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Systematic Review of the Microbiological Outcomes of Interventions to Improve Antibiotic Prescribing to Hospital Inpatients

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Abstract

Prudent antibiotic prescribing to hospital inpatients has the potential to reduce the incidences of antimicrobial resistance and healthcare-associated infection. We reviewed the literature from January 1980 to November 2003 to identify rigorous evaluations of interventions to improve hospital antibiotic prescribing. We identified 66 studies with interpretable data of which 16 reported 20 microbiological outcomes: Gram negative resistant bacteria (GNRB), 10 studies; *Clostridium difficile* associated diarrhoea (CDAD), 5 studies; vancomycin resistant enterococci (VRE), 3 studies and methicillin resistant *Staphylococcus aureus* (MRSA), 2 studies. Four studies provide good evidence that the intervention changed microbial outcomes with low risk of

alternative explanations, eight studies provide less convincing evidence and four studies were negative. The strongest and most consistent evidence was for CDAD but we were able to analyse only the immediate impact of interventions because of non-standardised durations of follow up. The ability to compare results of studies could be substantially improved by standardising methodology and reporting.

Article summary line:

Seven of 16 studies reporting microbiological outcome provide good evidence that interventions can reduce the incidences of *C. difficile* associated diarrhoea and antimicrobial resistance but the evidence base could be substantially improved by standardising methodology and reporting.

Background

Despite strenuous efforts to control antibiotic usage and to promote optimal prescribing, practitioners continue to prescribe excessively and it is estimated that up to 50% of antibiotic usage in hospitals is inappropriate(1-3). Antibiotic resistance is largely a consequence of the selective pressures of antibiotic usage and it is plausible that reducing these pressures by the judicious administration of antibiotics will facilitate a return of susceptible bacteria or, at least, will prevent or slow the pace of the emergence of resistant strains(4;5). Furthermore *Clostridium difficile* associated diarrhoea (CDAD) is a hospital acquired infection that is associated with antibiotic prescribing (6),(7;8) and reducing the incidences of CDAD is an additional potential benefit from improving hospital antibiotic prescribing.

Implementing and monitoring interventions to optimise antibiotic prescribing places a burden on hospital resources and their efficacies need to be confirmed.(9).

We have conducted a systematic review of interventions to improve antibiotic prescribing practices for hospital inpatients using the methods of the Cochrane

Effective Practice and Organisation of Care Group to assess validity (10). In this paper our primary objective is to evaluate the impact of interventions on reducing the incidence of colonisation with or infection caused by antimicrobial resistant pathogens or CDAD. In addition to the usual threats to the validity of interventions to change healthcare, infection control interventions are particularly prone to regression to the mean.(11) Simply put this refers to the natural tendency of extreme observations to return towards the average (mean) over time. An epidemic or outbreak is a sequence of unusually large number of cases of infection, so that the natural history of an epidemic is to increase, peak and then decline. Consequently regression to the mean is always a threat to the validity of evaluations of unplanned interventions that are initiated in response to an outbreak.

Methods

The full protocol is available in the Cochrane Library (10). We searched Medline, EMBASE, the Cochrane database and the EPOC specialised register from 1st January 1980 to 30th November 2003 for studies relating to antibiotic prescribing to hospital inpatients and additional studies were obtained from the bibliographies of retrieved articles, the Scientific Citation Index and personal files. We requested additional data from the authors when necessary. There were no language limitations for the literature review. We included all randomised and controlled clinical trials (RCT/CCT, designs where allocation to the intervention is determined either by an explicit random process [RCT] or by a non-random process such as date of birth or case note number), controlled before and after studies (CBA, a design where there is contemporaneous data collection before and after the intervention and an appropriate control site or activity) and interrupted time series (ITS, a design where there is a clearly defined point in time when the intervention occurred and at least three data

points before and three after the intervention). Data about microbiological outcomes were considered reliable if they met the same criteria. For example, if a paper included prescribing data that met the criteria for an ITS but provided only mean data about microbiological outcomes before and after the intervention then the microbiological data were not considered reliable. Two reviewers independently extracted data and assessed the quality of each study using the above standardised criteria.

Statistical considerations

There are many statistical methods that can be used to analyse ITS designs (eg ARIMA modelling or time series regression), however the design is often analysed inappropriately making interpretation of individual studies difficult (ref Ramsay IJTAHC). Methods of analysing ITS data were examined critically (ref Ramsay IJTAHC). The preferred method for short time series is segmented time series regression analysis, which is a statistical comparison of time trends before and after the intervention to identify either an immediate change in the level of the regression line or a sustained change in the slope of the line (12)(ref Ramsay). In this paper we have distinguished two intervention effects: immediate (a sudden change in the level of the regression line at the point of intervention) and sustained (a sustained change in the slope of the regression line from the start of the intervention phase. If the original paper did not include an appropriate analysis, the data were re-analysed using segmented time series regression. The following model was specified:

$$Y_t = B_0 + B_1 * \text{Preslope} + B_2 * \text{Postslope} + B_3 * \text{intervention} + e_t$$

Where Y_t is the outcome (eg CDAD incidence) in month t , Preslope is a continuous variable indicating time from the start of the study upto the last point in the pre intervention phase and coded constant thereafter. Postslope is coded 0 upto

and including the first point post intervention and coded sequentially from 1 thereafter. Intervention is coded 0 for pre intervention time points and 1 for post intervention timepoints. In this model, B_1 estimates the slope of the pre intervention data, B_2 estimates the slope of the post intervention data and B_3 estimates the change in level of outcome as the difference between the estimated first point post intervention and the extrapolated first point post intervention if the preintervention line was continued into the post intervention phase. The difference in slope is calculated by $B_2 - B_1$. The error term e_t was assumed to be first order autoregressive. Confidence intervals (95%) were calculated for all effect measures.

