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The burden of healthcare-associated Clostridium difficile infection in a non-metropolitan setting

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The burden of healthcare-associated *Clostridium difficile* infection in a non-metropolitan setting

Abstract

Objective: Healthcare-associated *Clostridium difficile* infection (HCA-CDI) remains a major cause of morbidity and mortality in industrialized countries. However, few data exist on the burden of HCA-CDI in multi-site non-metropolitan settings. This study examined the introduction of an antimicrobial stewardship programme (ASP) in relation to HCA-CDI rates, and the effect of HCA-CDI on length of stay (LOS) and hospital costs.

Methods: A comparative before-and-after intervention study of patients aged ≥ 16 years with HCA-CDI from December 2010 to April 2016 across the nine hospitals of a non-metropolitan health district in New South Wales, Australia was undertaken. The intervention comprised a multi-site ASP supported by a clinical decision support system, with subsequent introduction of email feedback of HCA-CDI cases to admitting medical officers.

Main outcome measures: HCA-CDI rates, comparative LOS and hospital costs, prior use of antimicrobials and proton pump inhibitors, and appropriateness of CDI treatment.

Results: HCA-CDI rates rose from 3.07 to 4.60 cases per 10,000 occupied bed-days pre-intervention, and remained stable at 4 cases per 10,000 occupied bed-days post-intervention ($P = 0.24$). Median LOS (17 vs six days; $P < 0.01$) and hospital costs (AU\$19,222 vs \$7861; $P < 0.01$) were significantly greater for HCA-CDI cases ($N = 91$) than for matched controls ($N = 172$). Half of the patients with severe HCA-CDI (4/8) did not receive initial appropriate treatment (oral vancomycin).

Conclusions: HCA-CDI placed a significant burden on the regional and rural health service through increased LOS and hospital costs. Interventions targeting HCA-CDI could be employed to consolidate the effects of ASPs.

Disciplines

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The burden of healthcare associated *Clostridium difficile* infection in a non-metropolitan setting

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Abstract

Objective

Clostridium difficile infection is a major cause of healthcare associated diarrhoea in industrialised countries and is associated with considerable morbidity and mortality. No data exist on the burden of healthcare associated *Clostridium difficile* infection (HCA-CDI) in multisite non-metropolitan settings. This study examined the introduction of an antimicrobial stewardship program (ASP) in relation to HCA-CDI rates and the effect of HCA-CDI on length of stay (LOS) and hospital costs.

Methods

A comparative before-and-after intervention study of patients aged 16 years and over with HCA-CDI from December 2010 to April 2016 across the nine hospitals of a regional and rural health district in New South Wales, Australia. The intervention consisted of a multisite ASP supported by a clinical decision support system, with subsequent introduction of email feedback of HCA-CDI cases to admitting medical officers. Main outcome measures: HCA-CDI rates; comparative LOS and hospital costs; prior antimicrobial and proton-pump inhibitor use; appropriateness of CDI treatment.

Results

HCA-CDI rates were stable at four cases per 10,000 occupied bed days following the intervention. Median LOS (17 vs. 6 days, $P < 0.01$) and hospital costs (AU\$19,222 vs. \$7,861, $P < 0.01$) were significantly greater for HCA-CDI cases ($N=91$) than for matched controls ($N=172$). Half of the patients with severe HCA-CDI (4/8) did not receive initial treatment concordant with Australian guidelines (oral vancomycin).

Conclusions

HCA-CDI placed a significant burden on our regional and rural health service through increased LOS and hospital costs. Interventions targeting HCA-CDI could be employed to consolidate the effects of ASPs.

