Impact of antimicrobial stewardship interventions on Clostridium difficile infection and clinical outcomes

Patton, Andrea; Davey, Peter; Harbarth, Stephen ; Nathwani, Dilip; Sneddon, Jacqueline; Marwick, Charis A.

Published in:
Journal of Antimicrobial Chemotherapy

DOI:
10.1093/jac/dkx413

Publication date:
2017

Document Version
Peer reviewed version

This is a pre-copyedited, author-produced version of an article accepted for publication in Journal of Antimicrobial Chemotherapy following peer review. The version of record is available online at: https://doi.org/10.1093/jac/dkx413

Impact of antimicrobial stewardship interventions on *Clostridium difficile* infection and clinical outcomes: segmented regression analyses

Andrea Patton[1, 2], Peter Davey[1], Stephan Harbarth[3], Dilip Nathwani[4], Jacqueline Sneddon[2], Charis A Marwick*[1, 4]

1. Population Health Sciences, School of Medicine, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee DD2 4BF, UK

2. Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland, Delta House, West Nile Street, Glasgow G1 2NP, UK

3. Infection control programme, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

4. Department of Infection and Immunodeficiency, East Block, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

*Corresponding author: Charis A Marwick c.z.marwick@dundee.ac.uk +44 (0)1382 383800

Population Health Sciences Division, Medical School, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee DD24BF

Short title: High risk antimicrobials and *C. difficile*

Main document word count: 3288

Synopsis

Background

Antimicrobial exposure is associated with increased risk of *Clostridium difficile* infection (CDI) but the impact of prescribing interventions on CDI and other outcomes is less clear.

Objectives

To evaluate the effect of an antimicrobial stewardship intervention targeting high risk antimicrobials (HRA), implemented in October 2008; to compare the findings to similar studies from a systematic review.

Population and methods

All patients admitted to Medicine and Surgery in Ninewells Hospital from October 2006 to September 2010 were included. Intervention effects on HRA use (dispensed DDD), CDI cases, and mortality rates, per 1000 admissions per month, were analysed separately in Medicine and Surgery using segmented regression of interrupted time series (ITS) data. Data from comparable published studies were re-analysed using the same method.

Results

Six months post-intervention, there were relative reductions in HRA use of 33% (95%CI 11 to 56) in Medicine and 32% (95%CI 19 to 46) in Surgery. At 12 months, there was an estimated reduction in CDI of 7.0 cases/1000 admissions (relative change -24% (95%CI -55 to 6)) in Medicine but no change in Surgery (estimated 0.1 fewer cases/1000 admissions (-2% (95%CI -116 to 112)). Mortality reduced throughout the study period, unaffected by the intervention. In all six comparable studies, HRA use reduced significantly but reductions in CDI rates were only statistically significant in two, and none measured mortality. Pre-intervention CDI rates and trends influenced intervention effect.

Conclusions

Despite large reductions in HRA prescribing and reductions in CDI, demonstrating real-world impact of stewardship interventions remains challenging.

Introduction

Clostridium difficile is the leading cause of healthcare-associated infective diarrhoea. *C. difficile* infection (CDI) is potentially life threatening and risk of infection is increased by recent exposure to antimicrobials.[1] In comparison with other antimicrobials, exposure to cephalosporins and clindamycin has been associated with higher risk of CDI in hospitals.[2] At population level, fluoroquinolone use has been associated with infection by fluoroquinolone-resistant epidemic strains and, in the UK, restriction of fluoroquinolones has been associated with reduction in total CDI, and in fluoroquinolone-resistant clones from 67% to 3% of all CDI.[3]

The direct impact of antimicrobial prescribing interventions on CDI rates is less clearly demonstrated. A recent systematic review of interventions to improve antibiotic prescribing for hospital inpatients[4] found no randomised controlled trials (RCTs) and 26 interrupted time series (ITS) studies that provided reliable data about the impact of interventions on both prescribing and microbial (CDI or resistant Gram-positive and Gram-negative bacteria) outcomes. Nine planned prescribing interventions (i.e. not in response to an outbreak) reported heterogeneous effects on CDI rates.[5-13]

In 2008, antimicrobial policy changes across Ninewells Hospital, Dundee were initiated, following national guidance on restriction of antimicrobials associated with a high risk of CDI (high risk antimicrobials [HRA]), designed to reduce prescribing of these agents. The aims of this study were to evaluate the impact of these policy changes on HRA prescribing rates, CDI, and mortality in Medical and Surgical Wards in Ninewells Hospital, using segmented regression analysis of ITS data, then to compare these findings with similar studies from the above systematic review in order to better understand variation in the impact of HRA prescribing interventions on CDI.

Methods

Setting and population

Ninewells Hospital is an 855-bed University hospital in the National Health Service (NHS) region of

Tayside, which had endemic CDI at a rate of 1.5 cases per 1000 acute occupied bed days in 2008. The study period was October 2006 to September 2010. We evaluated intervention effects in Medical and Surgical wards and included all patients aged ≥ 18 years admitted through the Acute Medical Unit or one of six general surgical wards. Further details of the setting, population and intervention are available in Table S1, reported according to the ORION statement recommendations.[14]

Intervention

Antimicrobials defined as HRA were identified from a previous time series analysis of relationship between antibiotic use and *C. difficile* infection rates in Ninewells Hospital.[15] In October 2008 the NHS Tayside policy for empirical treatment of infection changed to remove cefuroxime for any indication, include ceftriaxone only for meningitis, limit fluoroquinolones to a few specific indications and reduce use of clarithromycin, clindamycin and co-amoxiclav (Table S2). Cefuroxime was also removed from the policy for antibiotic prophylaxis in general surgery (Table S3).

The policy was implemented via provision of advice from clinical pharmacists at ward level supported by departmental presentations by the Chair of the Antimicrobial Management Group and Antimicrobial Pharmacist from October to December 2008 (Table S1).

Outcomes

Antimicrobial use data were obtained at ward level from the hospital pharmacy computer system and summarised as DDD per 1000 admissions per month, separately for Medicine and Surgery.

CDI data were obtained from the Infection Control Department and summarised as cases per 1000 admissions per month. The case definition was a patient with diarrhoea and toxin positive stool, without toxin positive stool in the previous 90 days. The laboratory diagnostic test changed nine months post-intervention but there were no changes to infection control policies over the study period (detailed in Table S1).

We measured 30-day mortality among all patients (deaths within 30 days of admission per 1000 admissions per month) and among patients who had a blood culture taken (deaths within 30 days of having a blood culture taken per 1000 patients with blood culture taken per month) as an indicator of sepsis mortality.[16] Patient-level hospital admissions and microbiology data were linked to the national register of deaths then anonymised by the Health Informatics Centre, University of Dundee.[17] Mortality was included as a balancing measure due to concerns from clinicians that a change in antimicrobial policy may result in inadequate treatment of patients with sepsis. We also examined post-operative acute kidney injury as a balancing measure, due to increased use of gentamicin as surgical prophylaxis in the new policy, and results are published elsewhere.[18]

Statistical analysis

We used segmented regression analysis of ITS data to estimate intervention effects, using lag terms to adjust models for autocorrelation present in residual terms, and using heteroskedastic robust standard errors when residual terms were not homoskedastic.[19] Effect sizes are the estimated absolute and relative changes, with 95% confidence intervals (CI), at six months (prescribing, mortality) or 12 months (CDI) post-intervention. Lower limits of 95%CI for estimated CDI rates that were negative were converted to zero. The absolute change is the difference between the modelled outcome at the specified post-intervention time point and the model estimate of the last preintervention data point, and the relative change is the absolute change as a percentage of the model estimate of the last pre-intervention data point. All analyses were carried out in IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.).

Comparison with studies from systematic review

Of a total 241 studies in the Cochrane systematic review, eight planned ITS studies provided reliable prescribing and CDI data, and had monthly or quarterly CDI rates for at least 12 months after the prescribing intervention.[5, 7-13] Six of these targeted HRA so were comparable with our intervention.[5, 8, 9, 11-13] The remaining two aimed to reduce use of all antibiotics.[7, 10] We made descriptive

comparisons (setting, selection of HRA, etc.) between our study and the six comparable studies, and reanalysed prescribing data from five, and CDI data from all six, studies using the same method described above to examine variation in effect (one study[11] did not present raw prescribing data to enable reanalysis). Pre-intervention CDI rates were converted to per 1000 occupied bed days (OBD) per month to enable comparison between studies. None of the six studies reported mortality. Due to the heterogeneity of study design and outcome measures among the ITS studies, formal meta-analysis was not applicable. We also reanalysed data from the two studies targeting all antibiotics (not just HRA) but these were less directly comparable to our study.

Ethics

All patient-identifiable data were anonymised by the Health Informatics Centre (HIC) according to Standard Operating Procedures (SOP) which have been agreed with the NHS Tayside Caldicott Guardian and East of Scotland Research Ethics Committee. Studies using anonymised data and following HIC SOP do not need individual ethics review. All analyses were carried out in an ISO27001 and Scottish Government accredited data Safe Haven.

