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Research Article

Clostridium difficile Infection: Incidence in an Australian Setting

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SUMMARY

Purpose: The aim of this study is to determine the incidence of *Clostridium difficile* infection (CDI) in an Australian hospital and highlight considerations for other Asian countries that are considering establishing or modifying existing CDI surveillance programs.
Methods: An observational study design with dynamic population was used. Data from all persons hospitalized for more than 48 hours over 4 years in a tertiary hospital in Australia were analyzed. Persons with healthcare associated, healthcare facility onset CDIs were identified. The calculation of the relative risk was performed to compare the occurrence of CDI in different groups.
Results: Of the total 58,942 admissions examined, 158 admissions had CDI. The incidence of CDI per 1,000 admissions for the entire study period was 2.68 (95% confidence interval [2.28, 3.13]). There was a statistically significant increase in the incidence of CDI in 2010 compared to that of 2007 ($p < .001$). The incidence of CDI increased from the 30–39-year age group onwards.
Conclusion: Comparisons between this study and others are challenging due to the lack of standardized definitions for CDI internationally. Noting the increases of CDI internationally and the associated mortality, there is increasing importance to monitor and report the incidence of this infection worldwide.
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Introduction

Clostridium difficile, a bacterium that is a common cause of diarrhea in hospitalized patients, can cause a variety of infections, ranging from mild diarrhea to pseudomembranous colitis. The incidence and severity of *C. difficile* infection (CDI) is increasing around the world, particularly in the northern hemisphere (Collins, Hawkey, & Riley, 2013). The primary mode of transmission of *C. difficile* is person to person via the fecal-oral route (National Health and Medical Research Council, 2010). *C. difficile* can exist in vegetative or spore form, with spores acting as a reservoir for transmission, particularly in the healthcare environment via the healthcare workers' hands (Dumford, Nerandzic, Eckstein, & Donskey, 2009; Stuart & Marshall, 2011). The ingestion of the organism does not necessarily result in infection due to the protective effects of the colonic flora (Cartman, Heap, Kuehne, Cockayne, & Minton, 2010). Disruption of the normal flora can occur following exposure to antibiotics, chemotherapy, antiperistaltic drugs, and gastroenterological surgery (Cartman et al., 2010; Kassavin, Pham, Pascarella, Yen-Hong, & Goldfarb, 2013; Kuijper, Coignard, & Tull, 2006). Antibiotics are thought to be an important risk factor for CDI, with a large number of studies supporting the association between antibiotics and CDI (Pepin, Valiquette, & Cossette, 2005; Polgreen et al., 2007; Thomas, Stevenson, & Riley, 2003).

Diagnosis of CDI occurs through the testing of fecal samples at a microbiology laboratory. The laboratory diagnosis of CDI is made through the detection of *C. difficile* by culture and/or by detection of its toxins. Treatment for symptomatic CDI usually involves stopping the use of antibiotics where possible and/or prescribing either vancomycin or metronidazole. Prevention of CDI primarily consists of three elements. First, appropriate antibiotic usage, including correct administration, is important. Second, early instigation and continued use of CDI prevention and control strategies, such as isolation of symptomatic persons, can assist in preventing the spread within a healthcare environment. Third, ensuring high standards of environmental cleanliness in healthcare settings can assist in the prevention and control of CDI (Van Gessel, Riley, & McGregor, 2009). Nurses play a key role in each of these three strategies. The importance of these measures and the ways to understand the risks that CDI pose to patients are best demonstrated through studies examining mortality.

Recent literature examining mortality and CDI indicates that CDI has a significant adverse effect on hospitalized patients (Karas, Enoch, & Aliyu, 2010; Mitchell & Gardner, 2012; Mitchell, Gardner, & Hiller, 2013). In two reviews examining this topic,

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only one study examining CDI and mortality in an Asian setting was found. Furthermore, there have been limited studies published in English that described the incidence of CDI in Asia (Collins et al., 2013). Studies investigating the incidence and mortality of CDI in settings outside of Europe and North America are needed so that the epidemiology of CDI in these regions can be understood with appropriate interventions planned. This paper describes a study exploring the incidence of CDI in a large Australian hospital. It also highlights important considerations for other Asian countries that are considering establishing or modifying existing CDI surveillance programs. In addition, it is hoped that by highlighting this infection in an Asian journal, it will encourage others to publish in this area and address the current gap in epidemiological knowledge in the region.