Keywords: *Clostridium difficile* infection, antimicrobial stewardship program, clinical decision support system, health care costs, length of stay

Introduction

Clostridium difficile infection (CDI) is a major cause of healthcare associated diarrhoea in industrialised countries and is associated with considerable morbidity and mortality.¹ In Australia, the annual incidence of hospital-identified CDI was 4.03 cases/10,000 patient days in 2012.² Risk is increased by antimicrobial use and/or immunosuppression.³ Other putative risk factors include gastrointestinal surgery, gastric acid-suppressive therapy and prolonged hospital stay.³

Healthcare associated *Clostridium difficile* infection (HCA-CDI) has been associated with increased length of stay (LOS), additional costs from hospitalisation⁴ and antimicrobial treatment,³ and indirect costs such as productivity losses.⁵

Most antimicrobials have been related to CDI, with lincosamides (e.g. clindamycin), third generation cephalosporins (e.g. ceftriaxone), and broad-spectrum penicillins (e.g. amoxicillin/clavulanic acid) showing strong associations.⁶ Fluoroquinolones have been particularly associated with the hypervirulent NAP1/027 strain.⁷ There is probable association between proton pump inhibitor (PPI) use and CDI, with the combination of PPIs and antimicrobials carrying a greater risk than either alone.⁸

Antimicrobial stewardship programs (ASPs) should be employed to reduce the incidence of HCA-CDI.¹ Despite HCA-CDI being an outcome measure for ASPs,

increasing community acquisition of CDI may cloud interpretation of HCA-CDI rates.² Antimicrobial stewardship (AMS) interventions targeting HCA-CDI have predominantly been conducted in metropolitan teaching hospitals, at single sites or within a defined clinical area.⁹⁻¹³ Very limited data exist on the burden of HCA-CDI in Australia, particularly in regional and rural settings.¹⁴ To our knowledge this is the first study to examine a multisite ASP in relation to HCA-CDI rates in the non-metropolitan setting.

The aims of our study were: to describe HCA-CDI rates before and after an ASP; to measure LOS and hospital costs in HCA-CDI patients across multiple hospital sites; to compare prior antimicrobial and PPI use in HCA-CDI patients with the background use; and to assess appropriateness of HCA-CDI antimicrobial treatment according to guidelines.

Methods

Setting

From December 2010 to April 2016, a comparative before-and-after intervention study on the burden of HCA-CDI was performed across the nine public hospitals (1000 total beds) of Illawarra Shoalhaven Local Health District (ISLHD) in south eastern New South Wales (NSW), Australia. The district services 390,000 residents across a catchment that begins one hour south of Sydney, and extends 250km along a coastal strip. The three largest hospitals comprise one principal referral hospital (550 beds), a large acute hospital (150 beds) and a medium acute hospital (100 beds). The remaining six hospitals are either small acute or mixed sub- and non-acute.¹⁵ This study employed Plan, Do, Study, Act (PDSA) quality improvement methodology.¹⁶

Antimicrobial Stewardship

In May and June 2012, an ASP supported by a computerised clinical decision support system (CDSS; GuidanceMS^{®17}) was uniformly implemented across the district's nine hospitals. In addition to the CDSS, the ASP involved a restriction policy, whereby broad spectrum antimicrobials were only stocked in pharmacy (with supply contingent on CDSS approval) or specialist areas (i.e. intensive care unit [ICU], emergency department, haematology/oncology ward). An education campaign

involved regular departmental presentations, and an intranet webpage was established to improve access to guidelines. Regular AMS rounds occurred at the three largest hospitals, and an antimicrobial advice telephone hotline was established across the district to support the smaller hospitals without onsite AMS clinicians. See **Figure 1** for the study flowchart. There were no major changes to infection control policies related to either *Clostridium difficile* or hand hygiene during the study period.

Following a review of HCA-CDI rates, in April 2013 the AMS team (infectious diseases doctors and pharmacists) introduced a targeted CDI intervention. The AMS pharmacist audited all CDI cases for the following: patient demographics, risk factors, antimicrobial treatment, severe disease,³ ICU admission, surgical intervention, and NAP1/027 strain. A feedback email was then sent to the attending medical officer (AMO) within two weeks (**Appendix A**). Qualitative analysis of email responses determined the level of acceptance by AMOs. Responses were categorised as clinical feedback, basic acknowledgment or defensive. The appropriateness of HCA-CDI treatment³ was assessed during AMS rounds or retrospectively from medical notes. Results were presented to the AMS, drug and therapeutics, and infection control committees.