Results

HRA

In NHS Tayside use of HRA per 1000 admissions per month in the pre-intervention period varied, mainly between 4000–7000 DDD in Medicine *versus* 2000-4000 DDD in Surgery (Figure 1A and 1B). In the pre-intervention period co-amoxiclav accounted for 36% of HRA in Medicine and Surgery. Other antimicrobial use, as % of all HRA, in Medicine versus Surgery was: cephalosporin 5 versus 13%, clarithromycin 32 versus 6%, fluoroquinolone 19 versus 30% and clindamycin 6 versus 7% (further details available in Table S4).

The intervention was associated with progressive reductions in HRA in Medicine (Figure 1A) and Surgery (Figure 1B). At six months post-intervention, use of HRA had reduced by 2094 DDD per 1000

admissions (relative reduction of 33% (CI 11 to 56%)) in Medicine, and by 1394 DDD per 1000 admissions (relative reduction of 32% (CI 19 to 46%)) in Surgery (Table 1).

CDI

In Medicine there was no significant pre-intervention trend in CDI rates, whereas in Surgery the rate was declining by 0.49 cases per 1000 admissions per month (CI 0.29 to 0.69) (Table 1). Immediately pre-intervention, there was a higher CDI rate in Medicine than Surgery at 22.0 versus 4.5 per 1000 admissions (Table 1).

The intervention was associated with a progressive decline in CDI rates in Medicine (Figure 1C) but not in Surgery (Figure 1D). At 12 months post-intervention CDI in Medicine reduced by 7.0 cases per 1000 admissions, although this was not quite statistically significant (relative change -24% (95%CI -55 to 6), Table 1). In Surgery, there was no change associated with the intervention after 12 months (model estimate -0.1 CDI cases per 1000 admissions, relative change -2% (95%CI -116 to 112%, Table 1), reflecting a levelling off from a downward pre-intervention trend (Figure 1D).

Mortality

All cause 30-day mortality declined post-intervention in Medicine and Surgery (Figure 2A and 2B, Table S5), but there was no statistically significance association with the intervention, with relative reductions of 8% (95%CI -24 to 9) in Medicine and 2% (95%CI -35 to 31) in Surgery at six months post-intervention. Mortality in patients who had blood cultures taken also declined in both Medicine and Surgery (Figures 2C and 2D, Table S5), but again there were no statistically significant changes associated with the intervention, with relative changes of -14% (95%CI -39 to 11) and -12% (95%CI 46 to 23), respectively, at six months post-intervention.

Comparable studies from systematic review

There were six studies targeting HRA with adequate (monthly or quarterly for at least 12 months) CDI data,[5, 8, 9, 11-13] one only included Medicine for the Elderly[9] but others included all wards. Five were based in the UK but the one US study included six intervention hospitals.[11] The definition of

HRA varied considerably between studies and hospitals and CDI case definitions varied slightly. Not all studies reported diagnostic methods or infection control practices (Table 2).

All interventions were associated with statistically significant reduction in HRA use (Table 1). Changes at six months post-intervention could not be estimated for one study,[11] but our re-analysis of data from the remaining five estimated relative reductions of 27% to 49%, all statistically significant (Table 1).

Immediate pre-intervention CDI rates ranged from 0.6 to 2.7 cases per 1000 OBD per month across all eight settings (including in Ninewells Hospital) (Table 2), and pre-intervention CDI rates were significantly reducing in three (Table 1). Re-analysis of CDI data from five of the six comparable studies estimated relative changes in CDI at 12 months post-intervention that were similar to the change in Medicine in Ninewells, but two had much wider confidence intervals: -40% (95%CI -124 to 43, Dancer[8]), -48% (95%CI -131 to 35, Talpaert[13]). Re-analysis of CDI data from the remaining study (Ostrowsky[11]) estimated much smaller relative changes, more similar to Surgery in Ninewells and with a similarly low immediate pre-intervention CDI rate (0.6 versus 0.8 per 1000 OBD per month (Table 2)). In only two of eight settings were estimated reductions in CDI at 12 months postintervention statistically significant (Fowler[9], Price[12]) and both had relatively flat pre-intervention trends (although Price has a significant downward trend, the change per month is numerically very small meaning the slope is very shallow) (Table 1).

Studies targeting total antimicrobial use

Re-analysis of data from one of two studies targeting total antimicrobial use, set in an 861 bed tertiary care hospital,[7] estimated a 25% (95%CI 19 to 30) relative reduction in antimicrobial use at six months post-intervention, and a 24% (95%CI -58 to 10) relative reduction in CDI at 12 months. There was no pre-intervention trend in CDI rate (0.02 (95%CI -0.16 to 0.20) cases per OBD per month) and a pre-intervention rate of 0.4 cases per 1000 OBD per month. In the other study, set in a 160 bed Long Term Care Facility,[10] re-analysis of published data estimated a 16% (95%CI 4 to 29) relative

reduction in antimicrobial use at six months post-intervention, and no change in in CDI at 12 months (relative change 1% (95%CI -73 to 76)). There was no pre-intervention trend in CDI rate (0.02 (95%CI -0.01 to

0.05) cases per OBD per month) and a pre-intervention rate of 1.0 case per 1000 OBD per month.

Discussion

In Ninewells Hospital, an intervention to reduce prescribing of antimicrobials associated with high risk of CDI resulted in large and significant reductions in prescribing of targeted antimicrobials in both clinical settings evaluated. The estimated effects on CDI were inconsistent, and influenced by preintervention rates and trends. Reanalysis of prescribing and CDI data from six similar previously published studies revealed similar large reductions in prescribing and inconsistent changes in CDI. In Ninewells Hospital, there was no evidence that the antimicrobial prescribing intervention was associated with any increase in 30-day mortality.

We analysed the effect of a real-world intervention in two clinical settings within our hospital using a statistically robust method for the analysis of quasi-experimental studies. The use of routine data enabled complete case identification and complete antimicrobial dispensing data. In addition to examining the intended process (HRA prescribing) and outcome (CDI) measures, we also included mortality as a balancing measure, which no other similar studies did. A further strength was the reanalysis of published data from all similar interventions identified in a recent systematic review[4] using the same methods, allowing direct comparison of effect and helping to explain variation in effect size.

In some segmented regression analyses, the assumption is that pre-intervention trends would have continued throughout the study period in the absence of an intervention and the projection of the pre-intervention trend used to estimate intervention effects. This can be problematic if the modelled projection breaches the limits of measurement, resulting in predicted negative incidence or proportions below zero or above 100%. Therefore, we projected the last pre-intervention time point

forward, assuming a flat post-intervention trend. In Surgery in Ninewells and one comparable study (Dancer[8]) CDI rates were statistically significantly reducing pre-intervention, and extrapolation of those trends would have breached zero by 12 months post-intervention, with the result that the estimated intervention effect would inevitably have been an increase in CDI.

In all the analysed interventions there were significant reductions in the use of HRA, but there were only significant reductions in CDI in two (Table 1). These results are in marked contrast to a previous systematic review, which concluded that Antibiotic Stewardship Programmes (ASP) were associated with a consistent, significant reduction in CDI (pooled risk ratio for CDI 0.48, CI 0.38 to 0.62).[20] That analysis was based on 16 studies, only four of which[9, 12, 13, 21] met inclusion criteria for the Cochrane systematic review.[4] One of those had ITS HRA prescribing data suitable for re-analysis but only aggregate CDI data so could not be included in this paper.[21] The other 12 studies were either uncontrolled before and after studies, which do not meet Cochrane criteria for inclusion in systematic reviews,[22] or ITS studies with methodological weaknesses. Analysing our Surgery data (Figure 1D) as uncontrolled before and after gives a relative risk of CDI post- *versus* pre-intervention of 0.50 (95%CI 0.36 to 0.70) but this difference is clearly attributable to a steady decline in CDI in the pre-intervention period rather than an intervention effect (Figure 1D). This highlights a difficulty in evaluating the impact of real-world antimicrobial stewardship interventions on downstream outcomes because there is often more than one prescribing intervention, healthcare professionals change behaviour before/without an intervention, and infection incidence is affected by outbreaks and infection control interventions.

In the eight settings we analysed, the pre-intervention CDI rates were lower for the two interventions with smaller estimated intervention effects (Ninewells Surgery, Ostrowsky[11]) and one with very wide confidence limits (Dancer[8]) (Table 2), and were already declining significantly in two of these (Ninewells Surgery, Dancer[8]) (Table 1). Declining CDI rates are likely multifactorial and, in addition to low baseline rates, make demonstrating an additional intervention effect very

challenging. A Scottish study, more recent than those included in the systematic reviews above, used non-linear time series analysis to estimate associations between a change in antimicrobial prescribing policy and CDI rates, taking infection control interventions into account, and found that compared to predicted rates, CDI prevalence density in hospitals fell by 68% (mean reduction 1·01 per 1000 occupied bed-days, 0·27–
1·76) following a change in antimicrobial policy.[23] Similarly emphasising the importance of antimicrobial stewardship in the control of CDI, a recent study in England, using whole genome sequencing of *C. difficile*, demonstrated that declining CDI rates were largely explained by reductions in fluoroquinolone-resistant strains.[24] The decline in fluoroquinolone-resistant CDI was significantly associated with declining fluoroquinolone prescribing rates rather than infection control.[24] Both these approaches provide robust evaluations of the impact of stewardship on CDI but the necessary data and analytical methods are not available for evaluation of most stewardship interventions.