Formal meta-analysis of results was not attempted given the differences in context, setting and type of outcomes. However, to gain an overall summary picture of the heterogeneity of effect sizes we standardised all measures so that they were all on the same scale. To do this, we divided the change in level and the change in slope by the pre-intervention standard deviation (SD) in each study. The resulting metric has no unit and in standard meta-analysis it is known as the standardised mean difference. Standardised effect sizes of 2 to 3 standard deviations were considered large, whereas an effect size of <0.5 standard deviation was considered of questionable clinical significance even if statistically significant (13). To visually display the heterogeneity of the standardised effect sizes, graphical plots of level effects versus slope effects for each study (with associated 95% confidence intervals) were generated.

Other Criteria for Assessment of Evidence

The statistical analysis assessed how likely it was that study results could simply have happened by chance and the Cochrane quality criteria assessed common threats to the validity of interventions to change practice or the organisation of care .

In order to assess other threats to validity of infection control interventions we used the format for reporting the results of included studies recommended by guidelines derived from a recent systematic review of isolation measures to control MRSA (14). Ideally we required studies to provide reliable data about the effect of interventions on both microbial and drug outcomes with clear case definition, description of infection control measures and other variables such as bed occupancy or staffing levels that could provide plausible alternative explanations for changes in microbial outcomes. We have provided a summary of the evidence from the included studies (Table 1) with more detailed information about each study in an appendix on the EID web site. We classified case definitions into colonization, infection or clinical isolates or a combination of two or more with the following definitions:

Colonization: the presence of a microorganism, usually detected by screening, at a host site (normally nonsterile, although the bladder urine of a catheterized patient may be an exception) without causing systemic signs of infection or a specific immune response.

Colonization by case note review: established by excluding infection diagnosed according to criteria adopted by the authors or defined by authoritative bodies, e.g., the CDC criteria for diagnosing nosocomial infections."

Infection: established by case note review according to criteria adopted by the authors or defined by authoritative bodies or by recording specific symptoms and/or signs, such as diarrhea in patients with CDAD."

Clinical isolates: recovery of a microorganism following culture of a clinical (not screening) specimen without specifying whether it represents colonization or infection.

Results

We identified 66 studies of interventions to improve antibiotic prescribing to hospital inpatients that met our inclusion criteria (15) and excluded 243 studies that were uncontrolled before and after studies (n=164) or inadequate ITS studies (n=79). Of the 66 included studies 16 reported reliable data about 20 microbiological outcomes: Gram negative resistant bacteria (GNRB), 10 studies; CDAD, 5 studies; vancomycin resistant enterococci (VRE), 3 studies and methicillin resistant *Staphylococcus aureus* (MRSA), 2 studies (Table 1). The setting for the intervention was the whole hospital in eight studies (16-23), a single service in two studies(24;25) and a unit or ward in six studies(26-31). One intervention was educational, with advice about changes in antibiotics (16), whereas the other 15 interventions were restrictive (Table 1). There were two RCTs (30;31)and one CCT (29); the remaining 13 studies used an ITS design.

Statistical validity

All three clinical trials involved appropriate statistical analysis (29),(30;31) whereas only two of the 13 ITS studies reported appropriate statistical analysis(16;26). Of the remaining 11 ITS studies five did not report statistical analysis and six reported inappropriate analysis using tests such as chi-square or t tests that assume independence between observations and take no account of time trends. Data from these 11 studies were re-analysed.

Evidence for effectiveness of interventions to improve antibiotic prescribing

Overall, four studies provide good evidence of control of the microbial outcome by change in prescribing. (16;26;29;30) All of these studies provide reliable data about antibiotic prescribing with significant changes in both microbial and drug outcomes following planned interventions. In addition two studies provided further protection

against regression to the mean by using a cross over design (26;29). Three of these studies have rigorous case definition based on prospective screening cultures plus full description of infection control measures.

Eight studies provide less convincing evidence. Two studies showed significant changes in prescribing that were associated with non-significant changes in CDAD(19;25). There are an additional six studies that report statistically significant improvement in microbial outcome but without reliable data about the effect of the intervention on prescribing (17;18;22;23;27;28). The importance of this omission is confirmed by the six studies that did include reliable data about prescribing because all of them showed that there was some prescription of restricted drugs during the intervention phase.(16;19;25;26;29;30)

There are four negative studies (20;21;24;31). One study provide good evidence of failure to control microbial outcomes despite a successful change in prescribing (31). One study reports an intervention that failed to change vancomycin use(21). The remaining two studies show no change in microbial outcome but do not provide reliable data about the effect of the intervention on prescribing (20;24).

