2017

Outcomes of multisite antimicrobial stewardship programme implementation with a shared clinical decision support system

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Abstract

Background: Studies evaluating antimicrobial stewardship programmes (ASPs) supported by computerized clinical decision support systems (CDSSs) have predominantly been conducted in single site metropolitan hospitals.

Objectives: To examine outcomes of multisite ASP implementation supported by a centrally deployed CDSS.

Methods: An interrupted time series study was conducted across five hospitals in New South Wales, Australia, from 2010 to 2014. Outcomes analysed were: effect of the intervention on targeted antimicrobial use, antimicrobial costs and healthcare-associated Clostridium difficile infection (HCA-CDI) rates. Infection-related length of stay (LOS) and standardized mortality ratios (SMRs) were also assessed.

Results: Post-intervention, antimicrobials targeted for increased use rose from 223 to 293 defined daily doses (DDDs)/1000 occupied bed days (OBDs)/month (+32%, $P < 0.01$). Conversely, antimicrobials targeted for decreased use fell from 254 to 196 DDDs/1000 OBDs/month (-23%; $P < 0.01$). These effects diminished over time. Antimicrobial costs decreased initially ($-$AUD\$64551/month; $P < 0.01$), then increased ($+$AUD\$7273/month; $P < 0.01$). HCA-CDI rates decreased post-intervention (-0.2 cases/10 000 OBDs/month; $P < 0.01$). Proportional LOS reductions for key infections (respiratory from 4.8 to 4.3 days, $P < 0.01$; septicaemia 6.8 to 6.1 days, $P < 0.01$) were similar to background LOS reductions (2.1 to 1.9 days). Similarly, infection-related SMRs (observed/expected deaths) decreased (respiratory from 1.1 to 0.75; septicaemia 1.25 to 0.8; background rate 1.19 to 0.90.

Conclusions: Implementation of a collaborative multisite ASP supported by a centrally deployed CDSS was associated with changes in targeted antimicrobial use, decreased antimicrobial costs, decreased HCA-CDI rates, and no observable increase in LOS or mortality. Ongoing targeted interventions are suggested to promote sustainability.

Disciplines
Medicine and Health Sciences

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Outcomes of multisite antimicrobial stewardship program implementation with a shared clinical decision support system

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43

44   **Synopsis**

45   **Background**

46   Studies evaluating antimicrobial stewardship programs (ASPs) supported by computerised

47   clinical decision support systems (CDSSs) have predominantly been conducted in single site

48   metropolitan hospitals. The aim of this study was to examine outcomes of multisite ASP

49   implementation supported by a centrally deployed CDSS.

50   **Methods**

51   An interrupted time series study of a CDSS-supported multisite ASP was conducted across

52   five hospitals in New South Wales, Australia from 2010 to 2014. Outcomes analysed were:

53   effect of the intervention on targeted antimicrobial use, antimicrobial costs, healthcare

54   associated *Clostridium difficile* infection (HCA-CDI) rates, infection-related length of stay

55   (LOS), and standardised mortality ratios (SMRs).

56   **Results**

57   Post-intervention, antimicrobials targeted for increased use rose from 223 to 293 defined

58   daily doses (DDDs)/1000 occupied bed days (OBDs)/month (+32%, $p<0.01$). Conversely,

59   antimicrobials targeted for decreased use fell from 254 to 196 DDDs/1000 OBDs/month (-

60   23%; $p<0.01$). These effects diminished over time. Antimicrobial costs decreased initially (-

61   AUD\$64,551/month; $p<0.01$), then increased (+AUD\$7,273/month; $p<0.01$). HCA-CDI rates

62   decreased post-intervention (-0.2 cases/10,000 OBDs/month; $p<0.01$). Proportional LOS

63   reductions for key infections (respiratory 4.8 to 4.3 days, $p<0.01$; septicaemia 6.8 to 6.1

64   days, $p<0.01$) were similar to background LOS reductions (2.1 to 1.9 days). Similarly,

65   infection-related SMRs (observed/expected deaths) decreased (respiratory 1.1 to 0.75,

66   p<0.01; septicaemia 1.25 to 0.8, p<0.01; background rate 1.19 to 0.90, p<0.01).

67   **Conclusions**

68   Implementation of collaborative multisite ASP supported by a centrally deployed CDSS was

69   associated with changes in targeted antimicrobial use, decreased antimicrobial costs,

70   decreased HCA-CDI rates, and no observable increase in LOS or mortality. Ongoing targeted

71   interventions are suggested to promote sustainability.

72   249 words including headings

73 Introduction

74 Antimicrobial stewardship programs (ASPs) aim to improve appropriateness of antimicrobial

75 prescribing with the goals of more effectively treating and preventing infections, while

76 curbing antimicrobial resistance and reducing adverse effects.[1, 2] Studies examining the

77 impact of ASPs have primarily been conducted in tertiary metropolitan hospitals.[3-8] There is

78 limited literature describing clinical outcomes from collaboratively implemented ASPs across

79 multiple hospital sites.[8-11] Previous single site ASP studies have demonstrated benefits using

80 a computerised clinical decision support system (CDSS), antimicrobial restriction, and

81 prospective audit and feedback.[3-6, 12] These benefits include a reduction in targeted

82 antimicrobial use,[4, 12, 13] antimicrobial drug acquisition costs,[4, 13, 14] and healthcare associated

83 *Clostridium difficile* infection (HCA-CDI) rates.[13, 15] An evidence gap exists for

84 implementation of ASPs across multiple sites using a centrally deployed CDSS.[2]

85 Metrics for evaluating ASPs include antimicrobial use, drug costs, adverse effects such as

86 HCA-CDI and antimicrobial resistance, length of stay (LOS), and mortality.[16, 17] Infection-

87 related outcomes related to community-acquired pneumonia (CAP), skin and soft tissue

88 infections and septicaemia have been also been recommended.[16] Although there are

89 confounders associated with their use as ASP metrics, LOS and mortality are useful

90 balancing measures to address potential unintended consequences.[12]

91 To our knowledge, no studies of multisite ASPs using a centrally deployed CDSS have

92 included non-metropolitan hospitals. The aims of this study were to evaluate the impact of a

93 CDSS-supported, multisite ASP on antimicrobial use, antimicrobial costs, HCA-CDI rates,

94 infection-related LOS, and standardised mortality ratios (SMRs).

95   **Methods**

96   **Setting**

97   In 2012 a multisite ASP supported by a centrally deployed CDSS was implemented in 12

98   hospital sites (**Figure 1**) across the South Eastern Sydney and Illawarra Shoalhaven Local

99   Health Districts, and Sydney Children's Hospital, all in New South Wales (NSW), Australia.

100 These districts cover a geographic area of 6,331 square kilometres and have an estimated

101 population of 1.17 million, extending from central Sydney to three hours' drive south.[18]

102 Comparable adult metrics were available for analysis in five hospitals, comprising 1900 beds,

103 as shown in **Figure 1**. The remaining hospitals were not included in the study for the

104 following reasons: small size, ASP implementation outside of study period, specialist (i.e.

105 obstetrics, paediatrics) or subacute admissions (**Figure 1**). Those attributes would not allow

106 comparison of outcomes such as antimicrobial use, LOS or HCA-CDI. The specialist paediatric

107 hospital contributed to the development of guidelines for paediatric services within the

108 other hospitals. Hospitals shared antimicrobial stewardship strategies, including a centrally

109 deployed CDSS (Guidance MS®, Melbourne Health[19]), educational material and similar

110 antimicrobial formulary restrictions. Further information on case complexity and case mix of

111 the included study hospitals is provided in **Supplementary Table 1**.

112 **Intervention**

113 An interrupted time series (ITS) study was conducted combining data from five acute

114 hospitals. The intervention point for the ASP was defined as the go-live date of the CDSS

115 with concurrent dissemination of standardised clinical guidelines at each site (May-July

116 2012). This occurred in the setting of a 6-month lead-in period of prior education and clinical

117   guideline development (**Figure 1**). The fully modifiable CDSS, Guidance MS® is an intranet

118   browser-based CDSS that guides prescribers on appropriate use and generates approvals for

119   antimicrobials.[19] Antimicrobial restriction (a key component of our ASP) within the CDSS is

120   determined on the basis of spectrum of action, potential toxicity or cost.[19] Implementation

121   of the CDSS used project methodology (PRINCE2®, ILX Group, Mulgrave, Victoria, Australia)

122   and was overseen by a multidisciplinary committee of medical, pharmacy, information

123   technology (IT), and executive staff. The committee met monthly via teleconference and

124   collaborated closely throughout the project implementation period (May 2011 - May 2012).