The selection of targeted HRA could plausibly influence the effectiveness of prescribing interventions. Meta-analyses of case control studies of patient-level CDI risk associated with specific antimicrobial exposure have varying results. In healthcare-associated CDI, exposure to cephalosporins, particularly third-generation (OR 3.20, 95%CI 1.80 to 5.71), and clindamycin (2.86, 2.04 to 4.02) had the highest associations, and fluoroquinolones (1.66, 1.17 to 2.35) had weaker associations out-with the context of resistant epidemic ribotypes.[2] In two meta-analyses of community-associated CDI, fluoroquinolone exposure was strongly associated (OR 5.65 (4.38 to 7.28)[25] and 5.50 (4.26 to 7.11)[26]), as were clindamycin (20.43 (8.50 to 49.09)[25] and 16.80 (7.48 to 37.76)[26]) and cephalosporins (4.47 (1.60 to 12.50)[25] and 5.68 (2.12 to 15.23)[26]). There were similarities in HRA selection across all eight settings we analysed (Table 2), but only Ostrowsky's study included piperacillin-tazobactam, and in that study cephalosporins were only targeted in two of six intervention sites and quinolones only in one (Table 1).[11] A recent ITS evaluation of multicentre antimicrobial stewardship in Australia, where targeted HRA were standardised across five hospitals,

demonstrated an associated reduction in CDI despite low rates pre-intervention.[27] A recent review of country-level data on the use of different cephalosporins and CDI rates across Europe, concludes that associations with CDI should be considered for individual cephalosporin agents, and argues that factors such as cumulative exposure are important,[3] which has been reported elsewhere.[28, 29] The use of certain cephalosporins in a controlled manner may be appropriate to maintain diversity and support long term sustainable stewardship.[30]

We measured mortality due to concerns raised by clinicians that the change in antimicrobial policy could have led to under-treatment of patients with sepsis and we found no evidence of worse outcomes with the intervention. There was declining mortality throughout the study period (Figure 2). Our intervention was co-incident with the start of the Scottish Patient Safety Programme (SPSP)[31] in 2008, which aimed to reduce hospital mortality through early recognition and management of deteriorating patients (although the SPSP Sepsis Collaborative only began in 2012). A local sepsis improvement initiative in 2009 in Ninewells Hospital was associated with reduced time to first antibiotic dose in Medicine and Surgery,[16] but not mortality (unpublished data, Marwick and Davey), in a smaller study using manually collected patient data. There are limitations in using mortality as a stewardship outcome, due to confounding, but it does have value as balancing measure and most studies do not report any clinical outcome data.[4] A very recent exception is a multicentre stewardship study which reported reductions in infection-specific mortality and length of stay, in line with similar reductions in all patients, providing reassurance that the intervention did not worsen outcome.[27] This is consistent with our findings and supports the use of all-cause mortality as an outcome in broadly implemented interventions.

Targeted restriction of HRA is an important stewardship intervention, particularly when CDI rates are high and when hyper-virulent strains of CDI are circulating within a population. Robust evaluation of the effect of real world stewardship interventions on outcomes other than prescribing remains methodologically challenging and worthy of further effort.[32] Pre-intervention outcome data should

be examined before resource-intense interventions and evaluations are undertaken, and all evaluations should include balancing measures. Although the included studies focused on restriction of HRA in relation to CDI, effective stewardship of all broad spectrum antimicrobials is important to reduce adverse effects including healthcare associated infection and the emergence of antimicrobial resistance.

Acknowledgements

We acknowledge NHS Tayside Pharmacy and Infection Control departments for providing data and the Health Informatics Centre, University of Dundee, for linking and anonymising study data. We acknowledge the Scottish Antimicrobial Prescribing Group for producing national guidance on restriction of high risk antibiotics and associated interventions and for developing the Project Initiation Document to secure funding for analysis of the Tayside data. Finally, we acknowledge Nathalie Vernaz for her original work on identifying high risk antimicrobials in NHS Tayside.[15]

Funding

This work was supported by the Scottish Government Healthcare Associated Infection Task Force, now operating as the Scottish Antimicrobial Resistance and Healthcare Associated Infection (SARHAI) Strategy Group { HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }{ HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }{ HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }{ HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }

{ HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }{ HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }{ HYPERLINK "http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h }{ HYPERLINK

"http://www.gov.scot/Topics/Health/Services/Preventing-Healthcare-Infections/Infection-Monitoring/SARHAI" \h **}**. AP was funded by a Health Foundation Improvement Science PhD studentship during this work. The funders had no role in the design or conduct of the study or writing the report.

Transparency declaration

AP no conflict; PD no conflict; DN has received lecture or advisory board honoraria from Astellas, Astra-Zeneca, Cubist, Durata and Pfizer and research grants from Pfizer, Astellas and Basilea; SH is a member of scientific advisory board of DNA Electronics, Bayer and Novartis and has received financial support for research on antimicrobial resistance from the European Commission (AIDA, COMBACTE, DRIVE-AB, R-Gnosis and SATURN network contracts), Geneva University Hospitals, B. Braun and Pfizer; JS is Project Lead for Scottish Antimicrobial Prescribing Group; CM has received support for conference attendance from Astellas and Eumedica and support for research from Pfizer and Astellas.

Contribution

All authors contributed to conception, design and interpretation of data. CM led on writing the manuscript and all authors contributed to critical revision and approval of the version for submission. AP was responsible for acquisition and analysis of data from NHS Tayside and re-analysis of data from published studies. PD and CM extracted all data from published studies.

References

1. Smits WK, Lyras D, Lacy DB et al. Clostridium difficile infection. *Nat Rev Dis Primers* 2016; **2**: 16020.
2. 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.
3. Wilcox MH, Chalmers JD, Nord CE et al. Role of cephalosporins in the era of Clostridium difficile infection. *J Antimicrob Chemother* 2016; **72**: 1-18.
4. Davey P, Marwick CA, Scott CL et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**: CD003543.
5. Aldeyab M, Kearney M, Scott M et al. An evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effect on the incidence of Clostridium difficile infection in hospital settings. *J Antimicrob Chemother* 2012; **67**: 2988-96.
6. Chan Y Y, Lin T Y, Huang C T et al. Implementation and outcomes of a hospital-wide computerised antimicrobial stewardship programme in a large medical centre in Taiwan. *Int J Antimicrob Agents* 2011; **38**: 486-92.
7. Cook P P, Rizzo S, Gooch M et al. Sustained reduction in antimicrobial use and decrease in methicillin-resistant Staphylococcus aureus and Clostridium difficile infections following implementation of an electronic medical record at a tertiary-care teaching hospital. *J Antimicrob Chemother* 2011; **66**: 205-9.
8. Dancer S, Kirkpatrick P, Corcoran D et al. Approaching zero: Temporal effects of a restrictive antibiotic policy on hospital-acquired Clostridium difficile, extended-spectrum beta-lactamase- producing coliforms and meticillin-resistant Staphylococcus aureus. *Int J Antimicrob Agents* 2013; **41**:

137-42.
9. Fowler S, Webber A, Cooper B S et al. Successful use of feedback to improve antibiotic prescribing and reduce Clostridium difficile infection: a controlled interrupted time series. *J Antimicrob Chemother* 2007; **59**: 990-5.
10. Jump R, Olds D, Seifi N et al. Effective antimicrobial stewardship in a long-term care facility through an infectious disease consultation service: keeping a LID on antibiotic use. *Infect Control Hosp Epidemiol* 2012; **33**: 1185-92.
11. Ostrowsky B, Ruiz R, Brown S et al. Lessons learned from implementing Clostridium difficilefocused antibiotic stewardship interventions. *Infect Control Hosp Epidemiol* 2014; **35**: S86-S95.
12. Price J, Cheek E, Lippett S et al. Impact of an intervention to control Clostridium difficile infection on hospital- and community-onset disease; an interrupted time series analysis. *Clin Microbiol Infect* 2010; **16**: 1297-302.
13. Talpaert MJ, Rao GG, Cooper BS et al. 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.
14. Stone SP, Cooper BS, Kibbler CC et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007; **7**: 282-8.
15. Vernaz N, Hill K, Leggeat S et al. Temporal effects of antibiotic use and *Clostridium difficile* infections. *J Antimicrob Chemother* 2009; **63**: 1272-5.
16. Marwick C, A., Guthrie B, Pringle J, E. et al. A multifaceted intervention to improve sepsis management in general hospital wards with evaluation using segmented regression of interrupted time series. *BMJ Qual Saf* 2013; **23**: e2.