***Clostridium difficile* laboratory testing**

From December 2010, our laboratory protocol subjected all diarrhoeal stools to *Clostridium difficile* testing. First line testing targeted glutamate dehydrogenase

(GDH) antigen and toxins A and B (C. Diff Quik Chek Complete®, Techlab, Blacksburg, VA, USA). If those tests were discordant, then a polymerase chain reaction (PCR; GeneXpert®, Cepheid, Sunnyvale, CA, USA) test was employed, which could also detect the NAP1/027 strain.

Effect of HCA-CDI on LOS and hospital costs

LOS and hospital cost analysis was performed only for the three acute hospitals due to a shortage of matched controls and other confounders for LOS at smaller hospitals (e.g. nursing home availability, social factors). Definitions for HCA-CDI were: HCA-healthcare facility onset, diarrhoea onset >48 hours after admission; HCA-community onset, diarrhoea onset in the community or <48 hours after admission, but within four weeks of last discharge.¹⁸ Demographic data for HCA-CDI cases did not differ significantly between hospitals, or between the two types of HCA-CDI (data not shown).

A post hoc analysis of LOS and hospital costs was conducted for those HCA-CDI cases identified from 1st April 2013 to 30th April 2014. Matched controls were identified from diagnosis-related group (DRG) data¹⁹ for HCA-CDI cases ($N=103$). Controls were identified from 1st January 2013 to 30th June 2014. Two controls were matched to each case by site, sex, age (± 5 years), and DRG (81 cases). Where two matched controls were not available, one control was identified (10 cases), resulting in 91 cases and 172 controls (**Figure 1**). DRGs were grouped and the most common

DRGs were reported. Additional analysis was performed on those HCA-CDI cases and controls with LOS of ≥ 8 days to address time-dependent biases (8 days equalled the median time to HCA-CDI onset).

Antimicrobial and PPI use

Antimicrobial use within one month prior to diagnosis among HCA-CDI patients was compared with background antimicrobial use data, regularly collected in Australia as part of standard surveillance reports. Those data (defined daily doses [DDDs] per 1000 occupied bed days [OBDs]) from the three acute hospitals were derived from the Australian National Antimicrobial Utilisation Surveillance Program (from pharmacy software) and the Australian National Antimicrobial Prescribing Survey (point prevalence survey in November 2013, seasonally corrected, antimicrobial class use as a percentage of total use). PPI use was also compared with background use (point prevalence survey 2013).

Statistical analyses

Interrupted time series analysis²⁰ was used to assess HCA-CDI rates at the three large hospitals (due to comparability of acute OBD data). Data were included from December 2010 (earliest time point with current CDI testing methods) to April 2016, with the intervention point defined as May 2012 (introduction of multisite ASP).

Separate analyses were performed for May 2012- Mar 2013 and April 2013 onwards (targeted CDI intervention). Since those periods did not reveal any significant differences (data not shown) the post-intervention period was reported as one interval. A chi-square test was used for proportions or Fisher's exact test where appropriate. A Mann-Whitney U-test was used to compare continuous variables such as LOS and hospital costs. Stata[®] Statistical Software Version 14 was used (Statacorp, College Station, Texas, USA). Significance was accepted as $P < 0.05$.

Ethics

Ethics approval was received from the joint University of Wollongong and Illawarra Shoalhaven Local Health District (ISLHD) Human Research Ethics Committee, approval number HE13/137.

Results

Figure 2 shows interrupted time series analysis of monthly HCA-CDI rates. The model-predicted HCA-CDI rate in December 2010 was 3.07 cases/10,000 OBDs. Prior to introduction of the ASP, the model-predicted rate was 4.6 cases/10,000 OBDs. Following ASP's introduction, and including the targeted email intervention, HCA-CDI rates remained stable at 4 cases/10,000 OBDs. None of those differences reached statistical significance. Detailed time series data are provided in **Appendix B**.

During the targeted intervention phase from April 2013 to April 2014, 120 primary HCA-CDI cases were identified. The median age was 73 years (interquartile range [IQR] 63-81yrs) and 51/120 patients were male (43%). Antimicrobials one month prior to HCA-CDI diagnosis were received by 107/120 patients (89%). Severe disease was identified in 8/120 (7%) cases; there were 8/120 (7%) ICU admissions, no surgical interventions, and no NAP1/027 strains.