CDAD

The most consistent evidence was for the five interventions designed to reduce the incidence of CDAD. Four were implemented in the whole hospital (16;17;19;23) and one in the care of the elderly service (25); all five targeted cephalosporin or clindamycin prescribing. All of the interventions were associated with a change in the expected direction (Figure 1a), which was a change in the incidence of CDAD in the same direction to change in cephalosporin or clindamycin use. For one intervention the expected direction was an increase in CDAD incidence after the introduction of

ceftriaxone (19); for all other interventions a decrease in CDAD incidence was expected to accompany decrease in cephalosporin or clindamycin use. These five studies reported a total of seven interventions. The immediate effect after six of the seven interventions was at least 0.5 SDs and five of these seven immediate effects were statistically significant (Figure 1a). Sustained changes after the intervention were more modest but all in the expected directions and four of seven were statistically significant (Figure 1a.). The five CDAD studies presented their results in different units: cases per month (23;25); cases per quarter (17;19) or cases per 1000 admissions per year (16). Consequently we were only able to compare effect sizes in numbers of CDAD cases per quarter by recalculating results from two studies (23;25). The antibiotic intervention was associated with a mean immediate reduction of 15.0 CDAD cases per quarter (range, 6 to 26) and a median sustained reduction of 3.2 CDAD cases per quarter (range, 1 to 6).

GNRB

The results of the 10 interventions designed to reduce the incidences of GNRB were less consistent. Three were implemented in the whole hospital (18;20;22), one was implemented on the neurology and neurosurgery service (24) and five in a single intensive care unit, four of which were paediatric (27-29;31) and one adult (30). One intervention was designed to reduce the duration of treatment with any antibiotic for ICU patients at low risk of pneumonia and this was associated with a significant reduction in the incidence of colonisation by any GNRB and in exposure to antibiotics (30). The remaining nine interventions involved changes in antibiotic treatment targeted mainly at aminoglycosides or cephalosporins. One RCT provided no evidence that antibiotic cycling reduced the incidence of GNRB in a neonatal ICU (31). The eight ITS studies reported nine outcomes (Figure 1b). The expected

direction of effect from a change in aminoglycoside or cephalosporin prescribing was usually a reduction in GNRB. For one intervention the expected direction of effect was an increase in the incidence of GNRB after re-introducing gentamicin (18). There was a change in level in the expected direction for all nine outcomes but the effect size was <0.5 SD in two studies and was not statistically significant in five (Figure 1b). In only three studies were the changes in slope in the expected direction and in only one was both statistically significant and >0.5 SD, which is likely to be clinically significant. Unlike the CDAD data it is not possible to express effects in a common unit. Some studies measured colonisation and others examined infection. Units of measurement were also variable (e.g. number of isolates, percentage of isolates, number of cases and number of cases per time period).

Gram-positive bacteria

Data for Gram-positive bacteria are very limited. One study provided convincing evidence that restriction of ceftazidime on a haematology unit was associated with significant reduction in risk of colonisation by VRE (26). However, reduction of cephalosporin use in a hospital was not associated with any change in the prevalence of VRE isolates (16). A third study targeted at VRE showed that implementation of a vancomycin order form had no significant impact on vancomycin prescribing, with a trend in the unintended direction (21). Two studies report effects on MRSA prevalence (16;20). Our segmented regression analysis showed that there was no significant change in response to a reduction in use of third generation cephalosporins (Table 1), although one of the papers claimed that there was a change (20).

Discussion

Our primary conclusion is that four of the 16 studies provide good evidence that changes in antibiotic prescribing to hospital inpatients can improve microbial outcomes (16;26)(29)(30). Eight of the remaining studies provide some evidence that antibiotic prescribing interventions can improve microbial outcomes but flaws in their design meant that there were plausible alternative explanations for the results (17-19;22;23;25;27;28). The remaining four studies were unequivocally negative (20;21;24;31).

Estimation of overall effect size was only possible for reduction in CDAD, where the evidence suggests that restriction of clindamycin or third generation cephalosporins resulted in an immediate reduction in prevalence by 15 cases per quarter with a further sustained reduction by 3 cases per quarter. It is usual to adjust prevalence for clinical activity, for example cases per 1000 admissions per quarter (7) but only one study provided this information (16). Furthermore there were potentially important differences in the case definitions of CDAD between the studies in our review.

The second conclusion is that finding valid studies required painstaking analysis of a huge volume of literature, most of which is fundamentally flawed (15). Even the included studies could be dramatically improved by following guidelines for standardised reporting (14). In particular, the unequal duration of post-intervention phases made it difficult to reliably compare the sustained effects of interventions, these being the most important outcome measures. The short and unequal duration of pre-intervention phases provides limited information about underlying pre-intervention trends. In order to understand how much of a change in prescribing is required to change outcome the intervention must be independent of other control

measures and be accompanied by reliable data about both prescribing and microbial outcomes.

