2011-2016

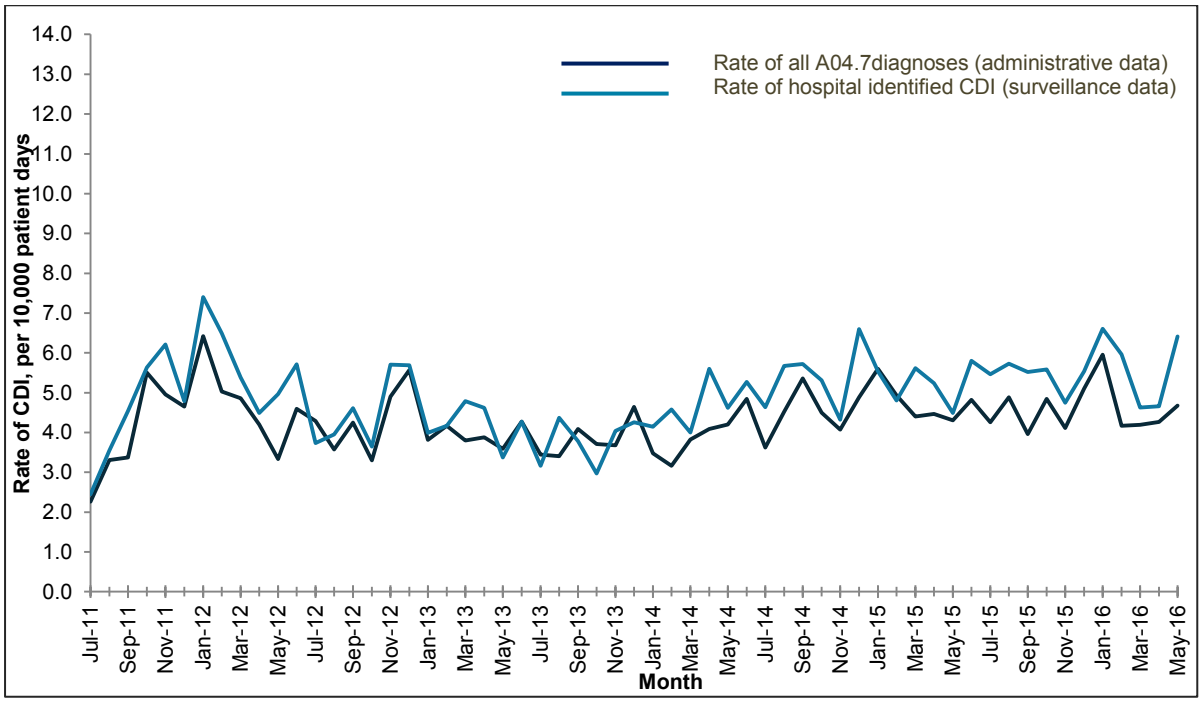


Commentary

The scale of these two datasets is small, at around 1.0 events per 10,000 patients days. The shape of the datasets is relatively flat. The gap between the two datasets for the entire data period is statistically significant ($p<0.05$).

Western Australia

Figure 14. Monthly rates of all A04.7 diagnoses and hospital-identified CDI in Western Australia, 2011-2016



Commentary

There is some similarity between the two datasets, characterised by a number of periods where the timing of peaks and troughs were aligned (December 2012 to March 2012, August 2012 to February 2013, May 2013 to July 2013, May 2014 to December 2014 and September 2015 to January 2016). Short periods of sustained convergence was observed between December 2012 to February 2013, May 2013 to July 2013 and January 2015 to February 2015. In general the rate of hospital-identified CDI was usually greater than the rate of all A04.7 diagnoses; the difference between the rates is statistically significant ($p= 0.00012$, $p<0.05$).

Discussion

Usefulness of administrative data for monitoring CDI rates

Using the data available in the APC-NMDS, the Commission has developed a mechanism to determine and monitor the national prevalence of CDI. This mechanism has enhanced understanding about the burden of CDI across the country. Knowing the national CDI burden enables the identification of critical changes in the spread of *C. difficile* and, in turn, can drive the development and roll out of targeted infection prevention and control and antimicrobial stewardship strategies to counter widespread increases in disease transmission and severity.

The main advantage of using administrative data to monitor CDI prevalence at the national level is that it can be done without causing any additional work burden for the states and territories. National monitoring CDI prevalence using administrative data requires no additional collation of any laboratory-based surveillance data. This is particularly advantageous for the ACT and NT, where there are no centralised surveillance systems in place. Furthermore, the ability to filter administrative data by principal/additional diagnosis code and condition onset flags is useful for identifying exposure, particularly in NSW and WA where exposure classification is not included in state CDI surveillance systems.

The comparability of administrative and the data captured by traditional HAI surveillance was evaluated. Visually, based on the alignment of data landmarks and scale of the data in Figures 6 to 14, there appeared to be a high level of similarity between the two datasets. Despite the visual similarity, the gap between the rate of hospital-identified CDI and the rate of all A04.7 diagnoses was statistically significant ($p<0.05$) in all states except South Australia and Tasmania. Furthermore, the gap between the rate of community CDI and the rate of additional A04.7diagnoses was also statistically significant ($p<0.05$) in Tasmania and Victoria but not in Queensland. It should be noted that there is potential for type 1 errors in these statistical analyses given the small number of CDI cases and diagnoses (i.e. the numerator) identified in each state relative to the size of the at-risk population (i.e. the denominator).

Limitations

This is a preliminary high level analysis of the usefulness of administrative data for monitoring CDI in Australia. Further analysis is required to validate whether administrative data is recording the same cases as the traditional HAI surveillance method. This type of validation requires comparison of individual cases rather than a comparison of aggregate data (which has been done in this report). It is difficult to do this validation at a national level given that data in the APC-NMDS is aggregate data with no individual patient identifiers. Validation may be easier at the state level where individual patient identifiers are maintained.