17. University of Dundee. Health Informatics Centre. http://medicine.dundee.ac.uk/healthinformatics-centre.
18. Bell S, Davey P, Nathwani D et al. Risk of AKI with Gentamicin as Surgical Prophylaxis. *Journal of the American Society of Nephrology* 2014; **25**: 2625-32.
19. Halbert W. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. *Econometrica* 1980; **48**: 817-38.
20. Feazel LM, Malhotra A, Perencevich EN et al. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. *J Antimicrob Chemother* 2014; **69**: 1748-54.
21. Elligsen M, Walker S, A., Pinto R et al. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. *Infect Control Hosp Epidemiol* 2012; **33**: 354-61.
22. Cochrane Effective Practice and Organisation of Care (EPOC) Group. EPOC Resources for review authors. http://epoc.cochrane.org/resources/epoc-resources-review-authors.
23. Lawes T, Lopez-Lozano JM, Nebot CA et al. Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of Clostridium difficile infections in a region of Scotland: a non-linear time-series analysis. *Lancet Infect Dis* 2016; **7**: 194-206.
24. Dingle KE, Didelot X, Quan TP et al. Effects of control interventions on *Clostridium difficile* infection in England: an observational study. *Lancet Infect Dis* 2017; **17**: 411-21.
25. Deshpande A, Pasupuleti V, Thota P et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *J Antimicrob Chemother* 2013; **68**: 1951-61.
26. Brown KA, Khanafer N, Daneman N et al. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrob Agents Chemother* 2013; **57**: 232632.
27. Bond SE, Chubaty AJ, Adhikari S et al. Outcomes of multisite antimicrobial stewardship programme implementation with a shared clinical decision support system. *J Antimicrob Chemother* 2017; **72**: 2110-8.
28. Kavanagh K, Pan J, Marwick C et al. Cumulative and temporal associations between antimicrobial prescribing and community-associated Clostridium difficile infection: population-based case-control study using administrative data. *J Antimicrob Chemother* 2016; **72**: 1193-201.
29. Marwick CA, Yu N, Lockhart MC et al. Community-associated Clostridium difficile infection among older people in Tayside, Scotland is associated with antibiotic exposure and care home residence: cohort study with nested case-control. *J Antimicrob Chemother* 2013; **68**: 2927-33.
30. Livermore DM. Of stewardship, motherhood and apple pie. *Int J Antimicrob Agents* 2014; **43**: 319-22.
31. Scottish Patient Safety Programme. http://www.scottishpatientsafetyprogramme.scot.nhs.uk/.
32. Graber CJ. *Clostridium difficile* infection: stewardship's lowest hanging fruit? *Lancet Infect Dis* 2017; **17**: 123-4.

Table 1: Baseline rates and estimated effect of interventions on HRA prescribing at six months and CDI at 12 months post-intervention from Medicine and Surgery in Ninewells Hospital and six comparable studies from a systematic review

Study	HRA data included	High risk antimicrobial (HRA) prescribing rates per month					*Clostridium difficile* infection (CDI) rates per month				
		Units	Pre-intervention		Change at 6 months		Units	Pre-intervention		Change at 12 months	
			Trend 95%CI	Rate[a] 95%CI	Absolute 95%CI	Relative (%) 95%CI		Trend 95%CI	Rate[a] 95%CI	Absolute 95%CI	Relative (%) 95%CI
Ninewells Medicine	All targeted	DDD/1000 admissions[b,c]	-70.4 -107, -33.8	4186 2831, 5540	-2094 -3488, -699	-33.3 -55.5, -11.1	Cases/1000 admissions[b]	-0.08 -0.40, 0.24	22.0 13.4, 30.6	-6.99 -15.8, 1.84	-24.1 -54.5, 6.36
Ninewells Surgery	All targeted	DDD/1000 admissions[b]	13.4 -10.6, 37.4	2917 2338, 3497	-1394 -1990, -797	-32.3 -46.2, -18.5	Cases/1000 admissions	-0.49 -0.69, -0.29	4.54 0[d], 9.70	-0.11 -5.41, 5.19	-2.37 -116.4, 111.6
Aldeyab 2012	All targeted	DDD/100 OBD[c]	0.13 0.05, 0.21	22.4 18.9, 25.9	-17.3 -20.9, -13.8	-43.6 -52.5, -34.7	Cases/100 OBD	0.001 -0.002, 0.004	0.10 0.04, 0.16	-0.03 -0.09, 0.03	-23.1 -71.1, 24.9
Dancer 2013	CRO	DDD/1000 OBD[b,c]	-3.35 -4.90, -1.80	26.6 13.4, 39.8	-25.7 -39.9, -11.5	-49.1 -76.3, -21.9	Cases/1000 OBD	-0.14 -0.28, -0.006	1.63 0[d], 3.76	-1.09 -3.36, 1.18	-40.1 -123.5, 43.4
Fowler 2007	AMC, CPS	Courses[e]/100 admissions	0.54 0.04, 1.04	46.8 37.1, 56.6	-17.7 -27.7, -7.59	-27.4 -43.0, -11.8	Cases[b]	0.02 -0.05, 0.09	3.42 1.79, 5.05	-2.86 -4.55, -1.17	-45.5 -72.4, -18.7
Ostrowsky 2014	All targeted	DDD/10,000 OBD	-	-	-0.016[f] P=0.015[f]	-	Cases/10,000 OBD	-0.04 -0.10, 0.02	5.46 3.99, 6.93	-0.48 -2.00, 1.04	-8.08 -33.7, 17.5
Price 2010	CPS, FQ	DDD[c]	-48.0 -116.2, 20.3	6375 5468, 7282	-2887 -3844, -1929	-31.2 -41.5, -20.8	Cases/1000 OBD	-0.05 -0.07, -0.02	1.02 0.57, 1.47	-0.60 -1.08, -0.12	-37.0 -66.4, -7.7
Talpaert 2011	AMC, CPS, FQ	DDD/1000 OBD[b]	8.84 0.08, 17.6	415.2 326.8, 503.5	-151.6 -247.7, -55.5	-26.7 -43.7, -9.8	Cases[b,c]	-0.35 -2.24, 1.54	27.6 0[d], 68.2	-25.5 -69.3, 18.4	-48.0 -130.5, 34.6

Abbreviations: AMC co-amoxiclav, CPS cephalosporins, CRO ceftriaxone, HRA high risk antimicrobials, FQ fluoroquinolones, OBD occupied bed days [a]Immediate pre-intervention rate = modelled rate at the last pre-intervention time point [b]Model adjusted for autocorrelation using lag terms

[c]Model uses heteroskedastic robust standard errors

[d]Lower limit of confidence limit was negative so adjusted to zero because a negative CDI rate is not possible

[e]Courses = number of seven-day courses

[f]Fixed effect co-efficient and p-value from segmented regression analysis in original publication, raw data were not available to allow reanalysis

Table 2: Setting, high risk antimicrobials selected, CDI rates, case definition and changes to diagnosis or infection control policies for Medicine and Surgery in Ninewells Hospital and six comparable studies from a systematic review

Study	Setting	Cephalosporins	Co-amoxiclav	Clindamycin	Clarithromycin	Fluoroquinolones	Piperacillin-tazobactam	Pre-intervention CDI rate (per 1000 OBD per month)	CDI case definition	Changes to CDI diagnostic test or infection control practices
Ninewells Hospital	Medicine	CRO, CXM	Yes	Yes	Yes	CIP, MXF	No	2.7*	Diarrhoea and +ve toxin, duplicates removed	Diagnostic test changed 9 months post intervention
Ninewells Hospital	Surgery	CRO, CXM	Yes	Yes	Yes	CIP, MXF	No	0.8*	Diarrhoea and +ve toxin, duplicates removed	Diagnostic test changed 9 months post intervention
Aldeyab 2012	UK, Whole hospital	CAZ, CRO, CTX, CXM	No	No	No	CIP, LVX, MXF, OXF	No	1.4	Diarrhoea and +ve toxin, duplicates removed	Screening age (>65 to >12y) and cleaning changed at start of intervention
Dancer 2013	UK, Whole hospital	CRO	No	No	No	CIP, LVX, MXF, OXF	No	0.8	HA diarrhoea (48h) and +ve test, duplicates removed	None
Fowler 2007	UK, Medicine for the Elderly	CAZ, CRO, CTX, CXM	Yes	No	No	All	No	2.1*	Diarrhoea and +ve toxin, duplicates not clear	None
Ostrowsky 2014	USA, Six hospitals	FEP, 2/6 sites	No	No	No	CIP, 1/6 sites	Yes, 6/6 sites	0.6	HA diarrhoea (48h) and +ve toxin, duplicates not clear	Not clear
Price 2010	UK, Whole hospital	CAZ, CRO, CTX, CXM	No	Yes	No	CIP, LVX, MXF, OXF	No	1.2	HA diarrhoea (48h) and +ve test, duplicates removed	Cohorting ward introduced at start of intervention

