Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M

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[Intervention Review]

Interventions to improve antibiotic prescribing practices for hospital inpatients

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ABSTRACT

Background

The first publication of this review in Issue 3, 2005 included studies up to November 2003. This update adds studies to December 2006 and focuses on application of a new method for meta-analysis of interrupted time series studies and application of new Cochrane Effective Practice and Organisation of Care (EPOC) Risk of Bias criteria to all studies in the review, including those studies in the previously published version. The aim of the review is to evaluate the impact of interventions from the perspective of antibiotic stewardship. The two objectives of antibiotic stewardship are first to ensure effective treatment for patients with bacterial infection and second support professionals and patients to reduce unnecessary use and minimize collateral damage.

Objectives

To estimate the effectiveness of professional interventions that, alone or in combination, are effective in antibiotic stewardship for hospital inpatients, to evaluate the impact of these interventions on reducing the incidence of antimicrobial-resistant pathogens or *Clostridium difficile* infection and their impact on clinical outcome.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE from 1980 to December 2006 and the EPOC specialized register in July 2007 and February 2009 and bibliographies of retrieved articles. The main comparison is between interventions that had a restrictive element and those that were purely persuasive. Restrictive interventions were implemented through restriction of the freedom of prescribers to select some antibiotics. Persuasive interventions used one or more of the following methods for changing professional behaviour: dissemination of educational resources, reminders, audit and feedback, or educational outreach. Restrictive interventions could contain persuasive elements.

Selection criteria

We included randomized clinical trials (RCTs), controlled clinical trials (CCT), controlled before-after (CBA) and interrupted time series studies (ITS). Interventions included any professional or structural interventions as defined by EPOC. The intervention had to include a component that aimed to improve antibiotic prescribing to hospital inpatients, either by increasing effective treatment or by reducing unnecessary treatment. The results had to include interpretable data about the effect of the intervention on antibiotic prescribing or microbial outcomes or relevant clinical outcomes.

Data collection and analysis

Two authors extracted data and assessed quality. We performed meta-regression of ITS studies to compare the results of persuasive and restrictive interventions. Persuasive interventions advised physicians about how to prescribe or gave them feedback about how they prescribed. Restrictive interventions put a limit on how they prescribed; for example, physicians had to have approval from an infection specialist in order to prescribe an antibiotic. We standardized the results of some ITS studies so that they are on the same scale (percent change in outcome), thereby facilitating comparisons of different interventions. To do this, we used the change in level and change in slope to estimate the effect size with increasing time after the intervention (one month, six months, one year, etc) as the percent change in level at each time point. We did not extrapolate beyond the end of data collection after the intervention. The meta-regression was performed using standard weighted linear regression with the standard errors of the coefficients adjusted where necessary.

Main results

For this update we included 89 studies that reported 95 interventions. Of the 89 studies, 56 were ITSs (of which 4 were controlled ITSs), 25 were RCT (of which 5 were cluster-RCTs), 5 were CBAs and 3 were CCTs (of which 1 was a cluster-CCT).

Most (80/95, 84%) of the interventions targeted the antibiotic prescribed (choice of antibiotic, timing of first dose and route of administration). The remaining 15 interventions aimed to change exposure of patients to antibiotics by targeting the decision to treat or the duration of treatment. Reliable data about impact on antibiotic prescribing data were available for 76 interventions (44 persuasive, 24 restrictive and 8 structural). For the persuasive interventions, the median change in antibiotic prescribing was 42.3% for the ITSs, 31.6% for the controlled ITSs, 17.7% for the CBAs, 3.5% for the cluster-RCTs and 24.7% for the RCTs. The restrictive interventions had a median effect size of 34.7% for the ITSs, 17.1% for the CBAs and 40.5% for the RCTs. The structural interventions had a median effect of 13.3% for the RCTs and 23.6% for the cluster-RCTs. Data about impact on microbial outcomes were available for 21 interventions but only 6 of these also had reliable data about impact on antibiotic prescribing.

Meta-analysis of 52 ITS studies was used to compare restrictive versus purely persuasive interventions. Restrictive interventions had significantly greater impact on prescribing outcomes at one month (32%, 95% confidence interval (CI) 2% to 61%, P = 0.03) and on microbial outcomes at 6 months (53%, 95% CI 31% to 75%, P = 0.001) but there were no significant differences at 12 or 24 months. Interventions intended to decrease excessive prescribing were associated with reduction in *Clostridium difficile* infections and colonization or infection with aminoglycoside- or cephalosporin-resistant gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis.* Meta-analysis of clinical outcomes showed that four interventions intended to increase effective prescribing for pneumonia were associated with significant reduction in mortality (risk ratio 0.89, 95% CI 0.82 to 0.97), whereas nine interventions intended to decrease excessive prescribing were not associated with significant increase in mortality (risk ratio 0.92, 95% CI 0.81 to 1.06).

Authors' conclusions

The results show that interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcome. This update provides more evidence about unintended clinical consequences of interventions and about the effect of interventions to reduce exposure of patients to antibiotics. The meta-analysis supports the use of restrictive interventions when the need is urgent, but suggests that persuasive and restrictive interventions are equally effective after six months.

PLAIN LANGUAGE SUMMARY

Improving how antibiotics are prescribed by physicians working in hospital settings.

Antibiotics are used to treat infections, such as pneumonia, that are caused by bacteria. Over time, however, many bacteria have become resistant to antibiotics. Antibiotic resistance is a serious problem for individual patients and healthcare systems; in hospitals, infections

caused by antibiotic-resistant bacteria are associated with higher rates of death, illness and prolonged hospital stay. Bacteria often become resistant because antibiotics are used too often and incorrectly. Studies have shown that about half of the time, physicians in hospital are not prescribing antibiotics properly. Hospital physicians may be unclear about the benefits and risks of prescribing antibiotics, including whether to prescribe an antibiotic, which antibiotic to prescribe, at what dose and for how long.

Many different methods of improving the prescribing of antibiotics in hospitals have been studied. In this review, 89 studies from 19 countries were analyzed to determine what methods work. The main comparison was between persuasive and restrictive methods. Persuasive methods advised physicians about how to prescribe or gave them feedback about how they prescribed. Restrictive methods put a limit on how they prescribed; for example, physicians had to have approval from an infection specialist in order to prescribe an antibiotic. Overall, the 89 studies showed that the methods improved prescribing. In addition, 21 studies showed that the methods decreased the number of infections in hospital. The restrictive methods appeared to have a larger effect than persuasive methods. In conclusion, this review has found a lot of evidence that methods can improve prescribing of antibiotics to patients in hospital, but we need more studies to fully assess the clinical benefits of these methods.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Interventions compared with none to improve antibiotic prescribing

Patient or population: Healthcare professionals
Settings: Secondary care (inpatients in acute, not long term care only)
Intervention: Any intended to improve antibiotic prescribing
Comparison: Usual care

Outcomes	Effect measure	Number of studies and health professionals	Quality of the evidence (GRADE)
Restrictive versus Persuasive interventions			
Appropriate prescribing of antibiotics	32% difference in effect size (restrictive-persuasive) at one month 95% CI 2 to 61% No significant difference at 6, 12 or 24 months	53 comparisons from 40 studies (all ITS) in 46 hospitals	**Low** ⊕⊕OO Indirect comparison between studies that provide data about effect of either persuasive or restrictive interventions
Microbial outcomes	53% difference in effect size (restrictive-persuasive) at 6 months 95% CI 31 to 75% No significant difference at 12 or 24 months	20 comparisons from 14 studies (all ITS) in 14 hospitals	**Low** ⊕⊕OO Indirect comparison between studies that provide data about effect of either persuasive or restrictive interventions
Interventions intended to decrease unnecessary antibiotic prescribing			
Patient outcomes	Risk of mortality for intervention versus control 0.92 (95% CI 0.81 to 1.06)	11 comparisons from 11 studies (7 RCT, 3 cluster-RCT, 1 cluster-CCT) in 20 hospitals with 9,817 patients	**Moderate** ⊕⊕⊕O High risk of bias especially around study design
	Difference (in days) in length of stay for intervention versus control -0.04 days (95% CI - 0.34 to 0.25)	6 comparisons from 6 studies (4 RCT, 2 cluster-RCT) in 8 hospitals with 8,071 patients	**Very Low** ⊕OOO Studies are very heterogeneous and have high risk of bias
	Risk of readmission for intervention versus control 1.26 (95%CI 1.02 to 1.57)	5 comparisons from 5 studies (4 RCT, 1 Cluster-RCT) in 12 hospitals with 5,856 patients	**Very Low** ⊕OOO Studies are very heterogeneous and have high risk of bias
Interventions intended to increase effective antibiotic prescribing for pneumonia			

Patient outcomes	Risk of mortality for intervention versus control 0.89 (95% CI 0.82 to 0.97)	4 comparisons from 4 studies (3 CBA, 1 RCT) in 104 hospitals with 22,526 patients	**Low** ⊕⊕OO High risk of bias especially around study design

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Abbreviations
CBA: controlled before and after; CCT: controlled clinical trial; CI: confidence interval; ITS: interrupted time series; RCT: randomized controlled trial.

BACKGROUND

Antibiotic resistance is now regarded as a major public health problem. In comparison with infections caused by susceptible bacteria, those caused by multidrug-resistant bacteria are associated with higher incidences of mortality and prolonged hospital stay (de Kraker 2010; de Kraker 2011a; de Kraker 2011b; Wolkewitz 2010). *Clostridium difficile* infection is another manifestation of the collateral damage caused by antimicrobial prescribing (Davey 2010). Such infections are also associated with increased costs, arising from the need to use more expensive antibiotics as therapy, prolonged hospital stay (de Kraker 2011a) and expenses related to screening and surveillance, eradication regimens and consumables (the gloves, gowns and aprons used to prevent cross-infection). The emergence of multidrug-resistant organisms limits the choice of therapy for patients with hospital-acquired infections and, ominously, for the first time since antibiotics were introduced we are faced with the prospect of not having effective treatment for some patients with bacterial infections (So 2010). A number of reports have proposed a range of measures designed to address the problem of increasing resistance (Behar 2000; EU 2002; Goldmann 1996; House of Lords 1998; House of Lords 2001; Lawton 2000; Shlaes 1997; SMACS 1998). Common to all the recommendations is the challenge to reduce inappropriate antibiotic prescribing, the implication being that antibiotic resistance is largely a consequence of the selective pressures of antibiotic usage and 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. At the same time, sepsis kills more people annually than myocardial infarction or breast, colon and lung cancer combined (Robson 2008), and delay in effective antibiotic treatment is associated with increased mortality (Daniels 2010; Kumar 2006). The term 'antibiotic stewardship' is used to capture the twin aims of ensuring effective treatment of patients with infection and minimizing collateral damage from antimicrobial use (Allerberger 2009; Davey 2010; Dellit 2007; MacDougall 2005).

There is evidence that antibiotic usage in hospitals is increasing, and that over a third of prescriptions are not compliant with evidence-based guidelines (Zarb 2011). In Denmark, antibiotic usage in hospitals increased by 18% between 1997 and 2001 (Muller-Pebody 2004). A similar study carried out in the Netherlands revealed that hospital antibiotic usage between 1997 and 2000 increased by 10.6%. However, more recent data from the Netherland showed that the number of hospital admissions as well as the antibiotic use has increased by 22% from 2003 to 2010. The authors interpreted these results as showing that total use and clinical activities were increasing in parallel. However, they noted that the use of penicillins with extended spectrum and quinolones increased from 2008 to 2011 and that this was not fully explained by increased clinical activity (SWAB 2011). Finally, a survey of 22 US academic centres found that there was a statistically significant increase in total antibacterial use between 2002 and 2006, from a mean of 798 days of therapy (DOTs) per 1000 patient days (PDs) to a mean of 855 DOTs per 1000 PDs (Polk 2007). The European Surveillance of Antimicrobial Consumption (ESAC) has established a method for point prevalence of antibiotic prescribing

in hospitals (Amadeo 2010; Ansari 2008) and the 2009 survey included data from 172 hospitals in 25 countries (Zarb 2011). These surveys have revealed important targets for improving the quality of antimicrobial prescribing to hospital inpatients. In the 2009 survey the indication for treatment was not recorded in case notes of 24% of patients and when an indication was recorded it was not compliant with local or national guidelines in 38% of patients. There was also evidence of excessive treatment of community-acquired infections and unnecessary prolongation of surgical antibiotic prophylaxis (Zarb 2011).

What should be done to improve antibiotic stewardship in hospitals? The Infectious Diseases Society of America and the Society of Hospital Epidemiologists of America have recommended measures to improve antibiotic prescribing in hospitals (Dellit 2007). However, the recommendations are based on only a small proportion of the published literature, and the literature that was assessed was not subjected to critical evaluation or systematic review. We have therefore reviewed the literature for evidence of the impact of interventions on the appropriateness of antimicrobial prescribing and on the prevalence of antimicrobial resistance and/or clinical outcome.

This review of interventions intended to improve prescribing of antibiotics to hospital inpatients complements a review of interventions to improve prescribing of antibiotics to patients in ambulatory care (Arnold 2005).

OBJECTIVES

The primary aim is to identify interventions that, alone, or in combination, are effective in improving antibiotic prescribing to hospital inpatients. We have used the term 'antibiotic stewardship' to address two objectives. The first objective is to ensure effective treatment for patients with bacterial infection. The second objective is to provide convincing evidence and information to educate and support professionals and patients to reduce unnecessary use and minimize collateral damage. Collateral damage means the increased risk of infection with antibiotic- resistant bacteria, and antibiotic resistant bacteria, which arises from damage to the normal bacterial flora after antibiotic treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized and nonrandomized controlled trials (RCTs and CCTs), controlled before-after studies (CBAs) and interrupted time series studies (ITSs) (with at least three data points before and after implementation of the intervention).

Types of participants

Healthcare professionals who prescribe antibiotics to hospital inpatients receiving acute care (including elective inpatient surgery). The review excludes interventions targeted at residents in nursing homes or other long-term healthcare settings.

Types of interventions

The following professional interventions in the Effective Practice and Organisation of Care Group (EPOC) scope were included:

1. Persuasive interventions: distribution of educational materials; educational meetings; local consensus processes; educational outreach visits; local opinion leaders; reminders provided verbally, on paper or on computer; audit and feedback.
2. Restrictive interventions:selective reporting of laboratory susceptibilities, formulary restriction, requiring prior authorization of prescriptions by infectious diseases physicians, microbiologists, pharmacists etc, therapeutic substitutions, automatic stop orders and antibiotic policy change strategies including cycling, rotation and cross-over studies.
3. Structural: changing from paper to computerized records, rapid laboratory testing, computerized decision support systems and the introduction or organization of quality monitoring mechanisms.

Studies that were clinical trials comparing the effectiveness of antibiotic treatments (for example intravenous (IV) versus oral administration of antibiotics) were considered invalid for this review.

Types of outcome measures

- Antibiotic prescribing process measures(decision to treat, choice of drug, dose, route or duration of treatment);
- Clinical outcome measures (mortality, length of hospital stay);
- Microbial outcome measure (colonization or infection with *Clostridium difficile* or antibiotic-resistant bacteria).

Search methods for identification of studies

For this update, we searched the Cochrane Central Register of Controlled Studies (CENTRAL), PubMed, EMBASE in 2006. We used search terms: antibiotics, premedication, guideline, clinical protocols, critical pathways, evidence based medicine, intervention. We also searched the EPOC Register in July 2007 and February 2009 (Appendix 1). The next update of this review will include fully documented search strategies.

Data collection and analysis

Selection of studies

Two authors (EB and PD) reviewed citations and abstracts retrieved in the search to identify all reports that included original data about interventions to change antibiotic prescribing. If either author had any doubt about eligibility, then both authors reviewed the full papers . The authors were not blinded to study author or location. We resolved disagreements by discussion and consensus. We then excluded studies that had no relevant and interpretable data presented or obtainable. 'Relevant data' was defined as an intervention that included a change in antibiotic treatment for hospital inpatients and at least one of the study's reported outcomes was directly attributable to change in antibiotic treatment. 'Interpretable data' was defined as follows: CBA, CCT or RCT designs had to include sufficient data to estimate effect size with 95% confidence interval (CI) as change in at least one relevant outcome after the intervention. For proportions this was either the numerator and denominator or the risk difference (or risk ratio or odds ratio). For continuous variables this was either the mean plus standard deviation or standard error, plus number in each group. ITS studies had to include a clearly defined intervention point.
We did not exclude studies because of high risk of bias.
We reached all decisions about minimum methodological criteria by consensus between the authors, and had them confirmed by the review editor, Lisa Bero.

Data extraction and management

Two review authors independently performed data abstraction using a template which included information on: study design, type of intervention, presence of controls, type of targeted behaviour, participants, setting, methods (unit of allocation, unit of analysis, study power, methodological quality, consumer involvement), outcomes, and results.

Explanation of terms used to describe interventions

Persuasive interventions

We applied the EPOC definitions for each intervention, with additional detail relevant to the context of this review. The persuasive interventions considered were:

1. Dissemination of educational materials in printed form or via educational meetings;
2. Reminders;
3. Audit and feedback;
4. Educational outreach (academic detailing or review and recommend change).

Restrictive interventions

Restrictive interventions correspond to the EPOC category of 'financial and healthcare system changes' used in the Cochrane review of interventions to improve antibiotic prescribing in ambulatory care (Arnold 2005). These interventions involve a change to the antibiotic formulary or policy implemented through an organizational change that restricts the freedom of prescribers to select some antibiotics. We identified four distinct types of restrictive interventions:

1. Compulsory order form - prescribers had to complete a form with clinical details to justify use of the restricted antibiotics;
2. Expert approval - the prescription for a restricted antibiotic had to be approved by an Infection specialist or by the Head of Department;
3. Restriction by removal - a restrictive policy was imposed in target wards, units or operating theatres, for example by removing restricted antibiotics from drug cupboards;
4. Review and make change - the difference between this intervention and review and recommend change (educational outreach) is that the reviewer changed the prescription rather than giving health professionals either a verbal or written recommendation that they should change the prescription.

In addition some studies included automatic stop orders (termination of prescriptions after a specified interval unless authorization was obtained to continue) but automatic stop orders were never used as the main intervention.
None of the restrictive interventions in our review included financial incentives or penalties.

Structural interventions

In this category we included the introduction of new technology for laboratory testing or changes to laboratory turnaround time that required substantive changes to the work patterns of the microbiology laboratory, or computerized decision support that required substantive changes to the hospital's information systems.

Assessment of the impact of interventions

We have used meta-analysis to make the following comparisons in assessing the impact of interventions on antibiotic prescribing and outcomes:
Comparison 1: effect of persuasive versus restrictive interventions on antibiotic prescribing;
Comparison 2: effect of persuasive versus restrictive interventions on microbial outcomes;
Comparison 3: effect of interventions intended to increase effective antibiotic treatment versus no intervention on clinical outcomes;
Comparison 4: effect of interventions intended to reduce unnecessary antibiotic treatment versus no intervention on clinical outcomes.

Assessment of risk of bias in included studies

We applied the 2009 revised EPOC risk of bias criteria to all papers in the review, including articles in the 2003 review (Cochrane EPOC 2013). We scored each study for risk of bias as 'Low' if all criteria were scored as 'Done', 'Medium' if one or two criteria were scored as 'Unclear' or 'Not Done', and 'High' if more than two criteria were scored as Unclear' or 'Not Done'.

The EPOC group criteria for a reliable primary outcome measure include "When there were two or more raters with at least 90% agreement or kappa greater than or equal to 0.8". However, kappa values may be as low as 0.39 for composite quality indicators even when data abstraction is carried out by trained abstractors, so the inter-rater reliability is likely to be the best possible (Scinto 2001). The key issue is whether or not the actual agreement is sufficient for the application of the quality indicator, so for composite measures such as quality or timing of antibiotic therapy we accepted kappa values as low as 0.6 (Marwick 2007; Williams 2006).

We applied three additional criteria to studies with microbial risk of outcome, based on the ORION statement: Guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection (Stone 2007, http://www.idrn.org/orion.php). The most important of these is the distinction between planned and unplanned intervention. An unplanned intervention is made in response to a problem, which makes interpretation of the effect of the intervention difficult because of regression to the mean, which is the natural tendency for extreme results to be followed by a return to normal. Regression to the mean is an important risk of bias for any unplanned intervention but is a particular problem for studies of infection because of the shape of the epidemic curve (Cooper 2003; Davey 2001). A classic example is the 1854 cholera epidemic in Golden Square, London, when the number of deaths per day fell from 140 to 20 in five days without any intervention (Davey 2001). The additional Microbial Outcome Criteria were:

1. Case definition: score as DONE if there is a clear definition either of infection or of colonization and there were no major changes in laboratory diagnostic methods during the study period.
2. Planned intervention: score as DONE if the intervention was planned to reduce endemic rates of colonization or infection and was not implemented in response to an outbreak.
3. Other infection control measures: score as DONE if infection control practices (hand hygiene, gowning or other personal protection) and isolation or cohorting policies are described and there were no changes coincident with the intervention to change antibiotic prescribing.

In the risk of bias tables these criteria are listed under 'other bias'. In the EPOC risk of bias tables, the microbial criteria count in two of the criteria: 'intervention independent of other changes' and 'other biases'. In the results tables of Microbial Outcomes (17a-d) we have included an assessment of microbial risk of bias based on the ORION criteria: low has no risks, medium has one and high has two or three microbial risks of bias.

Measures of treatment effect

Data are reported in natural units in the Characteristics of included studies tables and the Results section. We calculated the effects of interventions by study designs. When there is more than one study of the same study design, we calculated the effect size by taking the median value across studies. We have divided outcomes into four main groups: prescribing, clinical, microbiological and financial. 'Prescribing' includes the decision whether or not to prescribe an antibiotic, choice of drug, dosage, route of administration, dosing interval and duration of treatment. 'Clinical' includes length of hospital stay, incidence of readmissions, mortality and the occurrence of specific infections defined by clinical diagnosis (e.g. wound infection) without information about microbiological cause. 'Microbial' includes incidence of infection caused by specific bacteria (e.g. *Clostridium difficile* and colonization with or infection caused by antimicrobial-resistant bacteria). One study (Micek 2004) used the number of infections in the intensive care unit as a balancing measure of unintended consequences of a change in antibiotic policy. We have not included this as a microbial outcome. 'Financial' includes studies that provide information about both the cost of developing or implementing the intervention and about savings arising from the intervention.

For the included RCT or CBA studies, when possible we report pre-intervention and postintervention percentages for both study and control groups, and calculate the absolute change from baseline with 95% confidence intervals (CIs).

We examined the methods of analysis of ITS data critically. The preferred method is a statistical comparison of time trends before and after the intervention. If the original paper did not include an analysis of this type, we extracted the data presented in tables or graphs in the original paper and used them to perform new analyses where possible. We used segmented time-series regression analysis to estimate the effect of the intervention whilst taking account of time trend and autocorrelation among the observations. We obtained estimates for regression coefficients corresponding to two standardised effect sizes for each study: a change in level and a change in trend before and after the intervention. A change in level was defined as the difference between the observed level at the first intervention time point and that predicted by the pre-intervention time trend. A change in trend was defined as the difference between post- and pre-intervention slopes (Ramsay 2003). A negative change in level and slope indicates an intervention effect in terms of a reduction in infection rates. We evaluated the direct effect of the intervention using results reported one month after the intervention started. We also reported the level effects at six months, and yearly thereafter when possible. We standardized the results of some ITS studies so that they were on the same scale (per cent change in outcome), thereby facilitating comparisons of different interventions. To do this, we used the change in level

and change in slope to estimate the effect size with increasing time after the intervention (one month, six months, one year, etc) as the per cent change in level at each time point. We did not extrapolate beyond the end of data collection after the intervention. We anticipated that the eligible studies would exhibit significant heterogeneity, due to variations in target clinical behaviours, patient and provider populations, methodological features, characteristics of the interventions, and the contexts in which they were delivered. To address the source of variation in results due to the use of restrictive or persuasive interventions, we undertook a random-effects meta-regression analysis on study-level summary effect size at each time point.

We assessed the impact of interventions on microbial outcomes if the study provided reliable data about colonization or infection with *Clostridium difficile* or with antibiotic-resistant bacteria. We did not include microbial outcomes for studies that estimated the future impact of their intervention based on modelling (Paul 2006) or that used clinical definitions of infection that did not distinguish between resistant and sensitive bacteria (Micek 2004; Singh 2000).

We assessed the impact of interventions on clinical outcome for studies that provided reliable data about mortality or length of hospital stay. We did not include clinical outcomes for studies that estimated the impact of their intervention based on modelling (Barlow 2007).

Unit of analysis issues

If an RCT had not taken into account the effect of clustering in the analysis, we stated this in the risk of bias assessment but did not attempt re-analysis as the intervention and outcomes measured in the studies with unit of analysis errors differed from the studies in the meta-analyses. We therefore expected that the impact of unit of analysis issues would be minimal in this review, given that the evidence was primarily from ITS studies.

Data synthesis

The results for RCT, CBA and ITS studies were analyzed separately, and qualitatively described if possible. For the RCT data, if no significant heterogeneity was present ($I^2 < 70\%$) (Deeks 2011), a standard meta analysis approach using the Review Manager 5 data analysis programme was utilized to perform meta-analysis of binary (e.g. mortality) and continuous (e.g. length of stay) outcomes. If an RCT study had a unit of analysis error the study was excluded in a sensitivity analysis. We did not intend to formally meta-analyze the ITS studies, since we anticipated extreme heterogeneity.

When we found significant heterogeneity, we did not meta-analyze the results, but presented them as the median effect (interquartile range, (IQR)).