The utility of administrative data for monitoring and responding to CDI is challenged by two key factors. Firstly, the data available in the APC-NMDS is insufficient to fully illuminate the local epidemiology of CDI. While some risk factors, such as advanced age[25,26], co-morbidity status, and gastrointestinal surgery[48], are available in the APC-NMDS, other factors which are known to contribute to CDI onset, such as antibiotic exposure, residence in long term care[49], immunosuppression or chemotherapy[50], and gastric acid suppressive therapy[51], are either not included or are variably documented in the APC-NMDS. Furthermore, the APC-NMDS captures very little information about the risk factors for community-acquired CDI. This additional epidemiological information is critical for informing the development of targeted infection control strategies to mitigate the spread of CDI.

Secondly, there is a lag time of up to 12 months between the time of an A04.7 diagnosis being documented at the hospital and the time when the data become available for national monitoring. This means that administrative data is not available quickly enough to inform local action and change. Traditional HAI surveillance, on the other hand, provides timely patient-level information which can be used by a healthcare facility to identify the need for practice improvement. In addition, individual hospitals have more timely access to their patient administrative data and can use administrative data to complement other measurement tools to assess the effectiveness of infection control and antimicrobial stewardship activities and identify areas for practice improvement.

Publicly reported state-level infection surveillance data collected in Victoria and Western Australia between 2014 and 2016 indicates that the diagnosis rate of CDI in these jurisdictions is in the range of 3.2 to 4.3 infections per 10,000 patient days.[46, 52] These rates are comparable to the national rate of CDI diagnosis calculated from patient administrative data for the same period (3.8 to 4.3 diagnoses per 10,000 patient days) and indicates congruence between data collected by traditional surveillance methods and data collected in the APC-NMDS. Further work needs to be done, however, to determine whether there is a significant difference between the two datasets and to quantify the case validity, in terms of sensitivity and specificity, of CDI data collected in the APC-NMDS.

Key findings

The rate of CDI diagnosis in Australia

Between 2011 and 2016, the average CDI rate was 4.0 diagnoses per 10,000 patient days. The average CDI rate in year ending in June 2012 (the first year of data) was 4.2 diagnoses per 10,000 patient days whereas the rate in the year ending May 2016 (the last year of data) was 4.0 diagnoses per 10, 0000 patient days. The average CDI diagnosis rate in Australia is comparable to the infection rate reported in the UK in 2015-16, which was 4.1 infections per 10,000 patient days.[53]

There is a considerable resource burden associated with CDI

The average length of stay for separations where CDI was an additional diagnosis (21.6 days) is almost three times longer than average length of stay for separations where CDI was the principal diagnosis (7.9 days). It is difficult to ascertain whether the increased length of stay is directly attributable to the onset of CDI or other non-A04.7 diagnoses. One possible scenario is that the treatment of a non-A04.7 principle diagnosis (e.g. use of proton pump inhibitors and antibiotics) may promote the onset of CDI and that other additional non-A04.7 diagnoses or other clinical factors may further exacerbate the clinical impact of CDI.

The average length of stay associated with any A04.7 diagnoses was 16.9 days.
A recent study that use administrative data to look at the epidemiology of CDI within a smaller cohort of Australian patients estimated a similar length of stay of 17 days.[54] Further risk-adjustment is however, necessary to determine why the length of stay associated with CDI is longer.

The rate of severe CDI is low but it is increasing

The estimated rate of severe CDI in Australia is equivalent to 113 cases per year. Severe CDI is likely to represent less than 2% of all CDI cases seen in Australian hospitals, suggesting the vast majority of cases are likely to be characterised as *C. difficile* diarrhoea or colitis only. Based on the data collected in Victoria, the rate of severe disease has been

slowly increasing since 2012. Despite the increasing rate of severe disease, the mortality rate associated with severe disease has not increased.

Analysis of the severity data provided by VICNISS indicates that the proportion of CDI cases where severe disease has resulted in death is 0.7% (46/6566). This proportion is much smaller than the 7.3% mortality rate reported in recent Australian study that analysed patient administrative data.[54] There are several possible reasons for this disparity. It is possible that the majority of deaths associated with CDI may not be related to severe disease or death may occur before severe disease can be classified. Alternatively, this recent study was focussed on examining the incidence of CDI in a smaller cohort of individuals aged over 45 years old with high levels of comorbidity (65% of hospitalisations in this group had principal diagnoses related to digestive, cardiovascular, neoplasm or respiratory disease). This study also found that mortality was more likely to be associated with an additional A04.7 diagnosis than a principal A04.7 diagnosis. The authors of this study also pointed out that the study population may not be representative of the broader population requiring hospitalisation.

The mortality rate associated with severe CDI in Victoria is much lower than the mortality rate of other countries where the spread of severe CDI has become endemic. For example, the proportion of CDI associated with death is 6.46% in the United States.[55] In the United Kingdom the proportion of CDI associated with death is higher at 15.15%[56], however this proportion is based on all-cause mortality and may be a liberal estimation of the proportion of deaths attributable to CDI. Despite severe disease not yet being endemic in Australia, ongoing effort is needed across the country to maintain low rates of severe disease and mortality.

Pre-existing cases of CDI make up the majority of CDI found in Australian hospitals

The ability to filter administrative data by principal or additional diagnosis code and by condition onset flags has been useful for determining the burden of CDI directly attributable the health care delivery. The acquisition of CDI was attributed to health care delivery in 24.9% of separations where an A04.7 diagnosis was assigned. The remaining separations reflect acquisition prior to hospitalisation, either in the community or during a prior episode of care.