Methods

The aim of this study is to determine the incidence of CDI between January 1st, 2007 and December 30th, 2010 in an Australian hospital.

Study design

To address the research questions, a retrospective observational design with dynamic population is used.

Setting and sample

All persons aged 2 years or older and who were hospitalized at a tertiary referral hospital in Australia for more than 48 hours between January 1st, 2007 and December 31st, 2010 formed the study population. Persons in the study population are referred to as "admissions" throughout this paper. The hospital is a 500-bed hospital that provides a full range of services including an emergency department, intensive care, surgery, renal, children, chemotherapy and maternity services.

From the available data, those persons who developed CDI during their hospital stay were subsequently identified. A person was defined as having CDI if he or she had a positive stool sample result for *C. difficile* using either a laboratory assay (enzyme immunoassay or polymerase chain reaction) detecting toxin A and/or toxin B or culture, resulting in the isolation of *C. difficile* that is subsequently shown to produce toxin A and/or toxin B. The positive stool sample had to be collected more than 48 hours after admission to capture cases of healthcare-associated healthcare facility onset episodes of CDI (McDonald et al., 2007). All infectious episodes included in this study were such episodes. Any positive stool sample for *C. difficile* occurring in patients less than 2 years old or occurring within 8 weeks of the last positive test was excluded.

During the full study period, the microbiology department tested all diarrheal samples from the hospitalized patients, regardless of reason for hospitalization for *C. difficile*. Diarrhea was defined as an unformed stool that took the shape of the container.

Ethical considerations

Ethical approval for this research was granted by two human research ethics committees (Tasmanian Human Research Ethics Committee and Australian Catholic University).

Data collection

Data were retrieved from four different sources. These sources comprised data from the clinical coding department at the hospital, a government surveillance unit (The Tasmanian Infection Prevention and Control Unit [TIPCU]), the Infection Prevention and Control Unit at the hospital, and a review of the patient administration system and medical records of each person who has CDI during the period.

To identify the population, all admissions aged 2 years and older who were admitted to the hospital for more than 48 hours were identified by the clinical coding department at the request of the researcher. To allow for the identification of persons who developed CDI during their hospital stay, the TIPCU provided the researcher with details on all admissions who had an episode of CDI occurring at the hospital during the study period, consistent with the case definitions described earlier. Using the data provided by the TIPCU, further data were collected through a review of the records held on the hospital patient information system and on the individual medical records of those with CDI. The review of the medical records of each patient with CDI included reviewing medical and nursing documentation related to the frequency of diarrhea.

The Infection Prevention and Control Unit at the hospital collected data within the timeframe that a person with CDI was isolated under contact precautions. The researcher reviewed the data provided by this unit for when persons with CDI had contact precautions ceased. The rationale for using the cessation of contact precautions as a marker for infection cessation is described in more detail in the following section. Data using this process were only available from July 1st, 2009 until December 30th, 2010, as the infection control unit did not collect this data prior to July 1st, 2009. There were 11 instances within this timeframe where data were not available from the hospital infection control unit. Subsequently, a review of the medical notes of these admissions was conducted and pointed to the date a person was removed from isolation. Data on the isolation periods of a total of 72 persons (from July 1st, 2009 to December 30th, 2010) were obtained.

Data items collected

The data items collected included date of birth, sex, age, admission and discharge date, date of infection, date of infection cessation and the diagnosis-related group. The issue of defining CDI cessation in an individual is challenging. As *C. difficile* may continue to be detected from asymptomatic colonization, laboratory testing for the clearance of CDI is not recommended (Stuart et al., 2011). The researcher undertook a review of 20 medical notes of admissions with CDI and found that medical records failed to document a formed stool or cessation of diarrhea reliably. Based on the findings from the review of the 20 medical records, it was considered that the cessation of contact precautions for persons with CDI was a simple, reliable, and practical method of determining the cessation of CDI and was consistent with literature (National Health and Medical Research Council, 2010). Additionally, the decision to cease contact precautions was made after a review done by an infection control professional at the time of making this clinical decision.

Data analysis

Descriptive analysis on the characteristics of the admissions was performed using IBM SPSS Version 20.0 (International Business Machines Corporation, 2011). Distributions were analyzed using Q–Q plots and the Kolmogorov–Smirnov test. Univariate analysis was used to compare the clinical characteristics of persons with and without CDI using a chi-square test or Fisher's exact test where numbers were small. Incidence for calendar years and age groups was calculated by using mid p exact test. The calculation of the relative risk was performed to compare the occurrence of CDI in

different groups. Confidence interval (CI) was calculated using Taylor series.