125   This period was critical to optimise organisational readiness for implementation of a CDSS-

126   supported ASP.[1]

127   Clinical guidelines were standardised across the hospitals and incorporated into the CDSS.

128   The development of guidelines, educational content and decision support was shared by

129   adult and paediatric Infectious Diseases (ID) physicians and antimicrobial stewardship

130   pharmacists. This allowed for a standardised intervention that was tailored to hospital size

131   and level of acuity (**Figure 1**), thereby reducing individual hospital workload, allowing access

132   to clinical expertise at smaller sites and ensuring timely consensus on CDSS clinical content.

133   Staffing (ID physicians, pharmacists and microbiologists) varied across the hospital sites, so

134   intranet-based guidelines and an antibiotic advice hotline were used to promote access to

135   program resources. Standardised bimonthly nationally benchmarked antimicrobial usage

136   audits were reported to respective hospital antimicrobial stewardship committees.[20] Prior

137   to the study, antimicrobial stewardship activities were restricted to phone-based advice,

138   formal infectious diseases consults, some selective microbiology reporting and a phone-

139   based approval system at one study hospital (**Figure 1**). Study investigators classified the

140   most commonly used antimicrobial classes into two categories, either targeted for increased

141   or decreased use. Categorisation was based on the following factors: local antimicrobial

142   resistance patterns, local use compared with benchmarked hospitals,[20] risk of HCA-CDI and

143   other side effects, compliance with antibiotic guidelines,[21] and cost. Antimicrobials targeted

144   for increased use were benzylpenicillin, doxycycline and aminopenicillins, whereas

145   antimicrobials targeted for decreased use were third generation cephalosporins, macrolides,

146   anti-pseudomonal beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones,

147   and carbapenems. Some antimicrobials were targeted for increased use in some settings,

148   but decreased use in others. For example, local quality audits identified underdosing in

149   surgical prophylaxis, but unnecessarily long duration of therapy in other settings such as

150   cellulitis (data not shown). Such antimicrobials (i.e. first generation cephalosporins,

151   flucloxacillin, aminoglycosides, and vancomycin) were only included in the overall

152   antimicrobial use analysis.

153   There were no major changes to infection control policies related to either *Clostridium*

154   *difficile* or hand hygiene during the study period. Infection control measures recommended

155   by local policies included: isolation in single rooms; use of disposable gowns and gloves;

156   hand hygiene with alcohol-based hand rub and/or soap and water; and terminal cleaning

157   with chlorine-based disinfectant. Diagnostic testing methods were standardised from May

158   2010, and comprised first line testing with targeted glutamate dehydrogenase (GDH)

159   antigen and toxins A and B (C. Diff Quik Chek Complete®, Techlab, Blacksburg, VA, USA).

160   Discordant results occasioned the use of a polymerase chain reaction (PCR; GeneXpert®,

161   Cepheid, Sunnyvale, CA, USA) test. All diarrhoeal stools were subjected to testing from

162   December 2010 (seven months after the beginning of the pre-intervention period.

163 **Outcomes**

164 The effect of the intervention was assessed by: (1) change in antimicrobials targeted for

165 increased use (benzylpenicillin, doxycycline and aminopenicillins) expressed as defined daily

166 doses (DDDs) per 1000 occupied bed days (OBDs); (2) change in antimicrobials targeted for

167 decreased use (third generation cephalosporins, macrolides, anti-pseudomonal beta-

168 lactam/beta-lactamase inhibitor combinations, fluoroquinolones, and carbapenems;

169 DDDs/1000 OBDs);[22] (3) change in total monthly antimicrobial costs (Australian dollars

170 [AUD$]). High cost antifungals (liposomal amphotericin, anidulafungin, caspofungin,

171 posaconazole, and voriconazole) were analysed separately to the main antimicrobial group,

172 due to small variations in use accounting for large cost variations; (4) change in HCA-CDI

173 rates, defined as a positive laboratory test for toxigenic *Clostridium difficile* plus diarrhoea

174 onset greater than 48 hours after hospital admission (HCA-CDI cases per 10,000 OBDs);[23]

175 and (5) change in LOS and in-hospital SMR for respiratory tract infections, cellulitis, kidney

176 and urinary tract infections, and septicaemia, compared with background figures for all

177 conditions (infectious and non-infectious combined). Confounders for each of the above

178 measures were also investigated and reported where appropriate. Those included infection

179 outbreaks, updated guidelines, changes to drug acquisition costs and administrative

180 changes.

181 **Data sources**

182 Adult inpatient data were included from May 2010 to July 2014. Antimicrobial use and

183 acquisition cost data were obtained from pharmacy dispensing software, iPharmacy®

184 Versions 5.5 and 5.6 (CSC, Sydney, Australia). Antimicrobial use data were processed by the

185 National Antimicrobial Utilisation Surveillance Program (NAUSP)[20] using WHO classifications.

186   Occupied bed day data were sourced from the hospitals' performance units. HCA-CDI

187   numbers were provided by the infection control teams in line with standardised surveillance

188   and reporting.[23] LOS (using Australian refined diagnosis related groups[24]) and SMRs (using

189   principal diagnosis codes, based on International Classification of Diseases, 10th revision,

190   Australian modification[24]) were provided by the performance units for the following key

191   infections: respiratory infections/inflammations (predominantly pneumonia), cellulitis, and

192   kidney and urinary tract infections. Those were the commonest treatment indications for

193   antimicrobials in the 2014 Australian National Antimicrobial Prescribing Survey (NAPS).[25]

194   Septicaemia was also included due to its high mortality.[26] LOS and SMRs were compared for

195   the time periods 1 July 2010 – 30 June 2012 and 1 July 2012 – 30 June 2014, as only data

196   aligned with Australian financial years was available. Analysis of overall LOS excluded day

197   case haemodialysis admissions. Comparative case complexity and case mix of the study

198   hospitals was reported using National Weighted Activity Units (NWAUs)[27] and diagnosis

199   related groups (**Supplementary Table 1**).[24]

200   **Statistical analyses**

201   Interrupted time series (ITS) analysis with segmented linear regression was used to examine

202   the impact of the intervention on monthly antimicrobial use, costs and HCA-CDI, estimating

203   the immediate effects of the intervention and changes in trend.[28] To account for seasonal

204   variations, 24 time points one month apart were used pre- and post-intervention.[14] To allow

205   for statistical analysis of two years pre- and two years post-intervention, the intervention

206   point (go-live date of CDSS) was aligned for the five hospitals, with individual hospital data

207   included as **Supplementary Tables 2-11**. Definitions for ITS were: (1) initial level, model-

208   predicted level (antimicrobial use, cost, HCA-CDI) 24 months pre-intervention; (2) initial

209   trend, model-predicted monthly trend pre-intervention; (3) change in level (immediate

210   effect), model-predicted difference between the level at the end of the pre-intervention

211   period and commencement of the post-intervention period;[3] (4) change in trend, model-

212   predicted difference between monthly initial (pre-intervention) trend and post-intervention

213   trend. Autocorrelation using Newey-West approximation for standard errors was

214   investigated and an appropriate lag was used when necessary, in order to assess for

215   similarity between observations.[28] LOS was assessed using Mann-Whitney U-test. A logistic

216   regression model was used to calculate the number of expected deaths using: age; sex;

217   admission type (emergency or acute); admission source (acute transfer or other); principal

218   diagnosis, and Charlson Comorbidity Index (0, 1-2, or 3+).[29] Additional variables used in the

219   expected deaths analysis related to vascular surgery, cardiac surgery, neurosurgery, trauma

220   and transplant. Those figures were then used to calculate infection-related and total SMR

221   (actual deaths/expected deaths). SMRs (pre- and post-intervention) were expressed with

222   95% CIs. Statistical significance was considered $p<0.05$. Statistical analyses were performed

223   using Stata® Statistical Software: Release 14 (Statacorp 2015; College Station, TX, USA).