Of the emails sent to AMOs for 120 HCA-CDI cases from April 2013-14, 23 responses were received (19% response rate). Of those responses, 10 contained clinical feedback, 13 contained basic acknowledgement, and there were no defensive responses. Examples of clinical feedback responses were: "...in the setting of immune suppression and...other complications with chemo I am treating C diff..."; and, "the (antibiotic) was for aspiration... the PPI (was) longstanding...".

Median LOS was 11 days greater for HCA-CDI patients ($N=91$; 17 days [IQR 8-27]) than their matched controls ($N=172$; 6 days [IQR 3-12]; $P<0.01$). Also, median hospital cost was AU\$11,361 higher for the HCA-CDI group (\$19,222 [IQR \$7,817 - \$41,337]) compared to controls (\$7,861 [IQR \$3,477 - \$14,553]; $P<0.01$). The median time to onset of HCA-CDI was 8 days (IQR 4-14).

The median hospital cost for 48 HCA-CDI patients with $LOS \geq 8$ days was AU\$17,832 (IQR 9,472-28,840) vs. AU\$12,563 (9,072-20,086) for 70 controls with $LOS \geq 8$ days ($P=0.17$). For patients with $LOS \geq 8$ days, the median LOS was 16 days (IQR 10-26) for HCA-CDI cases vs. 15 days (IQR 12-26) for controls. After excluding non-treated patients ($N=6$) with available controls ($N=11$), the difference between HCA-CDI patients and controls persisted for median LOS (18 vs. 7 days; $P<0.01$) and cost (AU\$20,245 vs. \$8,924; $P<0.01$). The five most common primary DRG groups among 263 HCA-CDI cases and controls were: gastrointestinal ($N=18$ for cases, $N=36$ for controls), haematological malignancy ($N=9$, $N=17$), orthopaedic surgery ($N=8$, $N=15$), abdominal surgery ($N=6$, $N=10$), and cardiac ($N=5$, $N=9$).

Antimicrobial use among the HCA-CDI group at the three acute hospitals was compared with background antimicrobial use. Over-represented in HCA-CDI patients were third generation cephalosporins (e.g. ceftriaxone; 34% of total use in HCA-CDI patients vs. 11% of background use; $P<0.01$), beta-lactamase inhibitor combinations (e.g. piperacillin/tazobactam; 58% vs. 36%; $P=0.01$), nitroimidazoles (e.g.

metronidazole; 28% vs. 11%; $P<0.01$), and glycopeptides (e.g. vancomycin; 23% vs. 6%; $P<0.01$). Under-represented in HCA-CDI patients were beta lactamase resistant penicillins (e.g. flucloxacillin; 7% vs. 18%; $P=0.02$), beta lactamase sensitive penicillins (e.g. benzylpenicillin; 2% vs. 9%; $P=0.03$), extended spectrum penicillins (e.g. ampicillin; 14% vs. 33%; $P=0.03$), macrolides (e.g. azithromycin; 4% vs. 19%; $P<0.01$), and tetracyclines (e.g. doxycycline; 4% vs. 38%; $P<0.01$).

Vancomycin and metronidazole were over-represented in HCA-CDI patients, but are also recommended for CDI treatment. Those two classes were further analysed. For vancomycin, the most commonly co-prescribed antimicrobial was piperacillin/tazobactam (11/25) with febrile neutropenia the commonest known indication (9/11). Vancomycin use was intravenous in all of those cases. For metronidazole, the most commonly co-prescribed antimicrobial was ceftriaxone (13/35), predominantly for abdominal infections (10/13). There was an overall decrease in use of broad spectrum antimicrobials following implementation of the multisite ASP (data not shown). PPI use was documented in 83/120 (69%) HCA-CDI patients compared with 343/730 (47%) patients audited as part of the local 2013 point prevalence survey ($P<0.01$).

In non-severe HCA-CDI treated at the acute hospitals ($N=95$), oral metronidazole was initiated in 78 (82%) cases. Oral vancomycin plus oral metronidazole was used in eight (8%) cases, where metronidazole alone would have sufficed.³ No therapy was given in nine non-severe cases, due to cessation of diarrhoea with or without identification of an alternative correctable cause. In the severe HCA-CDI group

($N=8$), oral metronidazole was initiated in 4 (50%) cases, where oral vancomycin, intravenous metronidazole or a combination was indicated. In those cases a relevant AMS intervention was made.