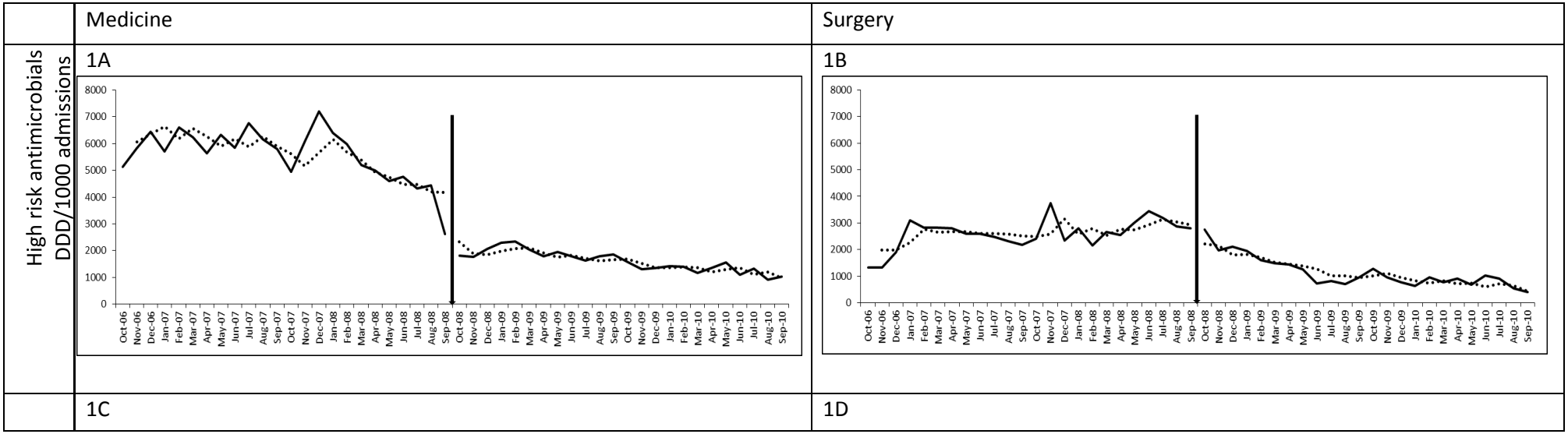
Talpaert 2011	UK, Whole hospital	CAZ, CRO, CTX, CXM	Yes	Yes	No	CIP, LVX, MXF, OXF	No	1.9*	Diarrhoea and +ve toxin, duplicates not clear	Isolation and cleaning policies changed at start of intervention

*OBD were estimated from data about number of admissions and mean length of stay in the pre-intervention period

Abbreviations: CAZ ceftazidime, CXM cefuroxime, CIP ciprofloxacin, CRO ceftriaxone, CTX ceftriaxone, FEP cefepime, HA hospital acquired, LVX levofloxacin, MXF moxifloxacin, OBD occupied bed days, OXF ofloxacin

Figures

Figure 1: Use of high risk antimicrobials (HRA) and *C. difficile* infection (CDI) rates pre- and post-intervention (introduction of HRA policy) in Medicine (1A,1C) and Surgery (1B,1D) in Ninewells Hospital. Solid lines indicate observed values and dashed lines indicate modelled values (modelled lines are straight when the model does not require adjustment for autocorrelation). Vertical arrows indicate the intervention time point.



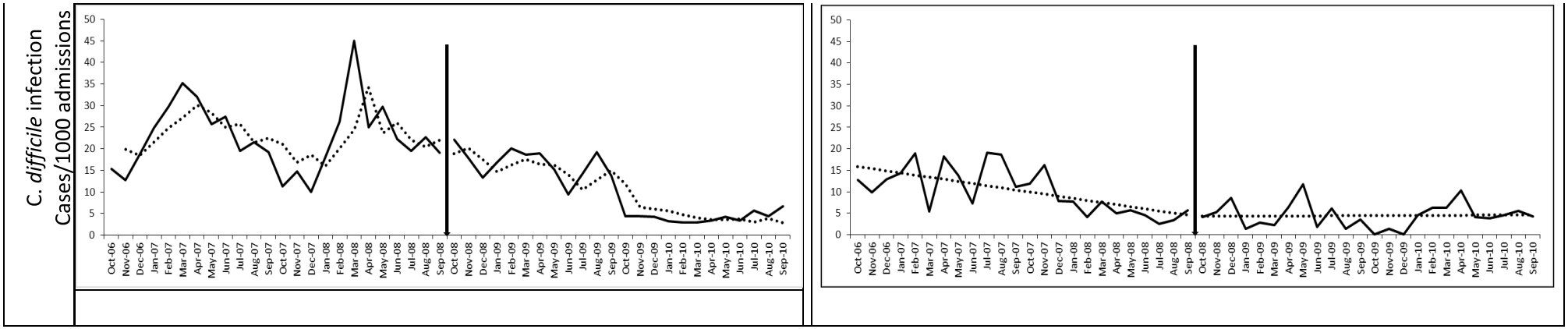
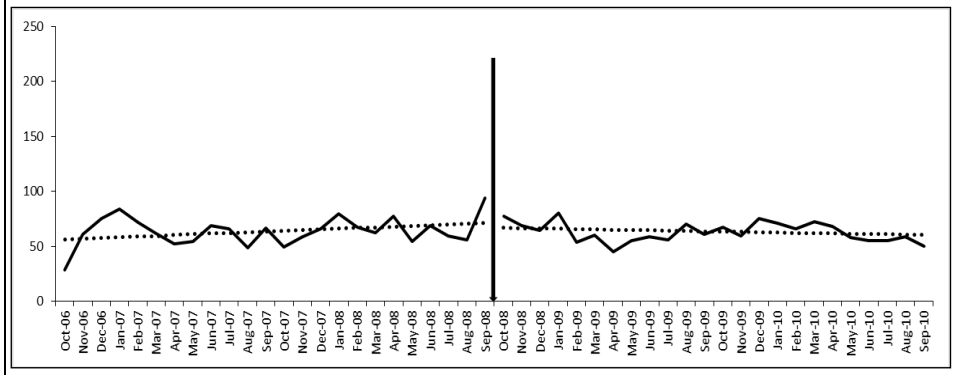
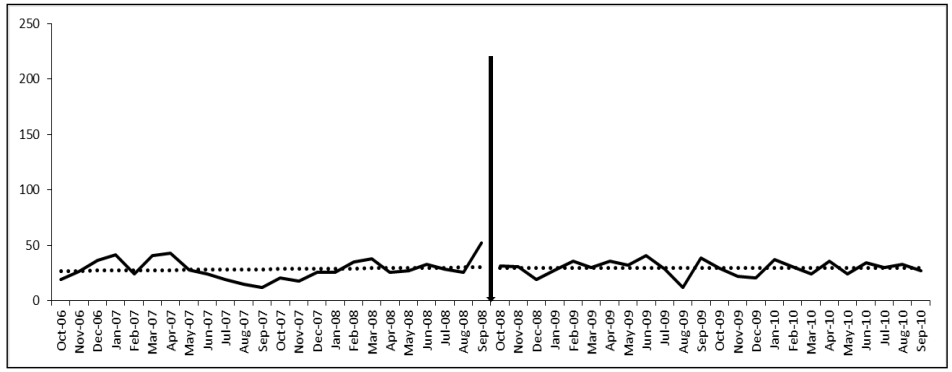
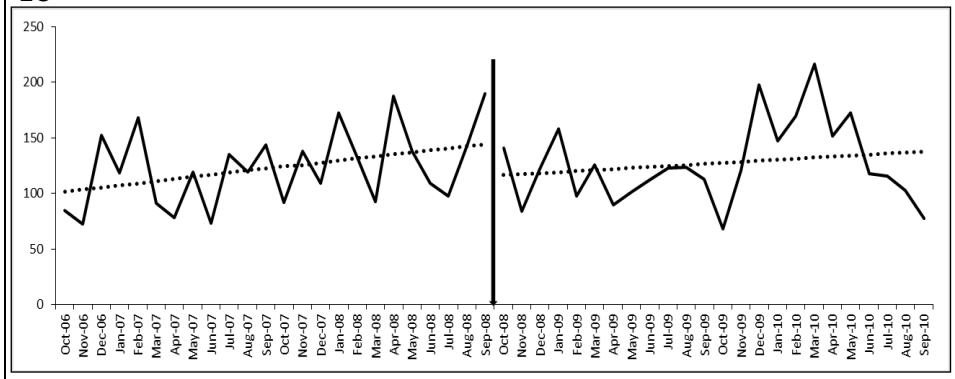
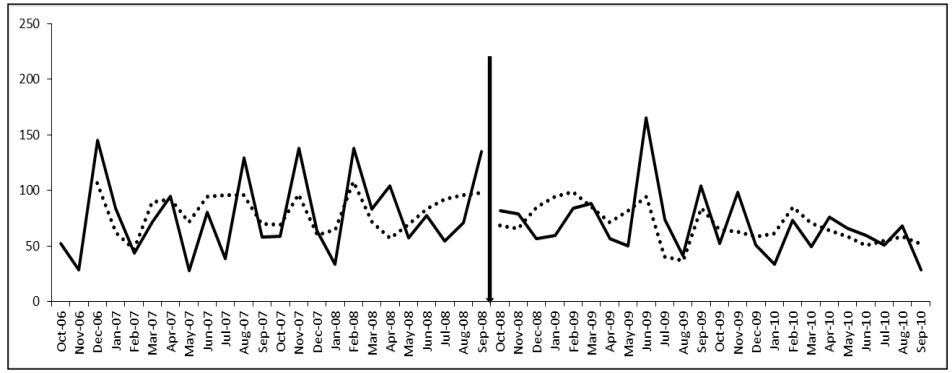