It is possible, in some instances, that hospital-acquired CDI may be the result of transmission from patients who have presented to hospital with pre-existing CDI. Confirming this hypothesis may be difficult given that additional data from strain typing and genome sequencing provides little clarity on the source of CDI in hospitals.[57] Should this hypothesis be proven, targeted infection control strategies, such as admission screening and early isolation[58, 59], may be necessary to prevent spread from pre-existing cases and reduce the burden of CDI acquired in hospital.

There is potential that the higher burden of pre-existing CDI is related to CDI transmission in the community. CDI transmission in the community may be a by-product of the high rates of antimicrobial prescribing and usage in the community.[60] The establishment of effective antimicrobial stewardship programs in community settings may have a strong effect in reducing the overall prevalence of CDI found in Australian hospitals. In lieu of no data available to confirm a direct link between antimicrobial usage and CDI rates in the community, it may be useful to measure the rate of community-acquired CDI in the evaluation of any antimicrobial stewardship effort undertaken in the community.

Future directions

1. Ongoing monitoring at a national level

It is recommended that administrative data be used at a national level on an ongoing basis to monitor the prevalence of CDI for informing on the relative increases and decreases in CDI prevalence.

Comparisons between administrative and traditional HAI surveillance datasets indicates that administrative data does reflect the same trends and landmarks as data collected through traditional HAI surveillance. This analysis has shown that administrative data for CDI is comparable to CDI surveillance data and may be useful in informing on the relative increases and decreases in CDI prevalence in the absence of a national CDI surveillance system.

Monitoring specifications

Several parameters for the ongoing monitoring of CDI administrative data have been considered. In order to develop a suitable mechanism for monitoring, options for data intervals, acceptability thresholds and data monitoring periods were applied to the three coding scenarios: all A04.7 diagnoses (presented in this report), principal A04.7 diagnoses and non-principal A04.7 diagnoses. Each scenario was modelled using data relevant to whole of country as well as a single state (Western Australia).

Data intervals

Recommended specification: Quarterly data intervals should be used for analysis

Earlier work examined whether a 12-month data interval was adequate for monitoring the national prevalence of CDI. This work indicated that a 12 month period was not sensitive enough to demonstrate seasonal changes in disease prevalence, which is important given that seasonality has an effect on the volume of CDI transmission.[46, 61]

As such, the use of monthly or quarterly data intervals was subsequently modelled (Figures 15 and 16). Use of a monthly data interval identified more events occurring outside of or nearing the control limits. These events were often single-point events (for example the peak at October-January 2013 and trough at April 14 in Figure 15). In comparison, use of a quarterly data interval was sensitive enough to identify sustained changes in in epidemiology (for example the peak in Q4, 2011and trough in Q2, 2011 in Figure 16) but robust enough to filter out single-point events.