Discussion

Our study describes the relationship between HCA-CDI rates and a multisite ASP supported by a CDSS, education and antimicrobial restriction combined with targeted audit and feedback. Implementation of an ASP was temporally associated with stable HCA-CDI rates. Targeted interventions may help to combat the waning of the initial impact of a program over time. We found that in an Australian non-metropolitan setting, LOS and hospital costs were significantly increased in HCA-CDI patients when compared with matched controls. Increased antimicrobial and PPI use in patients with HCA-CDI were consistent with previous reports.^{6, 8} Although the initial treatment of non-severe HCA-CDI cases predominantly matched guidelines, there was concerning use of oral metronidazole in half of the severe cases (albeit with small numbers). This was similar to previous findings elsewhere,²¹ likely resulting from under-recognition of severity criteria.^{3, 22}

HCA-CDI has been associated with increased LOS and hospital costs.⁴ Most studies evaluating these effects were either epidemiological studies^{23, 24} or performed in the metropolitan setting.¹⁰ To our knowledge this is the first study to combine evaluation of the burden of HCA-CDI with multisite ASP implementation in a regional and rural setting. Comparison with matched controls^{11, 25} allowed for a pragmatic approach to identifying additional LOS and hospital costs associated with HCA-CDI. For those patients with $\text{LOS} \geq 8$ days, there was a 42% increase in hospital costs in HCA-CDI patients compared with controls, despite similar LOS in those groups. This

highlighted the increased cost of caring for HCA-CDI patients additional to greater LOS, and alleviated the potential for time-dependent biases.

There were several limitations to this study. We included all positive *Clostridium difficile* tests during the targeted intervention phase, as the frequency of daily diarrhoeal episodes was unreliably documented. Alternative causes of diarrhoea may have been present in some patients carrying *Clostridium difficile*. We could not attribute the increase in LOS and hospital costs to HCA-CDI alone. Alternative statistical methods such as multi-state modelling²⁶ to account for time-dependent biases, and propensity matching⁴ to accurately estimate the impacts of CDI have been proposed. To account for those limitations, we applied the case-control methodology in two additional subsets: the “long-stay” patients (≥ 8 days, the median time-to-onset of HCA-CDI) and only those treated for HCA-CDI. Those results were in line with our primary evaluation, emphasising the high LOS and cost burden of HCA-CDI. As expected, gastrointestinal DRGs were overrepresented. In some cases the primary DRG may have been allocated to gastrointestinal due to CDI severity or duration.

Community cases could not be accurately assessed with the current study resources.

Of 120 HCA-CDI cases, only 91 were eventually analysed for LOS and cost.

Assessing the impact on HCA-CDI rates might have been confounded for antimicrobials (e.g. metronidazole, vancomycin) often given to treat CDI or co-administered with antimicrobials associated with HCA-CDI. Intravenous vancomycin has been associated with CDI²⁷; however, vancomycin was associated with CDI in this study only when combined with other antimicrobials. We did not evaluate

appropriateness of prior antimicrobial use, in order to define avoidable HCA-CDI cases. Detailed demographic data and prior antimicrobial use were not collected for controls, as this dataset was collected to allow for a post hoc analysis. Using background antimicrobial and PPI data allowed for larger numbers and accounted for the potential of bias due to under-reporting of those agents in control patients in whom CDI was not considered. However, detailed characteristics of patients from whom the background use data were derived were not available. The largest hospital accounted for two thirds of the total OBDs; hence its infection rate largely determined the overall rate. The response rate to emails was only 19%, limiting conclusions about their impact; however, responses were not requested in the initial email, and still some useful clinical feedback was received. Due to the hospitals' geographic disparity, email remained the most pragmatic feedback method.

Patient complexity in our hospitals may be lower compared with larger metropolitan hospitals, limiting generalisability to those settings. Further studies combining evaluation of ASPs with targeted CDI interventions would be useful, particularly in multisite and non-metropolitan settings. In this study we identified high risk antimicrobial classes that have formed targets for ongoing AMS activities.