Figure 2: 30-day mortality rates among all patients, and among patients who had blood cultures taken, pre- and post-intervention (introduction of HRA policy) in Medicine (2A,2C) and Surgery (2B,2D) in Ninewells Hospital. Solid lines indicate observed values and dashed lines indicate modelled values (modelled lines are straight when the model does not require adjustment for autocorrelation). Vertical arrows indicate the intervention time point.

		Surgery
Mortality Deaths per 1000 admissions	2A 	2B 
Blood culture mortality Deaths per 1000 blood cultures	2C 	2D 

Medicine

Table S1: Overview of study design: setting, population, nature and timing of antibiotic prescribing and infection control interventions

Setting: Nine adult medical wards and six adult surgical wards in a 855 bed University hospital

Dates: October 2006 to September 2010

Population characteristics:
Medical: 29,651 consecutive admissions through the Acute Medical Admissions Unit.
Surgical: 30,562 consecutive admissions to six general surgical wards (abdominal, urological and vascular surgery).
Endemic *C. difficile* infection at an average of 1.5 cases per 1000 acute occupied bed days in the pre-intervention period with no significant increase in the seven years from 2000-2006.
Few inter-hospital transfers from two other hospitals in Tayside with no change during the study period. No inter-hospital transfers from other regions.

	Antibiotic policy	**Audit and Feedback**	**Infection Control Policy**
Phase 1: 24 months (1 October 2006 to 30 September 2008)	Policy for use of ALERT antibiotics introduced in August 2000, implemented by advice from clinical pharmacists. (i) Carbapenems: imipenem and meropenem (ii) Glycopeptides: teicoplanin and vancomycin (iii) Intravenous (iv) amphotericin (iv) Ciprofloxacin (iv) (v) Linezolid (iv and oral) (vi) Piperacillin–tazobactam (Tazocin) (vii) Third-generation cephalosporins: ceftriaxone, cefotaxime and ceftazidime	Quarterly reports on ALERT antibiotic use by Clinical Group introduced in 2003. Reports expanded to include all antibiotics in April 2007. Quarterly reports on *C difficile* infections to clinical groups throughout Phase 1. Quarterly Infection Control reports with balanced scorecard to Clinical Groups and NHS Tayside Board from	Policy for isolation of any patient with diarrhoea and any patient with confirmed *C difficile* infection in single rooms with aprons and gloves worn for contact throughout Phase 1. Weekly hand hygiene audits by staff in study wards from 2005. Supplemented with bi-monthly audits by Infection Control practitioners as part of the National Hand Hygiene Campaign from 2007. Annual environmental infection control audits by Infection Control practitioners
Phase 2: 24 months (1 October 2008 to 30th September 2010)	ALERT antibiotic policy remained in place. Narrow spectrum antibiotic policy reducing use of cephalosporins, co-amoxiclav and quinolones. Cefuroxime and moxifloxacin restricted by removal from stock in wards and operating theatres. Policy implemented from October 2008 by advice from clinical pharmacists supported by departmental presentations by Chair of the Antimicrobial Management Group and Antimicrobial Pharmacist from October to December 2008	Quarterly reports on antibiotic use adapted to show use of restricted and recommended antibiotics. Compliance with the new antibiotic policy was also included in quarterly Infection Control reports and balanced scorecards to Clinical Groups and Clinical Governance Committees.	As Phase 1, no change in frequency of hand hygiene or other audits. NHS Tayside participated in the second phase of the Safer Patients Initiative and in the Scottish Patient Safety Programe and hand hygiene measures were in place throughout the pre- and post-intervention phases.

ALERT antibiotic policy (Phase 1): ALERT antibiotics limited to defined indications documented in the Antibiotic Policy. Pharmacists reviewed patients receiving ALERT antibiotics and recommended change
Antibiotic Man policy (Phase 2): designed to eliminate use of cefuroxime or moxifloxacin and reduce use of ceftriaxone, co-amoxiclav, ciprofloxacin, clarithromycin and clindamycin. ALERT antibiotic policy for use of ceftazidime, piperacillin-tazobactam or meropenem unchanged from Phase 1. The new policy promoted use of amoxicillin, co-trimoxazole, doxycycline and gentamicin for treatment (Table S2) and co-amoxyclav.
Intervention components: antibiotic policy available online (Tables S2 and S3), educational meetings, audit of drug supply to wards with quarterly feedback, restriction by removal (cefuroxime and moxifloxacin).

Isolation details (both phases): all participating wards have six single rooms. All other beds configured in six bedded bays. Wall mounted liquid soap and alcohol handrub dispenser and sink in each bay and side room with additional alcohol handrub dispensers for staff on trolleys.

Definition of *C difficile* infection (both phases): an episode of diarrhoea with a sample that was positive for toxin. Mandatory testing for *C difficile* in stool samples from all patients aged 65 or over introduced in Scotland in October 2007. Culture not routinely performed. Routine testing was by the automated EIA system VIDAS. As of 28 January 2009 all Vidas equivocal results had a Quik Chek Complete carried out in addition to the Vidas test and results interpreted as below:

VIDAS	Quik Chek GDH	Quik Chek TOX	REPORT
Equivocal	Positive	Negative	Cl. difficile toxin test indeterminate REP
Equivocal	Positive	Positive	Cl. difficile toxin detected
Equivocal	Negative	Negative	Cl. difficile toxin not detected
Equivocal	Negative	Positive	Cl. difficile toxin test indeterminate REP

Table S2: NHS Tayside Antibiotic Man introduced in October 2008

Hospital Adult Empirical Treatment of Infection Guidelines

NHS Tayside

NEWS ≥5 and INFECTION: THINK SEPSIS — **If 2 or more of the following AND clinical suspicion of infection**

COMPLETE SEPSIS 6 BUNDLE WITHIN 1 HOUR

Temperature >38°C or <36°C | Pulse rate >90 beats per minute | Altered mental state
Respiratory rate >20 breaths/min | WCC <4 or >12 | Known or suspected neutropenia

ALWAYS DOCUMENT INDICATION & DURATION IN NOTES AND MEDICINE CHART
REVIEW ANTIBIOTIC THERAPY DAILY- CAN YOU STOP? SWITCH? SIMPLIFY? STATE DURATION?

INDICATIONS FOR IV USE: Review IV therapy every 12-24 hours – see IVOST guideline

- 2 or more criteria as above out with range (temperature, respiratory rate, pulse, WCC)
- Febrile with neutropenia or immunosuppression
- Specific infections e.g. endocarditis, septic arthritis, abscess, meningitis, osteomyelitis
- Oral route compromised
- Post surgery – unable to tolerate 1 litre of oral fluids
- No oral formulation available

ANTIBIOTIC DOSES (UNLESS OTHERWISE STATED)
NOTE: ALL DOSES ASSUME NORMAL RENAL AND HEPATIC FUNCTION

ANTIBIOTIC	ORAL	IV
Amoxicillin	1g tds	1g tds
Co-trimoxazole	960mg bd	960mg bd
Co-amoxiclav	625mg tds	1.2g tds
Clarithromycin *	500mg bd	500mg bd
Metronidazole	400mg tds	500mg tds
Flucloxacillin	1g qds	1-2g qds

*Consider risk of prolonged QT interval and interactions e.g. statins

MICROMAN: FOR ANTIBIOTIC 'RULES OF THUMB' AND BASIC MICROBIOLOGY INFORMATION ON COMMON INFECTIONS

GENTAMICIN: IF IV THERAPY IS STILL INDICATED AFTER 72 HOURS OF GENTAMICIN (OR >24 HOURS IF POOR/DETERIORATING RENAL FUNCTION)
1. CHECK MICROBIOLOGY RESULTS & SENSITIVITIES 2. CONSIDER SWITCH TO AZTREONAM 3. IF REQUIRED ASK ID OR MICRO FOR ADVICE