To investigate potential reasons for heterogeneity, we performed meta-regression of ITS studies to compare the results of persuasive and restrictive interventions (Comparison 4). RCTs were not involved in the meta-regression because in the event the RCTs did not provide usable data for this comparison. The meta-regression was performed using standard weighted (by standard error of estimate) linear regression (see Cochrane Handbook). All differences were expressed as: (persuasive - restrictive).

We used Stata 11 for all statistical re-analyses and meta-regressions and Review Manager 5 for all data synthesis.

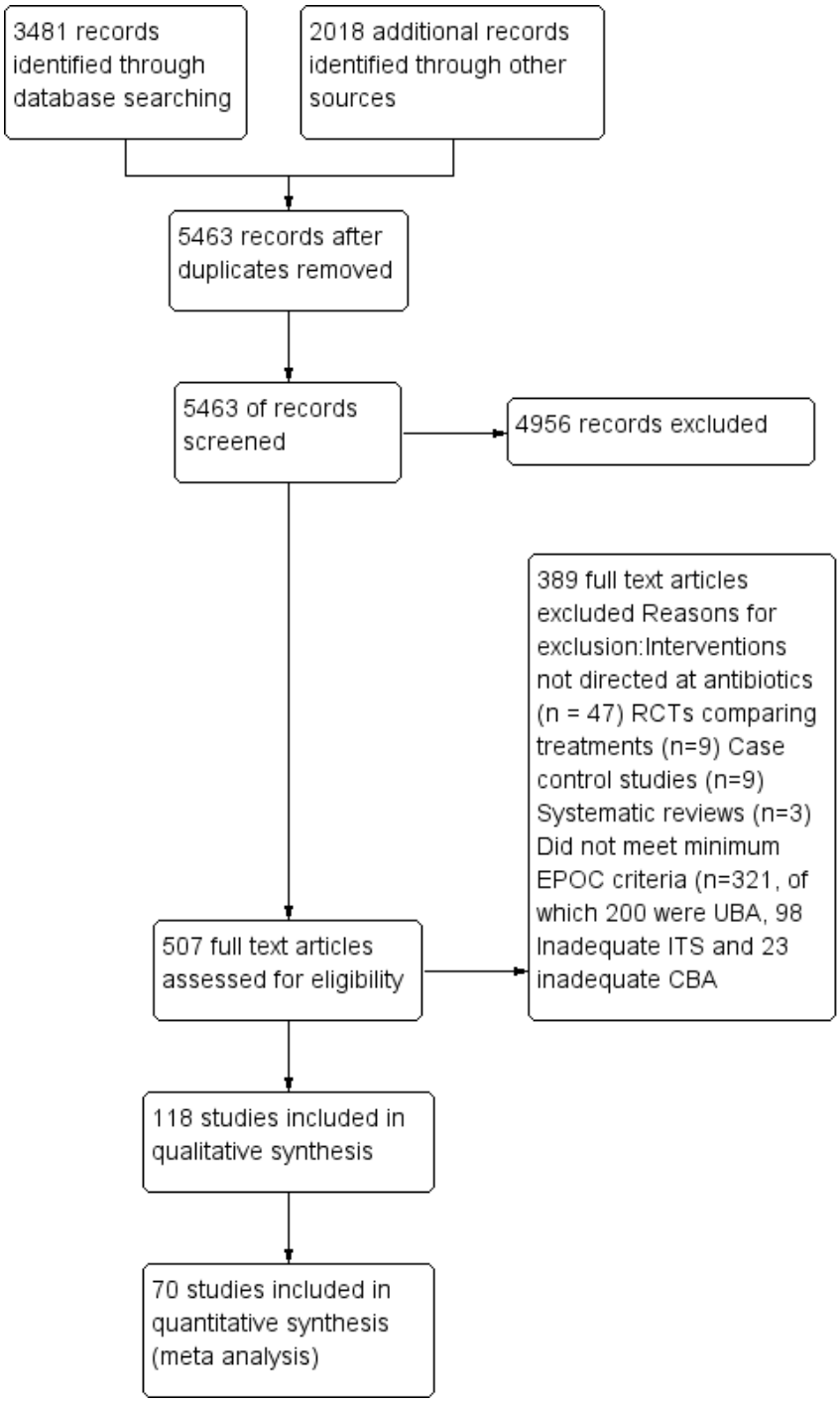
RESULTS

Description of studies

Results of the search

In this update, searching for literature to the end of 2006, we found 50 studies that were published prior to 2003 but were missed in the search for the previous version of the review. The combined results of both literature searches are described in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



The Cochrane EPOC Checklist was changed in January 2007 with the addition of the requirement for CBA studies to have at least two intervention and control sites. In the review update we have applied this new criterion to all studies and have eliminated 23 studies, of which 19 were included in the previous review (Barenfanger 2001; Bendall 1986; Bond 2005; Clapham 1988; Cordova 1986; Covinsky 1982; Eron 2001; Girotti 1990; Gyssens 1996; Herfindal 1983; Herfindal 1985; Khanderia 1986; Ludlam 1999; Parrino 1989; Przybylski 1997; Thornton 1991; Weingarten 1996; Weller 2002; Witte 1987) and four were published after 2003 (Capelastegui 2004; Martinez 2006; Ritchie 2004; von Gunten 2005).

Included studies

There were 89 studies listed in the Characteristics of included studies table. 56 were ITSs (of which four are controlled ITS studies (CITS): Barlow 2007; Charbonneau 2006; May 2000; Weinberg 2001). 20 were RCTs, 5 were CBAs, 2 were CCTs, 1 was a cluster-CCT and 5 were cluster-RCTs. Full details are given in the Characteristics of included studies table. The 89 studies report 95 interventions with reliable data about at least one outcome. Two studies report two interventions (Mol 2005; Perez 2003) and one study reports five interventions (Fridkin 2002).

Geographical Location of study

Fifty-two studies were from North America. The remaining 37 were from Europe (29, includes Israel), the Far East (3), South America (3) and Australia (2). There were two multinational studies (Franz 2004 took place in five countries: Australia, Austria, Belgium, Germany, Sweden; Paul 2006 took place in three countries: Germany, Israel, Italy). The number of studies by country (including the countries in the two multinational studies) is: Australia (3), Austria (1), Belgium (1), Brazil (1), Canada (4), Colombia (2), France (2), Germany (2), Hong Kong (1), Israel (2), Italy (1), Netherlands (6), Norway (1), Spain (2), Sweden (1), Switzerland (3),Thailand (2), UK (12) and USA (48).

Number of Hospital

A total of 69 (77%) studies were conducted in one hospital, 5 studies (6%) in two hospitals, 6 studies (7%) in 3 to 9 hospitals and 9 studies (10%) in ten or more hospitals.

Aims

The aim of the interventions was to optimize therapy either by (a) reducing the amount of antibiotic prescribed where this was considered excessive, or (b) increasing effective treatment by increasing the amount of antibiotic prescribed or improving the timing of administration where these were considered suboptimal. Of the 95 interventions, 79 aimed to decrease excessive antibiotic use, 11 aimed to increase effective treatment and 5 aimed to reduce inappropriate antibiotic use but did not distinguish between excessive or ineffective use (Bouza 2004; Bruins 2005; Burton 1991; Doern 1994; Trenholme 1989).

Nature of Intervention

Most interventions (87/95, 91%) were classified as professional, of which 39 were persuasive and 28 included at least one restrictive component. The remaining interventions were structural.

Target of Intervention

Most of the interventions (80/95, 84%) targeted the choice of antibiotic prescribed (drug selected, timing of first dose or route of administration). The remaining 15 interventions aimed to change exposure of patients to antibiotics by changing the decision to treat or the duration of treatment.

Six studies (Christ-Crain 2004; Christ-Crain 2006; Foy 2004; Franz 2004; Weinberg 2001; Wyatt 1998) targeted the decision to prescribe antibiotics. Three aimed to decrease the percentage of patients who received therapeutic antibiotics (Christ-Crain 2004; Christ-Crain 2006; Franz 2004) and three aimed to increase the percentage of patients who received antibiotic prophylaxis for surgery (Foy 2004; Weinberg 2001; Wyatt 1998).

Nine studies (Berild 2002; Fine 2003; Landgren 1988; Micek 2004; Oosterheert 2005; Senn 2004; Singh 2000; Van Kasteren 2005; Zanetti 2003) targeted the duration of antibiotic treatment or prophylaxis. Six aimed to decrease duration of therapeutic antibiotics (Berild 2002; Fine 2003; Micek 2004; Oosterheert 2005; Senn 2004; Singh 2000), two aimed to decrease duration of antibiotic prophylaxis for surgery (Landgren 1988; Van Kasteren 2005) and one aimed to increase duration of antibiotic prophylaxis for surgery (Zanetti 2003).

Deliverer of intervention

Of the 95 interventions, 37 (39%) were designed and delivered by a multidisciplinary team, 31 (33%) by specialist physicians (Infectious Diseases or Microbiology), 19 (20%) by pharmacists and 8 (8%) by department physicians (e.g. Department of Medicine or Surgery). The proportion of interventions that involved a multidisciplinary team is much higher in studies published from 2003 (11/21, 52%), compared with those published before 2003 (26/74, 35%).

Excluded studies

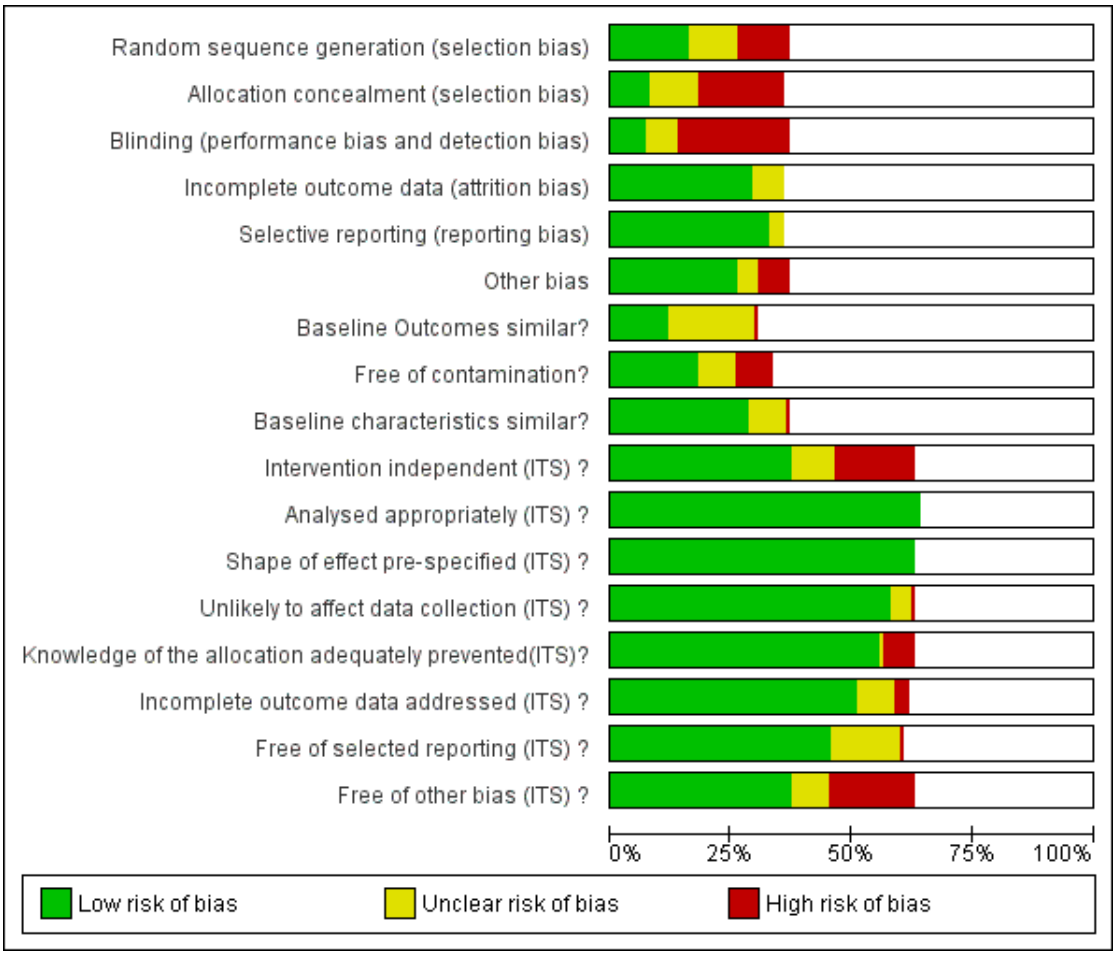
We excluded 29 studies from the review because they did not contain relevant or interpretable data (1 CBA, 11 RCTs, 3 CCTs and 11 ITSs) or were secondary publications (N = 3). Studies that did not contain relevant data were interventions that included antibiotic prescribing but did not provide data to assess the impact of the interventions or outcomes of interest. Studies that did not contain interpretable data were ITS designs with no clear point in time for the intervention, or RCTs with unacceptable selective reporting of results. See Characteristics of excluded studies for details of each study.

Risk of bias in included studies

Eighteen (20%) of the studies had low risk of bias, 31 (35%) studies had medium risk of bias and 40 (45%) had high risk of bias.

All five CBA studies had high risk of bias. High risk of bias was more common in CCTs, RCTs or CRCTs (22/28, 79%) than in ITS or CITS (13/56, 23%) (Figure 2). All 18 studies with low risk of bias were CITS or ITS (Figure 2) High risk of bias in CCTs, RCTs or CRCTs was much more likely in studies with two or fewer hospitals (19/22, 86%) versus three or more hospitals (3/6, 50%). There were only three ITS studies in more than two hospitals and all had medium risk of bias (Charbonneau 2006; Van Kasteren 2005; Wilson 1991).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



The three RCTs in two or fewer hospitals with medium risk of bias were Christ-Crain 2004, Christ-Crain 2006 and Senn 2004. The interventions were dissemination of laboratory test results (Christ-Crain 2004; Christ-Crain 2006) and a mailed questionnaire (Senn 2004). Because these interventions were targeted at doctors who were managing specific patients, the risks of allocation or contamination bias were relatively low compared with the other RCTs of interventions in one or two hospitals.

Allocation

Most of the RCTs had high risk of selection bias (Figure 2). The only RCTs that had low risk of selection bias were either cluster-RCTs (e.g. Paul 2006) or structural interventions, for which concealment of allocation is relatively straightforward.

Blinding

Most of the RCTs also had high risk of performance and detection bias (Figure 2).

Other potential sources of bias

Most RCTs did not provide information about baseline outcome (Figure 2). The importance of this risk of bias is illustrated by one study in which the intervention was a computer-generated reminder in the operating theatre about giving additional doses of antibiotic prophylaxis for prolonged operations (Zanetti 2003). The results show an increase in the use of additional doses and a reduction in wound infection in the control group in comparison with baseline. The authors attribute this result to contamination during development (surgeons were aware of the planned change) and implementation (surgeons who operated in the intervention theatre also operated in other theatres).

Effects of interventions

See: **Summary of findings for the main comparison**

Outcomes *of intervention*

For all outcomes we have included only data that are interpretable according to Cochrane EPOC criteria. Eighty interventions provide valid data about prescribing outcomes, 25 about clinical outcomes, 19 about microbiological outcomes and 10 about financial outcomes (the total adds up to more than 95 because some studies report more than one outcome per intervention).

Impact of persuasive interventions on prescribing outcomes

We report results as change in the direction of the intended effect, so a negative sign indicates that change in prescribing was in the opposite direction to the intended effect.

Overall, for the persuasive interventions, the median (interquartile range) change in antibiotic prescribing was 42.3% for the interrupted time series studies (ITSs), 31.6% for the controlled interrupted time series studies (CITSs), 17.7% for the controlled before-after studies (CBAs), 3.5% for the cluster-randomized controlled trials (CRCTs) and 24.7% for the randomized controlled trials (RCTs).

Fridkin 2002 reported on the impact of five interventions in different hospitals, three persuasive (educational materials, meetings, audit and feedback) and two restrictive (expert approval, restriction by removal). These are reported separately in Table 1; Table 2; Table 3.

Perez 2003 reported one persuasive intervention (reminders) in the same article as a restrictive intervention (compulsory order form). These interventions were both used in the same hospital but were targeted at different behaviours and are reported separately (Table 4; Table 5).

Dissemination of educational materials in printed form or via educational meetings (six interventions)

See Table 1. Five studies evaluated six interventions that used dissemination of educational materials as the main component (Fridkin 2002; May 2000; Stevenson 1988; Wilson 1991; Wyatt 1998). Of the five studies, one was a CRCT (Wyatt 1998), with an effect size of -3.1%; two studies were ITSs (Stevenson 1988; Wilson 1991), with a median effect size of 10.6%; one study was a CITS (May 2000), with an effect size of 42.5%; and two were CBAs (Fridkin 2002), with a median effect size of 16.1%. The findings had a high degree of clinical heterogeneity. All of the interventions showed a positive result except for the CRCT.

Reminders (eight interventions)

See Table 4. Eight studies evaluated eight interventions. All the interventions were associated with change in prescribing of at least 5% in the intended direction. Three of the studies were RCTs (Senn 2004; Shojania 1998; Zanetti 2003), with a median effect size of 27.4%. Five studies were ITSs (Avorn 1988; Halm 2004; Hulgan 2004; Madaras-Kelly 2006; Perez 2003), with a median effect size of 20%. The findings had a high degree of clinical heterogeneity.

Seven (87.5%) of the eight interventions were multifaceted, with additional educational materials (seven studies) and educational meetings or both (four studies).

Audit and feedback (nine interventions)

See Table 6. Nine studies evaluated nine interventions. Foy 2004 was a CRCT, with an effect size of 3.5%. Four of the studies were ITSs (Berild 2002; Kumana 2001; Mol 2005; Van Kasteren 2005), with an effect size of 32.7%. Two studies were CITSs (Barlow 2007; Weinberg 2001), with a median effect size of 24.3%. Two studies were CBAs (Chu 2003; Fridkin 2002), with a median effect size of 7.5%. The findings had a high degree of clinical heterogeneity.

Two studies reported no significant impact of audit and feedback, but both had design flaws. Fridkin 2002 reported that "evaluating periodic drug use" was an intervention to reduce vancomycin in 19 hospitals but provided no information about feedback of data to prescribers. The level of the intervention is described as hospital-wide rather than ICU-specific, with the implication that there was no feedback to ICU staff about their use of vancomycin. In Foy 2004 there was likely to be a ceiling effect because compliance with the guideline was very high (96.5%) in the control group.
All nine interventions were multifaceted with additional: educational materials (all interventions) and reminders (Barlow 2007; Kumana 2001). Audit and feedback was also an additional component in one study of review and recommend change (Abramowitz 1982) and in one restrictive intervention that used removal by restriction as the main component (Richards 2003).

Educational outreach (22 interventions)

See Table 2. There were 22 studies evaluated 22 interventions. Burton 1991 was not included in Table 2 because the effect size was measured as difference in peak aminoglycoside concentration, which was higher in the intervention group (5.3 versus 4.3 mg/l control, P = 0.001).
Most of the interventions in Table 2 (20/21, 95.2%) were associated with change in prescribing of at least 5% in the intended direction. Ten of the studies were RCTs including one CRCT (Bailey 1997; Bouza 2004; Dranitsaris 2001; Fine 2003; Fraser 1997; Gums 1999; Micek 2004; Naughton 2001; Solomon 2001; Walker 1998); the median effect size was 25%. Ten studies were ITSs (Abramowitz 1982; Adachi 1997; Ansari 2003; Hess 1990; Lee 1995; McLaughlin 2005; Mol 2005; Patel 1989; Richardson 2000; Skaer 1993), with a median effect size of 46.3%. Landgren 1988 was a CBA, with an effect size of 20%. The findings had a high degree of clinical heterogeneity.
However, three ITS studies reported large effect sizes (48.7 to 52.7%) that were not statistically significant by segmented regression analysis (McLaughlin 2005; Richardson 2000; Skaer 1993). Only one intervention (Bailey 1997, an RCT design) was completely ineffective, with a 9.8% increase in duration of intravenous antibiotics when the intended effect was a decrease.
One ITS study evaluated the incremental effect of academic detailing on audit and feedback (Mol 2005). Academic detailing was also used as an additional component in two ITS studies of restrictive interventions with compulsory order forms (Belliveau 1996; Salama 1996) and in one restrictive intervention with expert approval (McElnay 1995). Review and recommend change was also used as an additional component in one restrictive intervention (Inaraja 1986). Bouza 2004 directly compared a written recommendation in the patients' case notes with the written recommendation plus a direct conversation with the patient's physician and found that both interventions were similarly effective. Walker 1998 commented on the difficulty in making direct personal contact with prescribers at district hospitals.

Impact of restrictive interventions on prescribing outcomes

Overall, the restrictive interventions had a median effect size of 34.7% for the interrupted time series designs, 17.1% for the controlled before-after designs and 40.5% for the randomized controlled trials.

Compulsory order forms (five studies)

See Table 5. Five studies evaluated five interventions. All the studies were ITSs (Belliveau 1996; Perez 2003; Saizy-Callaert 2003; Salama 1996; Sirinavin 1998). Three (60%) reported interventions that were associated with change in prescribing of at least 5% in the intended direction. However, the findings had a high degree of clinical heterogeneity. The median effect size was 7.3% with an interquartile range of -0.1 to 28.2% (Table 5).
One compulsory order form intervention was completely ineffective at one year (Saizy-Callaert 2003). One intervention was associated with an initially significant reduction in vancomycin use, but this then reversed so that the net effect one year after the intervention was an increase in use (Belliveau 1996). In Perez 2003 the same intervention was associated with completely different effects on different drug groups in the same hospital.
All the interventions were multifaceted with additional: educational materials (four), educational meetings (five), reminders (four) and academic detailing (two).

Expert approval (nine studies)

Table 7.reports results on eight interventions on the effect of introducing expert approval and seven (87%) were associated with change in prescribing of at least 5% in the intended direction. Seven of the studies were ITSs (Huber 1982; Lautenbach 2003; McElnay 1995; McGowan 1976; Suwangool 1991; Woodward 1987; Young 1985), with a median effect size of 24.1%. Fridkin 2002 was a CBA, with an effect size of -2.8%. The findings had a high degree of clinical heterogeneity.
The ninth expert approval study (Himmelberg 1991) reported on the effect of removal of the need for expert approval, which our re-analysis showed that it was associated with a 162.2% increase in use of the nine previously restricted drugs (95% CI 97.7 to 226.6%), change in level P = 0.001, and change in slope P = 0.45. This study did not provide information about the effectiveness of the original restriction so has not been included in Table 6 or in the calculation of median effect.
Four (44%) of the expert approval interventions were multifaceted with additional educational materials or meetings (four studies), stop order (one study) and academic detailing (one study Table 7). Himmelberg 1991 was not multifaceted.

Removal by restriction (eight studies)

See Table 3. Eight included studies evaluated eight interventions. Removal by restriction was associated with large changes in the intended direction in all eight studies. Seven of the studies were ITSs (Bradley 1999; Everitt 1990; Inaraja 1986; McNulty 1997; Mercer 1999; Richards 2003; Toltzis 1998), with a median effect size of 60.7%. Fridkin 2002 was a CBA, with an effect size of 37%. The findings had a high degree of clinical heterogeneity. Of the three ITS designs with data at two time points, two showed sustained intervention effects (Richards 2003; Toltzis 1998), but one showed a transient effect (McElnay 1995). Six (75%) of the interventions were multifaceted with: additional educational materials or meetings (five studies), reminders (three studies), stop order (one study) or educational outreach (two studies).

Review and make change (four studies)

See Table 8. Four included studies evaluated four interventions. Two were RCTs (Borer 2004; Singh 2000), with a median effect size of 40.5%. Two were ITSs (Bunz 1990; Gupta 1989), with a median effect size of 94.3%. Review and make change was associated with large changes in the intended direction in all four studies. The findings had a high degree of clinical heterogeneity. None of these studies provided data at more than one time point. Of the four studies that used review and make change as the main method of dissemination, two (50%) were multifaceted with additional: educational materials (two studies), educational meetings (two studies), and reminders (two studies)

Impact of structural interventions on prescribing outcomes (eight studies)

The structural interventions had a median effect of 13.3% for the RCTs and 23.6% for the cluster-RCTs.

See Table 9. Six studies were RCTs (Bruins 2005; Christ-Crain 2006; Doern 1994; Franz 2004; Oosterheert 2005; Trenholme 1989), and two were CRCTs (Christ-Crain 2004; Paul 2006). Eight (89%) of nine structural interventions were associated with change in prescribing of at least 5% in the intended direction. For the RCTs, the median effect size was 13.3% with an interquartile range of 7.7% to 13.8%; for the cluster-RCTs, the median effect was 23.6% with an interquartile range of 15.9% to 31.2% (Table 9).

Three structural interventions introduced new tests for inflammatory markers (Christ-Crain 2004; Christ-Crain 2006; Franz 2004), which were associated with 13.5% to 38.8% reduction in the percentage of patients treated with antibiotics. These are the only interventions in this review that achieved this outcome. The other structural interventions introduced rapid microbiology reporting (Bruins 2005; Doern 1994; Trenholme 1989), a new polymerase chain reaction (PCR) test for detecting viruses or atypical bacteria (Oosterheert 2005), and a computerized decision support system (Paul 2006). Only one of these interventions was associated with reduction in exposure to antibiotics by discontinuing treatment earlier than originally planned but the effect was small (3.4% absolute reduction) and not statistically significant (Oosterheert 2005). Two of the rapid microbiology reporting interventions also included educational outreach. In Bruins 2005, same day delivery of a written, individual patient report to the ward had no additional impact over telephone reporting. Trenholme 1989 used educational outreach (a telephone consultation between an infectious diseases (ID) fellow and the prescriber) in both the intervention and control arms, so the intervention effect can be attributed to the microbiology results being available 24 hours earlier in the intervention arm. All eight structural interventions were multifaceted because they also included persuasive components: educational materials (five studies), reminders (four studies) or educational outreach (two studies).