Figure 15. Monthly rate of all A04.7 diagnoses, Australia 2011-16

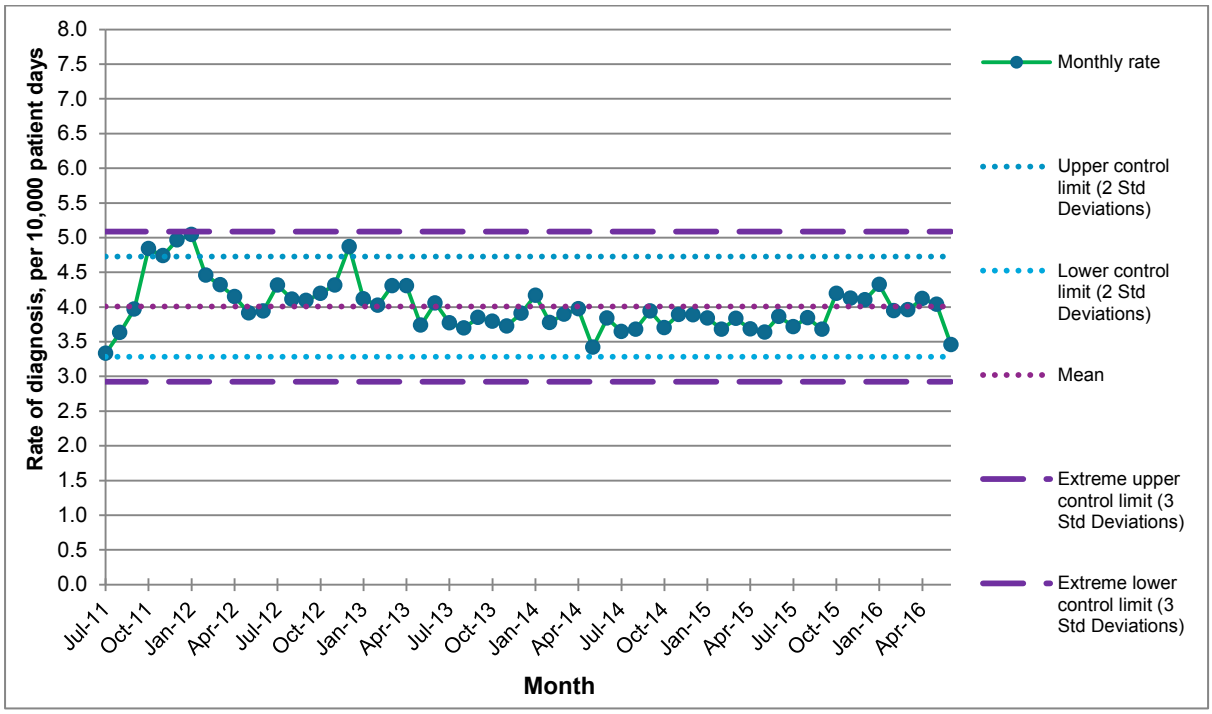
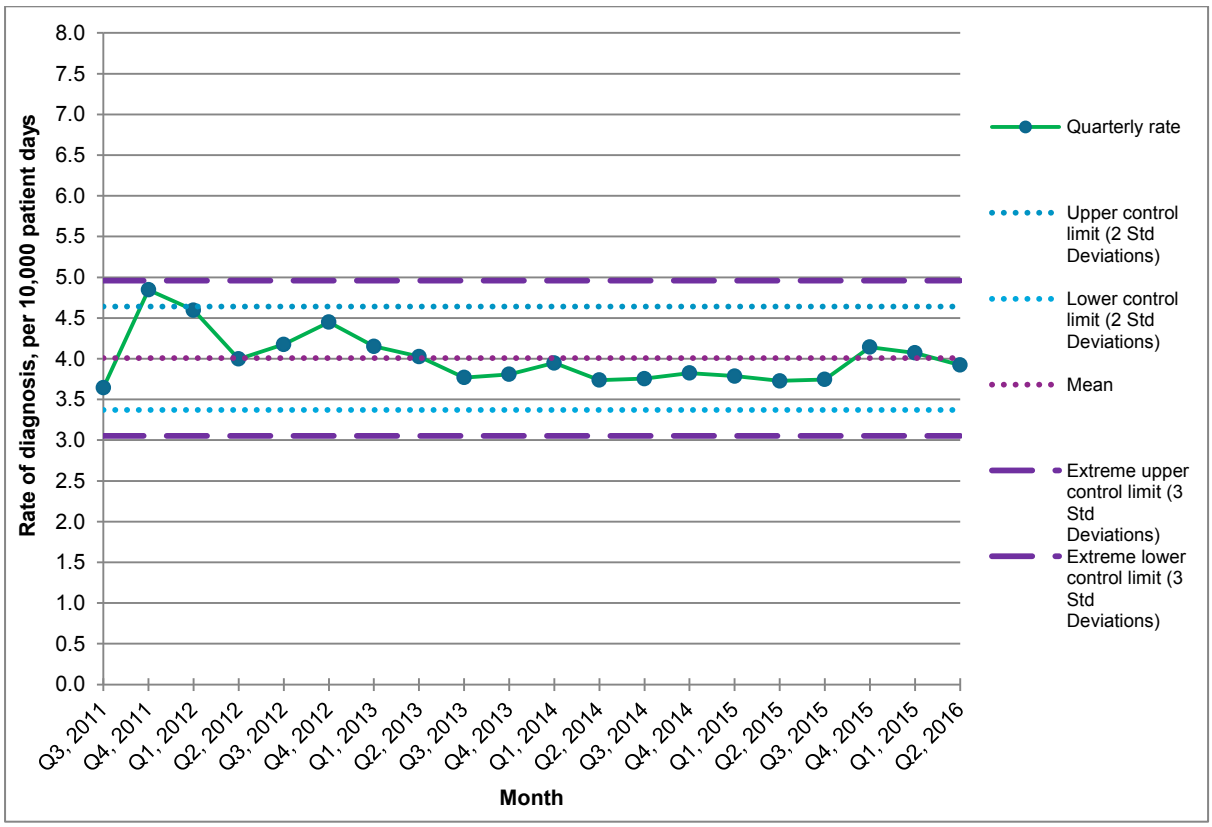


Figure 16. Quarterly rate of all A04.7 diagnoses, Australia 2011-16



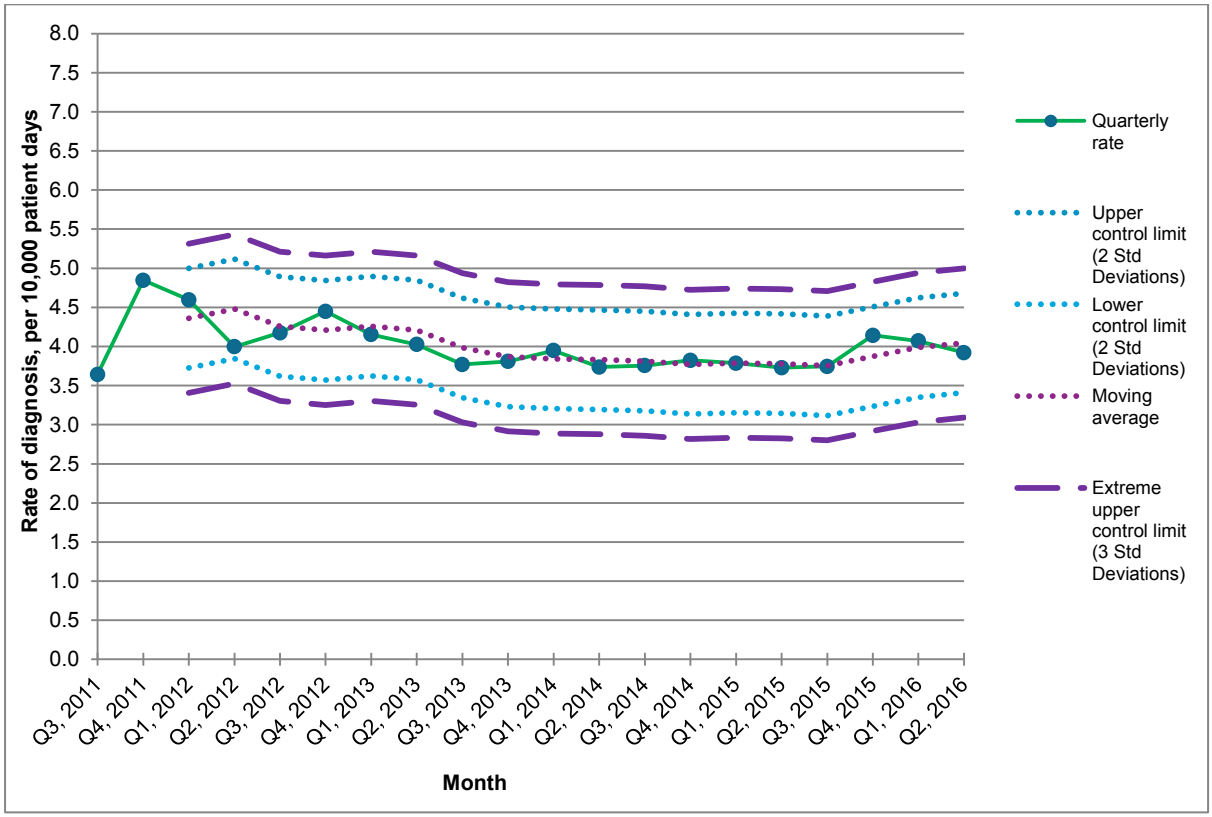
Data averages and control limits

Recommended specification: Data averages and control limits should be based on the entire data period