224   Ethics approval was obtained from the districts' Human Research Ethics Committees,

225   approval number HE13/137

226   **Results**

227   **Antimicrobial use**

228   Following the intervention, a rise in antimicrobials targeted for increased use of 70

229   DDDs/1000 OBDs (+32%; p<0.01) was observed, followed by a decline in trend of 3.5

230   DDDs/1000 OBDs per month (p<0.01). A concomitant reduction in antimicrobials targeted

231   for decreased use of 58 DDDs/1000 OBDs (-23%; p<0.01) was observed, followed by a rise in

232   trend of 3.4 DDDs/1000 OBDs per month (p<0.01; **Table 1, Figure 2**). No significant change

233   in level or trend was observed for overall antimicrobial use. There was a national shortage

234   of benzylpenicillin in 2010-11; ampicillin was recommended as an alternative for most

235   benzylpenicillin indications during this time. The national antimicrobial guidelines[21, 30] were

236   updated in 2010 and again in 2014.

237   **Antimicrobial costs**

238   There was a significant reduction in total monthly antimicrobial costs of AUD$64,551 (-17%;

239   p<0.01) post-intervention, followed by an increase in trend of AUD$7,273 per month

240   (p<0.01; **Table 2**). This corresponded to a reduction of AUD$1.70/OBD post-intervention (-

241   20%; p<0.01), with a subsequent increase in trend of AUD$0.26/OBD per month (p<0.01).

242   High cost antifungals demonstrated an immediate cost reduction (p<0.01), with no

243   significant increase in trend. Some changes in acquisition costs were noted prior to the

244   intervention, most notably a reduction in meropenem acquisition costs in mid-2011.

245   **HCA-CDI rates**

246   HCA-CDI rates were increasing pre-intervention from 2.8 to 6.2 cases/10,000 OBDs per

247   month (p<0.01). A reduction was demonstrated post-intervention (-1.2 cases/10,000

248 OBDs/month, p=0.15), followed by a decrease in trend (p<0.01; **Table 2, Figure 3**). There

249 were no systemic changes to hand hygiene, isolation or cleaning policies during the study

250 period. The rate of hand hygiene compliance had increased across facilities following

251 national initiatives prior to 2009. There were no notable HCA-CDI outbreaks from 2010-

252 2014.

253 **LOS**

254 Median LOS was reduced for respiratory infections (4.8 to 4.3 days, p<0.01), cellulitis (3.2 to

255 2.9 days, p<0.01), urinary and kidney infections (3.3 to 2.9 days, p<0.01), and septicaemia

256 (6.8 to 6.1 days, p<0.01; **Table 3**). Over the same time period, median LOS for all hospital

257 admissions also decreased from 2.1 to 1.9 days (p<0.01).

258 **In-hospital SMR**

259 SMRs decreased for respiratory infections (1.10 [95%CI 1.01-1.20] to 0.75 [0.68-0.82]

260 observed/expected deaths), urinary and kidney infections (0.78 [0.52-1.10] to 0.63 [0.42-

261 0.91]), and septicaemia (1.25 [1.12-1.38] to 0.80 [0.72-0.89]). Reductions in those infection-

262 related SMRs were in line with the reduction in background SMR (1.19 [1.15-1.23] to 0.90

263 [0.87-0.93]; **Table 3**). A small increase was observed for cellulitis (0.55 [0.28-0.95] to 0.66

264 [0.38-1.05]).

265

Discussion

266 **Discussion**

267 To our knowledge, this is the first study to evaluate implementation of a multisite ASP

268 supported by a centrally deployed CDSS. We found significant improvements in

269 antimicrobial use, demonstrated by changes in antimicrobials targeted for increased and

270 decreased use. There were significant reductions in antimicrobial costs and HCA-CDI rates.

271 Safety of the intervention was supported by decreased or unchanged LOS and SMRs for key

272 infections during the study period. The long-term impact of the intervention on

273 antimicrobial use and cost diminished over time, which suggests that ongoing program

274 reinforcement and targeted interventions may be required to alleviate "antimicrobial

275 stewardship fatigue". Changes in overall antimicrobial use prior to the main intervention

276 probably resulted from an intensive education campaign across the hospitals, with

277 heightened awareness of the impending change among clinicians. The importance of

278 readiness assessments prior to implementation was recognised, along with shared

279 interventions across the study hospitals. Those included antimicrobial stewardship ward

280 rounds with post-prescription review and feedback, consensus guidelines, and antimicrobial

281 restriction.

282 Some studies have evaluated ASPs across multiple hospital sites[8, 9, 31] and the utility of an

283 individual site CDSS for improvement in antimicrobial prescribing;[3, 32-34] however, the

284 combination of these two approaches is novel. Furthermore, this collaborative ASP was

285 applied to non-metropolitan settings with an established structure of support from a larger

286 hospital. Pooling data across five hospitals enhanced the potential to identify effects of the

287 ASP. Few randomised studies have been conducted to determine the effect of ASPs.[8, 12] Our

288 study used interrupted time series analysis, which is considered an alternative pragmatic

289   approach with strong quasi-experimental design.[35] Comparison with control hospitals would

290   have strengthened the study design; however, there were none available in the health

291   districts due to widespread implementation of the ASP.

292   Our study demonstrates that shared knowledge and expertise can be used to effectively

293   implement an ASP across multiple hospital sites spanning a wide geographic area. The

294   economies of scale enjoyed by the multisite approach allowed for collective interventions to

295   be employed with reduced workload at individual hospital sites. Multisite implementation

296   also alleviated some of the potential disadvantages of the CDSS, such as resources required

297   for implementation and maintenance.[2] An additional benefit of extensive multisite

298   intervention was consistency in antimicrobial prescribing guidelines, facilitating the training

299   of medical officers rotating through the facilities within the districts' different hospitals. A

300   consistent, multisite approach was also anticipated to enhance prescriber confidence and

301   facilitate the quality improvement culture necessary to effect longer term improvements in

302   antimicrobial prescribing.[36, 37]

303   ASPs are a key element of the approach to reducing HCA-CDI.[38] Importantly, our

304   intervention was associated with a reduction in HCA-CDI rates, as well as a decrease in trend

305   that persisted over time. This occurred in the context of increasing community CDI rates.[39]

306   The specialist paediatric hospital and paediatric wards from study sites were not included in

307   this analysis. Non-comparability of standard adult metrics such as DDDs results in difficulty

308   benchmarking antimicrobial use in children.[40] HCA-CDI cannot easily be assessed in the

309   paediatric population due to asymptomatic carriage in infants and lower rates of

310   symptomatic CDI in children.[41] Although quantitative paediatric data were not included in

311   this study, paediatric guideline and CDSS development were important for multisite ASP

312   implementation across the network of small rural to large metropolitan hospitals.

313   Maintaining cost effectiveness is of concern to administrators.[42] Placing drug costs as the

314   primary measure of cost analysis does not take into account changes in acquisition costs

315   (e.g. when drugs come off patent). In addition, the most appropriate antimicrobial is not

316   necessarily the lowest in price. Identifying other methods of cost benefit analysis is justified,

317   such as the impact of healthcare associated infections, and the increased cost of treating

318   resistant organisms.[43] Some cost savings were attributed to reductions in drug acquisition

319   costs, such as for meropenem in 2011. Paradoxically, the intervention was associated with

320   increased drug costs in some instances. Benzylpenicillin, targeted for increased use, had a

321   daily cost at usual dosing (1.2g intravenously 6 hourly) of AUD$25, compared with

322   ceftriaxone (targeted for decreased use; AUD$1.30 for 1g intravenously daily). In addition,

323   the post-intervention cost increase may have been driven by high cost antifungal use where

324   treatment of a small number of patients may result in a significant increase in drug costs.

325   Building works at some of the sites, leading to increased prophylaxis and treatment of

326   invasive fungal infections, may have led to this increase. However, antifungals were not a

327   main target of the collaborative ASP as they were already highly restricted prior to the

328   intervention. Costs of the intervention were not analysed as part of this study; there were

329   costs associated with purchasing the CDSS, and additional pharmacy and ID resources in

330   supporting the ASPs.