Results

Population size and incidence of infection

During the study period, there were 58,942 admissions of persons aged 2 years and older who stayed for 48 hours or longer at the Royal Hobart Hospital. These 58,492 admissions equated to a total of 493,626 bed days, defined as the sum of each individual person's length of stay in the hospital. The total number of admissions per annum at the hospital increased from 14,055 in 2007 to 15,185 in 2010, representing an 8% increase over the 4 years. Within this 4-year period, the largest seasonal increase in admissions occurred in spring, with a total of 16.5% more persons being admitted in 2010 compared to 2007.

There were 158 admissions with an episode of CDI in the calendar years 2007–2010. Despite removing duplicate samples occurring within 8 weeks of the previous positive samples, there were five instances of a secondary infection occurring in the same person during the 4-year study period. Further analysis of these five instances suggests that secondary cases were unrelated to the first case.

The annual incidence of CDI per 1,000 admissions for the calendar years 2007–2010 ranged from 1.71 (95% CI [1.12, 2.50]) to 3.89 (95% CI [2.96, 5.01]). The incidence of CDI per 1,000 admissions for the entire study period was 2.68 (95% CI [2.28, 3.13]). There was a statistically significant increase in the incidence of CDI in 2010 compared to that of 2007 ($p < .001$).

Demographic characteristics of study population

The distribution of age for the study population was not normal: $D(58, 784) = 0.08$, $p < .001$ (Kolmogorov–Smirnov test). As the size of the study is large, the distribution of age was confirmed as non-normally distributed using Q–Q plots. Table 1 displays the age and sex characteristics of the admissions.

Age stratification, which examined the incidence of CDI per 1,000 admissions, was performed. The results displayed in Figure 1 and Table 2 demonstrate the incidence of CDI by age group. The incidence of CDI increases from the 30–39 year age group until the 80–89 year age group. The incidence of CDI stratified by sex and age group is provided in Table 2.

The probability of a person admitted to the hospital during the study period as having CDI relative to their age group is displayed in Table 3. In calculating the relative risks displayed in Table 3, reference groups used were persons aged less than the stated age groups. Results are displayed in this manner to demonstrate the graduating relative risk. The graduating relative risk displayed in this manner can inform a decision as to the age groups CDI surveillance should be performed.

Comparisons were made between the diagnosis-related group categories assigned to persons with and without CDI. Significantly, more persons with the diagnosis-related group categories "nervous", "digestive", "kidney", and "neoplastic" diseases had CDI compared to persons without these categories did ($p < .01$). Conversely, those persons with diagnosis-related group categories of "mental health" and "pregnancy" were significantly less likely to have CDI ($p < .01$).

Table 1 *Demographic Characteristics of Those With and Without Clostridium difficile Infection (CDI).*

Characteristic	Admissions that developed CDI ($n = 158$) n (%)	Admissions that did not develop CDI ($n = 58{,}784$) n (%)	Total ($N = 58{,}942$)
Sex			
Male	79 (50.0)	25,915 (44.1)	25,994
Female	79 (50.0)	32,857 (55.9)	32,936
Intersex	–	11 (< 1%)	11
Not specified	–	1 (< 1%)	1
Age (yr)			
Median	67	55	55
Range	2–102	2–106	2–106
Age group			
2–9	3 (1.9)	1,523 (2.6)	1,526 (2.6)
10–19	6 (3.8)	3,471 (5.9)	3,477 (5.9)
20–29	3 (1.9)	7,977 (13.6)	7,980 (13.5)
30–39	5 (3.2)	6,928 (11.8)	6,933 (11.8)
40–49	13 (8.2)	5,748 (9.8)	5,761 (9.8)
50–59	24 (15.2)	6,759 (11.5)	6,783 (11.5)
60–69	31 (19.6)	8,609 (14.6)	8,640 (14.7)
70–79	38 (24.1)	9,159 (15.6)	9,197 (15.6)
80–89	30 (19.0)	7,057 (12.0)	7,087 (12.0)
≥ 90	5 (3.2)	1,553 (2.6)	1,558 (2.6)

Timing, duration of infection and documentation

For admissions that had an episode of CDI, the median time to infection from admission was 8 days, with a range of 2–104 days (75th percentile = 13 days). Available data on the length of time admissions had infection was incomplete. After reviewing information held by the Infection Prevention and Control Unit at the hospital and the medical and nursing notes, the time an admission was in isolation in hospital was only identified for 72 of the 158 instances of infection. For these 72 infections, the median time an admission had CDI was 5 days, with a range of 1–47 days. Twenty-five per cent of these admissions had CDI for 11 days or more. For admissions with CDI, there was limited information regarding the frequency of diarrhea in the medical and nursing notes. The use of a tool to measure the type and frequency of diarrhea was not found.