Only one of the interventions was designed to reduce overall exposure to antibiotics (30), all of the others being targeted at the choice of antibiotic. This study was conducted in an adult ICU but the same principle of using clinical scores to identify low risk patients, in whom antibiotic therapy could be stopped has been developed in other clinical settings(32-34) and the impact on microbiological outcomes should be investigated.

Crucially none of the studies provided evidence for cost-effectiveness or clinical outcome. Furthermore it is likely that the study designs did not have sufficient power to measure these outcomes. Only a minority of studies provided data about multiple microbiological species and one of these endpoints (incidence of cefotaxime-resistant *Acinetobacter* spp.) was in the opposite direction to that which was expected (20). Future studies should provide more data about cost and clinical outcomes. Notably, evidence is needed to show that interventions do not have adverse outcomes.

It seems likely that the potential for the success of antimicrobial interventions varies by organism (35;36). Anti-infectives are likely to play a large role in the selection of Enterobacteriaceae expressing ESBLs, a minimal role in the selection and transmission of MRSA, and an intermediate role in VRE. However, at present the available evidence is not sufficient to investigate these hypotheses.

Implications for practice

The evidence supports the theory that limiting the use of specific antibiotics will reduce the prevalences of resistant Gram-negative bacteria and CDAD. For Gram-positive bacteria there is a lack of evidence rather than evidence of no effect.

Ideally hospitals would like to know by how much they should limit their antibiotic prescriptions and what is the minimum that they must cut down to see a “real” effect. Unfortunately the available evidence is too limited to provide definitive answers to these questions, consequently hospitals must estimate the effect of their own interventions. The good news is that the data required for ITS analysis of the incidences of resistant bacteria or CDAD should be readily available in most hospitals. Healthcare providers need to invest in data analysis so that evaluation of antibiotic control in single hospitals becomes a routine measure of the quality of care rather than a research project.

Standardised reporting of outbreaks and interventions to control the incidence of antibiotic resistance or hospital acquired infection would greatly enhance the ability to combine results from hospitals in meta-analyses. Key issues include full description of other infection control measures, consistent and reproducible case definitions, the length of pre- and post-intervention phases and the time intervals between data points. Ideally data should be presented or made available in a way that allows re-analysis and where appropriate meta-analysis. Meta-analysis of single hospital studies is no substitute for good multi-centre studies but could be used to provide some evidence of reproducibility and hence to prioritise targets for definitive trials.

Priorities for research

The research agenda needs to move to multi-centre studies with randomised allocation to interventions. This will provide better evidence of external validity as well as the power to measure cost-effectiveness and exclude important unintended adverse clinical outcomes.

Development and pilot testing of the effectiveness of clinical decision rules for reducing unnecessary exposure to antibiotics should be a priority for research in single hospitals.

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Table 1: Summary of included studies.

Study	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Bradley et al 1999 (26)	Adult haematology unit in the UK, 261 patients who were not carriers of VRE at the start of the study	Prospective Interrupted Time Series with three phases of 4, 6 and 5 months. Planned intervention. Case definition: colonization. Other infection control measures: consistent through study.	Phase 1: ceftazidime for empirical antibiotic treatment Phase 2: antibiotic policy changed to piperacillin tazobactam. Phase 3: antibiotic policy changed back to ceftazidime.	Microbial: % of patients colonized with VRE fell from 57% in Phase 1 to 19% in Phase 2 then rose again to 36% in Phase 3, significant by Log Rank test. Drug: Significant reduction in ceftazidime use in Phase 2: immediate -227.8 patient days per month, $p<0.001$, sustained -19.3 patient days per month, $p=0.037$.	Statistically significant reduction in risk of colonisation with VRE associated with reduction in antibiotic prescribing. No major weaknesses in the study design.
Calil et al 2001 (27)	Neonatal unit in Brazil, 342 patients on a 30 bed unit (8 intensive care and 22 intermediate care beds).	Prospective Interrupted Time Series with two phases of 3 months each. Unplanned intervention. Case definition: colonization. Other infection control measures: were introduced during the study and it is not clear how they related to the antibiotic intervention.	Phase 1: usual care. Phase 2: implementation of infection control measures emphasizing hand washing and contact precautions plus an antibiotic policy restricting use of third generation cephalosporins.	Microbial: cases of of multi-resistant <i>E cloacae</i> colonization per month decreased in Phase 2: immediate -15.51 cases per month ($p=0.054$), sustained -2.73 cases per month ($p=0.138$). Drug: no reliable data.	Significant reduction in colonization but it is not possible to separate the effects of the infection control measures from the change in antibiotic policy. Several other potentially important weaknesses.
Carling et al 2003 (16)	Single medium sized community teaching hospital (affiliated to a University) in the USA. No obstetric unit or paediatric ICU.	Hybrid retrospective and prospective Interrupted Time Series with two phases of 36 and 84 months. Planned intervention. Case definition: infection with CDAD or resistant gram-negative bacteria, MRSA or VRE. Other infection control measures: consistent through study.	Phase 1: automatic 7 day stop order on all antibiotics, limited reporting of susceptibility tests, and educational programme. Phase 2: as Phase 1 plus review of patients receiving target antibiotics by pharmacist and ID physician, recommendations placed in the case notes.	Microbial: CDAD and resistant Enterobacteriaceae in cases per 1000 admissions. MRSA and VRE as % clinical isolates. Post intervention there were significant reductions for CDAD: immediate -1.47 cases, $p<0.001$; sustained -0.81 cases, $p=0.05$. Resistant Enterobacteriaceae also reduced: immediate -2.34 cases, $p=0.03$; sustained -1.34 cases, $p=0.01$. There was no significant change in the % isolates of MRSA or VRE. Drug: authors' regression analysis shows significant reduction in target antibiotics in Phase 2.	Significant reduction in CDAD cases and resistant Enterobacteriaceae associated with planned antibiotic intervention that resulted in significant changes in antibiotic use. Main weaknesses are the lack of detail about infection control and the case definition for resistant <i>Enterobacteriaceae</i> .