331   There were some other limitations to this study. Antimicrobial use patterns may also have

332   been affected by unforeseen drug shortages and changes to infection control practices.

333   There were no systematic changes to the infection control policies across the districts during

334   the study period, and no recognised outbreaks of CDI occurred during this time. Some

335   measures were not included due to a lack of comparable pre- and post-intervention data

336   across sites; these included the impact of antimicrobial stewardship ward rounds, point

337   prevalence survey results and antimicrobial resistance patterns. Antimicrobials analysed

338   included only those targeted for increased (e.g. benzylpenicillin) or decreased (e.g.

339   ceftriaxone) use. Not all antimicrobial classes were reported individually, such as

340   glycopeptides (e.g. vancomycin) and first generation cephalosporins (e.g. cephazolin,

341   cephalexin). Although often targeted in ASPs, based on national guidelines[21] there were

342   instances where these classes were targeted for either increased or decreased use. As such,

343   it was not clear whether the ASP would result in a change to use. Reserve antibacterial

344   agents such as linezolid and daptomycin were already highly restricted prior to the

345   intervention, requiring prior physician approval before use.

346   The effect of the intervention was not uniform across the sites. Reasons for this variability

347   may have included differences in maturity of existing antimicrobial stewardship initiatives

348   prior to the introduction of the CDSS, disparate levels of acuity, and variable patterns of

349   resistance. Pre-existing antimicrobial stewardship initiatives at all sites consisted of selective

350   microbiology reporting, limited ID and microbiology phone support, and some departmental

351   education, with one site additionally using a phone-based approval system (**Figure 1**). There

352   was variation in case complexity and case mix between study hospitals, which may have

353   justified some differences in antimicrobial use. Additionally, seasonal variation was evident

354   in the antimicrobial use patterns. Those confounders may have been alleviated by using

355   combined antimicrobial use data with sufficient pre- and post-intervention time points for

356   the ITS analysis. Data on antimicrobial use, cost and HCA-CDI data could not be aligned

357   perfectly in time with LOS and mortality data due to report limitations; however, the

358   maximum lag (for one hospital) was only 6 weeks over a 48 month period. Infection-related

359   and overall LOS decreased after the intervention, which may have been due to increased

360   use of hospital in the home services. There may have been potential confounders, such as

361   changes to funding and hospital admission models that affected LOS and SMR during the

362   intervention which were difficult to quantify. However, LOS and SMR were included as

363   important balancing measures as they could potentially be negatively impacted by changed

364   patterns of antimicrobial use. Statewide programs were also introduced by the New South

365   Wales Clinical Excellence Commission through 2010-2014 to improve management of

366   deteriorating patients (*Between the Flags* program) and recognition and management of

367   sepsis (*Sepsis Kills* program).[44] Those initiatives potentially contributed to the improvements

368   in LOS and SMR in the post-intervention period.

369   We anticipate that our findings would be generalisable to healthcare facilities with potential

370   for utilising shared resources, such as those with existing professional or political networks.

371   Additional studies using prospective methodological approaches in different settings would

372   help to validate our results.

373   **Conclusion**

374   Implementation of a multisite ASP supported by a centrally deployed CDSS was associated

375   with significant changes to targeted antimicrobial use, containment of antimicrobial

376   expenditure and reduction in HCA-CDI, without obvious adverse effects. Ongoing targeted

377   interventions involving education and behaviour change are required to sustain the benefits

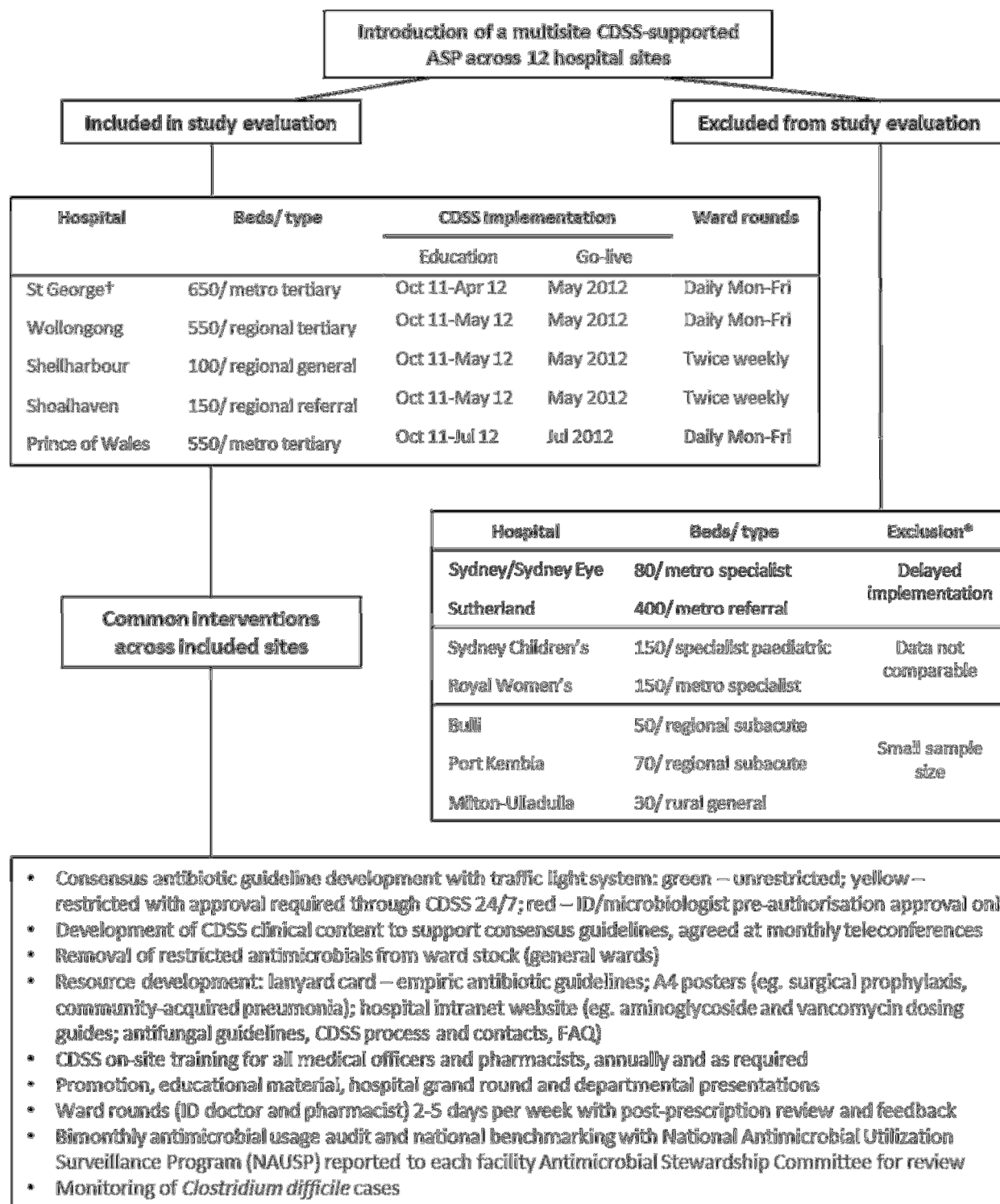378   of ASPs on hospital antimicrobial use.