Discussion

In this study, an increasing incidence of CDI was found, with a significant increase between 2007 and 2010. These findings are consistent with reports published by the TIPCU and other published literature of healthcare-associated healthcare facility onset CDI in Tasmania (Mitchell, McGregor, Wells, & Wilson, 2012). When comparing the incidence of CDI between organizations or countries, it is important to consider the methodological influences that affect the reliability and validity of the data (Mitchell & Gardner, 2014a). In the case of CDI, the study duration, denominator selection, testing effort, and testing methodology lead to ascertainment bias (Mitchell, Ware, McGregor, Brown, & Wells, 2011). With this in mind, there have been calls to standardize CDI testing and surveillance methods internationally (Mitchell et al., 2011). For countries yet to establish CDI surveillance or for those currently developing such programs, it is vital that they consider these points. This is particularly important in the Asian region, where CDI surveillance is still in its infancy.

The value of having standardized definitions for CDI and other healthcare associated infections cannot be underestimated. If healthcare associated infections data are used to underpin infection prevention programs and strategies, it is imperative that the data are collected and reported using consistent and reproducible methods (Mitchell & Gardner, 2014b). Failure to do so will make the evaluation of interventions to reduce healthcare associated infections more challenging, as it will be difficult to decipher the impact of interventions against the effect of issues, such as changes in the testing methodologies and testing efforts.

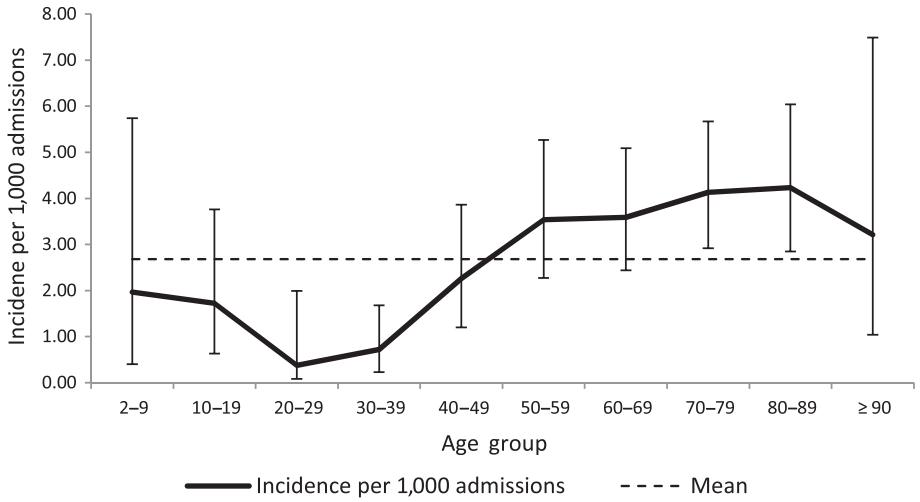


Figure 1. Incidence of *Clostridium difficile* infection per annum by age group. Error bars denote 95% confidence intervals.

Table 2 *Incidence of Clostridium difficile Infection Stratified by Sex and Age Group.*

Characteristic	Incidence per 1,000 admissions	95% confidence interval
Sex		
Male	1.34	1.07–1.66
Female	1.34	1.07–1.66
Age group (yr)		
2–9	1.97	0.40–5.74
10–19	1.73	0.63–3.76
20–29	0.38	0.08–1.99
30–39	0.72	0.23–1.68
40–49	2.26	1.20–3.86
50–59	3.54	2.27–5.27
60–69	3.59	2.44–5.09
70–79	4.13	2.92–5.67
80–89	4.23	2.85–6.04
≥ 90	3.21	1.04–7.49

Table 3 *Comparison of Relative Risk of Clostridium difficile Infection (CDI) by Age Group.*