Date averages and control limits were modelled using two approaches. The first approach was to calculate the data average and control limits using the entire data period, as seen in Figure 16. The second approach was to calculate a three-monthly moving average and to use the three-monthly moving average to calculate moving control limits. This approach is illustrated in Figure 17.

Rolling averages and control limits resulted in the data line being closer to the average rate than what was observed when static averages and control limits were used. This 'normalising' effect limits the usefulness of rolling averages and control limits for identifying critical changes in CDI prevalence.

Figure 17. Quarterly rate of all A04.7 diagnoses using a three monthly moving average and control limits, Australia 2011-16



Data monitoring period

Recommended specification: A data monitoring period of three years should be used.

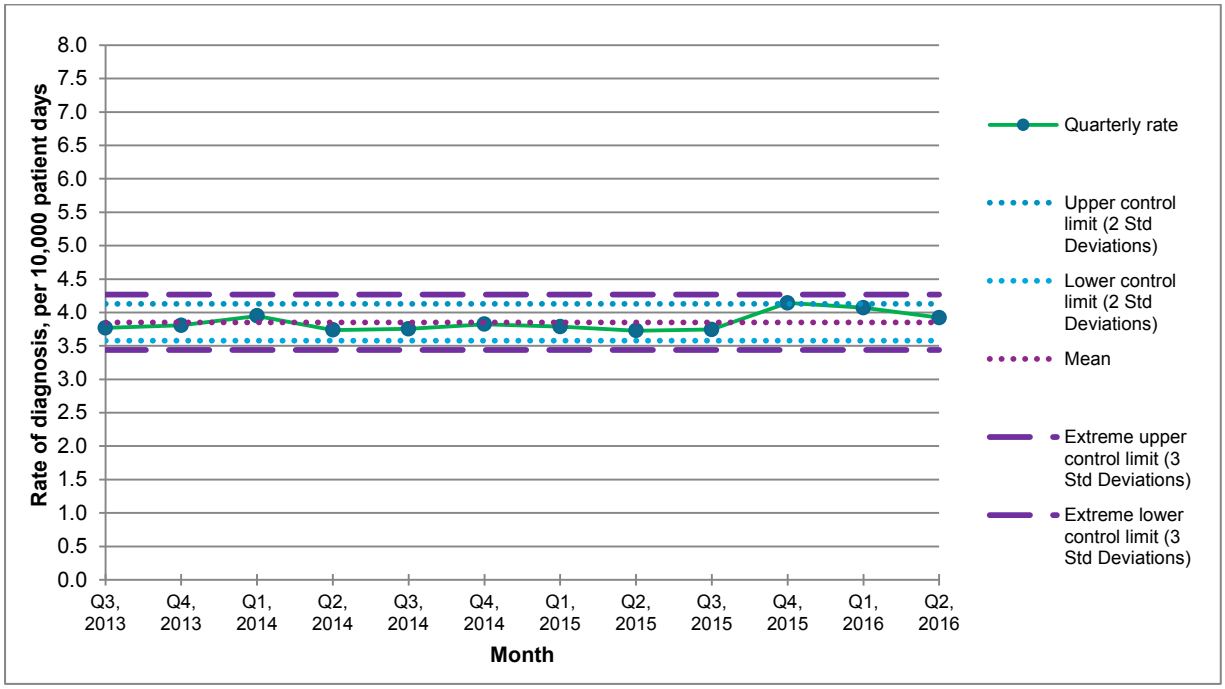
An alternative model was developed to test the effect of modelling data over a shorter period of three years instead of the whole period for which data was available, as seen in Figure 17. This alternative model is presented in Figure 18.

There are two key factors that support the use a three year data period:

- The reliability of administrative data has increased over time meaning that data collected from 2013 onwards is more reliable than data collected prior to 2013
- Data measures, such as the average mean and control limits, reflect more recent data trends and are less dominated by earlier historical events.

Tighter control limits were generated when a three year data period was used as the shorter dataset excluded the historical peaks that occurred in 2011 and 2012. As a result of these tighter controls, additional risk points at Q4 2015 and Q1 2016 were identified. This alternative approach has demonstrated the increased sensitivity that occurs when analysis is limited to a shorter but more recent dataset.

Figure 18. Quarterly rate of all A04.7 diagnoses, Australia Q3 2013 to Q2 2016



Coordinating responsibility

It is recommended that the Commission monitor the national CDI prevalence using the specifications described above. Changes in surveillance, laboratory diagnosis or coding procedures related to *Clostridium difficile* infection may affect the comparability between administrative data and laboratory-based surveillance data. The Commission should review the impact of these changes on the comparability between administrative data and traditional HAI surveillance data. To enable this comparison, states will need to provide traditional HAI surveillance data (i.e. counts of hospital identified CDI and if collected, exposure classification) to the Commission if such changes occur.

2. Local surveillance and exposure classification

It is recommended that health services continue to use traditional HAI surveillance and exposure classification processes to monitor and respond to local CDI trends.