Our study demonstrates the high burden of HCA-CDI in a non-metropolitan setting. While it confirms the association between high-risk antimicrobial use and HCA-CDI, it also identifies the possibility of under-recognition of CDI severity criteria during treatment initiation. Targeted audit and feedback interventions may be a useful way of

consolidating the effects of a multisite ASP, contributing to sustainability, which remains one of the major challenges of contemporary antimicrobial stewardship.

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Conflict of interest

None declared.

References

- [1] Valiquette L, Cossette B, Garant MP, Diab H, Pepin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis* 2007; **45 Suppl 2**: S112-21.
- [2] Slimings C, Armstrong P, Beckingham WD, *et al*. Increasing incidence of *Clostridium difficile* infection, Australia, 2011-2012. *Med J Aust* 2014; **200**: 272-6.
- [3] Cheng AC, Ferguson JK, Richards MJ, *et al*. Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection. *Med J Aust* 2011; **194**: 353-8.
- [4] Gabriel L, Beriot-Mathiot A. Hospitalization stay and costs attributable to *Clostridium difficile* infection: a critical review. *J Hosp Infect* 2014; **88**: 12-21.
- [5] McGlone SM, Bailey RR, Zimmer SM, *et al*. The economic burden of *Clostridium difficile*. *Clin Microbiol Infect* 2012; **18**: 282-9.
- [6] Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *J Antimicrob Chemother* 2014; **69**: 881-91.
- [7] Vardakas KZ, Konstantelias AA, Loizidis G, Rafailidis PI, Falagas ME. Risk factors for development of *Clostridium difficile* infection due to BI/NAP1/027 strain: a meta-analysis. *Int J Infect Dis* 2012; **16**: e768-73.
- [8] Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012; **107**: 1011-9.

- [9] Talpaert MJ, Gopal Rao G, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection. *J Antimicrob Chemother* 2011; **66**: 2168-74.
- [10] Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis. *J Antimicrob Chemother* 2014; **69**: 1748-54.
- [11] Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P. Costs of nosocomial *Clostridium difficile*-associated diarrhoea. *J Hosp Infect* 2008; **70**: 15-20.
- [12] Thomas C, Riley TV. Restriction of third generation cephalosporin use reduces the incidence of *Clostridium difficile*-associated diarrhoea in hospitalised patients. *Commun Dis Intell Q Rep* 2003; **27 Suppl**: S28-31.
- [13] Brumley PE, Malani AN, Kabara JJ, Pisani J, Collins CD. Effect of an antimicrobial stewardship bundle for patients with *Clostridium difficile* infection. *J Antimicrob Chemother* 2016; **71**: 836-40.
- [14] Riley TV, Codde JP, Rouse IL. Increased length of hospital stay due to *Clostridium difficile* associated diarrhoea. *Lancet* 1995; **345**: 455-6.
- [15] Australian Institute of Health and Welfare. *Australian Hospital Peer Groups*., Canberra: AIHW 2015. Available at: <http://www.aihw.gov.au/haag09-10/number-of-hospitals/> [Accessed October 2013].
- [16] NHS Institute for Innovation and Improvement. Quality and Service Improvement Tools: Plan Do Study Act. UK: NHS Institute 2008. Available at:

- http://www.institute.nhs.uk/quality_and_service_improvement_tools/quality_and_service_improvement_tools/plan_do_study_act.html [Accessed 31 March 2013].
- [17] Guidance Group. Guidance MS. Melbourne Health 2013. Available at: <http://www.guidancems.org.au/> [Accessed June 2016].
- [18] HAI Technical Working Group. *Implementation Guide for Surveillance of Clostridium difficile Infection*. Sydney, Australia: Australian Commission on Safety and Quality in Health Care 2013.
- [19] Australian Institute of Health and Welfare. Australia refined diagnosis-related groups data cubes. Australian Institute of Health and Welfare 2016; Diagnosis related group information. Available at: <http://www.aihw.gov.au/hospitals-data/ar-drg-data-cubes/> [Accessed June 2016].
- [20] Linden A. Conducting interrupted time series analysis for single and multiple group comparison. *Stata Journal* 2015; **15**: 480-500.
- [21] Jury LA, Tomas M, Kundrapu S, Sitzlar B, Donskey CJ. A *Clostridium difficile* infection (CDI) stewardship initiative improves adherence to practice guidelines for management of CDI. *Infect Control Hosp Epidemiol* 2013; **34**: 1222-4.
- [22] 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. *Intern Med J* 2016; **46**: 479-93.
- [23] Pakyz A, Carroll NV, Harpe SE, Oinonen M, Polk RE. Economic impact of *Clostridium difficile* infection in a multihospital cohort of academic health centers. *Pharmacotherapy* 2011; **31**: 546-51.