Age group (yr)[a]	Incidence	Admissions that developed CDI / Admissions	RR	95% CI[b]
≥ 80	4.06	35 / 8,610	1.66	1.14–2.40
≥ 70	4.11	73 / 17,769	1.98	1.44–2.70
≥ 60	3.94	104 / 26,378	2.36	1.70–3.27
≥ 50	3.86	128 / 33,137	3.29	2.21–4.90
≥ 40	3.63	141 / 38,885	4.23	2.56–7.00
≥ 30	3.19	146 / 45,813	3.44	1.91–6.19
≥ 20	2.77	149 / 53,790	3.53	1.80–6.88
≥ 10	2.71	155 / 57,261	1.36	0.43–4.24

Note. RR = relative risk; CI = confidence interval.
[a] Reference group are persons aged less than the stated age group.
[b] Confidence interval is calculated using Taylor series.

The incidence of CDI in our study appears to be higher than that reported in other Australian hospitals (Van Gessel, 2008). There is, however, limited data with which to compare the incidence of CDI in Australia. Internationally, it can be noted that the incidence found in this study is lower than that reported in many CDI surveillance systems in Europe and North America. In England, the reported rate for 2009–2010 was 3.7 per 10,000 bed days, down from 5.5 per 10,000 bed days in 2008–2009 (Health Protection Agency, 2011). It is important to note, however, that only samples from persons hospitalized for 4 days or more are reported in this figure for the English surveillance scheme. If this criterion is applied to this study, the incidence of CDI will reduce by approximately 16%, down to 2.26 per 1,000 admissions or 2.69 per 10,000 patient days. This demonstrates the importance of paying attention to the exclusion criteria when comparing CDI data and the need for a more standardized approach (Freeman et al., 2010). The higher incidence of CDI is not only seen with England, Scotland and Germany also reported higher rates of CDI (7.6 and 4.7 per 10,000 occupied bed days, respectively) (Gastmeier, Weitzel-Kage, Behnke, & Eckmanns, 2009; Health Protection Scotland, 2011). Conversely, there have been lower reported incidence rates of CDI in other European countries, such as Belgium (1.52 per 1,000 admissions) (Viseur, Lambert, Delmee, Van Broeck, & Catry, 2011) and the Netherlands (1.8 per 1,000 admissions) (Hensgens, Goorhuis, Notermans, van Benthem, & Kuijper , 2009). In North America, an incidence of 22.5 cases of CDI per 1,000 admissions has been reported (Loo et al., 2005), with more recent studies demonstrating an increasing incidence of CDI (Chandler, Hedberg, & Cieslak, 2007; Kazakova et al., 2006; Tan et al., 2007). Data on the incidence of CDI in Asia is limited (Collins et al., 2013). Noting the increases of CDI internationally and the associated mortality (Karas et al., 2010; Mitchell et al., 2013), there is increasing importance to monitor and report the incidence of this infection worldwide, particularly in Asia (Collins et al.; Ekma, Yee, & Aziz, 2012).

Issues relating to variations in laboratory testing and the potential impact that these have in research and in surveillance have been discussed earlier. There are two important factors to be taken into account when considering whether an increase in the incidence of CDI is “real”. These are testing effort and testing methodology. Testing effort refers to how many stool samples received by a laboratory are tested for CDI. This is dependent on what criteria are used before a test for CDI is performed. In this study, all diarrheal samples from the hospitalized individuals were tested for *C. difficile* during the study period, so this is unlikely to have a role in the calculated increase of CDI. However, the process of testing for CDI can vary considerably among institutions. For example, private microbiology laboratories may only test for *C. difficile* if the test is requested. This has the risk of ascertainment bias and is not often accounted for in CDI surveillance (Freeman et al., 2010). Testing methodology or the sensitivity of testing can play a role in identifying cases of CDI. In this study, the methodologies used for testing for *C. difficile* were highly sensitive and, in all situations, the laboratory testing for the *C. difficile* toxin used an assay. Therefore, the increase in healthcare-associated healthcare facility onset CDI over

time was unlikely to have been caused by changes in the testing effort or testing methodology. Alternatively, given the rigorous testing, there is also little chance of underestimation of infection in this study.