Effect of interventions on microbial outcomes (21 studies)

For all interventions the intended effect was a decrease in the microbial outcome. A total of 23 microbial outcomes were reported by 21 studies (Results Table 10; Table 11; Table 12): Carling 2003 reported four microbial outcomes but we have only included three (*Clostridium difficile* infections, infection with antibiotic-resistant gram-negative bacteria and methicillin-resistant Staphylococcus aureus (MRSA) infections). This study also reported on vancomycin-resistant enterococci (VRE) but there were no VRE infections until three years after the intervention began. The appearance of VRE infections in the hospital was attributed to transfer of colonized patients from other hospitals (Carling 2003).

Clostridium difficile infections (Five studies)

See Table 10. Five studies evaluated five interventions reported *Clostridium difficile* infections. All of the included studies were ITSs (Carling 2003; Climo 1998; Khan 2003; McNulty 1997; Pear 1994), showing a median effect size of 68%. All reported change in the intended direction by at least 15% and four by at least 50%. However, only McNulty 1997 had reliable data about intervention impact on prescribing. This study reported the largest intervention effect on *Clostridium difficile* infection but this was not statistically significant, probably because the study only had seven pre-intervention points. Only two of the studies had low risk of bias and these reported the smallest intervention effect on *Clostridium difficile* infection (Carling 2003; Khan 2003).

Antibiotic-resistant gram-negative bacteria (Nine studies)

See Table 11. Nine studies evaluated nine interventions reporting colonization or infection with antibiotic-resistant gram-negative bacteria. Seven were ITSs (Calil 2001; Carling 2003; de Champs

1994; Gerding 1985; Landman 1999; Leverstein 2001; Meyer 1993), with a median effect size of 47%. de Man 2000 was a CCCT, with an effect size of 68%. Toltzis 2002 was a CCT, with an effect size of -39%.

Although Toltzis 1998 found that cycling of antibiotics was associated with an increase in resistant gram-negative bacteria, the other eight studies all reported at least a 25% reduction in resistant gram-negative bacteria, but confidence intervals were wide and the effects were not statistically significant in two studies (Gerding 1985; Landman 1999). Moreover, none of the studies had reliable data about intervention impact on prescribing, and only two studies had low microbial risk of bias (Carling 2003; de Man 2000).

Antibiotic-resistant gram-positive bacteria (Seven studies)

See Table 12. Seven studies evaluated seven interventions reporting colonization or infection with antibiotic-resistant gram-positive bacteria. Six were ITSs (Bradley 1999; Carling 2003; Charbonneau 2006; Lautenbach 2003; Madaras-Kelly 2006; May 2000), with a median effect size of 24%. Fridkin 2002 was a CBA, with an effect size of 13.2%.

Six studies reported a statistically significant intervention effect with at least 10% difference in resistance between intervention and control groups. Moreover five studies included reliable data about intervention effects on antibiotic prescribing.

Madaras-Kelly 2006, with low microbial risk of bias, reported that a 50% statistically significant reduction in levofloxacin use (Table 2) was associated with a 21% statistically significant reduction in MRSA infections. Two other interventions also aimed to reduce MRSA infections by reducing fluoroquinolone use, but neither provided reliable data about antibiotic prescribing (Carling 2003; Charbonneau 2006).

Bradley 1999, with low microbial risk of bias, reported that a 61% reduction in ceftazidime use was associated with a statistically significant 25% reduction in vancomycin-resistant enterococci (VRE). However, the impact on ceftazidime prescribing had wide confidence intervals and was not statistically significant (Table 3).

Three studies reported that reduction in vancomycin use was associated with reduction in VRE (Fridkin 2002; Lautenbach 2003; May 2000). One study (Fridkin 2002 had medium microbial risk of bias and reported that two interventions that were each associated with statistically significant reduction in vancomycin use by 35% to 37% (Table 1; Table 3) were associated with a statistically significant 13.2% difference in VRE between the intervention and control hospitals. The other studies had high microbial risk of bias and reported effects on vancomycin prescribing that had wide confidence intervals and were not statistically significant (Lautenbach 2003; Table 7; May 2000; Table 1). In particular the difference in VRE rates pre- and postintervention in Lautenbach 2003 was probably due to the study reporting only three pre-intervention data points with a steep increase in VRE, followed by levelling of VRE rates in the postintervention years. These data probably showed the natural history of emergence of VRE in this hospital rather than the effect of the modest (19.6%) reduction in vancomycin use in the postintervention phase.

Meta-analysis of persuasive versus restrictive interventions (52 studies, Figure 3)

de Man 2000, a cluster CCT, was the only study of a restrictive intervention that did not use an ITS design. Consequently this meta-analysis was confined to a meta-regression of ITS studies.

A total of 56 ITS studies were identified, of which 52 included data for the meta-analysis. The other four studies (Barlow 2007; Charbonneau 2006; Perez 2003; Suwangool 1991) used appropriate statistical models but did not include estimates of variance for the effect size at any of our time points, and these could not be recalculated from the raw data in the papers. The outcomes for the remaining 52 studies were prescribing (N = 38), microbial (N = 14) and cost (N = 4); four studies had more than one outcome. Overall the studies showed a consistent impact on prescribing and microbial outcomes with at least 25% of studies showing an effect in the intended direction at each time point.

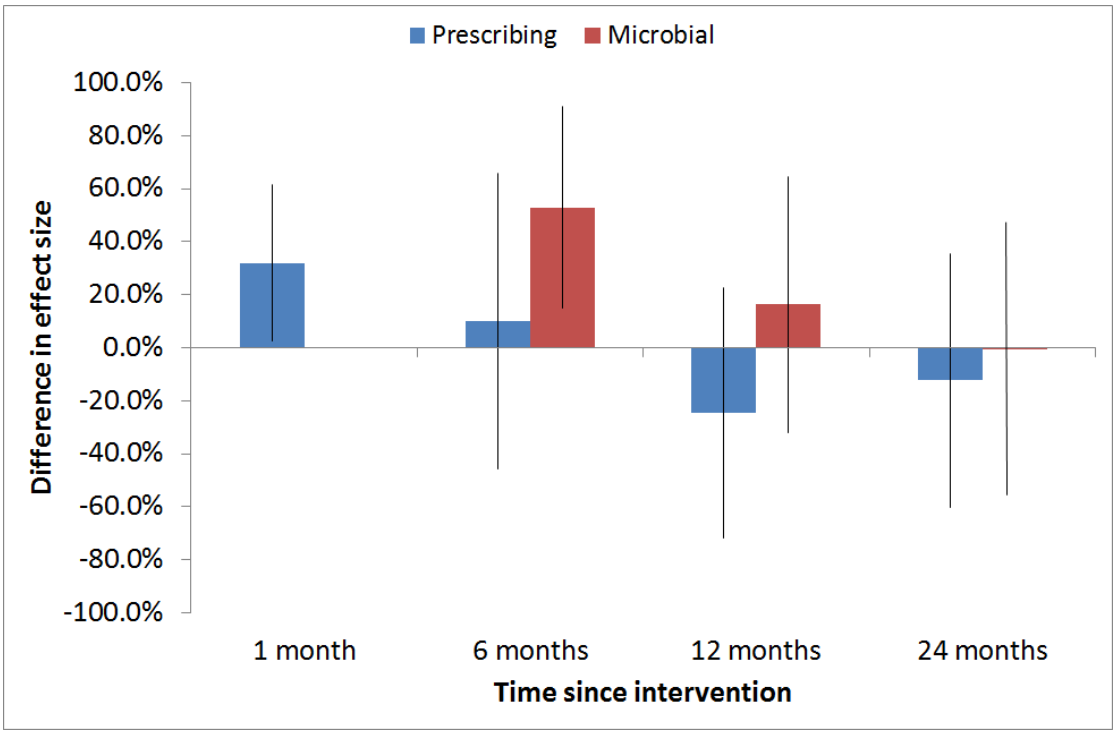
There were 23 studies of purely persuasive interventions: Abramowitz 1982; Adachi 1997; Ansari 2003; Avorn 1988; Berild 2002; Carling 2003; Dempsey 1995; Halm 2004; Hess 1990; Hulgan 2004; Kumana 2001; Lee 1995; Madaras-Kelly 2006; May 2000; McLaughlin 2005; Mol 2005; Patel 1989; Richardson 2000; Skaer 1993; Stevenson 1988; Van Kasteren 2005; Weinberg 2001; Wilson 1991.

There were 29 studies of restrictive interventions: Belliveau 1996; Bunz 1990; Bradley 1999; Calil 2001; Climo 1998; Everitt 1990; de Champs 1994; Gerding 1985; Gupta 1989; Himmelberg 1991; Huber 1982; Inaraja 1986; Khan 2003; Landman 1999; Lautenbach 2003; Leverstein 2001' McElnay 1995; McGowan 1976; McNulty 1997; Mercer 1999; Meyer 1993; Pear 1994; Richards 2003; Saizy-Callaert 2003; Salama 1996; Sirinavin 1998; Toltzis 1998; Woodward 1987; Young 1985.

Comparison 1: effect of restrictive versus persuasive interventions on prescribing outcomes

For prescribing outcomes the restrictive interventions had a statistically significantly greater effect at one month (+32.0%, 27 studies, 95% confidence interval (CI) +2.5% to +61.4%), but at six months the difference had diminished to +10.1% (15 studies, 95% CI -47.5% to +66.0%), and at 12 or 24 months the persuasive interventions had greater effect, though none of the 6-, 12- or 24-month differences were statistically significant. Difference at 12 months was -24.6% (18 studies, 95% CI -71.9% to +22.6%) and difference at 24 months was -12.3% (11 studies, 95% CI -60.2% to +35.5%), Figure 3.

Figure 3. Meta-regression of the difference in effect size between restrictive and persuasive interventions at 1, 6, 12 and 24 months after the intervention. The difference is Restrictive minus Persuasive so positive values for the difference indicate greater effect size for Restrictive interventions and negative values indicate greater effect size for Persuasive interventions. The bars show 95% CI for the mean difference



Comparison 2: effect of restrictive versus persuasive interventions on microbial outcomes

For microbial outcomes the restrictive interventions had a statistically significantly greater effect at 6 months (+53.0%, 9 studies, 95% CI +30.6 to +75.4%), but at 12 months the difference had diminished to +16.2% (8 studies, 95% CI -21.9% to +54.4%) and at 24 months there was a small difference of -0.7% in favour of persuasive interventions (3 studies, 95% CI -49.1 to +47.8%, Figure 3).

For cost outcomes there were too few studies to compare effects.

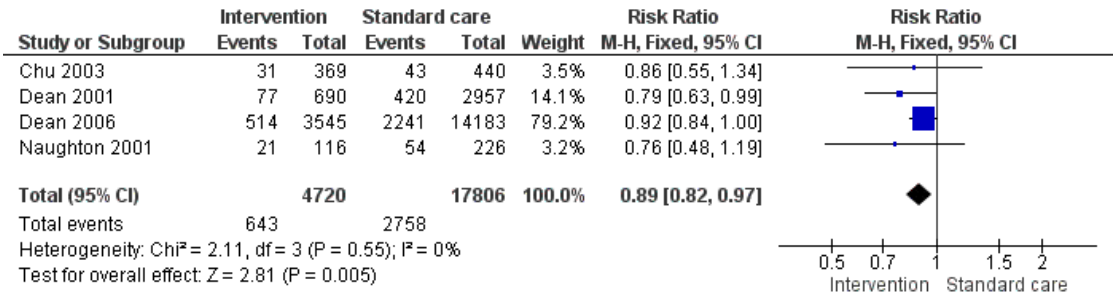
Comparison 3: effect on clinical outcomes of interventions that aimed to increase effective antibiotic treatment (11 studies, Figures 4 and 5)

Three interventions used rapid reporting of microbiology results with increase in appropriate antibiotic therapy as the prescribing outcome measure (Bouza 2004; Bruins 2005; Doern 1994). Doern 1994 reported a significant reduction in mortality (Odds Ratio (OR) 0.53, 95% CI 0.32 to 0.90, P = 0.02), while the other two studies reported nonsignificant increases in mortality. The combined result was a risk ratio (RR) of 0.92 (95% CI 0.69 to 1.22, P = 0.56, Figure 4). All three studies also reported length of stay, but there was no significant difference between the intervention and control patients in any study.

Figure 4. Forest plot of comparison: 1 Intended clinical outcomes, interventions intended to increase effective prescribing, outcome: 1.1 Mortality, interventions intended to increase appropriate antimicrobial therapy, all infections.

Five interventions were intended to increase guideline compliance for pneumonia, three for community-acquired pneumonia (Chu 2003; Dean 2001; Dean 2006) and two for nursing home-acquired pneumonia (Dempsey 1995; Naughton 2001). Four studies reported mortality and all four interventions were associated with a reduction in mortality, of which two were statistically significant (Dean 2001; Dean 2006). The combined result was a RR of 0.89 (95% CI 0.82 to 0.97, P = 0.005, Figure 5). Dean 2006 also reported a significant reduction in readmissions. Four studies reported length of stay (Chu 2003; Dean 2001; Dean 2006; Dempsey 1995), but the format did not allow meta-analysis. Chu 2003 reported mean length of stay without standard deviation (SD), showing a decrease in both intervention and control hospitals but with no significant difference between them (P = 0.47). Dean 2001 reported that length of stay among post-guideline inpatients was similar to statewide trends (0.3 days shorter compared with pre-guideline, 95% CI 20.2 to 0.8 days; P = 0.21). Dean 2006 reported that in a logistic regression model, the OR for length of stay longer than seven days at intervention hospitals was 1.22 (95% CI 1.13 to 1.31; P = 0.001) compared with control hospitals. Length of stay longer than seven days decreased significantly between pre-implementation and postimplementation periods at intervention hospitals (OR 0.88, 95% CI 1.13 to 1.31 [this is what is reported in the paper but must be wrong]; P = 0.004). Dempsey 1995 reported that their intervention was associated with a significant reduction in length of stay, however length of stay decreased throughout both the control and intervention periods and our segmented regression analysis did not show any significant change in level (P = 0.74) or slope (P = 0.81).

Figure 5. Forest plot of comparison: 1 Intended clinical outcomes, interventions intended to increase effective prescribing, outcome: 1.2 Mortality, interventions intended to increase antibiotic guideline compliance for pneumonia.



Two studies showed that increased appropriate use of antibiotics for prophylaxis in surgery was associated with significantly reduced postoperative surgical site infections (Weinberg 2001; Zanetti 2003).

Burton 1991 showed that an increase in effective gentamicin serum concentrations was associated with significant reduction in length of stay. However, this study had a unit of analysis error so the

confidence interval reported in the paper is too narrow. We did not include this study in any meta-analysis.

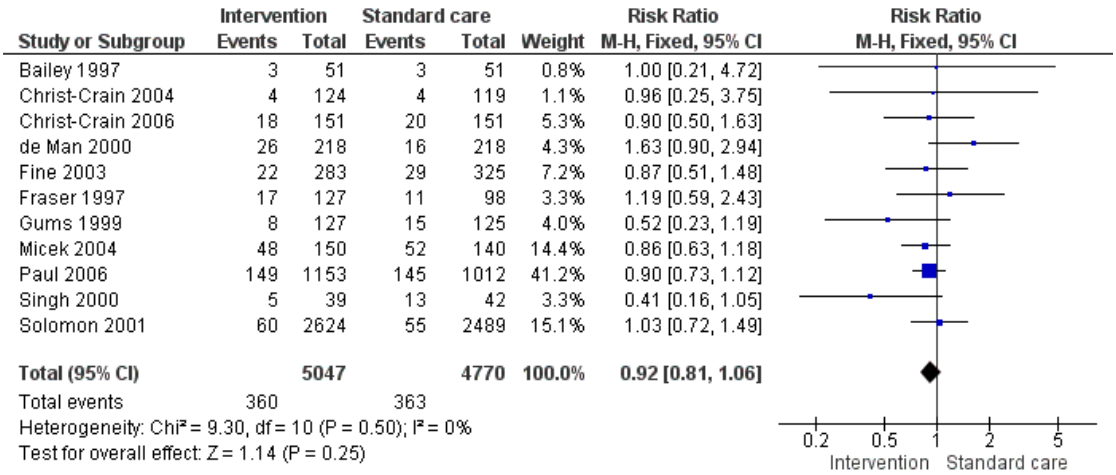
Comparison 4: effect on clinical outcomes of interventions intended to reduce excessive use of antimicrobials (14 studies, Figures 6-8)

In 14 studies clinical outcomes were used as a balancing measure, which is a term used in quality improvement to describe measures that address potential unintended consequences of changes to care processes (Lloyd 2004). In these studies the measures of clinical outcome were used to provide reassurance that reduction in what the authors had defined as excessive use of antibiotic prescribing was not associated with worse clinical outcomes.

Fourteen interventions that were intended to decrease antibiotic treatment reported clinical outcomes (Bailey 1997; Christ-Crain 2004; Christ-Crain 2006; de Man 2000; Fine 2003; Fraser 1997; Gums 1999; Micek 2004; Oosterheert 2005; Paul 2006; Singh 2000; Solomon 2001; Van Kasteren 2005; Walker 1998). However, one intervention was not associated with significant change in antibiotic prescribing (median duration of treatment 10 days in the intervention group versus nine days in the control group, the decreased duration as the intended effect (Oosterheert 2005)). We did not include this study in the meta-analyses.

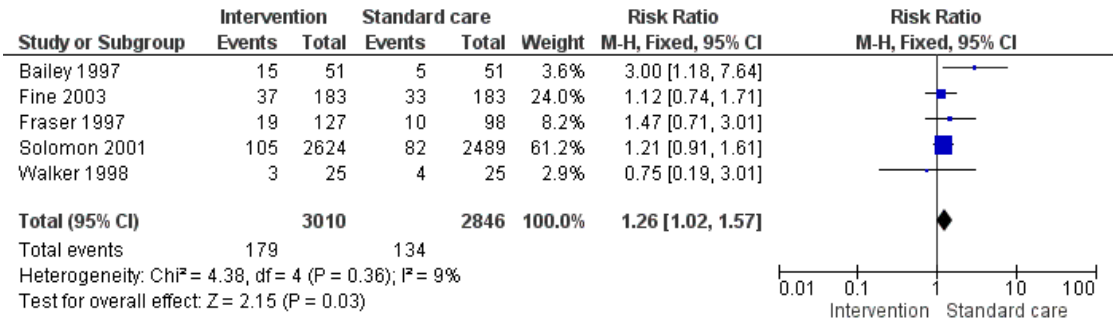
Eleven interventions associated with decrease in excessive antibiotic prescribing reported mortality as an outcome (Bailey 1997; Christ-Crain 2004; Christ-Crain 2006; de Man 2000; Fine 2003; Fraser 1997; Gums 1999; Micek 2004; Paul 2006; Singh 2000; Solomon 2001). Two were intended to reduce the number of patients who received antibiotics for lower respiratory tract infections (Christ-Crain 2004; Christ-Crain 2006), three to reduce use of target antibiotics for empirical therapy (de Man 2000; Gums 1999; Paul 2006), two to reduce total duration of antibiotic therapy (Micek 2004; Singh 2000), three to reduce duration of IV antibiotics (Bailey 1997; Fine 2003; Solomon 2001) and one to reduce cost of antibiotics (Fraser 1997). No single intervention was associated with a significant increase in mortality and the combined result was a RR of 0.92 (95% CI 0.81 to 1.06, P = 0.25, Figure 6).

Figure 6. Forest plot of comparison: 2 Clinical outcomes, interventions intended to decrease excessive prescribing, outcome: 2.1 Mortality, interventions intended to decrease excessive prescribing.



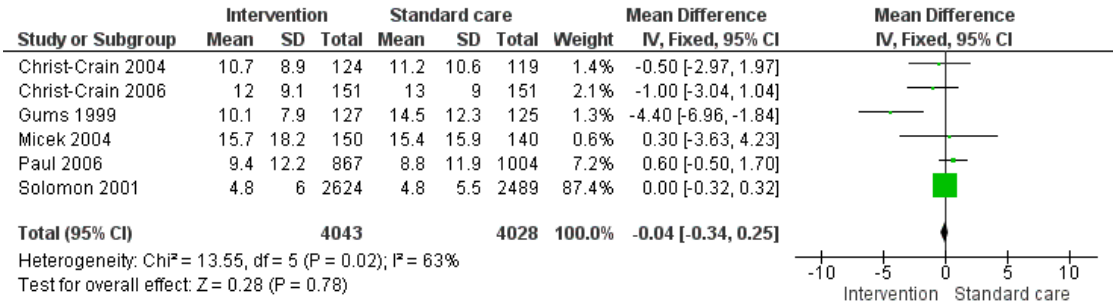
Five interventions reported readmission as an outcome (Bailey 1997; Fine 2003; Fraser 1997; Solomon 2001; Walker 1998). Four were intended to reduce duration of intravenous antibiotics (Bailey 1997; Fine 2003; Solomon 2001; Walker 1998) and one to reduce the cost of antibiotics (Fraser 1997). Bailey 1997 was associated with a significant increase in total readmissions (RR 3.00, 95% CI 1.18 to 7.64) but there was no significant increase in infection-related readmissions (RR 1.33, 95% CI 0.31 to 5.66, P = 0.5). The combined result was a RR for total readmissions of 1.26 (95% CI 1.02 to 1.57, P = 0.03, Figure 7).

Figure 7. Forest plot of comparison: 2 Clinical outcomes, interventions intended to decrease excessive prescribing, outcome: 2.2 Readmission, interventions intended to decrease excessive prescribing.



Length of stay was reported by six studies in a format that allowed meta-analysis: (Christ-Crain 2004; Christ-Crain 2006; Gums 1999; Micek 2004; Paul 2006; Solomon 2001). The combined intervention effect was a reduction in length of stay by 0.04 days (95% CI -0.34 to +0.25, P = 0.78, Figure 8). In addition, Fine 2003 reported the median and interquartile range for length of stay with hazard ratio (HR). The intervention was not associated with a significant increase in HR for length of stay (1.16, 95% CI 0.97 to 1.38, P = 0.11).

Figure 8. Forest plot of comparison: 2 Clinical outcomes, interventions intended to decrease excessive prescribing, outcome: 2.3 Lengh of stay, interventions intended to decrease excessive prescribing.



One intervention that resulted in significant reduction in duration of surgical antibiotic prophylaxis was not associated with a significant change in postoperative wound infection (Van Kasteren 2005).

One study reported that substitution of ceftazidime with cefotaxime was associated with a significant increase in cefotaxime resistant *Acinetobacter* infections (Landman 1999; Table 11). There were no other examples of measurement of unintended microbial outcomes.

Impact of interventions on healthcare costs

See Table 13. Only 10 studies (11%) provided reliable data

about both intervention costs and financial savings (Abramowitz 1982; Ansari 2003; Bailey 1997; Christ-Crain 2006; Gums 1999; Landgren 1988; Oosterheert 2005; Solomon 2001; Woodward 1987; Wyatt 1998). Other reports included statements such as the economic savings being "substantial in comparison to the modest costs" (Everitt 1990), or that modification of existing computer hardware or software incurred minimal costs (Zanetti 2003), without providing detail.

The limited information provided shows that intervention costs can be substantial. However, eight studies (Abramowitz 1982; Ansari 2003; Bailey 1997; Christ-Crain 2006; Gums 1999; Landgren 1988; Solomon 2001; Woodward 1987) reported that savings exceeded the cost of the intervention (Table 13). The two exceptions were interventions that did not have a significant impact on antibiotic prescribing (Oosterheert 2005; Wyatt 1998).

DISCUSSION

The primary aim of this review was to identify interventions that are effective in promoting prudent antibiotic prescribing to hospital inpatients.

Summary of main results

There are many positive findings in this review: the 89 studies were conducted in 19 countries on five continents. They show that a variety of persuasive and restrictive interventions have changed antibiotic treatment for hospital inpatients and that changes in prescribing can be associated with improvement in outcomes. Specifically, the review now provides evidence that increase in effective treatment can be associated with reduced mortality and that decrease in excessive antibiotic use can be associated with improvement in microbial outcome without compromising clinical outcomes. This update to the review provides stronger evidence about clinical outcomes and now includes 11 interventions that aimed to decrease exposure to antibiotics by reducing the percentage of patients that received treatment (Christ-Crain 2004; Christ-Crain 2006; Franz 2004) or by shortening duration of treatment (Berild 2002; Fine 2003; Micek 2004; Oosterheert 2005; Senn 2004; Singh 2000) or prophylaxis (Landgren 1988; Van Kasteren 2005). External validity has also improved, with 15 studies in three or more hospitals and 9 in 10 or more hospitals. However, on the negative side, the 89 studies represent only approximately one-fifth of the published literature, which is still dominated by uncontrolled before-after studies or inadequate interrupted time series (ITS) or controlled before-after (CBA) studies that do not provide interpretable data (Ramsay 2003). Even between 2003 and 2006 only 49% of published studies met the minimum criteria of the Cochrane Effective Practice and Organisation of Care (EPOC) Group.

Overall completeness and applicability of evidence

Should interventions be persuasive or restrictive?