AZTREONAM: FOR CERTAIN PATIENTS ONLY AS ALTERNATIVE TO GENTAMICIN – REFER TO GUIDANCE

PENICILLIN ALLERGY: TAKE ACCURATE HISTORY AND REFER TO GUIDANCE

CNS

MENINGITIS Ceftriaxone IV 2g bd + Dexamethasone IV 10mg qds for 4 days started with or just before first dose of antibiotics
- Aciclovir IV (10mg/kg tds) if encephalitis suspected
- Add Amoxicillin IV 2g 4 hourly if ≥ 60 years or immunocompromised

ENT

EPIGLOTTITIS/SUPRAGLOTTITIS Ceftriaxone IV 2g od — Refer to ENT Guidance for oral step down and treatment of other infections

LUNG

COMMUNITY ACQUIRED PNEUMONIA — **Assess CURB65 score**

0-2 Mild/Mod Amoxicillin 1g tds IV/PO **(5 days)** — If penicillin allergic:Doxycycline PO 200mg on day 1 then 100mg od (or IV Clarithromycin if NBM)
3-5 Severe Co-amoxiclav IV 1.2g tds + Doxycycline PO 100mg bd — If penicillin allergic: IV Levofloxacin 500mg bd
ICU/HDU or NBM Co-amoxiclav IV 1.2g tds + Clarithromycin IV 500mg bd — If penicillin allergic: IV Levofloxacin 500mg bd
Step down to Doxycycline 100mg bd for all patients with severe CAP — **TOTAL IV/PO 7 days**

HOSPITAL ACQUIRED PNEUMONIA OR ASPIRATION PNEUMONIA

Severe IV Amoxicillin + Metronidazole + Gentamicin — If penicillin allergic: IV Co-trimoxazole + Metronidazole +/- Gentamicin
Step down to PO Co-trimoxazole + Metronidazole (**TOTAL IV/PO 7 days**)
Non severe PO Amoxicillin + Metronidazole **(5 days)** — If penicillin allergic PO Co-trimoxazole + Metronidazole
Previous ICU admission or history of MRSA - seek advice

ACUTE EXACERBATION OF COPD — Give antibiotics if ↑ sputum purulence. If **no** ↑ sputum purulence then **no** antibiotics unless consolidation on CXR or signs of pneumonia.
1ST LINE Amoxicillin 500mg tds 2ND LINE Doxycycline 200mg on day 1 then 100mg daily **(5 days)**

ACUTE COUGH/ACUTE BRONCHITIS — Antibiotics give no significant benefit in clinical improvement but may be considered in the frail elderly.
1ST LINE Amoxicillin 500mg tds 2ND LINE Doxycycline 200mg on day 1 then 100mg daily **(5 days)**

HEART

ENDOCARDITIS • **Take appropriate blood cultures** • **Start empirical therapy and refer to ID/Microbiology**
• **Always check full endocarditis guidance for gentamicin/vancomycin dosing especially if reduced renal function** • **Do not use gentamicin chart**
Native valve indolent (Subacute): Amoxicillin IV 2g 4 hourly + Gentamicin 1mg/kg bd (use actual body weight - max 120mg/dose)
Native valve severe sepsis (Acute): Flucloxacillin IV 2g 6 hourly (4 hourly if >85kg)
Prosthetic valve or Suspected MRSA: Vancomycin IV + Rifampicin PO 600mg bd + Gentamicin IV 1mg/kg bd (use actual body weight - max 120mg/dose)
Native valve severe sepsis + risk factors for resistant pathogens (see full guidance):Vancomycin IV + Meropenem IV 2g tds (requires ID/Micro approval)

GI

CLOSTRIDIUM DIFFICILE INFECTION Refer to full guidance to assess severity
• Non severe: Metronidazole PO 400mg tds **(10 days)**
• Severe: Vancomycin 125mg qds PO/NG **(10 days)**
+/- IV Metronidazole
• Recurrent: positive CDI in previous 8 weeks - see **guidance**

ACUTE GASTROENTERITIS
No antibiotic treatment required. Seek advice if severe.

ACUTE PANCREATITIS
Antibiotics unlikely to affect outcome. Seek advice.

PERITONITIS/BILIARY TRACT/ INTRA-ABDOMINAL (TOTAL IV/PO 7-10 days)
IV Amoxicillin + Metronidazole + Gentamicin
then step down to PO Co-trimoxazole + Metronidazole
(If penicillin allergic IV Vancomycin + Metronidazole + Gentamicin
then step down to PO Co-trimoxazole + Metronidazole)

PROVEN SPONTANEOUS BACTERIAL PERITONITIS (5 - 7 days)
Severe disease: Piperacillin/Tazobactam IV 4.5g tds
then step down to Co-trimoxazole PO
Mild disease (incidental diagnosis on routine tap):
Co-trimoxazole PO

GU

CATHETERISED PATIENTS: DO NOT USE URINALYSIS. DO NOT TREAT UNLESS CLINICAL SIGNS/SYMPTOMS OF INFECTION. IF DEFINITE INFECTION TREAT AS PER COMPLICATED UTI.
UTI IN OLDER ADULTS: DO NOT USE URINALYSIS. DO NOT TREAT UNLESS CLINICAL SIGNS/SYMPTOMS OF INFECTION. IF DEFINITE INFECTION TREAT AS PER GUIDANCE BELOW.

UNCOMPLICATED FEMALE LOWER UTI — Nitrofurantoin 50mg qds or 100mg MR bd or Trimethoprim 200mg bd **(3 days)**
UNCATHETERISED MALE UTI — Nitrofurantoin 50mg qds or 100mg MR bd or Trimethoprim 200mg bd **(7 days)**
COMPLICATED UTI/PYELONEPHRITIS/UROSEPSIS — IV Amoxicillin + Gentamicin (If penicillin allergic IV Co-trimoxazole + Gentamicin)
Step down to PO Co-trimoxazole or as per sensitivities
TOTAL IV/PO 7 days (see separate guidance if **prostatitis** suspected or proven)

BONE/ SKIN

CELLULITIS Refer to full guidance to assess severity **TOTAL IV/PO 7 days**
Flucloxacillin 1g qds (If penicillin allergic: Doxycycline 100mg bd PO)
If history of MRSA or not responding: see MRSA guideline

DIABETIC FOOT INFECTION (7 days)
Refer to full guidance to assess severity and if antibiotics in last month
Mild: Flucloxacillin 1g qds or Doxycycline 100mg bd
Moderate: Flucloxacillin 1g qds + Metronidazole 400mg tds
or Doxycycline 100mg bd + Metronidazole 400mg tds

ACUTE SEPTIC ARTHRITIS/OSTEOMYELITIS (seek ID advice)
IV Flucloxacillin 2g qds

OPEN FRACTURE PROPHYLAXIS (including hand injuries)
IV Co-amoxiclav 1.2g tds (or IV Co-trimoxazole 960mg bd + Metronidazole 500mg tds) Start within 3 hours for max 72 hours

UNKNOWN SOURCE

IV Amoxicillin + Metronidazole + Gentamicin (consider adding Flucloxacillin/Vancomycin if concern re staphylococci)
Penicillin allergy: IV Vancomycin + Metronidazole + Gentamicin — **Neutropenic patients**: refer to guidance

Table S3: NHS Tayside policy for antibiotic prophylaxis in general surgery

ANTIBIOTIC PROPHYLAXIS IN GENERAL SURGERY

Written by: NHS Tayside Antimicrobial Management Group/Surgical Directorate
Date: 2008

NHS Tayside

The aim of surgical prophylaxis is to reduce rates of surgical site and healthcare-associated infections and so reduce surgical morbidity and mortality. There is however growing evidence that aspects of prescribing practice may themselves be associated with health-care associated infections, notably *Clostridium difficile* infection (CDI). The Scottish Antimicrobial Prescribing Group (SAPG), along with the Scottish Government, is monitoring surgical prophylaxis in order to reduce the rates of CDI and resistance.
SIGN guideline 104 (published in 2008 and updated 2014) has outlined which surgical procedures require prophylactic antibiotics based on a review of the available evidence. Principles of prophylaxis have also been outlined, including timing and duration of antibiotic administration. In conjunction with the surgical specialties within NHS Tayside the Antimicrobial Management Group has undertaken to review local prophylaxis policy and to formulate a uniform policy.