Study	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Climo 1998 (17)	Single 703 bed tertiary care hospital in the USA.	Hybrid retrospective and prospective Interrupted Time Series with two phases of 27 and 33 months. Unplanned intervention. Case definition: infection, CDAD. Other infection control measures: consistent through study.	Phase 1: infection control only Phase 2: infection control plus restriction of clindamycin.	Microbial: CDAD cases per quarter. The intervention was associated with significant reduction in CDAD cases per quarter: immediate -26.3 cases, $p < 0.001$; sustained -3.8 cases, $p < 0.001$. Drug: no reliable data.	Significant reduction in CDAD cases in Phase 2. However, this was an unplanned intervention, there are no reliable data about drug use and the study has several other potentially important weaknesses.
de Champs et al 1994 (28)	Single paediatric ICU with 15 ventilator beds and 28 intermediate care beds in France.	Prospective Interrupted Time Series with two phases of 7 and 12 months. Unplanned intervention. Case definition: infection by resistant <i>E. cloacae</i> . Other infection control measures: consistent through study.	Phase 1: barrier precautions only. Phase 2: barrier precautions plus removal of gentamicin from the unit and replacement by amikacin.	Microbial: The intervention was associated with significant reduction in resistant <i>E. cloacae</i> cases per month, immediate -7.47 cases, $p < 0.001$; sustained -1.00 cases, $p = 0.002$. Drug: no reliable data.	Significant reduction in <i>E. cloacae</i> cases in Phase 2. However, this was an unplanned intervention, there are no reliable data about drug use and the study has several other potentially important weaknesses.
de Man et al 2001 (29)	Two similar neonatal ICUs in the same hospital. The study enrolled 436 patients with a mean of 33 weeks gestation.	Prospective cluster controlled clinical trial with crossover with two phases of six months each. Planned intervention. Case definition: colonization plus clinical isolates. Other infection control measures: consistent through study.	Phase 1: Unit A used amoxicillin plus cefotaxime, Unit B used penicillin plus tobramycin. Phase 2: The antibiotic policies were swapped over: Unit A used penicillin plus tobramycin, Unit B used amoxicillin plus cefotaxime.	Microbial: The cefotaxime & amoxicillin regimen was associated with a relative risk of colonisation by Gram-negative bacteria resistant to cefotaxime or tobramycin of 2.98 (CI 1.64 to 5.38). Drug: Cefotaxime plus amoxicillin exposure was 26%-32% of patient days when that regimen was in place vs. 1% when penicillin plus tobramycin was in place.	Significantly increased risk of colonisation associated with the cefotaxime & amoxicillin regimen. However, risk of colonisation was also related to length of stay and this was significantly shorter in the penicillin plus tobramycin phase.
Gerding et al 1985 (18)	Single Veterans Administration hospital in the USA.	Prospective Interrupted Time Series with four phases of 4, 26, 12 and 12 months. Planned intervention. Case definition: clinical isolates. Other infection control measures: not described.	Phase 1: no restriction. Phase 2: gentamicin restricted. Phase 3: amikacin restricted. Phase 4: gentamicin restricted.	Microbial: % of all gram-negative aerobic bacilli resistant to gentamicin. Figure 1 of the paper shows resistance to gentamicin varied between 15% and 2% over the study, falling and rising with no clear relationship to changes in antibiotic policy. Drug: no reliable data.	Little evidence that the fluctuations in resistance to gentamicin were related to antibiotic policy changes. Several potentially important design weaknesses.