In the absence of direct comparisons any conclusions about the effectiveness of different interventions must be tentative. The problem of a lack of comparative studies is further compounded by the absence of standardization. In order to assess the sustained effect of any intervention we need data to assess change in level with the standard error (SE) for at least two time points. We suggest that for prescribing outcomes immediate effects should be assessed in the first six months, with sustained effects assessed at one year or longer. For microbial outcomes we suggest that immediate effects are assessed at six months with sustained effects assessed at one or two years. Our review suggests that restrictive interventions have a greater immediate impact than persuasive interventions. Previous EPOC reviews have not distinguished between these types of interventions and the frequent use of restrictive interventions may be peculiar to interventions relating to hospital prescribing. This finding is important because it supports restriction when the need is urgent (e.g. in an outbreak situation). However, this conclusion is based on indirect comparisons. The evidence base would be enormously enhanced by direct comparison, for example, by using time series analysis to measure the additional impact of a restrictive intervention added to that of a persuasive intervention. We also need more reassurance that restrictive interventions do not have unintended adverse clinical outcomes.

We considered further meta-analysis to see whether the addition of persuasive elements was associated with a more sustained intervention effect. We identified studies with data that allowed estimation of effect size at two or more time points. For microbial outcomes there is only one study in the review (McNulty 1997) that has a restrictive intervention with persuasive elements and effect size at both six and 12 months. Moreover there are only two studies in the review with data about microbial outcomes at 24 months postintervention (Carling 2003; Lautenbach 2003) and neither of these studies provides data about the immediate effect of the intervention. For prescribing outcomes effect size estimates at one and 12 months can be made for only one study of a purely restrictive intervention (Young 1985), and four studies of restrictive interventions with persuasive components (Belliveau 1996; Everitt 1990; McNulty 1997; Richards 2003).

Although there are not enough studies for meta-analysis of the effect of adding persuasive components to a restrictive intervention, there are two clear examples of multifaceted, restrictive interventions with diminishing effectiveness over time (Belliveau 1996; McNulty 1997). Hence the limited data show that the inclusion of persuasive components does not guarantee sustained effect for a restrictive intervention. The proportion of purely restrictive in-

terventions has not changed much over time: 4 of 9 studies (44%) published up to 1990; 8 of 15 studies (53%) published from 1991 to 2000, and 3 of 8 studies (38%) published from 2001 to 2006. There may be enough studies to compare sustained effects of different intervention types in the next update.

Despite the limitation of indirect comparisons, restrictive interventions do seem to have a greater immediate impact than persuasive interventions. The intervention effects reported for restriction by removal (Table 3) and for review and make change (Table 8) were more consistent than for compulsory order forms (Table 5) or expert approval (Table 7). It is plausible that it is easier for prescribers to find a way around order forms and expert approval. Documented examples include misrepresenting clinical information (Calfee 2003; Linkin 2007) and delaying treatment to circumvent expert approval by an ID service that was off duty from 10pm (LaRosa 2007). Nonetheless, prescribers will find a way around any restriction, for example by going to other wards if antibiotics are removed from their clinical area or by changing a prescription back to the original. Consequently hospitals should not assume that restriction will work and must collect data to monitor impact. In addition to reducing the intended effect of restrictive interventions, misrepresentation of clinical information can have additional consequences. For example, misrepresenting infections as hospital-acquired in order to meet the criteria for use of restricted antibiotics has resulted in a pseudo-outbreak of hospital-acquired infection (Calfee 2003).

A major limitation of the evidence about restrictive interventions is that only one study provides data about clinical outcomes (de Man 2000). If hospitals do restrict the clinical freedom of their physicians then it is critical that they are not compromising the outcomes for their patients.

Social marketing and behaviour change theories

The most resource-intensive persuasive interventions used educational outreach, and these were not always effective (Table 2). Two studies showed that academic detailing (Mol 2005) or review and recommend change (Bouza 2004) did not add significantly to the effect of simpler interventions (audit and feedback; Mol 2005, or reminders; Bouza 2004). Review and recommend change can be particularly resource-intensive because the system in some hospitals makes it difficult to identify and contact the doctor responsible for a specific prescription (Walker 1998). Consequently it is surprising that only one intervention in our review used a model for improvement based on involving the target professionals in setting priorities and in design and collection of measures for improvement (Weinberg 2001). In the quality improvement and patient safety literature there is growing evidence to support this type of intervention going back over a decade. In particular, successful interventions that are led by clinical teams may be easier to sustain and spread than interventions based on review and recommendation of change, which are inherently person-dependent (Nelson 1998). Recent systematic reviews have applied Control Theory (Gardner 2010; Michie 2009) or Feedback Intervention Theory (Hysong 2009) to meta-analysis, and have concluded that feedback is likely to be more effective if accompanied by action planning, helping participants to identify and overcome barriers to achieving their goals, which supports the model for improvement advocated by Nelson 1998.

There are several behavioural science theories which aim to explain why people behave in certain ways (Darnton 2008). These theories can be used in research to develop an understanding of the determinants of prescribing behaviours, in order to develop targeted interventions aiming to optimize prescribing. In public health, social marketing makes use of behavioural science theories and the principles of marketing to bring about change in health behaviours to reduce burden of disease in society. Social marketing at its core focuses on the target group to develop behaviour change interventions that are 'customer oriented', are based on theory, and are driven by primary research on what truly moves and motivates people (Morris 2009).Though the evidence on the application and utility of social marketing to change healthcare worker behaviours is limited, there is increasing evidence of use of some elements of social marketing contributing to interventions reported in antibiotic prescribing. Eight studies in this review could be classified as having elements of social marketing to investigate barriers to professional behaviour change as part of the intervention design (Barlow 2007; Dempsey 1995; Everitt 1990; Foy 2004; Mol 2005; Naughton 2001; Weinberg 2001; Wyatt 1998). However, none fulfilled the key additional element of explicit application of any behaviour change theory for the development of the interventions or the utilization of a defined strategy to market them. These results have been extended in a review of literature on social marketing applied to antibiotic stewardship published up to April 2011, which also found no evidence of the application of behavior change models (Charani 2011).

Structural interventions

Three structural interventions focused on rapid reporting of laboratory results. While conventional methods for culture and susceptibility testing are time-consuming, two of these interventions (Doern 1994; Trenholme 1989) suggested that same-day result reporting may have significant benefits for antibiotic stewardship, including quicker administration of appropriate therapy and quicker streamlining.

Three structural interventions focused on the introduction of tests of inflammatory markers (Christ-Crain 2004; Christ-Crain 2006; Franz 2004), and all three showed that the use of these tests may significantly reduce the use of antibiotics for patients with low risk of infection (Table 9). These are the only interventions in our review that reduced the number of patients who were treated with antibiotics in hospital, whereas rapid microbiology tests or polymerase chain reaction (PCR) tests for viruses had little impact

on total antibiotic use (Bruins 2005; Doern 1994; Oosterheert 2005; Trenholme 1989). The evidence base for procalcitonin has recently been reviewed, and identified six additional studies that will be relevant to the next update of our review (Schuetz 2012). Currently there is great emphasis on Point of Care Testing (POCT) that will allow informed antibiotic prescribing within one to two hours of presentation. In septic patients this could save lives (Kumar 2006) but there are many problems to overcome, not least expense. Risk assessment using an electronic decision support system may allow stratification of patients who would best benefit from such POCTs e.g. PCR of blood to increase detection of bacteraemia over conventional blood culture systems (Kofoed 2009), but this has yet to be tested in an intervention. Molecular POCTs are likely to be helpful in identifying specific organisms but identifying resistance profiles is more problematic; specific tests for vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and rifampin-resistant *Mycobacterium tuberculosis* are widely available, and those for some of the newer beta-lactamases such as New Delhi metallo-beta-lactamase 1 (NDM1) are a possibility. However these new technologies require careful assessment in well-designed intervention studies because the evidence that we have reviewed (Table 9) shows that simply increasing the speed of reporting test results does not necessarily change prescribing behaviour.

How do changes in prescribing influence other outcomes?

Microbial outcomes

The data show that interventions to change antibiotic prescribing were associated with decrease in *Clostridium difficile* (Table 10), resistant gram-negative bacterial (Table 11), MRSA and VRE (Table 12). However, only six interventions (29%) provided reliable data about change in antibiotic prescribing, which is a major weakness in the evidence base because there are not enough data to estimate the likely impact of change in prescribing on microbial outcomes.

Clinical outcomes

There has been a welcome increase in reporting clinical outcomes as a measure of unintended consequences of interventions that aim to reduce excessive prescribing. Failure to include measures of unintended consequences has been a long-standing problem with the use of performance data to change professional practice (Smith 1995). Limiting unintended consequences is an important goal of antimicrobial stewardship (McGowan 2012). However, the need for measures of unintended consequences is not specific to antimicrobial stewardship and extends beyond measures of clinical outcome. Recently 'Four Criteria for Accountability Measures That Address Processes of Care' have been proposed, of which one is 'Implementing the measure has little or no chance of inducing unintended adverse consequences' (Chassin 2010). The need for broader measures of unintended consequences is considered in more detail under construct validity in Quality of the evidence below.

In our review, all of the studies that included clinical outcomes as balancing measures were randomized controlled trials (RCTs) or cluster trials. In future information about balancing measures could be derived from routine data and included in ITS studies.

The most common measure of unintended clinical outcomes is mortality (Figure 6). Although it is reassuring to see no increase in total mortality associated with interventions that intend to reduce unnecessary antibiotic treatment, it would be preferable to develop indicators of mortality in patients with sepsis or defined infections. Five studies which included readmission as a balancing measure found that overall there was a significant increase in readmissions associated with the interventions (Figure 7). The study that reported the biggest change in total readmissions (Bailey 1997) also documented infection-related readmissions. These only accounted for 39% of readmissions within 30 days, and there was no significant difference between intervention and control groups for infection-related readmissions. It is unlikely that infection-related readmissions can be measured reliably from routine data (Davey 1995), which raises doubts about the validity of readmission as a balancing measure for interventions to reduce excessive antibiotic prescribing.

Intervention cost

It is disappointing that still only 10 of 89 studies (11%) provided information about the costs of intervention, which is the same proportion as reported by a review of guideline implementation, in which only 25 of 235 reports (11%) described intervention costs (Grimshaw 2004). A survey of the resources available for guideline implementation in the UK concluded that most healthcare organizations do not have a budget that is adequate to support complex dissemination or implementation strategies. Instead they expect that their organizations will achieve change through dissemination of educational materials and short (lunchtime) educational meetings (Grimshaw 2004). Even the limited information about resources needed to implement interventions clearly shows that these are unrealistic expectations (Table 13).

Quality of the evidence

We have considered three criteria for the included studies: internal validity, external validity and construct validity. Internal validity is concerned with problems such as bias or confounding in the study design. External validity is concerned with the extent to which results can be applied or generalized to people, settings or times other than those that were the subject of the study. Construct validity is concerned with the relationship between the study results

and a theoretical construct of antibiotic stewardship (McGowan 2012).

Internal validity

The risk of bias in the studies that we have reviewed is variable, but there is a core of 49 studies (55%) with low or medium risk of bias or confounding. These show that a variety of persuasive and restrictive interventions do change antibiotic prescribing and that this can improve clinical or microbiological outcomes. A major gap in the evidence is that only six studies provide reliable data about change in antibiotic prescribing and microbial outcome.

External Validity

The best evidence of external validity is provided by multicentre studies. In our review there are 15 studies that were done in three or more hospitals. Nine interventions aimed to decrease excessive antibiotic treatment (Charbonneau 2006; Fine 2003; Franz 2004; Fridkin 2002; Halm 2004; Landgren 1988; Paul 2006; Van Kasteren 2005; Wilson 1991) and included two cluster-RCTs (Fine 2003; Paul 2006). The remaining six studies were of interventions that aimed to increase effective antibiotic treatment (Chu 2003, Dean 2001; Dean 2006, Foy 2004, Naughton 2001, Wyatt 1998) and included two cluster-RCTs (Foy 2004; Wyatt 1998). Collectively these studies provide important evidence that interventions can work in multiple hospitals, both to decrease excessive prescribing (Charbonneau 2006; Franz 2004; Fridkin 2002; Landgren 1988; Paul 2006; Van Kasteren 2005) and to increase effective prescribing (Chu 2003; Dean 2001; Dean 2006).

Some evidence of external validity can be obtained by reproducing results from single hospitals in other hospitals but none of the single hospital studies is an exact reproduction of another study. However, we have been able to perform meta-regression of 52 ITS studies and meta-analysis of clinical outcomes, which is a major improvement in this update of the review.

The Holy Grail of implementation research is to provide health services with evidence about behaviour change that is similar to treatment trials, with robust estimates of effect size for well-defined groups of patients. Given the complexity of behaviour change strategies and healthcare organizations, it seems likely that local validation of interventions will always be required. Consequently hospitals will always have to evaluate their own interventions. We believe that the average hospital can aspire to low bias, high quality ITS evaluation of quality improvement interventions. These are data for improvement, not data for research. Nonetheless, improving the quality of ITS evaluations in single hospitals will lay the foundation for cluster-randomized trials with embedded time series (Brown 2006). Moreover, rigorous evaluation of interventions in single hospitals will help to set priorities for definitive research studies (Campbell 2007; MRC 2000).

Construct Validity

Construct validity is involved whenever a test is to be interpreted as a measure of some attribute or quality which is not operationally defined (Cronbach 1955). There is general agreement that antibiotic stewardship has two competing objectives: first to ensure effective treatment of patients with infection, and second to minimize collateral damage from antibiotic use (Davey 2010; Dellit 2007; McGowan 2012). However, collateral damage to the normal human bacterial flora is an inevitable consequence of any antibiotic use. Consequently a successful intervention to increase necessary use of antibiotics will also increase collateral damage to the flora of the patients in the intervention. More importantly the intervention may unintentionally increase unnecessary antibiotic treatment for other patients. This has been documented in the USA where a performance measure that was designed to reduce delays in treatment for patients with pneumonia unintentionally increased unnecessary antibiotic treatment of patients who did not have pneumonia (Wachter 2008). Another example of unintended consequences was a pseudo-outbreak of hospital-acquired infection caused by doctors misdiagnosing patients in order to circumvent a restrictive antibiotic stewardship programme (Calfee 2003). However, this problem is not peculiar to antibiotic stewardship. The need to consider unintended consequences of changing care processes is a feature of any improvement project (Lloyd 2004; Randolph 2009). This problem can be addressed through balancing measures, which assess these potential unintended consequences and assure teams that they have indeed improved the overall system of care, rather than optimizing one part of the system at the expense of another (Randolph 2009). We are concerned that this issue is not addressed by the current Cochrane EPOC methods and that a recent review about audit and feedback does not mention adverse effects, balancing measures or unintended consequences (Ivers 2012).

Indirect evidence may already exist to support the construct of unnecessary antibiotic treatment. For example guidelines based on a systematic review of the literature have found no evidence to support giving antibiotic prophylaxis for surgery for more than 24 hours after the procedure (SIGN 2008). Consequently it may not be necessary to measure wound infection as an outcome of an intervention to increase the proportion of patients who receive prophylaxis for less than 24 hours (Landgren 1988). It is reassuring to have direct evidence to show that an intervention that successfully reduced duration of surgical prophylaxis was not associated with increased wound infection rates (Van Kasteren 2005). However, increasing the proportion of patients who discontinue antibiotic prophylaxis within 24 hours of surgery is one of a set of performance measures that addresses all four key criteria for accountability measures relating to processes of care (Chassin 2010). Hence we believe that it would not be necessary to measure wound infection rates in future interventions to improve this performance measure.

None of the 11 studies that aimed to increase effective antibi-

otic prescribing included information about unintended consequences. In contrast this update to the review does provide some important new evidence about two aspects of interventions to reduce excessive prescribing. First the evidence about lack of unintended consequences is stronger with fifteen studies and three meta-analyses (Analysis 2.1; Analysis 2.2; Analysis 2.3). In particular there are now nine studies with data about mortality. Secondly, there are now three studies about reducing the percentage of patients who receive antibiotics, and eight studies about reducing the duration of antibiotic exposure without compromising clinical outcome. Nonetheless, more balancing measures of unintended consequences are required, especially the increase in resistance to antibiotics that are promoted in a policy change (Landman 1999; Meyer 1993).

In comparison with the 2005 review, this update comes closer to the aim of antibiotic stewardship because it provides more information about the safety of interventions to reduce excessive antibiotic prescribing and about the benefits of increasing effective prescribing,

CBA, CCT, RCT or ITS?

CCT or RCT designs were used in one or two hospitals in 22 studies. These designs provide very little protection against bias or confounding (Wagner 2002). Contamination from intervention to control arms is an important threat to the validity of RCTs conducted in a single hospital because of the rotation of junior staff. However because the majority of CCT or RCT studies in our review did not include baseline data, it is not possible to assess the degree of potential contamination. Even with baseline data, contamination is only one explanation for the observed improvement in the control groups. For example, Zanetti 2003 was conducted in a single hospital and showed marked improvement in both control and intervention groups. The authors suggested that contamination occurred and that it biased the results towards the null. However, a cluster-RCT performed in 25 hospitals (Wyatt 1998) also showed marked improvement in control and intervention arms, which is highly unlikely to have been due to contamination because of the study design. It is much more likely that the improvements in the control hospitals were due to increased awareness of the benefits of antibiotic prophylaxis in patients undergoing caesarean sections that was entirely independent of the intervention. An external secular trend can affect any study design but one of the key advantages of a cluster-randomized controlled trial is that it protects against contamination so that changes in the control group can be more reliably attributed to external secular trends. The only RCTs in fewer then three hospitals that had medium risk of bias were able to overcome the problems of allocation and contamination bias because the intervention was a laboratory test result that was only available for patients in the intervention arm (Christ-Crain 2004; Christ-Crain 2006) or by collecting baseline outcome data for two months before intervention to estimate the magnitude of possible observation bias (Senn 2004, Figure 3 in the original paper).

ITS represents a practical design for evaluating interventions in single hospitals that may provide better protection against bias and confounding than RCT and CBA designs (Wagner 2002). ITS studies have two features that are not present in CBA, RCT and CCT designs. Firstly, they provide information about pre-intervention trends and, secondly, they assess the extent to which the effect of an intervention is sustained. However, the information provided by studies would be enhanced enormously by using the same interval between points and by providing a minimum standard duration of pre- and postintervention phases. In this update, the meta-regression has been enhanced by calculation of effect sizes at 1, 6, 12 and 24 months. This allowed comparison of the immediate and sustained effects of restrictive versus persuasive interventions. However, this comparison would have been much stronger if more studies had provided data that allowed calculation of effect size at three or more time points. In future meta-analysis of time series data would be facilitated if all studies reported change in level with its standard error at 1, 6 and 12 months postintervention.

AUTHORS' CONCLUSIONS

Implications for practice

A wide variety of interventions has been shown to be successful in changing antibiotic prescribing to hospital inpatients.Our meta-analysis provides evidence that restrictive interventions work faster than persuasive interventions, which supports the use of restrictive interventions when the need is urgent. However, we also found evidence that the effectiveness of some restrictive interventions diminishes over time so when restriction is justified it may be helpful to win hearts and minds through additional persuasive components. However, like other EPOC reviews we found that complex, multifaceted interventions were not necessarily more effective than simpler interventions. Review and recommend change was the most labour-intensive persuasive intervention but the effectiveness was not necessarily greater than for other, less intensive persuasive interventions. One of the most successful persuasive interventions (Weinberg 2001) involved the providers in the design of the intervention and in the measurement of intervention effect, which in many settings is likely to be more sustainable than review of individual patients by a professional from outside the provider team (Nelson 1998).

Implications for research

Greater external validity can be achieved by evaluating interventions in multiple hospitals, especially interventions that aim to reduce excessive antimicrobial treatment. Interrupted Time Series

analysis is a valuable and practical method for evaluation of interventions in single hospitals. Standardizing methods for time series in single hospitals (for example, using monthly intervals, aiming for a minimum of one year of postintervention data and reporting intervention effects with standard error (SE) at 1, 6 and 12 months) would enhance the ability to compare results from single hospitals. Our new meta-regression method greatly enhanced comparison between studies and supports the use of restrictive interventions when the need is urgent. However, further meta-analysis will be enhanced by more standardized data.

We need more evidence about the effectiveness of interventions in a format that facilitates combining the results from several studies in order to provide robust estimates of effect size and assess the impact of effect modifiers. Combining results is likely to be particularly important in relation to clinical outcomes, studies from single hospitals usually being underpowered.

We found limited evidence from direct comparisons of the efficacies of different interventions, including simple versus multifaceted interventions. The ideal would be comparison by a cluster-randomized trial design, but such a design is expensive and must be directed towards high priority research questions. Multiphase time series data represents a more practical design format for generating reasonably robust data about the incremental impact of the components of multifaceted interventions (Wagner 2002), but this design was only used in one study (Mol 2005). In addition one RCT compared two levels of intervention with control (Bouza 2004).

The paucity of evidence about the cost effectiveness of guideline implementation in general is inexcusable and future studies should provide information about the resources required for development, dissemination and implementation of guidelines and other interventions (Grimshaw 2004).

It is strange that we have several examples of studies with clinical or microbiological outcomes that do not provide rigorous information about prescribing outcomes. There is some justification in a large multicentre study where mortality is the primary outcome measure (Dean 2001; Dean 2006), because measurement of prescribing outcomes would have added considerably to the cost of the study. However, in the majority of cases the problem was simply that the prescribing outcome data were described in terms of averages rather than as time series analyses, and correcting this would probably not have added significantly to the cost of the study.

Several of the studies that reported microbiological outcome data were unplanned interventions (Results Table 10; Table 11; Table 12). This is a serious risk of bias for any time series but is a particular problem with studies of infection because of the shape of the epidemic curve (Cooper 2003; Davey 2001).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abramowitz 1982

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: Medium**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians, number, age, gender, specialty and time since qualification NOT CLEAR PATIENTS: All adults in the hospital. Number, age, gender and ethnicity not clear A total of 269,168 patient days of AB use assessed CLINICAL PROBLEM: Receiving treatment with target antibiotics SETTING: Single University hospital in the USA
Interventions	FORMAT & DELIVERER: PERSUASIVE: Printed educational materials, audit and feedback, review and recommend change. Programme to promote carbenicillin instead of ticarcillin and cefazolin instead of cephalothin, cefamandole and cefoxitin. A letter detailing excessive cost of targeted drugs was circulated to the medical staff. Pharmacists reviewed each prescription for target drugs and recommended alternatives when necessary. During the first two months of the intervention follow-up discussions with data for the medical and surgical teams were conducted at weekly service rounds (audit and feedback) COMPARISON: Nine months pre-intervention DESIRED CHANGE: Reduction of established management. Change in regimen: reduction in use and cost of six target antibiotics TIMING: Single concurrent intervention per patient. Outcomes measured for six months, intervention maintained after the study
Outcomes	PRIMARY: Total cost of six target antibiotics (calculated from data in Tables 1 and 2) SECONDARY: Separate data are presented for four cephalosporins, ticarcillin and carbenicillin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Unclear risk	Not stated
Analysed appropriately (ITS) ?	Low risk	Reanalyzed. Not done in original paper (comparison of means, uncontrolled before-after)

Abramowitz 1982 (*Continued*)

Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine pharmacy systems database
Free of other bias (ITS) ?	Low risk	Price of target antibiotics constant over the study period

Adachi 1997

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age, specialty and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR 38 charts reviewed CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: Single hospital in the USA, University status NOT CLEAR
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change) with printed educational materials and reminder. Development of local guideline for appropriate vancomycin use by local ID specialist (based on CDC guideline) disseminated as memorandum and newsletter. Adapted into a vancomycin order sheet (reminder) that was used to monitor compliance with the guideline. Pharmacists also reviewed orders for vancomycin use against guideline and contacted physicians to reinforce appropriate use. COMPARISON: Five quarters (15 months) data before implementation of order sheet. DESIRED CHANGE: Reduction of established management (reduction in vancomycin use). TIMING: Outcomes measured for seven quarters (21 months) after implementation. Order sheet remained in place after the end of the study

Adachi 1997 (*Continued*)

Outcomes	PRIMARY: quarterly vancomycin purchases (ITS data). SECONDARY: cases of infection with VRE, BUT inadequate ITS data (two points pre- and seven points after start of vancomycin restriction)
Notes	EVIDENCE BASE: local guideline was based on guidance issued by Communicable Diseases Centre in 1994. OTHER: Cost of intervention NOT DONE.