- [24] Campbell R, Dean B, Nathanson B, Haidar T, Strauss M, Thomas S. Length of stay and hospital costs among high-risk patients with hospital-origin *Clostridium difficile*-associated diarrhea. *J Med Econ* 2013; **16**: 440-8.
- [25] Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *Clin Infect Dis* 2002; **34**: 346-53.
- [26] van Kleef E, Green N, Goldenberg SD, *et al.* Excess length of stay and mortality due to *Clostridium difficile* infection: a multi-state modelling approach. *J Hosp Infect* 2014; **88**: 213-7.
- [27] Hecht JR, Olinger EJ. Clostridium difficile colitis secondary to intravenous vancomycin. *Dig Dis Sci* 1989; **34**: 148-9.

Figure legends

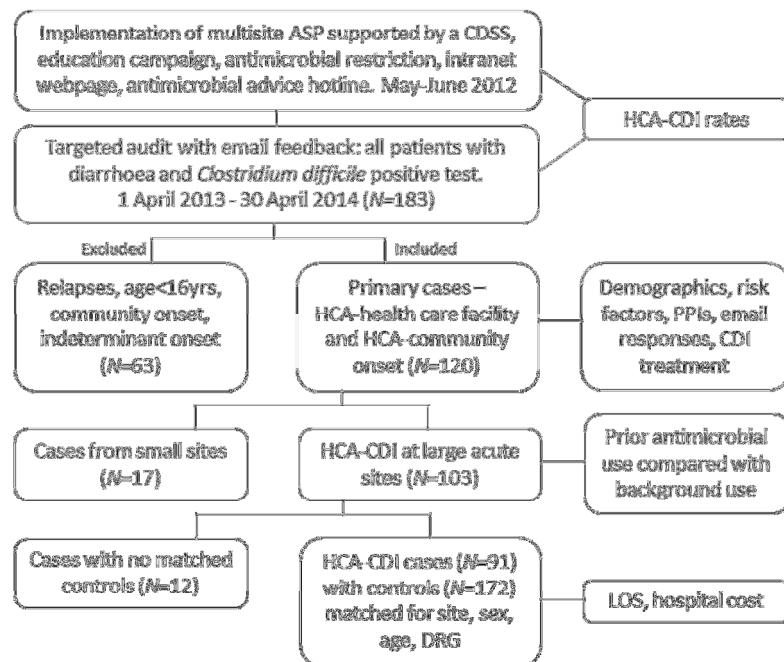


Figure 1: Study flowchart.

ASP, antimicrobial stewardship program; CDSS, clinical decision support system; HCA, healthcare associated; LOS, length of stay; risk factors, anti-peristaltic use, gastrointestinal surgery, immunosuppression; PPIs, proton pump inhibitors; HCA-CDI, healthcare associated *Clostridium difficile* infection; DRG, diagnosis-related group; background use, whole hospital prevalence data on antimicrobial use