Study	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Khan 2003 (19)	Single 800 bed non-teaching hospital in the UK.	Prospective Interrupted Time Series with three phases of 6, 13 and 5 months. Phase 2 planned, Phase 3 unplanned. Case definition: CDAD infection. Other infection control measures: consistent through study.	Phase 1: cefotaxime. Phase 2: ceftriaxone. Phase 3: levofloxacin.	Microbial: Phase 2 was associated with increase in CDAD cases per quarter: immediate +19.7 cases, $p=0.07$; sustained +4.7 cases $p=0.07$. Phase 3 was associated with sustained reduction in CDAD by -5.8 cases per quarter, $p=0.08$. Drug: no reliable data for Phase 1, significant reduction in ceftriaxone use (G per quarter) in Phase 3.	Non significant changes in CDAD were associated with the introduction and restriction of ceftriaxone. Regression to the mean is a plausible alternative explanation for changes in Phase 3 and reliable drug data are only provided for Phases 2 and 3..
Landman 1990 (20)	Single University hospital in the USA with 569 discharges per month from medical and surgical services.	Retrospective Interrupted Time Series with two phases of 29 and 23 months. Planned intervention. Case definition: clinical isolates of resistant bacteria. Other infection control measures: none specific to the bacteria under study.	Phase 1: unrestricted. Phase 2: restriction of third-generation cephalosporins, clindamycin and vancomycin by requiring approval by an ID physician.	Microbial: The intervention was not associated with a significant reduction in the incidence of either ceftazidime-resistant <i>Klebsiella pneumoniae</i> or MRSA. However, there was a significant sustained increase in cefotaxime-resistant <i>Acinetobacter</i> spp: by +0.337 new cases per 1,000 discharges. Drug: no reliable data.	The intervention was associated with a significant but unintended increase in one of the outcomes and no significant changes in the other. However there are important weaknesses in the study design.
Lautenbach 2003 (21)	Single 725 bed University hospital in the USA.	Hybrid retrospective and prospective IT with two phases of 36 and 84 months. Unplanned intervention. Case definition: clinical isolates of VRE. Other infection control measures: not described.	Phase 1: unrestricted use of antibiotics. Phase 2: use of vancomycin or third generation cephalosporins for >72h required approval by the Antimicrobial Management Team. After 24 months any use of vancomycin required approval.	Microbial: Regression analysis suggests that the intervention was associated with significant reduction in %VRE but this result was an artefact caused by the first point in the data (1% VRE) and only having three pre-intervention points. Drug: no significant change in vancomycin use (DDD/1000 patient days)	No evidence supporting control by antibiotic restriction because the restriction clearly did not reduce the use of vancomycin. No data about infection control measures and there are other important weaknesses in the study design.
Leverstein van Hall et al 2001 (24)	Neurology and neurosurgery wards in a single 858 bed University hospital in the Netherlands.	Prospective ITS with two phases of 1 and 2 months. Unplanned intervention. Case definition: colonization. Other infection control measures: consistent through study but only implemented four weeks before the start of antibiotic restriction.	Phase 1: stringent barrier precautions. Phase 2: restriction of all antibiotics by requiring approval by microbiology or ID. Only amikacin or carbanemems allowed for treatment of Gram-negative infection.	Microbial: % prevalence of intestinal colonization by gentamicin resistant <i>Enterobacteriaceae</i> was declining pre intervention: by -1.3 % per week and there was no significant change post-intervention. Drug: no reliable data.	No evidence supporting control by antibiotic restriction. There are several important weaknesses in the study design..
McNulty et al 1997 (25)	Care of the elderly unit in a single non-teaching hospital in the UK.	Prospective ITS with two phases of 7 and 16 months. Unplanned intervention. Case definition: infection, CDAD. Other infection control measures: consistent through study.	Phase 1: increased ward cleaning and patient isolation. Phase 2: restriction of cephalosporins by removal from ward stock; infection control measures as in Phase 1.	Microbial: Phase 2 was associated with non-significant reduction in CDAD: immediate -3.22, cases per month $p=0.120$; sustained -0.50 cases per month $p=0.230$. Drug: Intervention was associated with significant reduction in cefturoxime cost: immediate -£501.78 per month, $p=0.015$.	Non-significant reduction in CDAD cases. This was an unplanned intervention and the study has several other potentially important weaknesses.