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Low risk	> 1 year data pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Re-analysed. Not done in original paper (comparison of means, uncontrolled before and after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervenitonDone, intended effect was decrease in primary outcome
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Unclear risk	NOT CLEAR, no information about changes in price of vancomycin over the study period

Ansari 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: All wards in a single hospital PROVIDERS: All doctors in the hospital

Ansari 2003 (*Continued*)

	PATIENTS: All patients in the hospital CLINICAL PROBLEM: Antibiotics dispensed to hospital wards for administration for therapy or prophylaxis SETTING: a single University hospital in the UK. Total use was compared for two years before and after the intervention
Interventions	FORMAT & DELIVERER: PERSUASIVE: Antibiotic policy for Alert Antibiotics. Distribution by printed and web based materials with audit and feedback. DELIVERER: The policy was written by a multidisciplinary Antimicrobial Management Team. It was implemented by clinical pharmacists with immediate concurrent feedback to prescribers while their patient was still being treated COMPARISON: Two years before the introduction of the policy DESIRED CHANGE: Reduction of established management. Change in regimen: reduction in the inappropriate use of Alert antibiotics. Pre-intervention surveys of 794 patients identified 17% inappropriate use TIMING: After clinical decision making
Outcomes	PRIMARY: Total use of Alert antibiotics SECONDARY: Cost of antibiotics used adjusted for changes in price over the four year
Notes	EVIDENCE BASE: Criteria for appropriateness of target drugs documented in antibiotic policy, available on line OTHER: The cost of the first year of the intervention, which included setting up the programmes for extraction, formatting and analysis was GBP 15,143 and the cost of running the intervention in the second year was GBP 4990 (full details of intervention costs are in Table 3 of the paper). The total cost of the intervention (GBP 20,133) over the two years was therefore well below the most conservative estimate of the reduction in cost of Alert Antibiotics, which was GBP 133,296 (the lower boundary of the 95% CI for change in slope after the intervention, GBP 5554 per month times 24 months). However, assuming that the cost of Alert Antibiotics would have continued to increase without the intervention, the cost of Alert Antibiotics was estimated to have decreased by an average of GBP 23,852 per month (95% CI GBP 18,154 to GBP 29,549, P < 0. 0001)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	"In 2000, the Antibiotic Subcommittee of Tayside University Hospitals Trust devised an Alert Antibiotic Policy to reduce inappropriate use of key antibiotics, targeted because they should be reserved for infections caused by organisms that are resistant to first line antimicrobials." There were no other changes in local or national policy likely to influence use of Alert Antibiotics

Ansari 2003 (*Continued*)

Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis with adjustment for autocorrelation and seasonality
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	"The aim of this study was to use routine data from the pharmacy stock control computer to evaluate this intervention". Sources and methods of data collection were the same before and after the intervention
Knowledge of the allocation adequately prevented(ITS)?	Low risk	"After evaluation of the intervention according to patient records and its shortcomings, we decided to use the pharmacy stock data. During the 4 year period of analysis no restriction policy for dispensing the Alert Antibiotics was implemented by the hospital pharmacy, therefore the pharmacy data about dispensed Alert Antibiotics would provide us with the best available independent indicator for evaluation of the intervention."
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	"Correcting for autocorrelation avoids underestimating standard errors and overestimated significance of the effects of an intervention. For estimating seasonal autocorrelation, the autoregression model needs to evaluate correlations between error terms separated by multiples of 12 months. Accounting for seasonally correlated errors usually requires at least 24 monthly data points." Data about cost of antibiotics adjusted for price changes during study period

Avorn 1988

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at one teaching hospital. Clinical departments included NOT CLEAR. Number, level of training, age and time since graduation of providers NOT CLEAR PARTICIPANTS: Number, age, gender and ethnicity of patients NOT CLEAR CLINICAL PROBLEM: Patients receiving therapy with cefazolin, clindamycin or metronidazole SETTING: A 460-bed (page 1723, para 3) teaching hospital in the USA
Interventions	FORMAT & DELIVERER: PERSUASIVE: Parenteral antibiotic order form supported by educational sessions with house officers, nurses, unit secretaries and others throughout the hospital and by reminders (written "unadvertisements" mailed to all physicians and posters displayed on wards). The format was modified after pilot testing. Deliverer: the form was developed by a consensus process with a multidisciplinary team. The form was not restrictive COMPARISON: Twenty months pre-study DESIRED CHANGE: Reduction in establish management (reduction in inappropriately frequent dosing of cefazolin, clindamycin or metronidazole) TIMING: The order form was immediate and patient-specific. Data were collected for 25 months after the start of the study
Outcomes	PRIMARY: percentage of patients with kinetically incorrect dosing of cefazolin, clindamycin and metronidazole. SECONDARY: Estimated annual expenditure on the three drugs
Notes	EVIDENCE BASE: The study was designed after a review designed to identify suboptimal antibiotic prescribing at the hospital. Therapeutic recommendations were based on a literature review, which identified pharmacokinetic and observational clinical studies that supported less frequent dosing of the target antibiotics. OTHER: The costs of the programme were not measured, other than the cost of printing the form (USD 0.10 per multiple copy, perforated form)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	No price changes in the target antibiotics during the study period
Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Avorn 1988 (*Continued*)

Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Bailey 1997

Methods	STUDY DESIGN: RCT stratified by type of infection. Participants identified manually in Hospital A and automated in Hospital B QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at two teaching hospitals, excluding ICUs. Number, level of training, age and time since graduation NOT CLEAR PATIENTS: A Total of 102 inpatients. Age: 95% CI 51 to 81. Gender: 43% M (study group) and 61% M (Control group). Ethnicity NOT CLEAR CLINICAL PROBLEM: Patients receiving IV ABs for at least three days but excluded if in ICU or with uncontrolled infection or close to discharge SETTING: Two tertiary care USA teaching hospitals
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change). Physicians were contacted by a pharmacist with suggestions to change therapy targeted at each individual patient DESIRED CHANGE: Reduction of established management. Regimen, discontinuation of IV ABs (either stopped or switched to oral) TIMING: Single intervention per patient; follow-up until discharge. Intervention was in place for six months
Outcomes	PRIMARY: Mean IV antibiotic days SECONDARY: Cost, 30-day readmission (total and infection-related) and in hospital mortality
Notes	EVIDENCE BASE: Not clear OTHER: Labour costs (pharmacists' time) were estimated to be USD 15,000 per year at Hospital

Bailey 1997 (*Continued*)

	A and USD 7,000 per year at Hospital B at 1997 prices Extrapolating the average postrandomization costs to 200 patients per year at Hospital A, the estimated annual saving was USD 1600 per year (95% CI USD 3100 to USD 6300) Extrapolating the average postrandomization costs to 100 patients per year at Hospital B, the estimated annual saving was USD 4200 per year (95% CI USD 700 to USD 9000) 30-day readmission rates were significantly increased in the intervention patients at Hospital A, cause unknown but intervention stopped at end of trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Physicians of patients considered candidates for intervention were randomised to be either contacted by the clinical pharmacist ...or to be observed"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems found
Selective reporting (reporting bias)	Low risk	No problems found
Other bias	Low risk	Prices of antibiotics unlikely to change over the six-month study period
Baseline Outcomes similar?	Unclear risk	Not stated
Free of contamination?	Unclear risk	Not stated
Baseline characteristics similar?	Low risk	See Table 1 in study

Barlow 2007

Methods	STUDY DESIGN: Controlled ITS QUALITY: **Risk of bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Two hospitals PATIENTS: All patients presenting with pneumonia were recruited prospectively CLINICAL PROBLEM: Adults with community-acquired pneumonia

	SETTING: Two acute University hospitals within one Health Board in Scotland. Patients were enrolled from 1 November to 30 April in two consecutive years
Interventions	FORMAT & DELIVERER: PERSUASIVE: A care pathway for community-acquired pneumonia DELIVERER: The pathway was developed by a multidisciplinary group that included representatives from the intervention units. The pathway was delivered through information packs, educational sessions, reminders (wall posters) and regular feedback of results MARKETING: A structured survey of 83 members of the junior medical staff was conducted at the intervention site to identify barriers to implementation of the intervention. In addition, eight respondents to the survey were interviewed. The outcome of the survey and interviews was used to design the intervention and implementation strategy COMPARISON: Control hospital with no intervention DESIRED CHANGE: Increase established management. Regimen and timing (time to first antibiotic dose): increase in the percentage of patients who receive appropriate antibiotics within 4 h of admission TIMING: Before clinical decision-making
Outcomes	PRIMARY: appropriate antibiotics within 4 h of admission, adjusted for age, gender, comorbidity and severity SECONDARY: appropriate antibiotics; any antibiotic within 4 h of admission; cost effectiveness. Impact on mortality was estimated from the impact on the primary outcome measure but the study did not have enough power to assess impact on mortality directly
Notes	EVIDENCE BASE: DONE at least one supportive RCT referenced. The pathway was based on national guidelines with recommendations linked to evidence OTHER: Included economic evaluation with full costing of design, implementation and evaluation of the intervention. The reported intervention was conducted by a full time research fellow and included qualitative and quantitative staff surveys. The authors estimated the cost to another hospital of performing a more limited evaluation of the same intervention to be GBP 17,810

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	
Analysed appropriately (ITS) ?	Low risk	
Shape of effect pre-specified (ITS) ?	Low risk	
Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	High risk	

Barlow 2007 (*Continued*)

Incomplete outcome data addressed (ITS) ?	Low risk	
Free of selected reporting (ITS) ?	Low risk	
Free of other bias (ITS) ?	High risk	

Belliveau 1996

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at one teaching hospital, including five ICUs, one burn unit, three intermediate care areas and one bone marrow transplant unit. Number, level of training, age and time since graduation NOT CLEAR PATIENTS: Number, age, gender and ethnicity of patients over the 26 months of observation NOT CLEAR 386 courses of vancomycin evaluated CLINICAL PROBLEM: Patients receiving vancomycin therapy SETTING: A 388-bed teaching hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: use of vancomycin was restricted through a compulsory order form. If specific criteria were not met pharmacists suggested an alternative. If this was not accepted the case was referred to an ID pharmacist or ID physician. Duration also restricted with a stop order (three days empirical, seven days therapeutic and two doses for surgical prophylaxis) Persuasive: written guideline with educational meetings, reminders and academic detailing. Guideline from infectious diseases division approved by the antibiotic subcommittee. Disseminated through medical newsletter, memorandum from the chair of the hospital executive committee, signs posted on all nursing units and an announcement during the residents' morning report. "*In areas where pharmacists participate in physician rounds (general medicine, surgery) in service instruction was provided.*" COMPARISON: Data for 12 months pre-study DESIRED CHANGE: Reduction of established management. Regimen: reduction in inappropriate and total vancomycin use TIMING: Number of interventions per patient NOT CLEAR. Monthly data collected for 14 months after start of study
Outcomes	PRIMARY: Vancomycin doses per 100 patient days SECONDARY: None

Belliveau 1996 (*Continued*)

Notes	EVIDENCE BASE: Guidelines for vancomycin use were developed by the ID division based on US Communicable Diseases Centre guidance and approved after modification by the antibiotic subcommittee, the pharmacy and therapeutics committee, the hospital executive committee and the medical executive committee OTHER: cost of study NOT DONE

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Low risk	> 12 months pre-and postrestriction data
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper (comparison of means with t-test, uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention. Outcome data were collected from all patients
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Berild 2002

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians (paediatricians) in one hospital; number, level of training, age and time since graduation NOT CLEAR PATIENTS: Number, age, gender and ethnicity NOT CLEAR 304 children surveyed. CLINICAL PROBLEM: Children with infections requiring antibiotic therapy

Berild 2002 (*Continued*)

	SETTING: A 46-bed paediatric unit in a university hospital in Norway
Interventions	FORMAT & DELIVERER:PERSUASIVE (audit and feedback, guideline and educational meetings): Local guidelines for antibiotic usage (delivered by local expert), supplemented with lectures on rational prescribing to newly-employed doctors and meetings with ID physicians and microbiologists. Audit and feedback: "As a part of the surveys of hospital infections, all patients in the department were surveyed using eight point-prevalence studies every third month from June 1996 to June 1998. For all patients receiving antibiotics, date of birth, gender, reason for admittance, results of microbiological samples, name of antibiotics and dosage, diagnoses and symptoms leading to antibiotic use were recorded on special forms. Results of prevalence investigations were given orally and in paper leaflets to the staff shortly after each investigation." COMPARISON: Three years pre-intervention DESIRED CHANGE: Reduction of established management. Reduction in total antibiotic use and in usage of five specific groups of antibiotics TIMING: Guidelines issued to all doctors at start of intervention period or on taking up employment. Lectures four times yearly for new medical staff, and weekly meetings with ID physicians and microbiologists. Data were collected for four years after implementing the intervention
Outcomes	PRIMARY: Total antibiotic usage and usage of five specific groups of antibiotics SECONDARY: Annual antibiotic expenditure
Notes	EVIDENCE BASE: The evidence base for the guidelines for antibiotic prescribing are not specified OTHER: The numbers of patients/episodes of care and prescribers are not specified. There are no data on patient outcomes (the reduction in antibiotic usage may have exerted an adverse effect on patient outcome). The authors did not do any statistical analysis. There is no information on the cost of implementing the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Done, three years pre-intervention and two years post-intervention data
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper (run charts, Figure 1, with no statistical analysis)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period

Berild 2002 (*Continued*)

Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	Changes in antibiotic price were documented with their contribution to reduction in cost over the study period (Table 1 in study)

Borer 2004

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: Number not stated (physicians) PROVIDERS: ID specialists or physicians from other specialty PATIENTS: A total of 402 adults CLINICAL PROBLEM: Community-acquired fever SETTING: Single hospital in Israel; intervention was continued for four month from January to April 1999
Interventions	FORMAT & DELIVERER: RESTRICTIVE: ID physician reviewed patients who were receiving intravenous antibiotics in one ward and made changes to their antibiotic treatment DELIVERER: ID physician reviewed patients in one ward (Ward1) whereas other specialists visited the control ward (Ward 2) COMPARISON: IV specialist vs other specialist DESIRED CHANGE: Increase established management, Increase in appropriate use of antibiotics and in accuracy of diagnosis TIMING: At the time of clinical decision-making
Outcomes	PRIMARY: Use of restricted antibiotics; appropriateness of antibiotic therapy SECONDARY: Admission and discharge diagnosis: percentage of patients with diagnosis of 'fever of unknown origin' at admission and at discharge
Notes	EVIDENCE BASE: previous studies have suggested that consultation by ID physicians improves antibiotic management OTHER: RCT but most outcomes subjective. Single assessor. Not clear how blinded
Risk of bias	

Borer 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomisation was achieved, in that patient allocation from the emergency room to one of the six internal medicine wards was performed by a secretary, without consideration of demographic or clinical parameters, with the wards taking turns in a cyclic fashion (i.e., every six consecutively admitted patients were allocated to wards 1-6 according to the order in which they arrived and were treated in the emergency department."
Allocation concealment (selection bias)	High risk	The wards knew which group they were in at any time
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	Unclear risk	Not stated
Baseline Outcomes similar?	Low risk	Tables 1 and 2
Free of contamination?	Unclear risk	Not stated, staff likely to manage intervention and control patients
Baseline characteristics similar?	Unclear risk	Not stated

Bouza 2004

Methods	STUDY DESIGN: RCT QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: Microbiology department in one hospital PROVIDERS: Microbiology staff Blood samples from 297 patients divided into three groups: A conventional report (109 samples) B. A plus written alert C. A plus oral alert CLINICAL PROBLEM: Bacteraemia/fungaemia (blood stream infection)

	SETTING: Single hospital in Spain, general, teaching, and referral hospital with 1750 available beds covering an urban population of 650,000 persons. The intervention continued for six months, from February to July 2000
Interventions	FORMAT & DELIVERER: PERSUASIVE Educational outreach (review and recommend change). Compared three levels of contact with prescribing physicians: "Group A (i.e., conventional information provided). Immediately after the automatic detection of microbial growth, the physicians in charge are informed by telephone of the result of the Gram stain, and a written report is produced only after definitive identification and antimicrobial susceptibilities of the isolates are obtained Group B (i.e., written-alert report on the clinical chart). In this group of patients, the procedure for group A is complemented with a written-alert report issued at the bedside to be included with the clinical chart. The report includes a brief opinion on patient's situation based on the clinical records, including therapeutic recommendations Group C (i.e., oral-alert report provided). This procedure includes all the information provided to groups A and B together, as well as a direct conversation with the physician in charge.Advice given in different formats." DELIVERER: Microbiologists (specialist physicians) in writing or verbally COMPARISON: Conventional report alone DESIRED CHANGE: Increase in established management. Increase in the proportion of days on which adequate antibiotic treatment was received. Adequacy was defined according to seven criteria: (indication, coverage, spectrum, dose, interval, route and duration) TIMING: After clinical decision-making
Outcomes	PRIMARY: Proportion of days on which adequate treatment received SECONDARY: Adequacy of antibiotic therapy during early and late phase. Antibiotic cost, length of stay, mortality
Notes	EVIDENCE BASE: Previous observational studies have shown that many patients with blood stream infection receive inadequate therapy, even after microbiological results are available OTHER: Cost of intervention NOT DONE The study reported a significant association between appropriate antibiotic treatment and mortality, and that the risk of death increased 1.2-fold for each day until definitive microbiological information was available. However, their intervention was not associated with improvement in mortality or length of stay. They attribute this to the recommendations usually arriving more than four days after blood samples are obtained for culture, pointing to a probable need for earlier interventions and advice based only on the preliminary information available. This information should be conveyed by an infectious diseases specialist or a clinical microbiologist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We randomly classified the patients... into 3 different group by means of a computer assisted random list"

Bouza 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible with this study design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	High risk	NOT DONE, adequate prescription was defined by seven criteria, some of which required clinical judgement. The reliability of the primary outcome measure was not assessed
Baseline Outcomes similar?	Unclear risk	Not stated
Free of contamination?	High risk	All doctors in the hospital were distributed across all three study groups
Baseline characteristics similar?	Unclear risk	Not stated

Bradley 1999

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: physicians on an adult haematology unit. Number, level of training, age and time since graduation of providers NOT CLEAR PATIENTS: A total of 293 patients recruited; 31 patients were already carriers of GRE (glycopeptide resistant enterococci) and were excluded. Therefore, 261 patients (55% male) with mean age of 45 were recruited into the cohort. Ethnicity NOT CLEAR CLINICAL PROBLEM: Adult patients receiving treatment for haematological malignancy SETTING: Adult haematology unit with 35 beds in a University hospital in the UK
Interventions	FORMAT & DELIVERER: RESTRICTIVE: change in antibiotic policy, replacing ceftazidime with piperacillin/ tazobactam for the initial treatment of febrile neutropenia Persuasive infection control interventions included guidelines for domestic staff, education for patients about GRE and likely methods of transmission and educational seminars for nursing, medical and domestic staff to ensure that the heightened infection control measures were maintained COMPARISON: Four months pre-intervention DESIRED CHANGE: Modification of established management. Change in empiric

	antibiotic regimen TIMING: Patients were recruited over 17 months and followed up until discharge from hospital. Pre-intervention period four months. Change in antibiotic policy was sustained for eight months, then the policy was changed back to ceftazidime for a further five months
Outcomes	PRIMARY: Probability of remaining free of colonization by GRE by weeks of exposure on the ward from date of first admission SECONDARY: Antiboitic usage
Notes	EVIDENCE BASE: Previous observational studies have suggested that cephalosporin use is a risk factor for colonization by GRE. Piperacillin tazobactam was chosen as a substitute because it is more active than cephalosporins against enterococci and therefore would not tend to select for bowel overgrowth with these organisms OTHER: Cost effectiveness of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only four months pre-intervention data so secular changes possible
Analysed appropriately (ITS) ?	Low risk	Done in original paper: Kaplan Meier plot and log rank test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, screening protocol was the same throughout the study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, screening protocol was the same throughout the study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, screening protocol was the same throughout the study period
Free of selected reporting (ITS) ?	Low risk	Done, screening protocol was the same throughout the study period
Free of other bias (ITS) ?	Low risk	**Microbiology risk of bias criteria:** Case definition: DONE, colonization by screening; Planned intervention: DONE; Other infection control, isolation and IC practices: DONE, same throughout study

Bruins 2005

Methods	STUDY DESIGN: RCT QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians (numbers and characteristics not clear) PATIENTS: A total of 1883 patients randomized (1870 evaluated) CLINICAL PROBLEM: Inappropriate antibiotic therapy SETTING: Inpatients in one 1100 bed University hospital in the Netherlands. Data were collected over nine months from September 2000 to June 2001
Interventions	FORMAT & DELIVERER: STRUCTURAL, rapid laboratory testing. Information delivered by interpersonal (oral reporting of laboratory results) and paper (written reports of results) Three study periods (SP) SP1: rapid testing but no change in reporting SP2: rapid testing plus increased same day oral reporting SP3: rapid testing plus increased same day oral reporting plus extended working day, subcultures processed same day, extra mail delivery DELIVERER: Local expert body (microbiologists) COMPARISON: Clinically relevant isolates of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus* spp. were identified and their antibiotic susceptibilities were determined by conventional methods (control group) or by rapid testing (the Vitek 2 system) which reduced laboratory turnaround times (intervention group). In the intervention group the workflow was accelerated during three successive study periods in order to minimize turnaround times further DESIRED CHANGE: Increase of established management, reduce turnaround time for laboratory sampling and hence increase percentage of patients with appropriate antibiotic prescribing and improve patient outcomes TIMING: Either before clinical decision-making (initiation of antibiotic therapy) or after clinical decision-making (modification of empirical antibiotic therapy). The intervention was in place for nine months
Outcomes	PRIMARY: Turnaround times for microbiology tests and results SECONDARY: Clinical impact (total hospital mortality rate,length of hospital stay, length of ICU stay, percentage of patients with appropriate antibiotic treatment)
Notes	EVIDENCE BASE: DONE (two supportive RCTs referenced) OTHER: Intervention cost NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quasi-randomized. "Patients were randomised on the basis of the sum of the day and month of their date of birth....even numbers assigned to the control group.. odd number to the intervention group"

Bruins 2005 (*Continued*)

Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Free of contamination?	Low risk	
Baseline characteristics similar?	Low risk	

Bunz 1990

Methods	STUDY DESIGN: ITS (Figure 1), UBA (Fig 2 and Tables 1 - 2) and inadequate ITS (Figure 3) QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at one teaching hospital. Clinical departments included NOT CLEAR. Number, level of training, age and time since graduation of providers NOT CLEAR PATIENTS: Number, age, gender and ethnicity of patients contributing to ITS data NOT CLEAR A total of 989 prescriptions reviewed CLINICAL PROBLEM: Receiving metronidazole SETTING: Single University hospital in Canada
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Restriction by therapeutic substitution of metronidazole dosed 12-hourly for metronidazole doses more frequently Persuasion: Written materials, and reminder. The start of restriction was preceded by information period (two weeks) during which the rationale for the programme was explained in a newsletter sent via internal mail to all physicians, medical residents, medical student interns, nursing units and pharmacists. A detailed memo was also sent to all head nurses to explain the nursing-related implications COMPARISON: Five months pre-intervention DESIRED CHANGE: Increase in established management (dosing of metronidazole 12 hourly) TIMING: Single intervention per patient at the time of prescription. Data on metronidazole use collected for seven months from start of intervention. Intervention continued after the end of the study

Bunz 1990 (*Continued*)

Outcomes	PRIMARY: percentage of doses of metronidazole prescribed 12-hourly SECONDARY: UBA analysis of demography of a sample of 110 patients and of infection rates and mortality in the 12 months before-after intervention
Notes	EVIDENCE BASE: The case for 12-hourly dosing of metronidazole is described in detail, based on pharmacokinetics (disposition and elimination) and the minimum inhibitory concentrations for target bacteria OTHER: Costs of the intervention NOT CLEAR Financial savings UNRELIABLE. Estimated CAD 12,000 savings in metronidazole drug costs in five months after the start of the intervention but based on inadequate time series (one pre- and five postintervention points)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Done, although the pre- and postintervention phases were only a six month period one year prior to the intervention was chosen to control for any seasonal variation in prescribing patterns
Analysed appropriately (ITS) ?	Low risk	Re-analyzed Not done in original paper: run charts with no statistical analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, the analysis included all prescriptions for metronidazole
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Burton 1991

Methods	STUDY DESIGN: RCT **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: A total of 17 house staff teams in Internal Medicine or Surgery at one teaching hospital. Number, level of training, age and time since graduation NOT CLEAR PATIENTS: A total of 147 inpatients. Mean age 58 (Study group), 60 (Control group) . 99% were male. Ethnicity, 55 white, 16 black, 1 Hispanic in intervention group; 56 white, 19 black, 0 Hispanic in control group CLINICAL PROBLEM: Patients receiving IV amino glycosides SETTING: A 680-bed tertiary care affiliated hospital in the USA
Interventions	FORMAT & DELIVERER:PERSUASIVE, review and recommend change. Patients in the Sintervention group received initial doses and dose adjustment recommendations from physicians in Clinical Pharmacology according to serum aminoglycoside concentrations based on a Bayesian pharmacokinetic dosing programme. Patients in the control group had initial dosing and dose adjustment according to physician intuition and interpretation of serum aminoglycoside concentrations DESIRED CHANGE: Initiation of new management (i.e. the introduction of Therapeutic Drug Monitoring), Change in regimen in order to Improve outcome of aminoglycoside therapy TIMING: Immediate, concurrent study. Length of time during which outcomes were measured and length of post-study follow-up period NOT CLEAR
Outcomes	PRIMARY: Length of stay (LOS) is the dependent variable in the statistical analysis but four outcomes are reported without power calculation SECONDARY: Aminoglycoside levels; response to treatment; nephrotoxicity
Notes	EVIDENCE BASE: Two previous studies by the authors showed that their Bayesian dosing programme was more likely to achieve optimum serum aminoglycoside levels than standard dosing. Although 14 previous studies suggested that this was likely to improve outcome these were retrospective or uncontrolled OTHER: Cost data are only provided in the discussion, with inadequate description of resource components or unit prices. The estimated cost of the study was USD 297 per patient but the authors suggested that this was only ¼ of the savings likely to be achieved through reduced LOS No evaluable data for our analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random numbers table used to assign 9 of 17 house staff teams to the intervention group. Patients allocated to intervention or control groups based on house staff team to which they were admitted. The other 8 teams were assigned as control groups"