The detection of CDI in a health service requires an immediate infection prevention and control response. Traditional HAI surveillance remains the timeliest way for health services to get information about the incidence of CDI in their facilities in order to inform the direction and magnitude of infection prevention and control efforts. Therefore, surveillance of hospital-identified CDI should be continued by all health services.

All health services are encouraged to undertake enhanced surveillance of CDI (i.e. severity surveillance and exposure classification), however it is recognised that this process is time-consuming and often requires considerable resources. To encourage more health services to undertake enhanced surveillance, it is suggested that the surveillance of severe disease is prioritised over exposure classification, as severity surveillance can provide useful information for improving local case management and resource allocation. Exposure classification, however, should be considered if sudden changes in the rate of hospital-identified CDI are identified or if a CDI outbreak occurs.

States and territories should continue to support local health services in carrying out hospital-identified CDI surveillance and enhanced surveillance in line with the *Implementation Guide for Surveillance of Clostridium difficile Infection.*[26]

Acknowledgements

The Commission would like to acknowledge the contributions made by the following individuals and agencies in the preparation of this report:

Dr Lisa Hall, Queensland University of Technology
Dr Philip Russo, Deakin University
Associate Professor Brett Mitchell, Avondale College of Higher Education
Dr Andrew Stewardson, The Alfred Hospital and Monash University
Clinical Excellence Commission, NSW
Healthcare Associated Infection Unit, Communicable Disease Control Directorate, Western Australia
Department of Health, Queensland
SA Health Infection Control Service
Public Health Services, Department of Health and Human Services, Tasmania
VICNISS Healthcare Associated Infection Surveillance Coordinating Centre

Appendix 1

Table 6. International CDI incidence rates, 2012-2016

Country	CDI Incidence Rate, per 10,000 patient days				
	2012	2013	2014	2015	2016
Austria[62]		3.2			
Belgium[62]		2.7			
Denmark[62]		5.3			
Estonia[62]		1.2			
Finland[62]		4.4			
France[62]		3.8			
Germany[62]		3.6			
Hungary[62]		14.9			
Netherlands[62]		1.9			
Norway[62]		1.9			
Poland[62]		7.6			
Romania[62]		6.7			
Scotland[63] 15-64 yrs 65+yrs	 3.69 3.78	 3.45 3.50	 3.30 3.45	 3.82 3.12	 3.30 2.59
Serbia		10.0			
United Kingdom[53]	4.27 (FY12/13)	3.89 (FY13/14)	4.08 (FY14/15)	4.09 (FY15/16)	3.67 (FY16/17)
United States*[64]	14.6**	14.2**	14.2**	14.9**	-
Wales ENREF 65[65]	6.29 (FY12/13)	5.11 (FY13/14)	4.26 (FY14/15)	4.01 (FY15/16)	3.38* (FY16/17)

* Based on 10 US States

**Cases per 10,000 people in the population, not patient days

References

1. NICE. Clostridium difficile infection: risk with broad-spectrum antibiotics. [Online] 2015 [cited 31 July 2017]; Available from: https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence.
2. Lawson PA, Citron DM, Tyrrell KL and Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prévot 1938. *Anaerobe*. 2016; 40: 95-9.
3. Bloomfield LE and Riley TV. Epidemiology and risk factors for community-associated *Clostridium difficile* infection: A narrative review. *Infectious Diseases and Therapy*. 2016; 5: 231-51.
4. Awad MM, Johanesen PA, Carter GP, Rose E and Lyras D. *Clostridium difficile* virulence factors: Insights into an anaerobic spore-forming pathogen. *Gut Microbes*. 2014; 5: 579-93.
5. Abt MC, McKenney PT and Pamer EG. *Clostridium difficile* colitis: pathogenesis and host defence. *Nature Reviews Microbiology*. 2016; 14: 609-20.
6. Natarajan M, Walk ST, Young VB and Aronoff DM. A clinical and epidemiological review of non-toxigenic *Clostridium difficile*. *Anaerobe*. 2013; 22: 1-5.
7. Gerding DN, Johnson S, Rupnik M and Aktories K. *Clostridium difficile* binary toxin CDT: Mechanism, epidemiology, and potential clinical importance. *Gut Microbes*. 2014; 5: 15-27.
8. Aktories K, Schwan C and Jank T. *Clostridium difficile* Toxin Biology. *Annual Review of Microbiology*. 2017; 28: 090816-3458.
9. Pilate T, Verhaegen J, Van Ranst M and Saegeman V. Binary toxin and its clinical importance in *Clostridium difficile* infection, Belgium. *European Journal of Clinical Microbiology & Infectious Diseases*. 2016; 35: 1741-7.
10. Hensgens MPM and Kuijper EJ. *Clostridium difficile* infection caused by binary toxin–positive strains. *Emerging Infectious Diseases*. 2013; 19: 1539-40.
11. Napolitano LM and Edmiston CE. *Clostridium difficile* disease: Diagnosis, pathogenesis, and treatment update. *Surgery*. 2017; 162: 325-48.
12. Trubiano JA, Cheng AC, Korman TM, et al. Australasian Society of Infectious Diseases updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New Zealand. *Internal Medicine Journal*. 2016; 46: 479-93.
13. Henrich TJ, Krakower D, Bitton A and Yokoe DS. Clinical risk factors for severe *Clostridium difficile*–associated disease. *Emerging Infectious Diseases*. 2009; 15: 415-22.
14. Kachrimanidou M and Malisiovas N. *Clostridium difficil*e infection: A comprehensive review. *Critical Reviews in Microbiology*. 2011; 37: 178-87.
15. Cohen SH, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infection Control and Hospital Epidemiology*. 2011; 31: 431-55.
16. Aslam S, Hamill RJ and Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. *The Lancet Infectious Diseases*. 2005; 5: 549-57.
17. Therapeutic Guidelines. Antibiotic-associated diarrhoea. [Online] 2015 [cited 31 July 2017]; Available from: https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Antibiotic&topicfile=acute-gastroenteritis&guidelineName=Antibiotic&sectionId=toc_d1e798#toc_d1e798.
18. Dubberke ER, Carling P, Carrico R, et al. Strategies to prevent *Clostridium difficile* infections in acute care hospitals: 2014 update. *Infection and Hospital Epidemiology*. 2014; 35: S48-S65.
19. Patton A, Davey P, Harbarth S, Nathwani D, Sneddon J and Marwick CA. Impact of antimicrobial stewardship interventions on *Clostridium difficile* infection and clinical outcomes: segmented regression analyses. *Journal of Antimicrobial Chemotherapy*. 2017; *ePub*.
20. Lieberman JM. Appropriate antibiotic use and why it is important: the challenges of bacterial resistance. *Pediatric Infectious Diseases Journal*. 2003; 22: 1143-51.
21. National Health and Medical Research Council and Australian Commission on Safety and Quality in Health Care. Australian Guidelines for the Prevention and Control of Infection in Healthcare. [Online] 2010 [cited 9 October 2017]; Available from: http://www.nhmrc.gov.au/guidelines/publications/cd33.
22. Hanley E and Quoyle C. Approaches to surveillance of *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection in Australian states and territories. *Healthcare Infection*. 2015; 19: 141-6.
23. Australian Commission on Safety and Quality in Health Care. Consultation on surveillance and monitoring of Clostridium difficile infection in Australia. Discussion paper. [Online] 2015 [cited 17