393

394   **References**

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Introduction of a multisite CDSS-supported ASP across 12 hospital sites

Included in study evaluation

Hospital	Beds/ type	CDSS implementation		Ward rounds
		Education	Go-live	
St George†	650/ metro tertiary	Oct 11-Apr 12	May 2012	Daily Mon-Fri
Wollongong	550/ regional tertiary	Oct 11-May 12	May 2012	Daily Mon-Fri
Shellharbour	100/ regional general	Oct 11-May 12	May 2012	Twice weekly
Shoalhaven	150/ regional referral	Oct 11-May 12	May 2012	Twice weekly
Prince of Wales	550/ metro tertiary	Oct 11-Jul 12	Jul 2012	Daily Mon-Fri

Excluded from study evaluation

Hospital	Beds/ type	Exclusion*
Sydney/Sydney Eye	80/ metro specialist	Delayed implementation
Sutherland	400/ metro referral	
Sydney Children's	150/ specialist paediatric	Data not comparable
Royal Women's	150/ metro specialist	
Bulli	50/ regional subacute	Small sample size
Port Kembla	70/ regional subacute	
Milton-Ulladulla	30/ rural general	

Common interventions across included sites

- Consensus antibiotic guideline development with traffic light system: green – unrestricted; yellow – restricted with approval required through CDSS 24/7; red – ID/microbiologist pre-authorisation approval only
- Development of CDSS clinical content to support consensus guidelines, agreed at monthly teleconferences
- Removal of restricted antimicrobials from ward stock (general wards)
- Resource development: lanyard card – empiric antibiotic guidelines; A4 posters (eg. surgical prophylaxis, community-acquired pneumonia); hospital intranet website (eg. aminoglycoside and vancomycin dosing guides; antifungal guidelines, CDSS process and contacts, FAQ)
- CDSS on-site training for all medical officers and pharmacists, annually and as required
- Promotion, educational material, hospital grand round and departmental presentations
- Ward rounds (ID doctor and pharmacist) 2-5 days per week with post-prescription review and feedback
- Bimonthly antimicrobial usage audit and national benchmarking with National Antimicrobial Utilization Surveillance Program (NAUSP) reported to each facility Antimicrobial Stewardship Committee for review
- Monitoring of *Clostridium difficile* cases

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501

502   **Figure 1**: Population, clinical setting, nature and timing of interventions

503   *Cross* †Phone-based antimicrobial stewardship with formulary restriction implemented Nov

504   2008

505   *Star symbol* *Exclusions: delayed implementation, hospital sites had delayed recruitment of

506   specialist staff and inadequate reporting of antimicrobial benchmarking data; data not

507   comparable, specialist children's and women's hospitals with non-comparable patient and

508   case mix; small sample size, antimicrobial use and cost data not reported to the National

509   Antimicrobial Utilisation Surveillance Program (NAUSP); CDI, LOS and mortality data not

510   analysed due to small sample size and high proportion of sub-acute admissions

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Antimicrobials targeted for increased use

Regression with Newey-West standard errors - lag(1)

Antimicrobials targeted for decreased use

Regression with Newey-West standard errors - lag(0)

All antimicrobials

Regression with Newey-West standard errors - lag(1)

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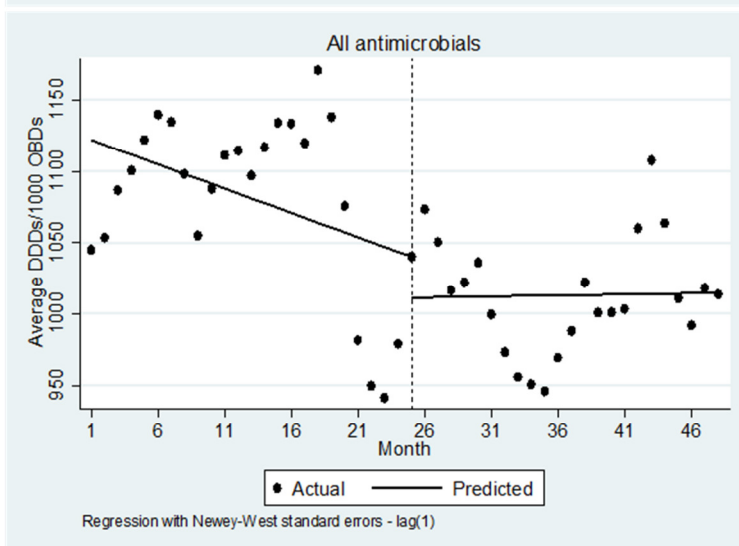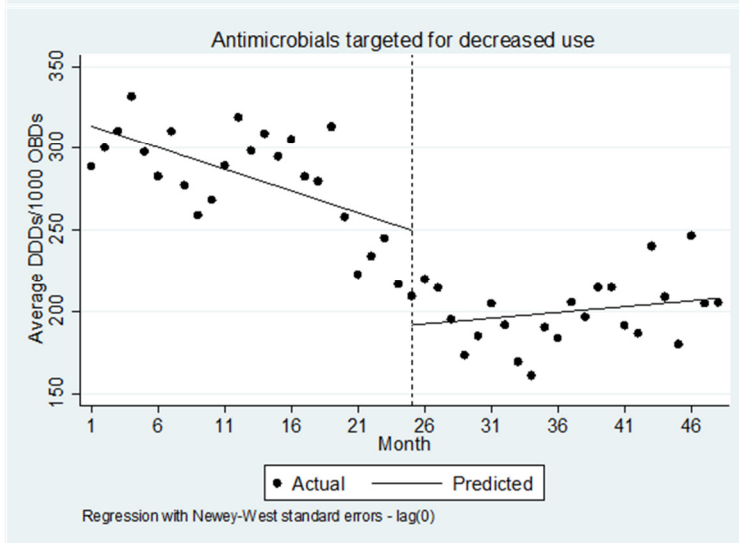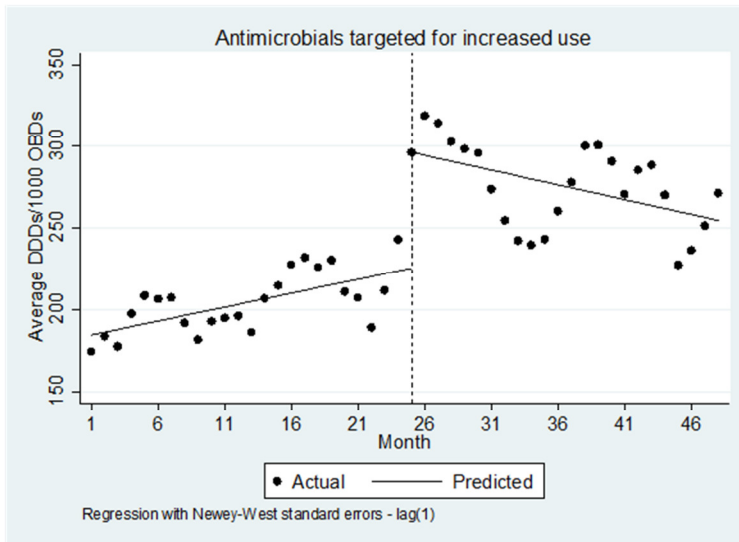
515 **Figure 2**: Impact of CDSS-supported multisite ASP on monthly antimicrobial use

516 Abbreviations: DDDs, defined daily doses; OBDs, occupied bed days

517 Targeted for increased use: benzylpenicillin, doxycycline, aminopenicillins (amoxicillin and

518 ampicillin); targeted for decreased use: third generation cephalosporins (ceftriaxone,

519 cefotaxime), macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin), anti-

520 pseudomonal penicillins (piperacillin/tazobactam, ticarcillin/clavulanic acid),

521 fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin); carbapenems (ertapenem,

522 doripenem, imipenem/cilastatin, meropenem) total antimicrobials, all antimicrobials

523 excluding antifungals and antivirals; vertical line is introduction of a CDSS-supported ASP,

524 including antimicrobial restriction and education.

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528   **Figure 3**: Impact of CDSS-supported multisite ASP on monthly healthcare associated

529   *Clostridium difficile* infection rates

530   Abbreviations: HCA-CDI, healthcare associated *Clostridium difficile* infection

531   Two years of monthly HCA-CDI rates pre- and post-intervention; vertical line is introduction

532   of a CDSS-supported ASP.