Burton 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not stated but unlikely: nine house staff teams were in the intervention group, eight control, groups swapped over after four months
Blinding (performance bias and detection bias) All outcomes	High risk	"Blinding as to patient status was not performed.."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems found
Selective reporting (reporting bias)	Low risk	No problems found
Other bias	High risk	Unit of analysis error for length of stay (LOS). This was a cluster-RCT but LOS was analysed at patient level
Baseline Outcomes similar?	Unclear risk	not measured before interventions
Free of contamination?	High risk	NOT DONE, nine house staff teams were in the intervention group, eight control, groups swapped over after four months
Baseline characteristics similar?	Low risk	See Table 2 in paper

Calil 2001

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Staff in a neonatal unit. Age, gender, level of training and time since qualification NOT CLEAR PATIENTS: A total of 342 patients on a 30-bed neonatal unit (8 intensive care and 22 intermediate care beds). Age: 43% neonates were premature. gender NOT CLEAR CLINICAL PROBLEM: Requiring neonatal care SETTING: One neonatal care unit in a University Hospital in Brazil
Interventions	FORMAT & DELIVERER: Restrictive: Introduction of a new antibiotic policy, eliminating use of third generation cephalosporins. Intervention also included training of the entire healthcare team (nurses, physiotherapists and physicians) to avoid cross-colonization, emphasizing hand hygiene and Contact Precautions. Before the intervention infection control education was only delivered to nurses on admission to the service COMPARISON: Three months pre-intervention data DESIRED CHANGE: Initiation of new management (new antibiotic policy)

	TIMING: Detailed observations were made for three months after the implementation of the policy. Limited data are presented for four years after the end of the study
Outcomes	PRIMARY: Monthly incidence of *E cloacae* infections SECONDARY: None, no reliable data about antibiotic use
Notes	EVIDENCE BASE: Three previous studies relating previous use of third generation cephalosporins to an increase in the rates of colonization and infection by multiresistant *Enterobacter spp.* OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	More than one year of data before and after intervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with logistic regression analysis of relationship between antibiotic prescribing and resistance
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about changes in sampling or testing protocol over study period
Free of other bias (ITS) ?	High risk	NOT DONE **Microbial Risk of Bias Criteria:**.Case definition**:** Infection, monthly infections with *Enterobacter cloacae*; Unplanned intervention ; Other infection control measures: barrier precautions, isolation of patients and personal IC procedures fully described and same in both phases

Carling 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: All patients at the hospital PROVIDERS: Number, age, gender, ethnicity, time since qualification NOT CLEAR PARTICIPANTS: Number, age, gender, ethnicity NOT CLEAR CLINICAL PROBLEM: NOT CLEAR SETTING: Single medium-sized community teaching hospital (affiliated to a University) in the USA. No obstetric unit or paediatric ICU
Interventions	FORMAT: PERSUASIVE: educational outreach (review and recommend change) with printed educational materials. Multifaceted, local consensus-based policy with individual case review by Antimicrobial Management Team (ID physician and ID pharmacist). Three elements: choice of antibiotic, duration (discontinue after two to three days if no confirmed infection) and switch from IV to oral. DELIVERER: Policy implemented by an antimicrobial management team led by an ID physician working with a clinical pharmacist with training in ID. Review of all patients receiving aztreonam or third generation cephalosporins. COMPARISON: three years pre-intervention DESIRED CHANGE: Reduction in established management (reduction in use of target drugs) TIMING: Immediate, concurrent, patient-specific feedback.
Outcomes	PRIMARY: Prevalence of *Clostridium difficile*, ceftazidime-resistant Enterobacteriaceae, MRSA and VRE. However, data for VRE are not reliable (see Risk of Bias Table) SECONDARY: Use and cost of target antibiotics (third-generation cephalosporins, aztreonam, parenteral fluoroquinolones, or imipenem) but inadequate ITS for prescribing data
Notes	EVIDENCE BASE: Four previous studies about the effectiveness of antibiotic management teams. OTHER: Costs of intervention: one full time pharmacist and 0.25 FTE of an ID Physician

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Three years pre-intervention data
Analysed appropriately (ITS) ?	Low risk	Done in original paper: regression analysis with adjustment for autocorrelation. Analysis repeated by review team because of incomplete reporting of results
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Carling 2003 (*Continued*)

Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about changes in sampling or testing protocol over study period
Free of other bias (ITS) ?	Low risk	VRE isolation unlikely to have influenced *C difficile* or resistant gram-negative bacteria. **Microbial Risk of Bias Criteria:** Planned intervention: DONE Implementation of antimicrobial management team in response to increase in use of target drugs. Case definition**:** DONE for *C.difficile* infection (diarrhoea and toxin positive) or infection with clinical isolates of gram-negative bacteria resistant to ceftazidime, or MRSA (CDC definition of nosocomial infection). Other infection control measures: DONE For *C. difficile* contact precautions and procedures for cleansing equipment and patient care areas remained unchanged . Other infection control processes are not described in detail but may have changed during the study period (e.g. VRE isolation introduced after intervention) **Data about VRE infections NOT RELIABLE:** there were no cases in the pre-intervention phase and none in the first three years postintervention but there was an outbreak in the fourth and fifth postintervention years caused by admission of patients from other hospitals who were colonized with VRE

Charbonneau 2006

Methods	STUDY DESIGN: Controlled ITS QUALITY: **Risk of Bias: MEDIUM**

Charbonneau 2006 (*Continued*)

Participants	NUMBER & CHARACTERISTICS: Four hospitals, one intervention and three control PROVIDERS: Physicians PATIENTS: Unit of analysis is isolates CLINICAL PROBLEM: Infection with MRSA SETTING: Intervention in one large teaching hospital in NW France. Additional data about three control hospitals. Intervention continued for one year, January to December 2001 with two years data before and after the intervention period
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Expert approval. Therapeutic substitution of fluoroquinolones by other drugs specified by a protocol validated by local ID experts. If no effective alternative was available an ID consultant had to approve a fluoroquinolone prescription Persuasive: Dissemination of printed materials. Protocol was distributed to all antibiotic prescribers, including residents and senior physicians DELIVERER: ID physician endorsed protocol and authorised fluoroquinolones if required COMPARISON: Three other hospitals using national guidelines DESIRED CHANGE: Reduction in established management (reduction in use of quinolones in order to reduce MRSA) TIMING: Before clinical decision-making
Outcomes	PRIMARY: Reduction of MRSA infections SECONDARY: Reduction of fluoroquinolones
Notes	EVIDENCE BASE: Previous published reports of correlation between MRSA and fluoroquinolones use OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	One year post- and two years pre-intervention data so secular changes unlikely. Infection control protocols were unchanged pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Done in original paper: The study is analyzed as a CBA adjusting for confounders and slope and level. The ITS analyses are correct but the results are not well reported
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period

Charbonneau 2006 (*Continued*)

Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about changes in sampling or testing protocol over study period
Free of other bias (ITS) ?	Low risk	**Microbial Risk of Bias Criteria:** Planned intervention: DONE Case definition: DONE clear case definition of clinical infection: "A new case was defined as a case in a patient with no previous history of MRSA or ESBL-EB colonization or infection who was infected with MRSA or ESBL-EB no less than 48 h after hospital admission." Other infection control measures: DONE "The measures recommended by French national guidelines for the prevention of nosocomial infections were implemented in the 4 study hospitals several years before the study began"

Christ-Crain 2004

Methods	STUDY DESIGN: cluster-RCT QUALITY: **Risk of bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Single hospital PATIENTS: A total of 597 patients randomized, 243 were eligible and included CLINICAL PROBLEM: suspected lower respiratory tract infection (LRTI) SETTING: A single University Hospital in Switzerland. Four months: 16 December 2002 to 13 April 2003
Interventions	FORMAT & DELIVERER: STRUCTURAL AND PERSUASIVE Structural: introduction of testing for procalcitonin, a marker of inflammatory response that may distinguish between bacterial infections and viral infections or nonspecific inflammatory diseases Persuasive: written antibiotic policy based on procalcitonin level with reminder of recommended action on reporting of prosectioning test result DELIVERER: antibiotic policy written by the Department of Internal Medicine and Division of Pneumonology COMPARISON: weeks with no procalcitonin measures DESIRED CHANGE: Introduction of new management (procalcitonin test)

Christ-Crain 2004 (*Continued*)

	TIMING: At time of clinical decision-making
Outcomes	PRIMARY: Relative risk of antibiotic exposure measured in percentage and patient-days SECONDARY: Length of stay (LOS), clinical and laboratory outcome
Notes	EVIDENCE BASE: DONE Observational studies suggested that procalcitonin was a sensitive and specific marker for infection OTHER: cost of intervention NOT DONE. No information about the cost of the test or of implementation of the policy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We randomly assigned eligible patients... ...according to a computer generated week wise randomisation scheme"
Allocation concealment (selection bias)	Unclear risk	"We randomly assigned eligible patients either standard antimicrobial therapy (standard group) or procalcitonin-guided antimicrobial treatment (pro calcitonin group) according to a computer-generated week wise randomisation scheme". No information about concealment of allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"Single blinded intervention trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Antibiotic data from all treated patients
Selective reporting (reporting bias)	Low risk	Objecive outcome measure in all patients
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Unclear risk	Not stated
Free of contamination?	Low risk	Although same doctors treated patients in nonintervention weeks they did not have data about procalcitonin results
Baseline characteristics similar?	Low risk	Done, Tables 1 and 2 in the original paper

Christ-Crain 2006

Methods	STUDY DESIGN: RCT QUALITY: **Risk of bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians, number and grade NOT CLEAR PATIENTS: 302 (151 each group) CLINICAL PROBLEM: Suspected community-acquired pneumonia (CAP) SETTING: University hospital Basel, Switzerland. Intervention continued for 16 months, November 2003 to February 2005
Interventions	FORMAT & DELIVERER: STRUCTURAL AND PERSUASIVE Structural: To assess procalcitonin guidance for the initiation and duration of antibiotic therapy Persuasive: written materials and reminder. Guideline for procalcitonin antibiotic pathway to reduce unnecessary empiric antibiotic treatment and reduce duration of treatment DELIVERER: NOT CLEAR, the origins of the standard and procalcitonin-guided antibiotic policies are not described COMPARISON: Antibiotic treatment guided by procalcitonin markers or usual care DESIRED CHANGE: Introduction of new management (procalcitonin test) TIMING: Before clinical decision-making. Intervention was in place for 16 months
Outcomes	PRIMARY: Relative risk of antibiotic exposure SECONDARY: Total antibiotic use. Duration of antibiotic course. Antibiotic cost per patient Clinical success, mortality and length of hospital stay
Notes	EVIDENCE BASE: Published papers about procalcitonin and other biomarkers OTHER: Part-funded by three commercial companies. Costs DONE Median costs of antibiotics in the procalcitonin group were USD 100 per patient, as compared with USD 190 per patient in the control group (Table 3). In the procalcitonin group, the marker was measured 529 times (151 on admission, 21 at follow-up after 6 to 24 h, 139 on Day 4, 128 on Day 6, and 90 on Day 8), thus 3.5 times per patient. The use of procalcitonin for antibiotic stewardship in CAP would become cost saving below USD 25 per analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to one of the two groups by sealed opaque envelopes", no information about generation of randomisation sequence
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes"

Christ-Crain 2006 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Free of contamination?	Low risk	Same doctors in the intervention and control weeks but they did not have access to pro-calcitonin results in the control weeks
Baseline characteristics similar?	Low risk	Done, Table 1 in the original paper

Chu 2003

Methods	STUDY DESIGN: CBA QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: A total of 20 intervention hospitals, 16 control. PROVIDERS: Number, level of training, clinical specialty, age and time since graduation of physicians NOT CLEAR PARTICIPANTS: 2154 episodes in 2087 patients. Mean age about 74, (ranged 27 to 106), 94% white, 41% to 49% male CLINICAL PROBLEM: Community-acquired pneumonia SETTING: A total of 36 small (< 200 beds) rural, non-University community hospitals in USA
Interventions	PERSUASIVE: assistance with development of individual hospital quality improvement plan; audit and feedback of pre-intervention data with benchmarking results from other hospitals. Single feedback at the start of the intervention phase COMPARISON: A total of 16 control hospitals DESIRED CHANGE: Increase in established management (use of CAP guidelines) TIMING: the intervention was implemented at intervention hospitals over three months. Postintervention data were collected from 100% of patients at intervention and control hospitals for seven months after the end of the intervention phase
Outcomes	PRIMARY: Process measures sputum and blood cultures within 4 hours, antibiotics within 4 hours, first antibiotic in emergency room. SECONDARY: mortality and LOS.
Notes	EVIDENCE BASE: Evidence from 11 previous studies about effect of external feedback on quality of care for pneumonia. OTHER: No power calculation done so may have been underpowered. Also improvements in outcome mortality, duration of stay but not

	significant difference from control hospital and not designed to look at this e.g. there were also changes in antibiotics used. Only blood cultures and first antibiotics in emergency room in 'by-hospital analysis' (CI includes one for sputum and first dose < 4). Also no control of outside feedback from QI0. Data was cross-sectional so not able to assess improvement with time. The intervention was implemented at the control hospitals at the end of the study and was associated with similar process changes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Control cohort study (CBA)
Allocation concealment (selection bias)	High risk	Control cohort study (CBA)
Blinding (performance bias and detection bias) All outcomes	High risk	Control cohort study (CBA)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Objective primary outcome collected on all patients
Selective reporting (reporting bias)	Low risk	Objective primary outcome collected on all patients
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Low risk	Tables 1 and 2
Free of contamination?	Low risk	Intervention and control were at different sites
Baseline characteristics similar?	Low risk	Tables 3 and 4

Climo 1998

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Single hospital, all physicians, number, age, specialties and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital, number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: All patients in the hospital SETTING: A 703-bed tertiary care, University hospital in the USA

Climo 1998 (*Continued*)

Interventions	FORMAT & DELIVERER: RESTRICTIVE: Use of clindamycin required prior approval of prescription by an ID Consultant (Page 992) COMPARISON: Data for nine quarters (27 months) before clindamycin restriction DESIRED CHANGE: Reduction of established management (reduction in use of target antibiotics) TIMING: Single intervention implemented after failure of standard infection control measures. Outcomes were measured for 11 quarters (33 months) after the start of clindamycin restriction. Clindamycin restriction was maintained after the end of the study
Outcomes	PRIMARY: Cases of *Clostridium difficile*-associated diarrhoea (CDAD) per quarter (ITS data). SECONDARY: Prevalence of clindamycin-resistant *Clostridium difficile*. Data about drug use NOT CLEAR, use of clindamycin, cost of clindamycin and other antibiotics only presented as mean before-after intervention (UBA data)
Notes	EVIDENCE BASE: Effect of clindamycin restriction on cases of CDAD had been reported previously (Pear 1994). Costs associated with CDAD were taken from a published observational study (Kofsky 1991).OTHER: Compared with the year before clindamycin restriction, clindamycin costs decreased by USD 27,791 to USD 32,305 in the three years after but costs of other anti-anaerobic drugs increased by USD 32,173 to USD 52,198 (Table page 993). The authors estimate savings USD 2000 attributable to each case of CDAD avoided and calculate that there would be net savings provided that the cost per case of CDAD is > USD 200. However they do not provide information about the costs of implementing the restriction

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Low risk	Done, infection control measures fully described and same in both phases
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with t-test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period

Climo 1998 (*Continued*)

Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about changes in sampling or testing protocol over study period
Free of other bias (ITS) ?	High risk	NOT DONE **Microbial Risk of Bias Criteria:** Planned intervention: NOT DONE; Case definition: DONE Infection, diarrhoea and toxin positive Other infection control measures: DONE barrier precautions, isolation of patients with CDAD and personal IC procedures fully described and same in both phases

de Champs 1994

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians on a paediatric ICU with 15 ventilator beds and 28 intermediate care beds. Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: A total of 636 neonates < 28 days old on admission and treated with empirical antibiotics. Total number of admissions 861 children of which 714 were neonates. Gender and ethnicity NOT CLEAR CLINICAL PROBLEM: neonates requiring intensive care including empirical antibiotic treatment SETTING: Paediatric intensive care unit in a University hospital in France
Interventions	FORMAT & DELIVERER: RESTRICTIVE: change in antibiotic policy from gentamicin to amikacin COMPARISON: seven months before the policy change DESIRED CHANGE: Initiation of new management (new restrictive antibiotic policy) TIMING: Single intervention per patient. Patients were followed up until discharge from the unit. The antibiotic policy was maintained for 12 months
Outcomes	PRIMARY: Monthly incidence of infection with multiresistant *Enterobacter cloacae* SECONDARY: Nosocomial infections and mortality
Notes	EVIDENCE BASE: previous studies suggested that substituting amikacin for gentamicin was associated with reduction in risk of colonization by gentamicin-resistant gram-negative bacteria. OTHER: cost effectiveness of intervention NOT DONE.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

de Champs 1994 (*Continued*)

Intervention independent (ITS) ?	High risk	Only seven months pre-intervention data so secular/seasonal changes possible. Very complex case definition with no information about how this was applied reliably across the pre- and postintervention periods
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with t-test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Unclear risk	Case definition included clinical interpretation
Knowledge of the allocation adequately prevented(ITS)?	Unclear risk	NOT CLEAR because of case definition
Incomplete outcome data addressed (ITS) ?	Unclear risk	Availability of all data required for the case definition not documented
Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about changes in sampling or testing protocol over study period
Free of other bias (ITS) ?	High risk	**Microbial outcome risk of bias:**Unplanned intervention: Implementation of change in response to emergence of gentamicin resistant *Enterobacter cloacae;* Case definition: Infection from clinical or screening isolates combined with seven clinical criteria and five additional laboratory criteria assessed by a resident paediatrician and a consultant microbiologist and verified by a consultant paediatrician. Reliability of this outcome measure not clear; all clinical criteria and one lab criteria (DIC) undefined. Other infection control measures: well documented, no changes during the study period

de Man 2000

Methods	STUDY DESIGN: Cluster-CCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians on two neonatal intensive care units in the same hospital. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: 436 patients, mean 33 weeks gestation. Episodes of care, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Sick newborn requiring ventilation with suspected septicaemia SETTING: Two NICUs in one University hospital in the Netherlands
Interventions	FORMAT & DELIVERER: RESTRICTIVE: change in antibiotic policy from penicillin and tobramycin to amoxicillin & cefotaxime. Full details of antibiotic policy for each study phase in Table 4 COMPARISON: cross-over design DESIRED CHANGE: Initiation of new management (new restrictive antibiotic policy) TIMING: Immediate concurrent intervention. During the first six months of the study unit A used the amoxicillin and cefotaxime regimen while unit B used the penicillin and tobramycin regimen. During the second six months the units switched antibiotic regimens
Outcomes	PRIMARY: colonization by gram-negative bacteria resistant to the empiric therapy of the unit ([colonizing events/patient days at risk] x 1000). SECONDARY: colonization by gram-negative bacilli resistant to cefotaxime or tobramycin, use of target and other antibiotics, length of NICU stay and mortality
Notes	EVIDENCE BASE: Four observational studies reporting an association between use of third generation cephalosporins and colonization of resistant gram-negative bacteria. OTHER: cost effectiveness NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Cluster-CCT
Allocation concealment (selection bias)	High risk	Not done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No explicit statement about complete screening data for all patients
Other bias	Low risk	

Baseline Outcomes similar?	Low risk	Not done, no data about colonisation rates at baseline
Baseline characteristics similar?	Low risk	

Dean 2001

Methods	STUDY DESIGN: CBA comparing patients of physicians affiliated to Intermountain Health Care (IHC) vs patients of nonaffiliated physicians on the same sites and on different sites QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All inpatient and outpatient services in the state of Utah. Number of providers, level of training, age and time since graduation NOT CLEAR. PARTICIPANTS: 22,985 Medicare beneficiaries aged 65 or more with 28,661 episodes of community-acquired pneumonia of which 7719 were hospitalized. About 55% female. Ethnicity NOT CLEAR. CLINICAL PROBLEM: Community-acquired pneumonia (CAP) SETTING: Hospital size varied from a 14-bed facility staffed by three family physicians to a 520-bed teaching hospital, all in Utah USA
Interventions	FORMAT & DELIVERER: PERSUASIVE: "Guideline implementation included formal presentations, academic detailing, letters, reminders by pharmaceutical representatives, preprinted outpatient and admission order sheets (Figures 1 and 2) and reporting of outcome data to providers". COMPARISON: Patients cared for by physicians not affiliated to Intermountain Health Care (IHC), either at IHC hospitals or at other hospitals. DESIRED CHANGE: Initiation of new management (CAP care pathway intended to reduce mortality from CAP) TIMING: Immediate > 1 episode of CAP in 19% of patients. Data collected for two years pre- & post guideline implementation. Patients followed up 30 days
Outcomes	PRIMARY: 30-day mortality. SECONDARY: Length of stay (LOS)
Notes	EVIDENCE BASE: Guidelines developed by a multidisciplinary team by combining local practices with American Thoracic Society guidelines (American Thoracic Society 1993). OTHER: Detailed data about processes of care were not collected. However, among all patients admitted to IHC hospitals, guideline implementation was associated with an increase in treatment of CAP with a guideline recommended antibiotic from 28% to 56%. Since the end of data collection (1997) this has increased to 85%. Data about costs and cost-effectiveness of intervention NOT DONE

Risk of bias

Dean 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	CBA
Allocation concealment (selection bias)	High risk	CBA
Blinding (performance bias and detection bias) All outcomes	High risk	CBA
Incomplete outcome data (attrition bias) All outcomes	Low risk	Objective outcome measure collected on all patients
Selective reporting (reporting bias)	Low risk	Objective outcome measure collected on all patients
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Low risk	Table 1
Free of contamination?	Unclear risk	NOT CLEAR, some hospitals had both intervention and control physicians. IHC provides 50% of regional healthcare delivery in Utah. In rural IHC hospitals 90% of pneumonia admissions were cared for by IHC-affiliated physicians, whereas in urban IHC hospitals only 44% of pneumonia admissions were cared for by IHC-affiliated physicians. Non-affiliated physicians caring for patients at IHC hospitals may have been influenced by guideline implementation at these hospitals
Baseline characteristics similar?	Low risk	Table 1

Dean 2006

Methods	STUDY DESIGN: CBA QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: A total of 35 hospitals in Utah, 16 from Intermountain Healthcare (IHC) and 19 from other systems PATIENTS: A total of 17,728 patients aged > 66 years CLINICAL PROBLEM: Admitted with community-acquired pneumonia (CAP) SETTING: All hospitals in Utah. Data were collected over 10 years (1993 to 2003)

Interventions	FORMAT: PERSUASIVE, multifaceted "Guideline implementation included formal presentations, academic detailing, standardized outpatient and inpatient order sheets, frequent reminders via several methods, and reporting of outcome data to providers" DELIVERER: Local experts (clinicians and administrative staff) COMPARISON: Hospitals without the guideline DESIRED CHANGE: Initiation of new management (CAP care pathway intended to reduce mortality from CAP) TIMING: Before clinical decision-making
Outcomes	PRIMARY: 30-day mortality SECONDARY: Compliance with policy, LOS, 30-day readmission
Notes	EVIDENCE BASE: DONE. Supported by at least one referenced RCT (Marrie et al) Guideline was based on national guidelines OTHER: Insufficient data to calculate pneumonia severity scores (CURB65 or PSI). As the characteristics of the study and control group populations are not provided it is not clear if they were comparable. It is not clear if the outcome measures were comparable in the study and control groups before implementation of the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	CBA
Allocation concealment (selection bias)	High risk	CBA
Blinding (performance bias and detection bias) All outcomes	High risk	CBA
Incomplete outcome data (attrition bias) All outcomes	Low risk	Electronic record linkage used.
Selective reporting (reporting bias)	Low risk	30-day mortality was primary outcome
Other bias	Low risk	Objective primary outcome measure
Baseline Outcomes similar?	Low risk	Table 3
Free of contamination?	Low risk	NOT CLEAR, some hospitals had both intervention and control physicians. The 100,000 annual inpatient admissions of Intermountain Healthcare represent almost one half of Utah hospital admissions. Intermountain Healthcare has an employed

		physician group and several non-Medicare health maintenance organization insurance plans, but many nonemployed physicians and non-health maintenance organization patients also utilize its facilities. Non-affiliated physicians caring for patients at IHC hospitals may have been influenced by guideline implementation at these hospitals
Baseline characteristics similar?	Unclear risk	Not stated

Dempsey 1995

Methods	STUDY DESIGN:ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Clinical guidelines for nursing home-acquired pneumonia were created for physicians and presented to all staff (physicians, nursing, pharmacy, and ancillary) in involved departments (Emergency, Pulmonology, Infectious Diseases, Family Practice, Internal Medicine) Number, level of training, age and time since graduation of physicians NOT CLEAR PARTICIPANTS: Number, age, gender and ethnicity NOT CLEAR. 225 patients studied retrospectively CLINICAL PROBLEM: Patients with nursing home-acquired pneumonia SETTING: an 814-bed teaching and referral centre in the USA.
Interventions	FORMAT & DELIVERER: PERSUASIVE: Dissemination of clinical guideline developed by multidisciplinary team who delivered the guideline through meetings with audit and monthly feedback to all medical staff, ancillary departments and committees. COMPARISON: Data for three months pre-intervention (January-March 1993) DESIRED CHANGE: Increase in established management (earlier initiation of appropriate antibiotics, intended to decrease length of stay and financial charges per case) TIMING: Monthly feedback of aggregate data about clinical and financial outcomes for nine months after dissemination of the guidelines (April to December 1993)
Outcomes	PRIMARY: Length of stay (LOS) per case of nursing home-acquired pneumonia. SECONDARY: and financial charge per case of nursing home-acquired pneumonia
Notes	EVIDENCE BASE: The guideline was developed by a multidisciplinary team, who conducted interviews to identify issues and concerns about the management of nursing home-acquired pneumonia. This information was supplemented with a retrospective baseline study of 225 patients with nursing home-acquired pneumonia hospitalized between October 1991 and March 1992 plus a review of the literature about microbial aetiology. OTHER: No statistical analyses of the time series data were presented in the original