May 2017]; Available from: https://www.safetyandquality.gov.au/wp-content/uploads/2015/05/Surveillance-and-Monitoring-of-CDI-in-Australia-April-2015.pdf.
24. Australian Commission on Safety and Quality in Health Care. Surveillance and monitoring of *Clostridium difficile* infection in Australia. [TRIM record] 2015 [cited 1 August 2017]; Available from: D15-32398.
25. Australian Commission on Safety and Quality in Health Care. Inter Jurisdictional Committee Meeting 39. Agenda Item 8.4. Update on the consultation on surveillance and monitoring of *Clostridium difficile* infection in Australia. [TRIM record] 2015 [cited 1 August 2017]; Available from: D16-7912.
26. Australian Commission on Safety and Quality in Healthcare. Implementation Guide for Surveillance of *Clostridium difficile* infection. [Online] 2013 [cited 1 August 2017]; Available from: https://www.safetyandquality.gov.au/wp-content/uploads/2012/02/1303-CDI-Implementation_Guide-_V10.pdf.
27. Council of Australian Governments. National Health Reform Agreement. [Online] 2011 [cited 1 August 2017]; Available from: http://www.federalfinancialrelations.gov.au/content/npa/health/_archive/national-agreement.pdf.
28. Australian Institute of Health and Welfare. Performance and Accountability Framework. [Online] 2011 [cited 1 August 2017]; Available from: http://www.aihw.gov.au/health-performance/performance-and-accountability-framework/.
29. Australian Commission on Safety and Quality in Health Care. National Survey of *Clostridium difficile* infection. [TRIM record: 63462] 2012 [cited 25 August 2017]; Available from.
30. Australian Commission on Safety and Quality in Health Care. National Safety and Quality Health Service Standards. [Online] 2012 [cited 9 October 2017]; Available from: https://www.safetyandquality.gov.au/wp-content/uploads/2011/09/NSQHS-Standards-Sept-2012.pdf.
31. O'Connor JR, Johnson S and Gerding DN. *Clostridium difficile* infection caused by the epidemic BI/NAP1/027 Strain. *Gastroenterology*. 2009; 136: 1913-24.
32. Valiente E, Cairns MD and Wren BW. The Clostridium difficile PCR ribotype 027 lineage: a pathogen on the move. *Clinical Microbiology and Infection*. 2014; 20: 396-404.
33. Freeman J, Bauer MP, Baines SD, et al. The changing epidemiology of *Clostridium difficile* infections. *Clinical Microbiology Reviews*. 2010; 23: 529-49.
34. Health Protection Agency and Department of Health. *Clostridium difficile* infection: How to deal with the problem. [Online] 2008 [cited Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/340851/Clostridium_difficile_infection_how_to_deal_with_the_problem.pdf.
35. Public Health England. *C. difficile* infections: quarterly counts by acute trust and CCG, and financial year counts and rates by acute trust and CCG, up to financial year 2016 to 2017 (Table 8a: Financial year counts and rates of *C. difficile* infection (patients aged 2 years and over)) - All reported cases. [Internet] 2017 [cited 19 January 2018]; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/625307/C_difficile_annual_tables_2017.ods.
36. Knight DR, Giglio S, Huntington PG, et al. Surveillance for antimicrobial resistance in Australian isolates of *Clostridium difficile*, 2013-14. *Journal of Antimicrobial Chemotherapy*. 2015; 70: 2992-9.
37. Eyre DW, Tracey L, Elliott B, et al. Emergence and spread of predominantly community-onset *Clostridium difficile* PCR ribotype 244 infection in Australia, 2010 to 2012. *Euro Surveillance*. 2015; 20: 21059.
38. Australian Institute of Health and Welfare. Admitted patient care NMDS 2016-17. [Online] 2016 [cited 4 August 2017]; Available from: http://meteor.aihw.gov.au/content/index.phtml/itemId/612171.
39. Independent Hospital Pricing Authority. Data Collection. [Online] 2017 [cited 4 August 2017]; Available from: https://www.ihpa.gov.au/what-we-do/data-collection.
40. *ICD-10-AM/ACHI/ACS.* 9th ed. 2015.
41. Australian Institute of Health and Welfare. Principal diagnosis data cubes [http://www.aihw.gov.au/hospitals-data/principal-diagnosis-data-cubes/] 2017 [cited Available from.
42. Australian Institute of Health and Welfare. Episode of admitted patient care - condition onset flag, code N. [Online] 2016 [cited 4 August 2017]; Available from: http://meteor.aihw.gov.au/content/index.phtml/itemId/496512.