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Table 1: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use

Antimicrobial	Pre-intervention							Post-intervention							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Combined targeted for increased use	182[a]	170	195	1.7[a]	0.7	2.8	<0.01	71[a]	43	98	<0.01	-3.5[a]	-5.3	-1.7	<0.01
Combined targeted for decreased use	316	298	334	-2.6	-4.1	-1.2	<0.01	-58	-87	-29	<0.01	3.4	1.4	5.3	<0.01
Total antimicrobial use	1125[a]	1033	1184	-3.4[a]	-8.9	2.1	0.22	-29[a]	-129	71	0.57	3.55[a]	-2.6	9.7	0.25

Antimicrobial use (level) expressed as average defined daily doses/1000 occupied bed days for five hospitals, as reported to NAUSP; trends: positive value represents increase, negative value represents decrease; 95% confidence intervals expressed as LCI (lower confidence interval) and UCI (upper confidence interval); [a]adjusted for first order autocorrelation; targeted for increased use: benzylpenicillin, doxycycline, aminopenicillins (amoxycillin, ampicillin); targeted for decreased use: third generation cephalosporins (ceftazidime, cefotaxime, ceftriaxone); macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin); anti-pseudomonal penicillins (piperacillin/tazobactam, ticarcillin/clavulanic acid); fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin); carbapenems (meropenem, ertapenem, doripenem, imipenem/cilastatin); individual hospital data provided in **Supplementary Tables 2-6**.
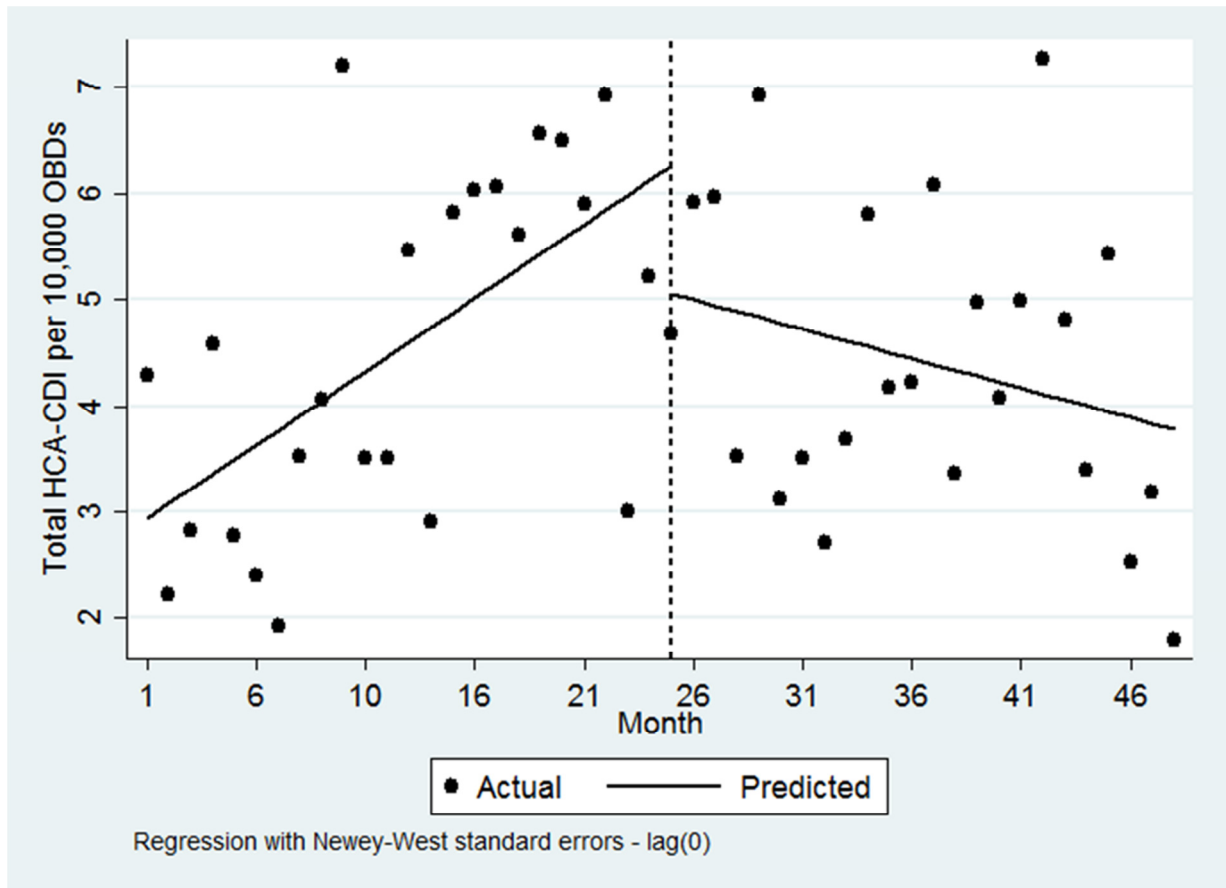
Table 2: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare associated *Clostridium difficile* infection

Variable	Pre-intervention							Post-intervention							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total[b] costs ($AU)	**463375**[a]	417101	509649	**-3196**[a]	-5759	-633	0.02	**-64551**[a]	-106056	-23044	<0.01	**7273**[a]	3899	10649	<0.01
Costs per OBD ($AU)	**9.9**	8.7	11.1	**-0.07**	-0.14	-0.01	<0.01	**-1.7**	-2.6	-0.8	<0.01	**0.26**	0.18	0.34	<0.01
Antifungal[c] costs ($AU)	**92575**	67721	117429	**2021**	376	3666	0.02	**-50270**	-86637	-13903	<0.01	**1117**	-1504	3738	0.40
HCA-CDI per 10,000 OBDs	**2.8**	1.7	3.9	**0.14**	0.06	0.22	<0.01	**-1.2**	-2.8	0.4	0.15	**-0.2**	-0.3	0.1	<0.01

Abbreviations: OBD, occupied bed day; $AU, Australian dollars; HCA CDI, healthcare associated *Clostridium difficile* infection.

[a]adjusted for first order autocorrelation; trends: positive value represents increase, negative value represents decrease; [b]antibacterial, antifungal, antiviral [c]high cost antifungals: liposomal amphotericin, anidulafungin, caspofungin, posaconazole, voriconazole; individual hospital data provided in **Supplementary Tables 7-11.**

Table 3: Length of stay and standardised mortality ratio by clinical infection group

Outcome measure	Length of stay					Standardised mortality ratio			
	July 10 – June 12		July 12 – June 14			July 10 – June 12		July 12 – June 14	
	Episodes	Median LOS (IQR), days	Episodes	Median LOS (IQR), days	p value	Standardised mortality ratio (95% CI)	Actual/ expected deaths	Standardised mortality ratio (95% CI)	Actual/ expected deaths
Respiratory infections	5,489	4.8 (2.8-7.8)	5640	4.3 (2.5-7.1)	<0.01	1.10 (1.01-1.20)	534/485	0.75 (0.68-0.82)	436/584
Cellulitis	3,696	3.2 (1.6-5.8)	3757	2.9 (1.2-5.0)	<0.01	0.55 (0.28-0.95)	12/22	0.66 (0.38-1.05)	17/26
Urinary and kidney infections	4,323	3.3 (1.2-5.2)	4364	2.9 (1.0-5.2)	<0.01	0.78 (0.52-1.10)	30/39	0.63 (0.42-0.91)	29/46
Septicaemia	1,610	6.8 (4.0-11.7)	2441	6.1 (3.5-10.9)	<0.01	1.25 (1.12-1.38)	350/281	0.80 (0.72-0.89)	359/450
Overall	224,021	2.1 (0.6-5.6)	242,383	1.9 (0.5-5.0)	<0.01	1.19 (1.15-1.23)	3795/3193	0.90 (0.87-0.93)	3647/4063

Abbreviations: LOS, length of stay; IQR, interquartile range; CI, confidence interval

Respiratory infections/inflammations, code E62; cellulitis, code J64; urinary and kidney infections, code, L63; septicaemia, code T60; overall

LOS excludes haemodialysis day admissions. Codes for LOS used Australian refined diagnosis related group definitions; codes for SMR used

principal diagnosis codes, based on International Classification of Diseases, 10th revision, Australian modification.