Dempsey 1995 (*Continued*)

	paper	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	
Analysed appropriately (ITS) ?	Low risk	
Shape of effect pre-specified (ITS) ?	Low risk	
Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	Low risk	
Incomplete outcome data addressed (ITS) ?	Unclear risk	No explicit statement about complete follow-up
Free of selected reporting (ITS) ?	Low risk	
Free of other bias (ITS) ?	Low risk	

Doern 1994

Methods	STUDY DESIGN: CCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital in Medicine, Surgery, Paediatrics and Other specialties. Number, age and time since qualification NOT CLEAR. PARTICIPANTS: A total of 573 patients, mean age 51.3 intervention and 53.7 Control, 52% male intervention and 46% male control. Ethnicity NOT CLEAR CLINICAL PROBLEM: Patients with positive bacterial cultures SETTING: Single University hospital in the USA
Interventions	FORMAT & DELIVERER: STRUCTURAL AND PERSUASIVE Structural: Intervention was reporting of Rapid Antimicrobial Susceptibility Testing performed on the day of recognition of bacterial growth Persuasive: Reporting of results for intervention and control patients included "telephone reporting to the physician who had requested the test by members of the laboratory's technologist staff for blood cultures, normally sterile body fluids, catheter tips with > 15 colonies, specimens obtained in the operating room and selected other important specimens". All other test results were reported on a computerized system COMPARISON: Overnight antimicrobial susceptibility testing DESIRED CHANGE: Initiation of new management (rapid laboratory testing)

Doern 1994 (*Continued*)

	TIMING: Single concurrent intervention per patient. Outcomes were collected until hospital discharge. Patients were enrolled for one year
Outcomes	PRIMARY: Percentage of patients with antibiotic treatment changed within 24 hours SECONDARY: Time to reporting of antibiotic susceptibility results, length of stay (LOS) , mortality, and total costs of care
Notes	EVIDENCE BASE: Three previous published studies on the impact of rapid testing on use of antibiotics (two positive, one negative) but none on the impact of rapid bacterial identification on clinical outcome OTHER: Mean costs per patient were USD 15,062 intervention and USD 21,644 control (P = 0.012). Significant differences were observed in all three subcategories of cost: laboratory tests, pharmacy and other costs (imaging and services such as respiratory, physiotherapy and nutrition) OTHER: Cost of the intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	'Specimens assigned to one of two categories based on the first letter of the last name of the patient. (A through K and L through Z)"
Allocation concealment (selection bias)	High risk	Not done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data reported on all patients
Selective reporting (reporting bias)	Low risk	No problems noted
Other bias	Low risk	Antibiotic prices unlikely to change over the one year study period
Baseline Outcomes similar?	Unclear risk	Only measured postintervention.
Free of contamination?	Low risk	Intervention (rapid reporting of microbiology results) unlikely to have had an impact on management of control patients
Baseline characteristics similar?	Low risk	Done, Table 1 of original paper

Dranitsaris 2001

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Prescribers were residents (77%), fellows (6%), or staff (14%) assigned to seven services. Status of prescriber was missing for 3% of episodes. Age, gender and time since qualification NOT CLEAR PARTICIPANTS: A total of 323 episodes randomized and 309 evaluated. Patients could be enrolled more than once. Mean age: 66 intervention, 65 control. Male 56% intervention, 62% control. Ethnicity NOT CLEAR. CLINICAL PROBLEM: Adult patients with infections requiring IV cefotaxime SETTING: Two hospitals in Canada, University status NOT CLEAR
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change) to promote printed hospital guideline on appropriate use of cefotaxime developed by an expert antibiotic subcommittee of the Pharmacy and Therapeutics Committee (Appendix 1). Clinical pharmacists contacted prescribers if cefotaxime use did not meet the guideline and discussed changes in treatment COMPARISON: No educational outreach DESIRED CHANGE: Reduction of established management (reduction in use of cefotaxime) TIMING: Proximity to Clinical Decision Making immediate. Study lasted six months
Outcomes	PRIMARY: Percentage of cefotaxime prescriptions that were consistent with guideline for both indication and dosage SECONDARY: Mean duration of therapy and cost per treatment course
Notes	EVIDENCE BASE: Guidelines for appropriate cefotaxime use were developed by an expert antibiotic subcommittee of the Pharmacy & Therapeutics Committee using a systematic literature review process OTHER: Cost of intervention NOT DONE. Multivariate analysis identified four variables that were significantly associated with appropriate prescribing: Staff physician (vs resident), longer duration of therapy, increasing patient age, renal insufficiency and immuno-suppression. However, these variables plus intervention group only accounted for 12% of variability in appropriateness of cefotaxime scripts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised on a one to one basis via a computer generated list"
Allocation concealment (selection bias)	Low risk	Randomizations carried out in central pharmacy and "telephone on a consecutive basis"

Dranitsaris 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Not done, acknowledged as a limitation by authors on Page 179
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Table 3; all patients included
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	
Baseline characteristics similar?	Low risk	

Everitt 1990

Methods	STUDY DESIGN: ITS ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians in Obstetrics & Gynaecology, mixed experience (house staff and attending staff). Number, age and years since qualification NOT CLEAR PARTICIPANTS: A total of 2783 episodes of care in women but number, age and ethnicity not clear CLINICAL PROBLEM: Caesarean section SETTING: Single teaching hospital in the USA. Number of beds NOT CLEAR
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Cefoxitin was removed from the supply shelf in the labour and delivery area Persuasive: Printed materials, meetings and reminder. Educational: guidelines circulated to key department leaders who discussed them in conferences and grand rounds with house staff and attending staff. Cefazolin was recommended for prophylaxis on an educational antibiotic order form COMPARISON: Data for nine months pre-study DESIRED CHANGE: Reduction in established management (switch from cefoxitin to cefazolin for prophylaxis in cesarean section). TIMING: Immediate (order form). Data collected for 25 months post-study
Outcomes	PRIMARY: Relative use of cefazolin or cefoxitin in caesarean sections that received < 5 g of either drug perioperatively. SECONDARY: Estimated financial savings
Notes	EVIDENCE BASE: Local guidelines based on informal open-ended interviews held with house officers to determine their beliefs and practices and an extensive literature search on the appropriate use of prophylactic antibiotics for caesarean section and hysterectomy. OTHER: The economic savings were reported to be "substantial in comparison to the modest costs" (of the study) but these costs were not quantified

Everitt 1990 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only nine months pre-intervention data so secular/seasonal changes possible
Analysed appropriately (ITS) ?	Low risk	Done in original paper, segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	Antibiotic costs adjusted to 1986 prices over the whole study period

Fine 2003

Methods	STUDY DESIGN: Cluster-RCT QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: Seven hospitals, 325 control and 283 intervention patients PROVIDERS: Physicians PATIENTS: With community-acquired pneumonia (CAP) CLINICAL PROBLEM: Duration of IV antibiotic therapy and (LOS) SETTING: Seven nonprofit hospitals in Pittsburgh, Pennsylvania, mixed teaching and nonteaching
Interventions	FORMAT: PERSUASIVE: Educational outreach (review and recommend change) to promote printed guideline about duration of IV therapy for CAP with reminder in the case record DELIVERER: Guideline delivered by mail to intervention and control

Fine 2003 (*Continued*)

	For intervention physicians only: reminder in case record plus nurse contact to tell physician about recommendation plus offer to take verbal order for switch to oral therapy plus offer of home nursing care. COMPARISON: Guideline only DESIRED CHANGE: Reduction in established management (decrease days on IV antibiotics and decreased LOS for patients with CAP) TIMING: Daily monitoring
Outcomes	PRIMARY: Duration of IV antibiotic therapy SECONDARY: Mortality
Notes	EVIDENCE BASE: Evidence based on review of the literature and consensus of an eight-member national guideline panel

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Physician groups were randomly assigned after stratification for practice type, group size and patient volume but details not clear
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Baseline Outcomes similar?	Unclear risk	No data about LOS prior to intervention
Free of contamination?	Low risk	
Baseline characteristics similar?	Low risk	

Foy 2004

Methods	STUDY DESIGN: CLUSTER-RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: All 26 hospital gynaecology units in Scotland providing induced abortion care, 1474 case notes were reviewed PROVIDERS: Clinicians PATIENTS: 1474 patients

Foy 2004 (*Continued*)

	CLINICAL PROBLEM: Induced abortion SETTING: Care during termination of pregnancy
Interventions	FORMAT: Multifaceted guideline intervention for five key result areas, one based on antibiotic prophylaxis: 1. Attendance of an assessment appointment within five days of referral. 2. Ascertainment of cervical cytology history at pre-abortion assessment. 3. Use of antibiotic prophylaxis or screening for lower genital tract infection. 4. Use of misoprostol for cervical priming and for early and mid-trimester medical abortion. 5. Supply of contraception at discharge. Guideline disseminated to all fellows and members of RCOG in the intervention and control hospitals. Following randomization no further contact with control units. Invervention units had audit findings presented at unit educational meetings with discussion of barriers to change and potential solutions MARKETING: Barriers to improved care were identified during semi-structured interviews with lead consultants and by a postal survey of medical, nursing and midwifery staff DELIVERER: Clinicians COMPARISON: No guideline DESIRED CHANGE: Increase in established management (increase in percentage of patients who received prophylactic antibiotics or screening for lower genital tract infection) TIMING: Feedback after care had been delivered.
Outcomes	PRIMARY: Odds ratio of receiving prophylactic antibiotics or screening for lower genital tract infection with vs without guideline SECONDARY: None relevant to this review
Notes	EVIDENCE BASE: Based on RCOG guidelines (2000) OTHER: Mean cost of the intervention was GBP 2067, with the audit and feedback component accounting for half of this cost. Note that the audit and feedback was for five different aspects of care and use of prophylactic antibiotics was just one aspect

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The units in each matched pair were randomised .....by an independent statistician"
Allocation concealment (selection bias)	Unclear risk	It is unlikely that full allocation concealment is possible with this study design
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible

Foy 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Tables 2 and 3, number of patients reported for all outcome data
Selective reporting (reporting bias)	Low risk	Tables 2 and 3, number of patients reported for all outcome data
Other bias	High risk	Ceiling effect for antimicrobial outcome
Baseline Outcomes similar?	Unclear risk	Not stated, no information about pre-randomization outcomes
Free of contamination?	Low risk	Cluster-randomization by hospital
Baseline characteristics similar?	Low risk	Table 1

Franz 2004

Methods	STUDY DESIGN: RCT QUALITY: **Risk of bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians in neonatal units PATIENTS: A total of 1291 neonates < 72 hours of age CLINICAL PROBLEM: Suspected bacterial infection SETTING: Eight centres in five countries (Australia, Austria, Belgium, Germany, Sweden), teaching status mixed
Interventions	FORMAT: STRUCTURAL AND PERSUASIVE Structural: Testing for Interleukin-8 (IL-8) in combination with C-reactive protein (CRP) Persuasive: Written materials. Algorithm in the form of a flow diagram for decision-making based on test results (Figure 2) DELIVERER: IL-8 and/or CRP results delivered by participating laboratories COMPARISON: Standard care based on local guidelines DESIRED CHANGE: Initiation of new management (test for IL-8, intended to reduce number of infants who received unnecessary postnatal antibiotic therapy) TIMING: IL-8 results were available on diagnosis of infection
Outcomes	PRIMARY: Number of newborn infants who received antibiotic therapy SECONDARY: Number of infants with infection missed at initial evaluation
Notes	EVIDENCE BASE: Preliminary reports about IL-8. OTHER: Sensitivity and specificity of IL-8 and CRP documented with suggested care pathway based on IL-8 > 70 pg/ml and/or CRP > 10mg/l. Cost of intervention and tests NOT DONE

Risk of bias

Franz 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned to 1 or 2 diagnostic algorithms using sealed opaque envelopes"
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Done, IL-8 results were only provided to physicians in the intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Free of contamination?	Low risk	
Baseline characteristics similar?	Low risk	

Fraser 1997

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Medical, surgery, intensive care, haematology and oncology. Paediatric and obstetric patients were excluded. Number, age and years since qualification NOT CLEAR PARTICIPANTS: A total of 127 in intervention group (I) and 98 in control group (C) ; mean age 64.6 (I), 65.4 (C); female 49.6% (I), 39.8% (C), ethnicity not clear. CLINICAL PROBLEM: Adult inpatients receiving one or more of 10 designated parenteral antibiotics for three or more consecutive days. SETTING: Single teaching hospital in the USA
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change): an ID fellow and a clinical pharmacist placed suggestions for change to antibiotics in the medical records (e.g. switch to oral, change drugs or stop). Patient-specific, antibiotic-related suggestions were placed in the medical progress note section of the medical record on a removable notecard.The statement, "The patient has not been examined by us and the above suggestion(s) should be taken within this context" was included on the note card to recognize the limitations of using the medical record as the primary source of patient information. We emphasized the educational component of this effort by offering the rationale for each recommendation on the note card. Diagnostic studies were not suggested.The suggestion was removed from the medical record

	within 24 hours, and the response of the physician to that suggestion was noted COMPARISON: Control group with no intervention. DESIRED CHANGE: Reduction in established management (reduction in cost of antibiotics with no adverse effect on clinical outcome) TIMING: Suggestions were removed from case records after 24 hours. Patients were eligible for multiple reviews and were visited on alternate days until three days after completion of antibiotics. Outcome variables were collected up to 30 days postdischarge. The intervention was in place for three months
Outcomes	PRIMARY: Antibiotic charges (USD) per patient. SECONDARY: Clinical response at three days after completion of antibiotics; retreatment with antibiotics within seven days; inpatient mortality; readmission within 30 days of discharge
Notes	EVIDENCE BASE: DONE (switch to oral therapy was the most common recommendation and criteria were based on the results of three RCTs: Chan 1995, Solomkin 1996, Siegel 1996) OTHER: Cost of Intervention NOT CLEAR: both the pharmacist and the ID fellow each spent two hours per day on the Intervention but the other costs of development and dissemination are not described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients randomised...using an unblocked computer generated random number table"
Allocation concealment (selection bias)	High risk	Not possible; "The patient population was assigned to 1 of 4 medical service groups based on where they were treated at randomizations"
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	For primary outcomes not secondary
Selective reporting (reporting bias)	Low risk	Based on microbial repose and other clinical parameters
Other bias	Low risk	No problems noted
Baseline Outcomes similar?	Unclear risk	No information about baseline outcomes pretrial in the allocated groups

Fraser 1997 (*Continued*)

Free of contamination?	High risk	Doctors likely to have cared for patients in all groups
Baseline characteristics similar?	Low risk	Table 1

Fridkin 2002

Methods	STUDY DESIGN: CBA QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: There were 50 intensive care units (ICUs) in the study but main results compare data from 31 ICUs that implemented one of five interventions PROVIDERS: A total of 50 ICUs were located in 20 hospitals. ICUs included medical, surgical and specialized (e.g. cardiothoracic, neurosurgical or trauma) CLINICAL PROBLEM: Vancomycin use, prevalence of VRE. SETTING: Hospitals in the USA participating in the ICU surveillance component of National Nosocomial Infection Surveillance (NNIS)
Interventions	FORMAT: RESTRICTIV AND EPERSUASIVE: Provision of local monitoring data to improve quality and reduce vancomycin use or VRE. Five interventions were used by 3 to 19 hospitals (some used more than one). Three interventions were hospital-wide and two were Unit-specific ***Hospital-wide interventions (22 ICUs)*** Intervention 1 (persuasive): guideline distribution by newsletter or mail (persuasive), nine ICUs Intervention 2 (persuasive): audit and feedback of aggregated data about use of vancomycin at the hospital level. Method and frequency of feedback not clear Intervention 3 (restrictive): prior approval for vancomycin use (restrictive): three ICUs ***Unit specific interventions (11 ICUs)*** Intervention 4 (persuasive): ICU-specific education on appropriate vancomycin use, nine ICUs. Method and frequency of education not clear, use of feedback not clear Intervention 5 (restrictive): Removal of vancomycin from operating theatres to prevent use in prophylaxis for cardiac surgery (restrictive), three ICUs DELIVERER: Infection control practitioners COMPARISON: National benchmark data DESIRED CHANGE: Reduction in established management (reduction in vancomycin use and in percentage of VRE) TIMING: Interventions were at the point of prescribing but feedback of data about other hospitals was retrospective
Outcomes	PRIMARY: DDDs of vancomycin SECONDARY: percentages of VRE and of MRSA.
Notes	EVIDENCE BASE: Not stated

Risk of bias

Fridkin 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	CBA-not randomized
Allocation concealment (selection bias)	High risk	CBA-not randomized
Blinding (performance bias and detection bias) All outcomes	High risk	CBA, allocation not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not clear, " Susceptibility reports from isolates obtained as part of infection-control surveillance were excluded." Criteria for exclusion of isolates are not described and may not have been consistent across all hospitals
Selective reporting (reporting bias)	Low risk	Not clear, "Susceptibility reports from isolates obtained as part of infection-control surveillance were excluded." Criteria for exclusion of isolates are not described and could have led to reporting bias
Other bias	Unclear risk	NOT CLEAR **Microbial Risk of Bias Criteria:** Case definition: percentage VRE or percentage MRSA in clinical isolates; Planned intervention: DONE; Other infection control Isolation: NOT CLEAR; IC practices: NOT CLEAR Data were collected about infection control changes in response to feedback of data but the paper does not report any results
Baseline Outcomes similar?	Unclear risk	Not stated
Free of contamination?	Low risk	Interventions were at different hospitals from control sites
Baseline characteristics similar?	Unclear risk	Not stated

Gerding 1985

Methods	STUDY DESIGN: ITS and UBA QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All prescribers in the hospital, number and details NOT CLEAR PARTICIPANTS: All patients in the hospital, NOT CLEAR 291,000 isolates assessed during study period. CLINICAL PROBLEM: Requiring aminoglycoside treatment SETTING: time series data about resistance from one Veterans Administration hospital in the USA. UBA data about resistance from 14 other similar hospitals
Interventions	FORMAT & DELIVERER: RESTRICTIVE: expert approval. Details lacking in the original paper but the author provided additional information. The Pharmacy & Therapeutics committee determined which aminoglycoside (gentamicin or amikacin) would be the agent on formulary for the hospital. All other aminoglycosides required prior approval through a call to the Infectious Diseases fellow or faculty on call COMPARISON: pre-intervention time series. DESIRED CHANGE: change in established management (cycling of gentamicin and amikacin) TIMING: Four segments to time series: gentamicin four months, amikacin 26 months, gentamicin 12 months, amikacin 12 months
Outcomes	PRIMARY: resistance to gentamicin and aminoglycoside use.
Notes	EVIDENCE BASE: Three publications about impact of long-term amikacin use on gentamicin resistance. None of these are included in this review. Two are purely descriptive and one has inadequate time series data about the effect of switching from gentamicin to amikacin (Wielunsky 1983). OTHER: Cost of intervention and monitoring NOT DONE.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Unclear risk	Only four months pre-intervention data so secular/seasonal changes possible. No information about infection control measures
Analysed appropriately (ITS) ?	Low risk	
Shape of effect pre-specified (ITS) ?	Low risk	
Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	Low risk	

Gerding 1985 (*Continued*)

Incomplete outcome data addressed (ITS) ?	Low risk	
Free of other bias (ITS) ?	Unclear risk	NOT CLEAR **Microbial outcome risk of bias:** Planned intervention. DONE Implementation in response to emergence of gentamicin resistance over the previous five years; Case definition: DONE Infection from clinical isolates; Other infection control measures: NOT CLEAR, no information provided

Gums 1999

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital, number, age and time since qualification NOT CLEAR. PARTICIPANTS: A total of 272 patients CLINICAL PROBLEM: Patients receiving inappropriate antibiotic therapy judged on culture results, risk of toxicity or drug interaction, drug cost and duration of treatment. SETTING: Single 275-bed community hospital with a family practice residency programme in the USA
Interventions	FORMAT & DELIVERER: PERSUASIVE: Each patient receiving inappropriate therapy was randomized. Intervention patients received a consultation from the multidisciplinary ID service with a typed summary in the patient chart within two hours of randomization. COMPARISON: Control group received no intervention DESIRED CHANGE: Reduction of established management (reduction in inappropriate antibiotic use intended to reduce LOS). TIMING: Concurrent, patient-specific intervention. Patients were followed until discharge or inpatient death. Patients were enrolled for 19 months
Outcomes	PRIMARY: LOS after randomization SECONDARY: Charges for antibiotics, laboratory and radiology services, total patient charges and mortality
Notes	EVIDENCE BASE: Previous observational studies showed an association between inappropriate antibiotic therapy and LOS or hospital charges. OTHER: Mean total hospital charges were USD 9153 intervention vs USD 12,207 control. Cost of the intervention was estimated at USD 22,000 per year. Actual financial savings to the hospital were estimated at a median of USD 2642 per intervention so that the programme was likely to be cost-saving with only 10 interventions per year

Gums 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not clear; "eligible patients were blindly randomised to the intervention or control group"
Allocation concealment (selection bias)	High risk	Not possible to conceal allocation because all intervention patients had a consultation, whereas no control patients did
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear, despite objective primary outcome measure (LOS) it is not clearly stated that record linkage was without knowledge of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems found, data were analyzed from 93% of randomized patients
Selective reporting (reporting bias)	Low risk	No problems found
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Low risk	Done for primary outcome
Free of contamination?	Low risk	Patients were randomized to receive a consultation from an ID specialist (intervention) or no consultation (control), so no contamination likely
Baseline characteristics similar?	Low risk	Done, Table 1 of the original paper

Gupta 1989

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: A total of 3535 treatment courses with cefazolin. Number, age, gender and ethnicity of patients NOT CLEAR CLINICAL PROBLEM: Patients receiving cefazolin SETTING: 1000-bed University hospital in Canada.