Principles of Antibiotic Prophylaxis Policy

1. **Indication for prophylaxis** should comply with SIGN 104 guideline i.e. when 'highly recommended', 'recommended' or 'considered' within guideline.
2. **Timing of antibiotic(s)**:
    - Optimum timing is intravenous dose given or infusion completed 60 minutes prior to skin incision
    - Sub-optimal if >1 hour prior to skin incision or post-skin incision
3. **Recording of antibiotic** prescription in 'once only' section of medicine chart to avoid multiple dosing
4. **Frequency of administration** should be single dose only unless:
    - 1.5 litres intra-operative blood loss - re-dose following fluid replacement (see administration guidance table)
    - operation prolonged (see administration guidance table)
    - specifically stated in following guidelines
5. **Documentation in medical notes** of reason for antibiotic administration beyond single dose or state intention for antibiotic treatment course
6. **Choice of agent** should:

- Avoid cephalosporins, clindamycin, quinolones and co-amoxiclav wherever possible
- Use narrow spectrum agents when possible to minimise impact on resistance and CDI
- Take into account local resistance patterns
- Provision of alternatives for beta-lactam allergy

7. **De-colonisation therapy/MRSA positive**
   If a patient is identified as MRSA positive from screening swabs within 3 weeks of anticipated date of elective surgery then a decolonisation program should be started as per MRSA protocol. The decolonisation regimen should also be restarted the day they come into hospital for 5 days to reduce the microbial load perioperatively. For surgical prophylaxis for primary operations vancomycin infusion should be added to the regime recommended in the table below (except for breast surgery where it would be used as a replacement). If they have an MRSA infection prior to elective surgery the approach is the same as for any other infection.
8. **Complex individual prophylaxis** issues should be discussed with Microbiology or Infectious Diseases pre-operatively and recorded in medical notes 9. **Compliance with local policy** is required and monitored by NHS Tayside. Any deviation from policy must be recorded in the appropriate medical records.

For details of antibiotic administration see last page.

Type of Surgery	**Procedure**	**SIGN 104 Recommendation**	**Antibiotic(s)**	**Comments** **(if patient is MRSA positive refer to section 7 above)**
Breast Surgery	Breast Cancer Surgery Breast Reshaping Procedures	Locally 'Recommended'	Flucloxacillin IV	If penicillin allergic use Clindamycin IV
	Breast Surgery with Implant (reconstructive or aesthetic)	'Recommended'	Flucloxacillin IV	If penicillin allergic use Clindamycin IV
Vascular Surgery				See separate Vascular Unit Policy
Head and Neck Surgery	Thyroidectomy	'Not recommended'		Clean, benign surgery
Upper Gastro-intestinal	Oesophageal Surgery Stomach and Duodenal Surgery Gastric Bypass Surgery Small Intestine Surgery	'Recommended'	Gentamicin IV + Metronidazole IV	**If patient is receiving dialysis, an eGFR <30ml/min, Cr >350 or acute kidney injury consider using co-amoxiclav instead**. If patient has any renal issues, as above, and penicillin allergy please seek ID or Microbiology advice on choice of antibiotic prophylaxis.
Hepatobiliary	Bile Duct Surgery Pancreatic Surgery Liver Surgery	'Recommended'	Gentamicin IV + Metronidazole IV	**If patient is receiving dialysis, has an eGFR <30ml/min, Cr >350 or acute kidney injury consider using co-amoxiclav instead.** If patient has any renal issues, as above, and penicillin allergy please seek ID or

	Gall Bladder Surgery (open)			Microbiology advice on choice of antibiotic prophylaxis.
	Gall Bladder Surgery (laparoscopic)	'Not recommended' but should be 'considered' in 'high risk' patients	If required use: Gentamicin IV + Metronidazole IV	'High risk': intraoperative cholangiogram, bile spillage, conversion to laparotomy, acute cholecystitis/pancreatitis, jaundice, pregnancy, immunosuppression, insertion of prosthetic devices. **If patient is receiving dialysis, has an eGFR <30ml/min, Cr >350 or acute kidney injury consider using co-amoxiclav instead.** If patient has any renal issues, as above, and penicillin allergy please seek ID or Microbiology advice on choice of antibiotic prophylaxis.
Lower Gastro-intestinal	Appendectomy Colorectal Surgery	'Highly recommended'	Gentamicin IV + Metronidazole IV	**If patient is receiving dialysis, has an eGFR <30ml/min, Cr >350 or acute kidney injury consider using co-amoxiclav instead.** If patient has any renal issues, as above, and penicillin allergy please seek ID or Microbiology advice on choice of antibiotic prophylaxis.
Abdomen	Hernia repair-groin • Inguinal/femoral with or without mesh • Laparoscopic with or without mesh Hernia repair (incisional with or without mesh)	'Not recommended'		
	Open/laparoscopic surgery with mesh (e.g. gastric band or rectoplexy)	'Not recommended' but should be 'considered' in 'high risk' patients	If required use: Gentamicin IV + Metronidazole IV	'High risk': pregnancy, immunosuppression, insertion of prosthetic devices. **If patient is receiving dialysis, has an eGFR <30ml/min, Cr >350 or acute kidney injury consider using co-amoxiclav instead.** If patient has any renal issues, as above, and penicillin allergy please seek ID or Microbiology advice on choice of antibiotic prophylaxis.
	Diagnostic endoscopic procedures	'Not recommended'		
	Therapeutic endoscopic procedures (ERCP)	'Not recommended' but should be 'considered' in 'high risk' patients	If required use: Gentamicin IV + Metronidazole IV	'High risk': pregnancy, immunosuppression, insertion of prosthetic devices. **If patient is receiving dialysis, has an eGFR <30ml/min, Cr >350 or acute kidney injury consider using co-amoxiclav instead.** If patient has any renal issues, as above, and penicillin allergy please seek ID or Microbiology advice on choice of antibiotic prophylaxis.

Spleen	Splenectomy	'Not recommended'		

IV Antibiotic Administration Guidance:

Antibiotic	Dose	Administration	Prolonged surgery	>1.5L blood loss redose after fluid replacement
Metronidazole	BMI <30 500mg BMI ≥30 1g	Infusion over 20 minutes Infusion over 40 minutes (at least 500mg to be infused before knife to skin)	Redose 500mg after 8 hours	500mg
Gentamicin	4mg/kg Use ideal body weight (IBW) if >20% overweight IBW = (males: 50kg, females: 45.5kg) +0.9kg for every cm >150cm	Bolus over at least 5 mins or infusion Can also be added to metronidazole infusion bag	Redosing not required	Redosing not required
Flucloxacillin	1g	Bolus over 3-5 minutes	Redose 500mg after 4 hours	500mg
Clindamycin	600mg	Infusion over 20 minutes	Redose 300mg after 4 hours	300mg
Co-amoxiclav	1.2g	Bolus over 3-5 minutes	Redose 600mg after 4 hours	600mg
Vancomycin	1g	Infusion over 100-120 minutes in 250ml sodium chloride 0.9%	Redose after 12 hours	500mg

Table S4: Use of HRA in Medicine and Surgery in Ninewells Hospital pre- and post-intervention in DDD per 1000 admissions per month.

	Medicine					Surgery				
Drug	Pre-intervention	% total	Post-intervention	% total	Difference (post-pre)	Pre-intervention	% total	Post-intervention	% total	Difference (post-pre)
Ceftriaxone	202	4.1%	129	9.1%	-73	16	0.6%	15	1.8%	-104
Cefuroxime	62	1.2%	2 (0 from 13 months)	0.2%	-60	315	12.3%	19 (0 from 13 months)	2.2%	-296
Ciprofloxacin	634	12.7%	355	25.0%	-279	750	29.2%	273	32.5%	-477
Moxifloxacin	309	6.2%	5 (0 from 10 months)	0.3%	-304	19	0.7%	0	0.0%	-19
Clarithromycin	1610	32.3%	356	25.0%	-1254	162	6.3%	45	5.4%	-117
Clindamycin	311	6.2%	215	15.1%	-96	176	6.8%	90	10.8%	-85
Co-amoxiclav	1773	35.6%	270	19.0%	-1503	916	35.7%	267	31.8%	-649
Total	4979		1421		-3558	2354		710		-1644

Ceftazidime was not targeted but was already part of the ALERT antibiotic policy. In Medicine ceftazidime use was 78 DDD per 1000 admissions per month in the pre-intervention period and increased to 89 in the post-intervention period (difference +11, compared with much larger reductions in all targeted antimicrobials in Table). Ceftazidime was not used at all in Surgery pre- or post-intervention.

Table S5: Mortality among all admissions and among patients who had blood cultures taken, in Medicine and Surgery in Ninewells Hospital

Group	**Units (per month)**	**Pre-intervention trend**	**Baseline rate***	**Absolute change at 6 months**	**Relative change at 6 months**
Ninewells Medicine	Deaths within 30 days per 1000 admissions	0.6	71.2	-5.7 (-18.7 to 7.2)	-7.5% (-24.4 to 9.4)
Ninewells Surgery		0.2	30.1	-0.6 (-10.8 to 9.7)	-1.9% (-35.2% to 31.4%)
Ninewells Medicine Blood cultures	Deaths within 30 days per 1000 blood culture patients	2.0	144.4	-23.5 (-65.5 to 18.5)	-14.0% (-39.0% to 11.0%)
Ninewells Surgery Blood cultures		0.5	97.8	-12.9 [i, ii] (-50.9 to 25.1)	-11.7% (-46.0 to 22.7)

[i] Model has been adjusted for autocorrelation using lag terms, [ii] Model has heteroskedastic robust SE terms