The findings from this study suggest that the incidence of CDI increases with age, from 30 years old up until the age of 90. The reason for the incidence of CDI not continuing to increase past 90 years of age is almost certainly an artifact of the small number of admissions with CDI occurring in this age group in this study. Consistent with this study, increasing age is a well-established risk factor for CDI (DuPont, Garey, Caeiro, & Jiang, 2008; McDonald, Owings, & Jernigan, 2006). A variation in the proportion of a hospitalized population that is older may affect the incidence of CDI (McFarland, Surawicz, & Stamm, 1990; Starr, Martin, McCoubrey, Gibson, & Poxton, 2003; Vaishnavi, 2009). Internationally, there are some surveillance programs that specifically focus on CDI in persons aged 65 years and over. For example, in both England and Wales, the incidence of CDI in persons aged 65 and over is higher than in all persons aged 2 years and over (Health Protection Agency, 2011; Welsh Healthcare Associated Infection Programme, 2011). Data extrapolated from the Health Protection Agency suggest that the relative risk for CDI was 2.27 ($p < .001$, 95% CI [2.20, 2.34]), comparing those aged 65 and over to those aged less than 65 years in England (Health Protection Agency).

The trend of a higher incidence of CDI in persons aged 65 and older is repeated in this study, which reports an incidence of 4.22 per 1,000 admissions (95% CI [3.41, 5.16]) for this age group. The relative risk of CDI in persons aged 65 and over in this study, compared to persons less than 65 years old, is 2.42 ($p < .001$, 95% CI [1.75, 3.38]), a similar finding to the CDI surveillance in England. In this study, the relative risks for CDI by age group are also compared for each decade of life. The groups with the highest relative risk are persons aged 40 years and older compared to persons who are less than 40 years old. It is not possible to calculate the relative risk for CDI in different age groups for England and Wales based on the available data. Nonetheless, the findings of this study pose the question as to whether the “65 and over” age group is the most appropriate age group for targeted CDI surveillance because it appears that the risk of contracting CDI begins to increase significantly for patients as young as 40 years of age. This has clear implications for countries establishing or considering modifications to existing CDI surveillance programs.

Results from this study also suggest that the median time to infection from admission was 8 days. For nurses, this highlights the importance of being aware of the signs and symptoms of CDI around this period, particularly for susceptible or at risk groups. Prompt isolation of patients with diarrhea and early specimen collection will reduce the risk of transmission and lead to the opportunity for early diagnosis and treatment. Upon reviewing the medical and nursing notes of persons with CDI in this study, poor standards of documentation were found. Specifically, there was a lack of documentation describing patients’ symptoms, such as diarrhea. Standardized tools are available for describing diarrhea, for example the Bristol Stool Chart (Lagrotteria, Holmes, Smieja, Smaill, & Lee, 2006). The type of stool and frequency of diarrhea are important pieces for decision making for infection control professionals and clinicians and nurses standards of documentation can go a long way to improving this situation.

Implications

There are several implications of this study for practice, future research and policy. For policy, this study demonstrates the need for using standardized definitions for CDI and to survey an entire hospital population for CDI, not just those in more advanced age groups. These points should be considered for those planning or modifying CDI surveillance programs. The paper identified the risk of CDI increasing with advancing age. Future research could examine what specific host factors related to advancing age contribute most to this increased risk. For clinical practice, this study demonstrates the impact CDI can have and support prevention and control measures, often led by nurses. These could include but not be limited to antibiotic stewardship (Charani & Holmes, 2013), maintaining standards of environmental cleanliness (Rutala & Weber, 2013) and the early identification and isolation of patients suspected of having CDI.

Conclusion

The incidence of CDI found in this study is lower than those reported in most countries in the northern hemisphere but higher than those reported from limited Australian data. The increase in CDI is part of a trend experienced internationally in recent years. These points are significant as the author’s findings suggest that the impact of CDI is not yet fully realized in Australia or more widely across Asia due to limited published data. We may yet experience increases in CDI as have occurred in other countries. In order to better interpret the trends and the epidemiology of CDI, the issue of variations in microbiological testing methodologies becomes an important issue. Differences in the testing methodologies make comparisons intrinsically difficult and there is a need for standardized practice in this area internationally. When planning or modifying CDI surveillance programs, testing methodologies should be understood to better determine the limitations of the program and subsequent interpretation of the results. Results from this study found that the risk of CDI increases with age. However, not all surveillance programs survey the population at most risk. Surveillance of CDI should include those aged 2 years and over, rather than be limited to older adults. In so doing, the population at most risk will be surveyed and appropriate health and infection prevention and control interventions can be implemented.

Conflict of Interest

The author declares no conflict of interest.

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