43. Independent Hospital Pricing Authority. Risk adjustment model for Hospital Acquired Complications - Technical Specifications. [Online] 2017 [cited 15 December 2017]; Available from: https://www.ihpa.gov.au/sites/g/files/net636/f/risk_adjustment_model_for_hospital_acquired_complications_-_technical_specifications_v1.0_july_2017_pdf.pdf.
44. Australian Commission on Safety and Quality in Health Care. National definition and calculation of Hospital identified *Clostridium difficile* infection. [Internet] 2012 [cited 23 October 2017]; Available from: https://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/national-hai-surveillance-initiative/national-definition-and-calculation-of-hospital-identified-clostridium-difficile-infection/.
45. Australian Institute of Health and Welfare. Establishment - number of patient days, total N [N(7)]. [Online] 2005 [cited 2018]; Available from: http://meteor.aihw.gov.au/content/index.phtml/itemId/270045.
46. Worth LJ, Spelman T, Bull AL, Brett JA and Richards MJ. Epidemiology of *Clostridium difficile* infections in Australia: enhanced surveillance to evaluate time trends and severity of illness in Victoria, 2010-2014. *Journal of Hospital Infection*. 2016; 93: 280-5.
47. Bull AL, Worth LJ and Richards MJ. Implementation of standardised surveillance for *Clostridium difficile* infections in Australia: initial report from the Victorian Healthcare Associated Infection Surveillance System. *Internal Medicine Journal*. 2012; 42: 715-8.
48. National Health Performance Authority. MyHospitals. In: MyHospitals. 2015. http://www.myhospitals.gov.au. Accessed 9th March 2015.
49. Fisher A and Varendran R. Letter: clinical predictors of *Clostridium difficile* infection – advanced age and residential status are important factors for prediction and prevention. *Alimentary Pharmacology & Therapeutics*. 2014; 41: 232-7.
50. Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. *Annals of Internal Medicine*. 2006; 145: 758-64.
51. Trifan A, Stanciu C, Girleanu I, et al. Proton pump inhibitors therapy and risk of *Clostridium difficil*e infection: Systematic review and meta-analysis. *World Journal of Gastroenterology*. 2017; 23: 6500-15.
52. HISWA. Healthcare Infection Surveillance Western Australia Annual Report 2015-16. [Online] 2016 [cited 2018]; Available from: http://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Infectious%20diseases/PDF/HISWA/AR-2015-16-Final-10072017-updated.pdf.
53. Public Health England. *C. difficile* infections: quarterly counts by acute trust and CCG, and financial year counts and rates by acute trust and CCG, up to financial year 2016 to 2017. [Online] 2017 [cited 2 August 2017]; Available from: https://www.gov.uk/government/statistics/clostridium-difficile-infection-annual-data.
54. Chen Y, Glass K, Liu B, Korda RJ, Riley TV and Kirk MD. Burden of C*lostridium difficile* infection: associated hospitalization in a cohort of middle-aged and older adults. *American Journal of Infection Control*. 2017: *In Press*.
55. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *New England Journal of Medicine*. 2015; 372: 825-34.
56. Public Health England. Thirty-day all-cause fatality subsequent to MRSA, MSSA and *E.coli* bacteraemia and *C.difficile* infection, 2016/17. [Online] 2017 [cited 16 June 2017]; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/637436/HCAI_thirty_day_all_cause_fatality_report_2016_2017.pdf.
57. Eyre DW, Cule ML, Wilson DJ, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *New England Journal of Medicine*. 2013; 369: 1195-205.
58. Longtin Y, Paquet-Bolduc B, Gilca R, et al. Effect of detecting and isolating *Clostridium difficile* carriers at hospital admission on the incidence of *C. difficile* infections: a quasi-experimental controlled study. *JAMA Internal Medicine*. 2016; 176: 796-804.
59. Maghdoori S and Moghadas SM. Assessing the effect of patient screening and isolation on curtailing *Clostridium difficile* infection in hospital settings. *BMC Infectious Diseases*. 2017; 17: 384.
60. Australian Commission on Safety and Quality in Health Care. AURA 2017 Second Australian report on antimicrobial use and resistance in human health. [Online] 2017 [cited 10 August 2017]; Available from: https://www.safetyandquality.gov.au/publications/second-australian-report-on-antimicrobial-use-and-resistance-in-human-health/.

61. Furuya-Kanamori L, McKenzie SJ, Yakob L, et al. *Clostridium difficile* infection seasonality: patterns across hemispheres and continents - a systematic review. *PLoS One*. 2015; 10: e0120730. doi: 10.1371/journal.pone.. eCollection 2015.
62. van Dorp SM, Kinross P, Gastmeier P, et al. Standardised surveillance of *Clostridium difficile* infection in European acute care hospitals: a pilot study, 2013. *Eurosurveillance*. 2016; 21: pii=30293.
63. Health Protection Scotland. Healthcare Associated Infection. Annual Report 2016. [Online] 2016 [cited 2 August 2017]; Available from: http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=5934.
64. Centers for Disease Control and Prevention. *Clostridium difficile* Infection (CDI) Tracking. [Online] 2015 [cited 13 February 2018]; Available from: https://www.cdc.gov/hai/eip/clostridium-difficile.html.
65. Public Health Wales. *Clostridium difficile* and *Staphylococcus aureus* bacteraemia Surveillance Update. [Online] 2017 [cited 2 August 2017]; Available from: http://www.wales.nhs.uk/sites3/page.cfm?orgid=379&pid=67899.