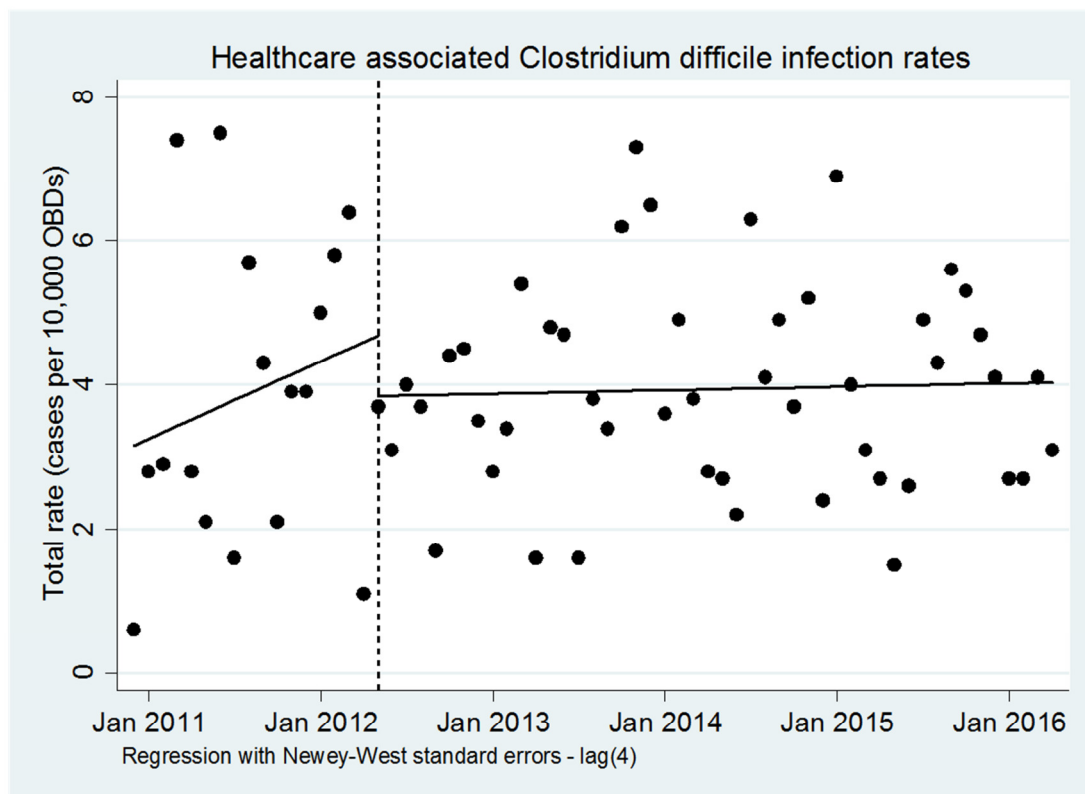


Figure 2: HCA-CDI rates for the three acute hospitals in Illawarra Shoalhaven Local Health District, Australia from December 2010 to April 2016

Vertical line, implementation of antimicrobial stewardship program; HCA-CDI, healthcare associated *Clostridium difficile* infection; OBD, occupied bed day.

Appendix A: Exemplar feedback email to admitting medical officer on *Clostridium difficile* infection case

Dear Doctor,

As part of routine antimicrobial stewardship activities we are conducting a prospective audit into all episodes of *C. diff* diarrhoea across the district.

Your patient X (MRN: 111111) was diagnosed with C. diff diarrhoea on dd/mm/yyyy.

Potential risk factors for your patient included:

(As appropriate)

- Proton pump inhibitor use –
- Anti-peristaltic use –
- Prior GI surgery –
- Immunosuppression –
- Antimicrobial use within one month prior to diagnosis –

Details of antimicrobial treatment of CDI.

I've attached a copy of the audit form for your information. Please don't hesitate to contact me if you have any questions.

Regards,

AMS pharmacist

Appendix B: HCA-CDI rates before and after implementation of an ASP

	Pre-ASP (Dec 2010 to April 2012)			Post-ASP (May 2012 to April 2016)			
	Initial level	Initial trend	p-value	Change in level	p-value	Change in trend	p-value
HCA CDI per 10,000 OBDs, n	3.07 ^a	0.09 ^a	0.23	-0.83 ^a	0.24	-0.08 ^a	0.26
(LCI, UCI)	(1.51-4.65)	(-0.06-0.24)		(-2.25-0.58)		(-0.24-0.07)	

Initial level, number of cases of HCA-CDI per 10,000 occupied bed days per month; initial trend, rate of increase per month; change in level, immediate difference between pre-intervention and post-intervention cases; change in trend, difference between pre-intervention and post-intervention trend by month; ASP, antimicrobial stewardship program, detail described in Methods; HCA-CDI, healthcare associated *Clostridium difficile* infection, data included for the three large acute hospitals of the health district; OBDs, occupied bed days; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval; ^aadjusted for first order autocorrelation;