Supplementary Table 1: Case complexity and case mix of study hospitals for the Australian financial year 2013-2014

Hospital	Total acute episodes	Total acute NWAU(16)	Average NWAU(16) per acute episode	Top five DRGs by volume
Prince of Wales	32,699	49,513	1.51	Chest pain; cellulitis; other digestive system diagnosis; respiratory infection/ inflammation; injuries
Shellharbour	8,213	11,246	1.37	Respiratory infection/ inflammation; schizophrenia disorders; chronic obstructive airway disease; hernia procedures; personality disorder and acute reactions
Shoalhaven	10,970	12,678	1.16	Uncomplicated neonatal admission; vaginal delivery; respiratory infection/ inflammation; chronic obstructive airway disease; caesarean delivery
St George	39,234	57,138	1.46	Uncomplicated neonatal admission; vaginal delivery; chest pain; respiratory infection/ inflammation; oesophagitis and gastroenteritis
Wollongong	36,951	50,813	1.38	Uncomplicated neonatal admission; vaginal delivery; respiratory infection/ inflammation; cellulitis; caesarean delivery

Australian financial year, 1 July 2013 to 30 June 2014; total acute episodes excludes haemodialysis, due to a large number of episodes without significant antimicrobial use; NWAU(16), National weighted activity unit (2015/16), a measure of comparing and valuing each public hospital service, to determine the overall complexity and relative resource payment for services funded on an activity basis. DRGs, Australian-refined diagnosis related group.

Supplementary Table 2: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, Prince of Wales Hospital

	Antimicrobial	Pre-intervention							Post-intervention							
		Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	19[a]	11	28	**0.5**	-0.1	1.2	0.1	**4.9**	-8.6	18.4	0.5	**-0.3**	-1.2	0.6	0.5
	Doxycycline	10[a]	5	15	**2**	1.5	2.5	<0.01	**4.4**	-6.8	15.6	0.4	**-1.8**	-2.6	-0.9	<0.01
	Aminopenicillins	146[a]	129	163	**-0.8**	-1.8	0.3	0.15	**3.0**	9.3	47.5	<0.01	**0.4**	-1.0	1.7	0.6
	Combined	175[a]	148	202	**1.78**	0.1	3.4	0.04	**38**	14.0	61.4	<0.01	**-1.68**	-4.1	0.68	0.15
Targeted for decreased use	3rd gen cephalosporins	75[a]	68	83	**-0.6**	-1.0	-0.3	<0.01	**1.7**	-4.7	8.2	0.6	**0.8**	0.2	1.5	0.01
	Macrolides	95[a]	80	111	**-0.6**	-1.6	0.4	0.2	**-13**	-35	8.8	0.2	**0.4**	-1.2	1.9	0.6
	Anti-pseudomonal penicillins	28[a]	23	33	**0.7**	0.4	1.0	<0.01	**-4.9**	-13	3.3	0.24	**-0.67**	-1.1	-0.2	<0.01
	Fluoroquinolones	72	62	81	**-1.8**	-1.4	-0.2	0.01	**-0.2**	-12	12	0.98	**0.1**	-1	1.1	0.87
	Carbapenems	25	17	34	**0.4**	-0.2	1.0	0.2	**3.4**	-7.4	14	0.5	**-0.5**	-1.3	0.3	0.25
	Combined	296	270	322	**-0.9**	-2.7	0.8	0.3	**-13**	-47	21	0.4	**0.1**	-2.4	2.5	0.9
	Total antimicrobial use	1109[a]	1078	1140	**0.8**	-3.2	1.6	0.5	**69**	20	119	<0.01	**3.6**	-0.8	8.1	0.1

Antimicrobial use (level) expressed as average defined daily doses/1000 occupied bed days, as reported to NAUSP; 95% confidence intervals expressed as LCI (lower confidence interval) and UCI (upper confidence interval); trends: positive value represents increase, negative value represents decrease.

Supplementary Table 3: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, Shellharbour Hospital

	Antimicrobial	Pre-intervention							Post-intervention							
		Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	13	-1.1	26	0.17	-0.8	1.2	0.7	35	17	53	<0.01	-1.4	-2.7	-0.1	0.03
	Doxycycline	22[a]	8	35	5.2	3.9	6.5	<0.01	74	33	115	<0.01	-7	-10	-4	<0.01
	Aminopenicillins	98[a]	80	117	-0.2	-1.6	1.2	0.75	53	25	81	<0.01	-1.3	-2.9	0.3	0.1
	Combined	132[a]	96	168	5.2	2.5	7.8	<0.01	162	99	226	<0.01	-9.9	-14.2	-5.6	<0.01
Targeted for decreased use	3rd gen cephalosporins	94	78	110	-1.2	-2.9	0.6	0.19	-29	-59	2	0.06	2.1	0.3	3.9	0.02
	Macrolides	295	259	331	-6.1	-8.7	-3.4	<0.01	-65	-127	-3.4	0.04	5.7	2.9	8.4	<0.01
	Anti-pseudomonal penicillins	17	13	21	0.03	-0.3	0.3	0.88	-8	-15	-1	0.02	0.25	-0.2	0.7	0.28
	Fluoroquinolones	55	35	75	-0.001	-1.6	1.6	1	-30	-58	-1	0.04	0.7	-1.3	2.6	0.5
	Carbapenems	5	2	7	-0.05	-0.2	0.1	0.57	-1.5	-5	2	0.41	0.2	-0.1	0.5	0.18

Combined	**466**	400	530	**-7.3**	-13	-1.2	0.02	**-133**	-245	-22	0.02	**8.9**	1.9	16	0.01
Total antimicrobial use	**1295**[a]	1191	1399	**-8**	-18	3	0.14	**-42**	-252	167	0.7	**6.7**	-5.3	18	0.27

Supplementary Table 4: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, Shoalhaven Hospital

	Antimicrobial	Pre-intervention							Post-intervention							
		Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	**36**	22	49	**0.03**	-1.1	1.2	1	**9**	-13	31	0.8	**-0.2**	-1.5	1.1	0.7
	Doxycycline	**108**[a]	71	143	**0.4**	-1.7	2.6	0.7	**54**	26	81	<0.01	**-1.1**	-3.5	1.3	0.4
	Aminopenicillins	**202**[a]	190	214	**-2.4**	-3.3	-1.5	<0.01	**19**	-11	49	0.2	**2.2**	0.2	4.1	0.03
	Combined	**344**[a]	302	387	**-2.0**	-4.4	0.5	0.12	**82**	32	131	<0.01	**0.8**	-3.0	4.6	0.68
Targeted for decreased use	3rd gen cephalosporins	**54**	42	67	**0.3**	-0.5	1.0	0.5	**-16**	-27	-6	<0.01	**-0.5**	-1.4	0.4	0.24
	Macrolides	**170**	153	187	**-3.2**	-4.4	-1.9	<0.01	**-40**	-84	3	0.07	**5.1**	-0.3	11	0.06
	Anti-pseudomonal penicillins	**21**	16	26	**-0.01**	-0.3	0.3	0.97	**-5**	-12	1.7	0.14	**0.63**	-0.02	1.3	0.06
	Fluoroquinolones	**66**	57	75	**-1**	-1.7	-0.3	<0.01	**-13**	-30	3.4	0.12	**0.85**	-0.2	1.9	0.12
	Carbapenems	**9**[a]	6	11	**-0.2**	-0.3	-0.01	0.04	**-2**	-6.5	2.5	0.37	**0.4**	0.1	0.8	0.02
	Combined	**320**	293	346	**-4.1**	-5.8	-2.3	<0.01	**-77**	-128	-27	<0.01	**6.5**	0.9	12	0.02
	Total antimicrobial use	**1508**[a]	1391	1625	**-15**	-24	-7	<0.01	**-104**	-249	40	0.15	**17**	8	27	<0.01

Supplementary Table 5: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, St George Hospital