Study	Setting and population	Design	Main interventions	Outcomes	Assessment of evidence
Meyer et al 1993 (22)	A single 487 bed University hospital in the USA.	Hybrid retrospective and prospective ITS with two phases of 14 and 11 months. Unplanned intervention. Case definition: infection plus colonization. Other infection control measures: barrier precautions implemented at the same time as ceftazidime restriction.	Phase 1: usual care. Phase 2: barrier precautions for infected or colonized patients plus restriction of ceftazidime. Case notes were reviewed for 133 of the 142 patients with resistant isolates, of whom 52 (39%) met CDC criteria for nosocomial infection.	Microbial: Number of cases of ceftazidime resistant <i>K pneumoniae</i> per 1000 average daily census. Phase 2 was associated with significant reduction: immediate -38.6 cases, p<0.0001; sustained -6.2 cases, p<0.0001. Drug: Drug data are provided for different periods (22 months pre and 6 months post) but do show a significant reduction in the number of patients receiving ceftazidime: immediate -26.4 patients, p=.003; sustained -10.21 patients, p<0.001.	Significant reduction in ceftazidime resistant <i>K pneumoniae</i> in Phase 2 with significant reduction in ceftazidime use. However, it is impossible to separate the effect of ceftazidime restriction from the infection control measures. Regression to the mean is another plausible explanation.
Pear et al 1994 (23)	A single University hospital in the USA with an average daily census of 168 patients.	Hybrid retrospective and prospective ITS with two phases of 40 and 14 months. Unplanned intervention. Case definition: infection, CDAD. Other infection control measures: consistent across study.	Phase 1: hospital staff education, increased use of gloves and improved environmental hygiene. Phase 2: restriction of clindamycin by prior approval by ID physician; infection control measures maintained as in Phase 1.	Microbial: Number of CDAD cases per month. Phase 2 was associated with significant reduction, immediate -3.68 cases per month, p=0.041, sustained -0.32 cases per month, p=0.134). Drug: no reliable data.	Significant reduction in CDAD in Phase 2 but this was an unplanned intervention and there are no reliable data about drug use.
Singh et al 2000 (30)	Adult surgical and medical ICUs in a single University affiliated Veterans Administration hospital in the USA. 81 patients included, mean age 69 years.	Randomised trial with follow up of patients until they were discharged from ICU or died. Planned intervention. Case definition: colonization plus clinical isolates. Other infection control measures: not described but it is reasonable to assume that they were consistent for the intervention and control patients.	Control group: Choice, number and duration of antibiotics at the discretion of the care providers. Intervention group: patients received standardised initial therapy (ciprofloxacin IV for 3 days) with assessment at 3 days when antibiotics were stopped if the patient was judged to be at low risk of pneumonia based on the CPIS score.	Microbial: % patients colonized or infected with resistant bacteria. Relative risk for intervention vs. control: 0.36, CI 0.14-0.89 Drug: Relative risk of receiving antibiotics for > 3days, intervention vs. control: 0.29, CI 0.17-0.48. Clinical: ; length of ICU stay (9.4 days Intervention vs 14.7 days Control; P =0.04); Non significant reduction in mortality: relative risk of 30 day mortality: 0.41, CI 0.16-1.05	Statistically significant reduction in risk of colonisation and infection with resistant bacteria associated with reduction in antibiotic prescribing. Clinical non-inferiority of the Intervention regimen was confirmed. No major weaknesses.
Toltzis et al 2002 (31)	Single 38-bed neonatal intensive care unit in a University hospital in the USA; 1062 episodes of care in infants with mean age 35 weeks.	Randomised trial with follow up of patients until they were discharged from ICU or died. Planned intervention. Case definition: colonization. Other infection control measures: not described but it is reasonable to assume that they were consistent for the intervention and control patients.	Control group: prescribing according to individual preference of physicians. Intervention group: monthly rotation between gentamicin, followed by piperacillin-tazobactam followed by ceftazidime followed by gentamicin again etc.	Microbial: % of patients colonized with resistant bacteria. Relative risk was greater in the Intervention group: 1.40, CI 0.95-2.05. Drug: The Control patients received predominantly gentamicin. The Intervention group received the intended antibiotics on 84% of all antibiotic days. No difference in total antibiotic use. Clinical: All cause mortality was similar: 3.2% Intervention vs 2.3% Control.	No evidence supporting control of resistance by antibiotic cycling. No major weaknesses. The authors provide four alternative explanations other than failure of cycling: 1. NICU population 2. Rotation too rapid 3. Inclusion of ceftazidime 4. Use of ampicillin in all regimens

Figure 1a: Standardised immediate and sustained effects for *Clostridium difficile* Associated Diarrhoea

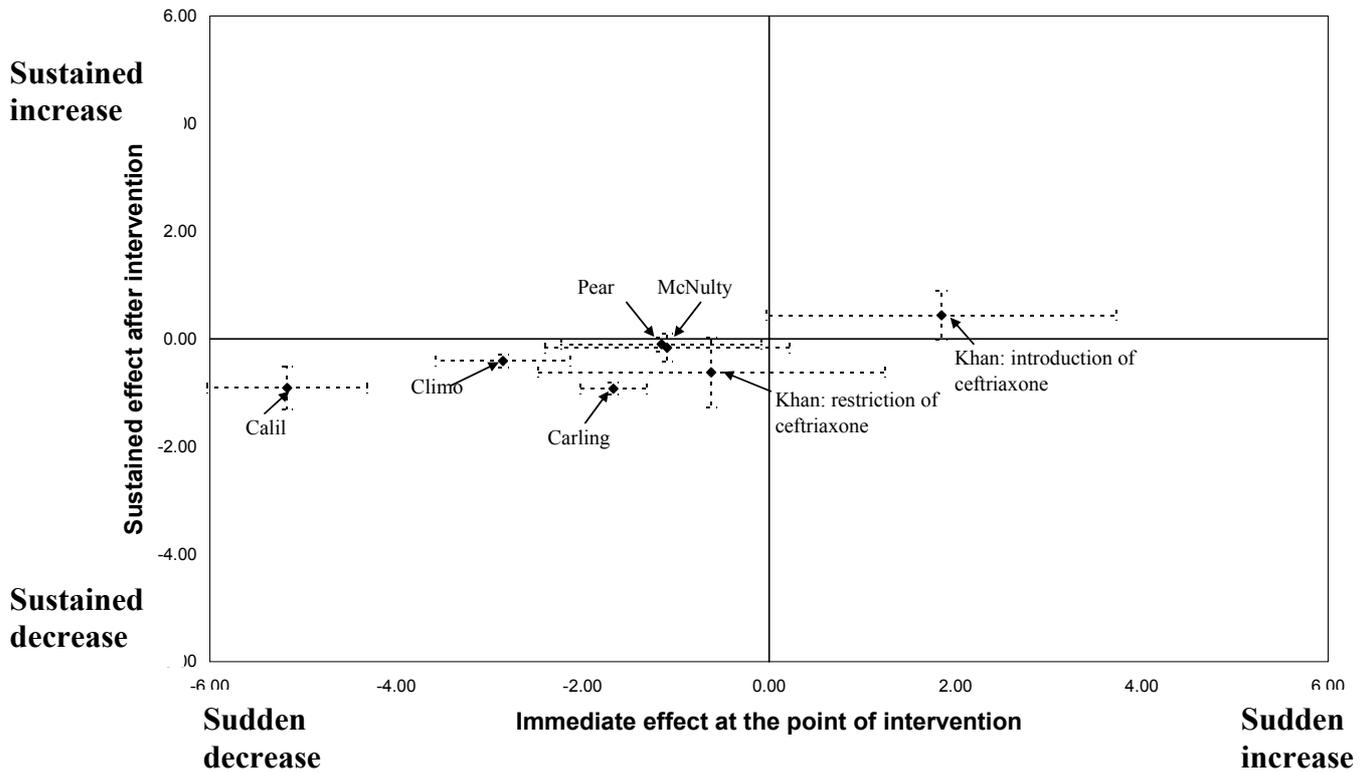
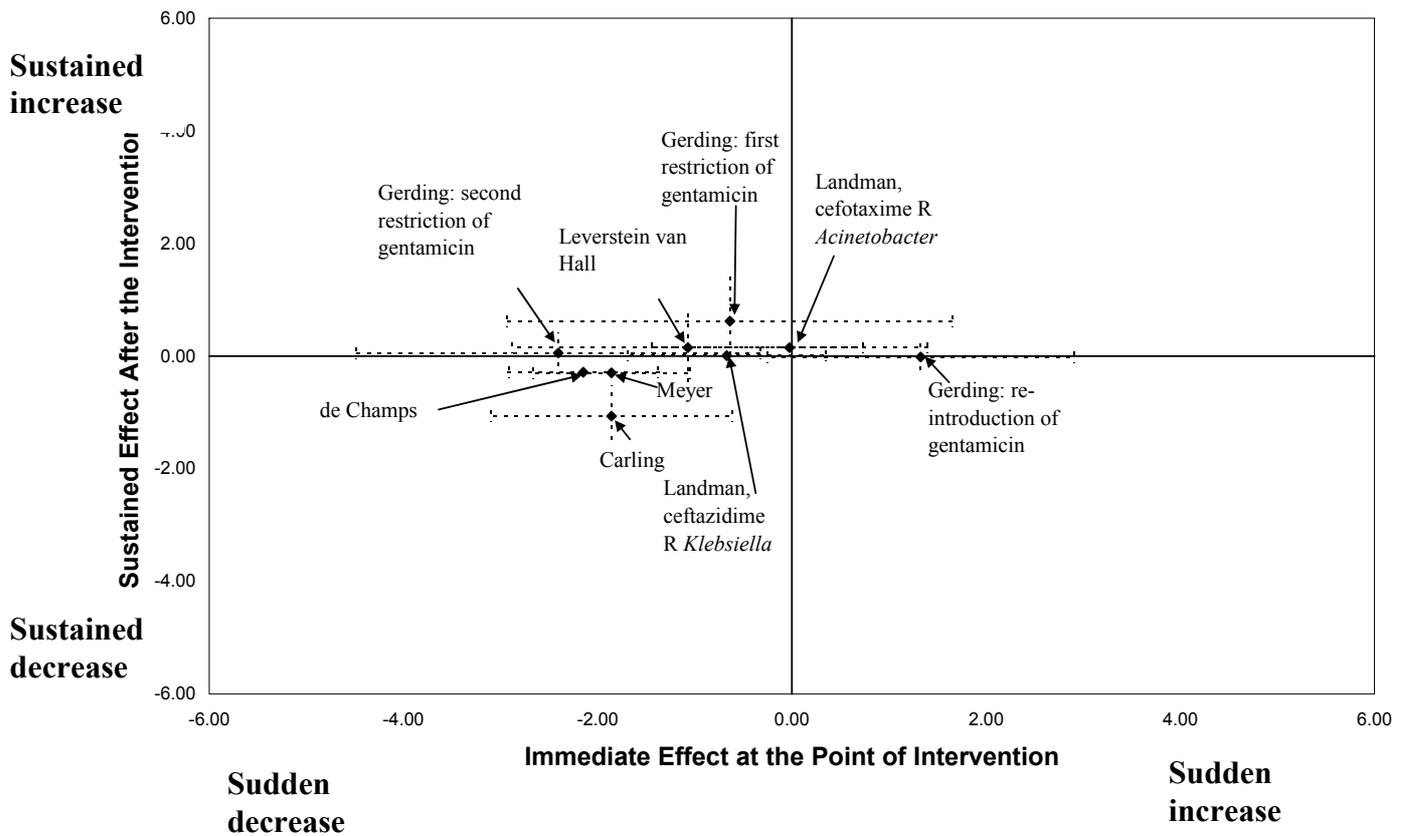


Figure 1b: Standardised immediate and sustained effects for resistant Gram-negative bacteria.



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