	Antimicrobial	Pre-intervention							Post-intervention							
		Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	**20**[a]	14	27	**0.7**	0.2	1.2	<0.01	**-16**	-24	-7	<0.01	**-0.1**	-0.7	0.4	0.6
	Doxycycline	**1.4**[a]	-2.9	5.6	**1.1**	0.84	1.43	<0.01	**-0.1**	-8.5	8.3	0.98	**-1.0**	-1.6	-0.5	<0.01
	Aminopenicillins	**75**[a]	69	81	**2.0**	1.28	2.69	<0.01	**8.1**	-6.8	23.0	0.3	**-3.8**	-4.7	3.0	<0.01
	Combined	**96**[a]	85	107	**3.8**	2.8	4.9	<0.01	**-7.6**	-27.8	12.6	0.45	**-5.0**	-6.3	-3.8	<0.01
Targeted for decreased use	3rd gen cephalosporins	**44**	37	50	**0.5**	0	1.06	0.051	**-4.0**	-14	6.1	0.43	**-0.9**	-1.5	-0.3	<0.01
	Macrolides	**80**	68	90	**0.9**	-0.1	1.9	0.09	**-6.4**	-28	15	0.56	**-2.0**	-3.4	-0.7	<0.01
	Anti-pseudomonal penicillins	**18**[a]	15	20	**0.8**	0.6	1.0	<0.01	**-7**	-12	-2	<0.01	**-0.08**	-0.4	0.2	0.6
	Fluoroquinolones	**29**[a]	24	34	**0.2**	-0.1	0.5	0.13	**-5**	-9	-1	0.02	**-0.1**	-0.5	0.2	0.43
	Carbapenems	**13**[a]	10	15	**0.1**	-0.02	0.3	0.09	**3.2**	-2.4	8.8	0.25	**-0.1**	-0.4	0.2	0.5
	Combined	**183**	165	202	**2.5**	0.8	4.3	<0.01	**-19**	-54	15	0.27	**-3.3**	-5.4	-1.2	<0.01
	Total antimicrobial use	**633**	590	676	**14**	11	18	<0.01	**-43**	-98	12	0.12	**-17**	-20	-13	<0.01

Supplementary Table 6: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, Wollongong Hospital

	Antimicrobial	Pre-intervention							Post-intervention							
		Initial level	LCI	UCI	**Initial trend**	LCI	UCI	p value	**Change in level**	LCI	UCI	p value	**Change in trend**	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	**20**	15	26	**-0.3**	-0.7	0.06	0.1	**18**	11	25	<0.01	**-0.05**	-0.6	0.5	0.8
	Doxycycline	**30[a]**	19	40	**1.2**	0.1	2.3	0.03	**35**	8	61	0.01	**-2.5**	-4	-1	<0.01
	Aminopenicillins	**114[a]**	104	124	**-1.2**	-2.1	-0.3	0.01	**27**	11	44	<0.01	**0.8**	-0.3	1.9	0.15
	Combined	**164[a]**	143	186	**-0.3**	-2.3	1.8	0.8	**80**	39	120	<0.01	**-1.8**	-4.4	0.8	0.18
Targeted for decreased use	3rd gen cephalosporins	**51**	42	61	**-0.3**	-0.9	0.4	0.4	**-8**	-17	1	0.08	**0.56**	-0.2	1.3	0.12
	Macrolides	**123**	110	137	**-1.9**	-3.0	-0.9	<0.01	**-13**	-34	8.5	0.23	**1.5**	0.4	2.5	<0.01
	Anti-pseudomonal penicillins	**49[a]**	41	58	**-0.3**	-0.9	0.2	0.24	**-7**	-15	1.5	0.1	**0.7**	0.05	1.3	0.04
	Fluoroquinolones	**73**	63	83	**-1**	-1.8	-0.3	<0.01	**-16**	-30	-4	0.01	**1.3**	0.5	2.1	<0.01
	Carbapenems	**19[a]**	15	23	**0.01**	-0.2	0.2	0.87	**-3**	-10	3	0.3	**0.6**	0.2	1.0	<0.01
	Combined	**316**	283	349	**-3.6**	-6.0	-1.2	<0.01	**-48**	-88	-7	<0.01	**4.6**	1.8	7.4	<0.01
	Total antimicrobial use	**1081[a]**	1008	1156	**-7**	-15	0.2	0.06	**-22**	-159	114	0.74	**6.4**	-1.8	14.6	0.12

Supplementary Table 7: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection rates, Prince of Wales Hospital

Variable	Pre-intervention							Post-intervention							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs ($AU)	174984[a]	135818	214149	-2006	-4201	188	0.07	-7440	-37329	22449	0.62	2853	297	5410	0.03
Total costs per OBD ($AU)	12	10	14	-0.15	-0.3	-0.003	0.045	-1.5	-3.5	0.5	0.15	0.55	0.35	0.75	<0.01
Antifungal[b] costs ($AU)	56110[a]	-705	2803	87	-1218	1391	0.9	-13288	-34951	8375	0.22	1049	-705	2803	0.23
HCA CDI per 10000 OBDs (n)	5.5	3.6	7.5	0.08	-0.05	0.2	0.2	0.4	-3.2	4.0	0.8	-0.24	-0.5	-0.01	0.04

Abbreviations: OBD, occupied bed day; $AU, Australian dollars; HCA CDI, healthcare associated *Clostridium difficile* infection.

[a]adjusted for first order autocorrelation; [b]high cost antifungals, liposomal amphotericin, caspofungin, voriconazole, posaconazole, anidulafungin.

Supplementary Table 8: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection rates, Shellharbour Hospital

Variable	Pre-intervention							Post-intervention							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs ($AU)	**12274**	10351	14196	**-37**	-196	123	0.65	**-2708**	-6074	657	0.11	**36**	-175	247	0.73
Total costs per OBD ($AU)	**4.3**[a]	3.5	5.0	**-0.02**	-0.08	0.05	0.6	**-0.85**	-2	0.3	0.15	**0.05**	-0.02	0.11	0.16
Antifungal[b] costs ($AU)	**-88**	-129	31	**51**	-29	130	0.2	**-1177**	-2893	540	0.17	**-49**	129	31	0.22
HCA CDI per 10000 OBDs (n)	**1.1**	-1.2	3.4	**0.1**	-0.02	0.25	0.09	**-2.5**	-5.6	0.5	0.1	**-0.1**	-0.3	0.1	0.4

Supplementary Table 9: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection rates, Shoalhaven Hospital

Variable	Pre-intervention							Post-intervention change							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs ($AU)	28629	21020	36238	-624	-1037	-210	<0.01	89	-4122	4299	0.97	639	201	1077	<0.01
Total costs per OBD ($AU)	8.5	6.2	109	-0.2	-0.3	-0.1	<0.01	0.14	-1.1	1.4	0.83	0.24	0.1	0.4	<0.01
Antifungal[b] costs ($AU)	4409[a]	23	386	-213	-368	-58	<0.01	2225	404	4046	0.02	204	22.5	386	0.03
HCA CDI per 10000 OBDs (n)	1.7	-0.3	3.7	0.1	-0.04	0.3	0.14	-0.1	-3.6	3.4	0.95	-0.2	-0.4	0.1	0.17

Supplementary Table 10: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection rates, St George Hospital

Variable	Pre-intervention							Post-intervention change							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs ($AU)	**104693**[a]	84724	124662	**1688**	206	3170	0.03	**-61611**	-85528	-37694	<0.01	**828**	-873	2529	0.33
Total costs per OBD ($AU)	**7.1**[a]	5.95	8.33	**0.19**	0.02	0.22	0.02	**-4.7**	-6.5	-2.9	<0.01	**0.1**	-0.01	0.23	0.06
Antifungal[b] costs ($AU)	**11112**	-6465	28689	**1998**	390	3606	0.02	**-46943**	-74954	-18932	<0.01	**-300**	-2011	1411	0.73
HCA CDI per 10000 OBDs (n)	**4.1**	1.9	6.3	**0.2**	0.07	0.36	<0.01	**-1.9**	-4.5	0.7	0.15	**-0.4**	-0.6	-0.2	<0.01

Supplementary Table 11: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection rates, Wollongong Hospital

Variable	Pre-intervention							Post-intervention change							
	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs ($AU)	**142796**	122788	162803	**-2218**	-3396	-1040	<0.01	**7120**	-19333	33573	0.6	**2917**	1138	4667	<0.01
Total costs per OBD ($AU)	**12.3**	10.6	14.1	**-0.2**	-0.3	-0.1	<0.01	**0.5**	-1.6	2.6	0.6	**0.27**	0.12	0.41	<0.01
Antifungal[b] costs ($AU)	**21032**	-1051	1476	**98**	-713	908	0.8	**8912**	-6418	24242	0.25	**212**	-1051	1476	0.74
HCA CDI per 10000 OBDs (n)	**1.6**	0.5	2.6	**0.15**	0.06	0.24	<0.01	**-1.9**	-4.1	0.33	0.09	**-0.08**	-0.21	0.06	0.25