Gupta 1989 (*Continued*)

Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Therapeutic substitution initiated by pharmacy when they received an order for cefazolin dosed < every eight hours. The order was stamped with conversion information, returned to the nursing station and placed in the doctor's orders section of the chart Persuasion: Written materials, meetings and reminder. The rationale for the programme was explained in a newsletter distributed to all staff three weeks before the start of the restriction. Detailed memos were sent to all nursing units twice in the three weeks before restriction started. These memos described the nursing-related implications of the intervention. Meetings were held with pharmacy staff to explain the intervention. Two weeks after the start of the restriction of the programme a reminder was issued to all staff in the same newsletter COMPARISON: Three months pre-intervention data DESIRED CHANGE: Reduction of established management (cefazolin doses prescribed at < eight-hour intervals) TIMING: Single intervention per patient. Outcomes were measured for eight months. The intervention remained in place at the end of the study
Outcomes	PRIMARY: % of cefazolin doses prescribed at < eight-hour intervals SECONDARY: None
Notes	EVIDENCE BASE: Dosing recommendation for cefazolin based on pharmacokinetic and pharmacodynamic studies. OTHER: The authors claim to have compared the restrictive intervention with an educational intervention. However this (newsletter and memos to nursing staff) was only in place for three weeks before the restrictive intervention was implemented so it is not possible to compare the two

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only three months pre-intervention data so secular/seasonal changes possible
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper, x^2 test on mean before-after
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period

Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Halm 2004

Methods	STUDY DESIGN: ITS QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Four University Hospitals. Number and characteristics of physicians NOT CLEAR PATIENTS: A total of 2094 consecutive patients CLINICAL PROBLEM: Adults with community-acquired pneumonia SETTING: New York, USA. December 1999 to April 2001, five months pre- and five months post-intervention
Interventions	FORMAT: PERSUASIVE (guideline, care pathway, educational meetings and reminders). "Specific techniques included the development and dissemination of hospital-specific, evidence based practice guidelines and critical pathways, educational sessions with attending physicians and house officers, distribution of pocket reminder cards, and use of standardized orders sets and bilingual patient education materials" DELIVERER: Multidisciplinary team of opinion leaders with physicians (pulmonary and ID, emergency medicine, general internal medicine), nurses, respiratory therapists and pharmacists COMPARISON: Pre-intervention phase DESIRED CHANGE: Increase of established management (improvement in uptake of guideline recommendations for appropriate antibiotic therapy with increase in percentage of patients who received an antibiotic regimen in the first 24 hours that covered both typical and atypical organisms). The guideline also aimed to reduce the percentage of patients discharged before they reached clinical stability TIMING: Before clinical decision-making
Outcomes	PRIMARY: Percentage of patients treated with appropriate antibiotics SECONDARY: All other outcomes only had mean before-after data, not eligible
Notes	EVIDENCE BASE: DONE: Supported by one RCT and national guidelines OTHER: Percentage of patients with appropriate antibiotics was the only outcome with reliable data, all others were UBA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Halm 2004 (*Continued*)

Intervention independent (ITS) ?	High risk	NOT DONE, subjective outcome measure, not blinded.
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with χ^2 test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data collection same pre- and postintervention
Knowledge of the allocation adequately prevented(ITS)?	High risk	NOT DONE, subjective outcome measure, not blinded
Incomplete outcome data addressed (ITS) ?	Unclear risk	Not stated whether outcome data collected on all patients
Free of selected reporting (ITS) ?	Unclear risk	Not stated whether outcome data collected on all patients
Free of other bias (ITS) ?	High risk	NOT DONE, the only reliable data for analysis are about compliance with the antibiotic policy, which was 80% at baseline. Serious risk of ceiling effect

Hess 1990

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age, gender, services and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Receiving cefazolin therapy SETTING: A 719-bed tertiary care medical centre in the USA. University status NOT CLEAR
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach to promote written guidelines. Several interventions are mentioned but Standardized Dosing is the only one with both sufficient ITS data and clear intervention point. Dissemination of guidelines, then pharmacists who received orders for dosing target drugs more frequently than eight hours contacted physicians to discuss

	COMPARISON: Four quarters (12 months) pre-intervention DESIRED CHANGE: Reduction of established management (reduction in dosing of cefazolin < eight-hourly) TIMING: Immediate, concurrent intervention per patient. Outcomes were measured for four quarters (12 months) after start of intervention, which remained in place at the end of the study
Outcomes	PRIMARY: Cefazolin expenditure per patient day SECONDARY: None
Notes	EVIDENCE BASE: "Literature reports that an eight hour dosing interval sufficed for most infections." Pharmacy and Therapeutics Committee-approved recommendations for eight-hour dosing with exceptions for patients with endocarditis, osteomyelitis or septic shock. OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	12 months data pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper, no statistical analysis and only comparison was between mean (uncontrolled) before and after
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Unclear risk	On page 588 the authors state that "a proportion of these savings can be attributed to a decrease in acquisition cost" but do not say how much

Himmelberg 1991

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR. PARTICIPANTS: Mean age of patients receiving restricted drugs 53 years before and 55 years after removal of restriction. Number of courses of treatment 413 before and 1064 after removal of restriction. Number, gender and ethnicity of patients NOT CLEAR CLINICAL PROBLEM: Patients receiving restricted antibiotics: amikacin, aztreonam, cefoperazone, cefotaxime, ceftazidime, ceftriaxone, imipenem, piperacillin, ticarcillin-clavulanate SETTING: A 660-bed tertiary care teaching hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Until June 1988 use of nine antibiotics was restricted, requiring approval by the on-call fellow or staff physician in adult or paediatric Infectious Diseases. Restriction ceased from July 1988 because of staff shortages. COMPARISON: Six months in the restriction period (July to December 1987) were compared with six months after restriction was lifted (July to December 1988). DESIRED CHANGE: Reduction in established management (hypothesis was that removal of restriction would be associated with increase in drug use). TIMING: The restriction was an immediate, patient-specific intervention. Follow-up was six months after removal of the restriction
Outcomes	PRIMARY: Number of courses and cost of restricted drugs SECONDARY: Cost of unrestricted drugs
Notes	EVIDENCE BASE: NOT CLEAR OTHER:

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Data collected in same months in two consecutive years
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with t-test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period

Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Huber 1982

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at a large federal hospital. Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: Number and characteristics of patients and episodes NOT CLEAR CLINICAL PROBLEM: Appropriateness of inpatient prescribing of cephalexin SETTING: One USA Teaching Hospital
Interventions	FORMAT & DELIVERER: RESTRICTIVE: each prescription had to be counter-signed by the Chief of Staff from January 1977; this restriction was still in force at the end of the study (December 1981). COMPARISON: Pre-study data (annual for three years) DESIRED CHANGE: Reduction in established management (decrease in cephalexin prescribing) TIMING: Number of studies per patient NOT CLEAR. Effect of study measured for five years after initiation
Outcomes	PRIMARY: Cephalexin dosing units SECONDARY: None measured
Notes	EVIDENCE BASE: Not Clear OTHER: No statistical analyses of the time series data were presented in the original paper. Paper reports interventions on six other drugs: three cephalosporins (cephalothin, cephapirin and cefazolin) and three benzodiazepines (diazepam, chlordiazepoxide and oxazepam). Cephalexin was chosen for the review because it was the only one with a clear intervention point. The authors do not comment on changes in other oral antibiotics with cephalexin restriction OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Huber 1982 (*Continued*)

Intervention independent (ITS) ?	Low risk	> two years data pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: no statistical analysis of time series, presented as chart
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Hulgan 2004

Methods	STUDY DESIGN: ITS QUALITY: **Risk of bias: LOW**
Participants	NUMBER & CHARACTERISTICS: A total of 15,194 orders for quinolones during study period PROVIDERS: Physicians PATIENTS: All who required quinolones. CLINICAL PROBLEM: Use of IV and oral quinolones. Volume and cost SETTING: University hospital in the USA February 2001 to June 2003
Interventions	FORMAT: PERSUASIVE Reminder. Computerized decision support system (CDSS) to increase proportion of oral quinolone orders for hospitalised patients. The reminder was delivered as part of an existing order entry system. "Upon recognizing a relevant order, the CDSS searched the patient's current active orders for the presence of an oral medication or a solid diet. An order for either of these combined with the absence of a 'nothing by mouth' (NPO) order identified the patient as being 'able to take oral medications'. Prescribers entering an order for an oral quinolone in a patient 'able to take oral medications', or an order for an iv quinolone in patients not 'able to take oral medications' were allowed to complete their order through a menu of doses and

	suggested indications based on quinolone choice and renal function order for an iv quinolone was initiated in a patient identified as being 'able to take oral medications', the intervention presented the prescriber with a statement suggesting that the patient could potentially tolerate an oral quinolone. To place an order for an iv quinolone despite a recommendation to use an oral form, the prescriber selected from a list of predefined reasons for the use of iv, or entered a free-text indication" DELIVERER: Computerized Decision Support at point of prescribing,designed by specialist physicians and pharmacists (AMT) COMPARISON: Pre-intervention phase DESIRED CHANGE: Increase in established management (increase in oral quinolone orders) TIMING: After clinical decision-making
Outcomes	PRIMARY: Number of orders for oral quinolone. SECONDARY: Cost savings
Notes	EVIDENCE BASE: Systematic review of computerized decision support OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Objective outcome measure
Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was increase in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	One year of data pre- and postintervention
Free of other bias (ITS) ?	Low risk	Objective primary outcome, cost analysis adjusted to 2003 prices

Inaraja 1986

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: All patients receiving antibiotics. Number, age, gender and ethnicity of patients NOT CLEAR CLINICAL PROBLEM: Patients receiving antibiotics SETTING: A 447-bed University hospital in Spain
Interventions	FORMAT & DELIVERER: RESTRICTIVE. Restriction of cephalosporin use with the aim of promoting cefazolin as first choice cephalosporin introduced in month nine (Figure 6). Method of restriction and deliverer NOT CLEAR. Educational: review of all antibiotic prescriptions by pharmacist with recommendation for change was present throughout the 12 months COMPARISON: Nine months pre-intervention data DESIRED CHANGE: Reduction of established management (reduction in cephalosporin cost) TIMING: No feedback to prescribers other than advice from pharmacist. Number of pharmacist contacts NOT CLEAR Outcomes were measured for three months. Intervention status after the end of the study
Outcomes	PRIMARY: Cephalosporin use measured with costs as a percentage of cephalosporins plus penicillins plus aminoglycosides. No data about changes in absolute drug costs SECONDARY: None
Notes	EVIDENCE BASE: NOT CLEAR OTHER: Reduction in use of cephalosporins was accompanied by increase in use of penicillins and aminoglycosides. Cost of interventions NOT CLEAR. "Approximately one to two hours per day is needed for the pharmacist This is to complete review of antibiotic treatments, identify any problem medication order and contact physicians for discussion in a 447-bed hospital in which 37% of patients are receiving antibiotics". Information about cost of restriction NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Unclear risk	Only 12 months data (nine months pre- and three months postintervention) so cannot control for seasonal effects
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)

Inaraja 1986 (*Continued*)

Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Khan 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Specialties: general medicine, renal medicine, elderly care, neurology, oncology, general surgery, orthopaedics, neurosurgery, obstetrics & gynaecology, burns, ophthalmology, ENT. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: inpatients between 1995 and 2000. Number, age, gender and ethnicity of patients NOT CLEAR CLINICAL PROBLEM: *Clostridium difficile*-associated diarrhoea (CDAD) SETTING: A 800-bed non-teaching hospital in the UK
Interventions	RESTRICTIVE FORMAT & DELIVERER: RESTRICTIVE: change in antibiotic policy, from cefotaxime to ceftriaxone. Method of restriction NOT CLEAR, "ceftriaxone replaced cefotaxime on the medical wards" implies removal. COMPARISON: six quarters (18 months) before policy change DESIRED CHANGE: Modification of Established Management. Intended effect was cost reduction and convenience of once daily dosing. However, the article reports an increase in CDAD as an unintended consequence. TIMING: feedback NOT CLEAR, no information about feedback of information to prescribers Duration DONE: policy change was in place for 12 quarters (three years). An additional five quarters (15 months) data are presented after levofloxacin was substituted for ceftriaxone

Outcomes	PRIMARY: Incidence of CDAD SECONDARY: Impact of intervention on drug use NOT CLEAR because data about ceftriaxone consumption are only given for post-intervention 1 phases
Notes	EVIDENCE BASE: The change in policy from cefotaxime to ceftriaxone was based on evidence of equal efficacy with lower acquisition and administration costs. for ceftriaxone. OTHER: Costs of intervention or of CDAD diarrhoea NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	> 1 year data in each of the three phases
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: no statistical analysis, mean cases per quarter compared between periods
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done: "The standard operating procedure for selection and processing stool specimens did not change over the study period. All stool specimens from inpatients with liquid or bloody diarrhoea and those receiving antibiotic therapy were tested for C. difficile toxin. C. difficile toxin was detected by cytotoxic activity on a fibroblast cell line, with specific neutralization by Clostridium sordelli antiserum"
Free of other bias (ITS) ?	High risk	NOT DONE for the intervention that was intended to reduce *C difficile* infection in Phase 3 **Microbial outcome risk of bias:** Planned intervention: NOT DONE for unplanned intervention Phase 3 Case

		definition: DONE *C difficile* infection; all stool specimens from inpatients with liquid or bloody diarrhoea and those receiving antibiotic therapy were tested for *C. difficile* toxin. Other infection control measures: DONE, well described and same in all three phases

Kumana 2001

Methods	STUDY DESIGN: ITS QUALITY: **Risk of bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Single hospital, two departments were in the intervention group and all other departments served as control. PATIENTS: All patients in the hospital CLINICAL PROBLEM: Patients receiving glycopeptides (teicoplanin or vancomycin) SETTING: Single hospital in Hong Kong. Two years pre- and one year postintervention
Interventions	FORMAT: PERSUASIVE guideline publicized at departmental rounds and meetings followed by immediate concurrent feedback about use (reminder, a memo to prescriber about inappropriate glycopeptides prescribing) DELIVERER: Research nurse or clinical pharmacist collected data, which was reviewed by a multidisciplinary panel. They issued a memo detailing any errant prescribing signed by a consultant physician or microbiologist on the same day to the prescriber and to the supervising medical officer. COMPARISON: There were 32 months of pre-intervention data in the intervention departments plus contemporary data from rest of hospital DESIRED CHANGE: reduction in unnecessary use of glycopeptides TIMING: DONE before clinical decision-making (introduction of guidelines for appropriate and inappropriate use of glycopeptides) and within 24 hours of decision-making (individual concurrent feedback). Data for 11 months postintervention
Outcomes	PRIMARY: DDD per month of glycopeptides SECONDARY: Audit of patients who died following *Staph aureus* bacteraemia
Notes	EVIDENCE BASE: DONE Guidelines for appropriate glycopeptide use from Centers for Disease Control in the USA OTHER: Cost of intervention NOT DONE.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Done, 32 months pre- and 11 months postintervention so secular or seasonal ef-

Kumana 2001 (*Continued*)

		fects unlikely
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before and after) with χ^2 test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	11 months postintervention data, 32 months pre-intervention data
Free of other bias (ITS) ?	Low risk	Reliable primary outcome

Landgren 1988

Methods	STUDY DESIGN: CBA QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All surgeons at 12 hospitals. Number, age, gender and time since qualification NOT CLEAR PARTICIPANTS: 9417 patients of whom 2613 received antibiotic prophylaxis CLINICAL PROBLEM: Patients receiving surgical antibiotic prophylaxis SETTING: A total of 12 hospitals, 4 university, 2 suburban general and 6 rural, in Australia
Interventions	FORMAT & DELIVERER: PERSUASIVE: campaign with five elements: 1: reminder (message pad); 2: wall poster; 3: lecture; 4: videotape shown at meetings or in lounges; 5: academic visit from the project pharmacist. COMPARISON: Six hospitals were used as control in year 1, then intervention and control hospitals were crossed over in year 2 DESIRED CHANGE: Reduction of established management (reduction in duration of surgical antibiotic prophylaxis) TIMING: Feedback DONE, immediate concurrent academic detailing from project pharmacist. Duration DONE: baseline data collected at all 12 hospitals, follow-up at six months after first intervention, then after a further 12 months, after the second

Landgren 1988 (*Continued*)

	intervention
Outcomes	PRIMARY: Appropriate duration of prophylaxis SECONDARY: Timing of prophylaxis. Financial savings
Notes	EVIDENCE BASE: Recommendations for duration and timing were based on Melbourne Antibiotic Guidelines (5th Edition, 1988). OTHER: The first Intervention was associated with a AUD 43,474 decrease in cost of prophylactic antibiotics in intervention hospitals but a AUD 25,960 increase in control, a total estimated annual saving of AUD 69,434. The second intervention was also associated with an estimated annual saving of AUD 55,636. These savings (total AUD 125,070) from the two interventions were considerably greater than their combined cost (AUD 71,950)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	CBA "hospitals were paired being matched as far as possible for type size and surgical load"
Allocation concealment (selection bias)	High risk	Not done, CBA
Blinding (performance bias and detection bias) All outcomes	High risk	Not stated; all hospitals in same Australian state, CBA so not possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement
Selective reporting (reporting bias)	Low risk	Objective primary outcome measure on all patients
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Low risk	Done, pre-intervention data for primary outcome similar in intervention and control hospitals
Free of contamination?	Low risk	Intervention and control sites were different hospitals
Baseline characteristics similar?	Unclear risk	Only information is about characteristics of hospital (teaching, rural etc), no data about case mix and unlikely to change over study period

Landman 1999

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at a large University hospital. Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: All patients in the hospital (569 discharges per month from medical and surgical services). Number and characteristics of patients and episodes NOT CLEAR CLINICAL PROBLEM: requiring antibiotic treatment SETTING: University hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Use of third-generation cephalosporins, clindamycin and vancomycin required approval by an infectious diseases physician COMPARISON: 29 months pre-intervention DESIRED CHANGE: Reduction of established management (reduction in target antibiotics with the aim of reducing infections with antibiotic resistant bacteria) TIMING: Immediate, concurrent patient-specific intervention. The intervention was maintained for 23 months and data collected throughout this period
Outcomes	PRIMARY: Incidence (new cases per 1000 discharges per month) of ceftazidime-resistant Klebsiella pneumoniae, MRSA and cefotaxime-resistant Acinetobacter species (ITS data) . SECONDARY: Impact of intervention on use of individual drugs (decreased usage of cephalosporins, imipenem, clindamycin,and vancomycin and increased usage of b-lactam/b-lactamase-inhibitor antibiotics), and total antibiotic cost NOT CLEAR, only mean before and after (UBA) data provided
Notes	EVIDENCE BASE: Two previous reports of association between cephalosporin restriction and reduction in incidence of infection with cephalosporin-resistant bacteria. One included in this review (Meyer 1993) and one rejected as an inadequate ITS (Pena 1998) . OTHER: No change in monthly cost of antibiotics after the intervention. Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Reliable primary outcome
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with t-test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Landman 1999 (*Continued*)

Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Unclear risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about protocols for clinical sampling or testing
Free of other bias (ITS) ?	High risk	Change in IC practices at start of intervention **Microbial outcome Risk of Bias:** Case definition: DONE Clinical isolates Planned intervention: DONE, the change in antibiotic policy was made in response to increase in VRE, there was no pre-intervention change in the outcome organisms Isolation: DONE No change in isolation or resistant bacteria within two years of the start of the intervention Infection Control practices: NOT DONE. at the start of the intervention contact precautions were changed to include patients with *C difficile* infection.

Lautenbach 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians at a large University hospital. Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: All patients in the hospital. Number and characteristics of patients and episodes NOT CLEAR CLINICAL PROBLEM: requiring antibiotic treatment SETTING: A 725-bed University hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE Restrictive: Use of vancomycin required approval by the hospital's antimicrobial management programme. Initial restriction was that use > 72 hours required approval but after two years all use required approval COMPARISON: three years data before the intervention DESIRED CHANGE: reduction of established management (reduction in vancomycin use)

Lautenbach 2003 (*Continued*)

	TIMING:DONE immediate, concurrent intervention. The restriction was maintained for seven years
Outcomes	PRIMARY: Vancomycin use in DDD per 1000 patient days SECONDARY: Proportion of enterococci resistant to vancomycin
Notes	EVIDENCE BASE: Four studies reporting an association between use of vancomycin and prevalence of VRE OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	
Analysed appropriately (ITS) ?	Low risk	
Shape of effect pre-specified (ITS) ?	Low risk	
Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	Low risk	
Incomplete outcome data addressed (ITS) ?	Low risk	
Free of selected reporting (ITS) ?	Low risk	
Free of other bias (ITS) ?	High risk	**Microbial outcome risk of bias:** Planned intervention: High Risk: Unplanned intervention, implementation in response to emergence of VRE over the previous three years. Case definition: Low Risk, Infection from clinical isolates. Other infection control measures: Low Risk, no change to infection control procedures during the intervention phase

Lee 1995

Methods	STUDY DESIGN:ITS QUALITY: **Risk of Bias: Medium**

Lee 1995 (*Continued*)

Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PATIENTS: Number, age, gender and ethnicity of patients NOT CLEAR. A total of 480 patients reviewed during study period CLINICAL PROBLEM: Patients receiving ceftriaxone SETTING: A hospital in the USA, teaching status NOT CLEAR
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change), written guidelines, educational meetings, reminders plus immediate concurrent review of patients by a multidisciplinary antibiotic review team (AMT): an ID physician plus a pharmacist. Educational data presented during medical staff sectional meetings. Reminder letters sent to obstetrics, gastroenterology and surgery departments COMPARISON: eight months before the introduction of AMT were compared with four months after DESIRED CHANGE: Reduction in established management (substitution of ceftriaxone by cefotaxime) TIMING: DONE The intervention was immediate and patient-specific, occurring on three days each week. Follow-up was four months after introduction of the AMT
Outcomes	PRIMARY: Grams of ceftriaxone and cefotaxime. SECONDARY: None
Notes	EVIDENCE BASE: NOT CLEAR OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	
Analysed appropriately (ITS) ?	Low risk	
Shape of effect pre-specified (ITS) ?	Low risk	
Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	Low risk	
Incomplete outcome data addressed (ITS) ?	Low risk	
Free of selected reporting (ITS) ?	Low risk	
Free of other bias (ITS) ?	Low risk	

Leverstein 2001

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Departments of Neurology and Neurosurgery, details of providers NOT CLEAR PARTICIPANTS: All patients in the departments (40 beds neurosurgery, 59 beds neurology), details NOT CLEAR CLINICAL PROBLEM: Colonization with gentamicin-resistant Enterobacteriaceae SETTING: One 858-bed University hospital in the Netherlands
Interventions	FORMAT: RESTRICTIVE Restriction on all antibiotic prescriptions in the Department of Neurosurgery required authorization plus only amikacin or carbapenems allowed for treatment of gram-negative infection. Restriction started four months after start of stringent barrier precautions and one year after reinforcement of hospital control measures DELIVERER: all antimicrobial prescriptions required authorization by microbiologist or ID specialist. Prohibited antibiotics were removed from ward stocks COMPARISON: four months pre-intervention, from the start of stringent barrier precautions DESIRED CHANGE: reduction in established management (reduction in use of target antibiotics with the aim of reducing infection with gentamicin-resistant bacteria) TIMING: intervention continued for eight months
Outcomes	PRIMARY: prevalence of gentamicin-resistant Enterobacteriaceae in weekly screening stool swabs SECONDARY: impact of intervention on use of antibiotics NOT CLEAR, data are only provided as mean use before and after intervention (UBA data only)
Notes	EVIDENCE BASE: previous publications about infection control and antibiotic restriction OTHER: cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	NOT DONE, major changes in infection control four weeks before the antibiotic restriction. Separate effect cannot be estimated because no screening before change in infection control
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: No statistical analysis, time series data presented as run chart
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Leverstein 2001 (*Continued*)

Unlikely to affect data collection (ITS) ?	Low risk	Screening protocol was the same pre- and postintervention
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Screening protocol was the same pre- and postintervention
Incomplete outcome data addressed (ITS) ?	Unclear risk	NOT CLEAR, no explicit statement about complete screening samples for all patients
Free of selected reporting (ITS) ?	Unclear risk	NOT CLEAR, no explicit statement about complete screening samples for all patients
Free of other bias (ITS) ?	High risk	**Microbial Outcome Risk of Bias Criteria:** Case definition: DONE colonization by screening Planned intervention: NOT DONE, in response to increase in GRE Other infection control practices: NOT done Changes four weeks before antibiotic restriction Isolation: isolation of gentamicin resistant *Enterobacteriaceae*-positive patients in either side-rooms or cohorted with other positive patients IC practices: Increase in education plus several new hygiene practices: disposable washing gloves, elbow-directed soap dispensers; a new room-cleaning protocol. Hygiene was emphasized and more stringent barrier precautions

Madaras-Kelly 2006

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All prescribers and staff. The hospital had 87 beds that consists of a 10-bed medical-surgical intensive care unit, a 23-bed medical-surgical step-down unit, a 14-bed general medical surgical unit, a 9-bed psychiatric unit, and a 31-bed attached extended care unit PATIENTS: All inpatients CLINICAL PROBLEM: Patients receiving antibiotic treatment and patients with MRSA infections SETTING: University-affiliated veterans hospital in the USA. July 2001 to June 2004
Interventions	FORMAT: PERSUASIVE Computer-generated reminder to limit use of fluoroquinolones. "The intervention was a prompt that was inserted next to fluoroquinolone selections on the electronic order-entry screen accessed by physicians to prescribe medica-

	tions. In addition, if a physician chose to order a fluoroquinolone, the subsequent screen asked them to confirm their need for a fluoroquinolone. The prompt asked physicians to prescribe alternative antibiotic agents when possible in place of fluoroquinolones in accordance with local antibiotic use guidelines of the infectious diseases service at the Boise Veterans Affairs Medical Center" The reminder augmented printed educational materials (guideline) and educational meetings (in-service training sessions for residents) that emphasized an association between addition of levofloxacin to the hospital formulary in the late fall of 1998 and a subsequent increase in isolation of MRSA DELIVERER: Physician-directed computer intervention with content from the hospital antibiotic policy. The intervention was done "in conjunction with activities of the antibiotic management team, such as dissemination of local prescribing guidelines, educational promotion, and positive feedback relative to the decreased MRSA infection rate" (AMT) COMPARISON: pre-intervention phase DESIRED CHANGE: Reduction in established management (reduction in use of fluoroquinolones with the aim of reducing MRSA infections) TIMING: Before clinical decision-making
Outcomes	PRIMARY: MRSA infection rate (number per 1,000 patient days) SECONDARY: Changes in MRSA, coagulase negative staphylococci, enterococci, *C. difficile* and gram-negative organisms. Segmented regression analysis of change in use of levofloxacin, ciprofloxacin and other antibiotics (Table 1)
Notes	EVIDENCE BASE: Published studies and recommendations by Society of Healthcare Epidemiologists of America (SHEA) OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Unclear risk	Data collected for 11 months postintervention. Season included as a variable in the model and summer found to be associated with lower MRSA infection rate. Coincident with infection control intervention for norovirus outbreak, infection control variables included in the model and significantly associated with lower MRSA rate
Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Unlikely to affect data collection (ITS) ?	Unclear risk	Not clear, no information about protocols for sampling or testing for MRSA over the study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Objective data about MRSA
Incomplete outcome data addressed (ITS) ?	Low risk	Identification of cases was the same in the pre- and post-intervention phases
Free of selected reporting (ITS) ?	Low risk	In addition to the primary outcome of MRSA infections the Figure shows percentage of MRSA for all *Staph aureus* isolates with a reduction coincident with the intervention.
Free of other bias (ITS) ?	High risk	NOT DONE data are MRSA infection rates in six-month time periods based on very small numbers of cases (80 cases in 3½ years) **Microbial Outcome Risk of Bias:** Case definition: MRSA infection. Screening for nosocomial infections was performed through daily review of hospital admissions and discharges, intravenous antibiotic use by patients admitted to the emergency department, and laboratory reports with case confirmation by review of medical records. "An infection was assumed to be caused by MRSA if cultures of blood, intravenous line, sputum, urine, tissue, or stool obtained at the time of symptom development yielded MRSA." Planned intervention: YES. Intervention introduced in July 2003 in response to May 2003 SHEA recommendations that institutions where MRSA is endemic should consider limiting the use of broad spectrum antibiotics, especially fluoroquinolones; Other infection control: NOT DONE: antibiotic intervention coincident with environmental decontamination and hand hygiene campaign because of norovirus outbreak. Data about some infection control variables showed no change after start of intervention

May 2000

Methods	STUDY DESIGN: Controlled ITS QUALITY: **Risk of bias: HIGH** Data analyzed appropriately: NOT DONE Poisson regression on VRE infection rate from each year
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Staff of Trauma & Burns ICU (TBICU), Medical ICU (MICU) and Surgical ICU (SICU) PATIENTS: All patients in these ICUs CLINICAL PROBLEM: Adults needing intensive care SETTING: Single > 500-bed University hospital in the USA. Quarterly data for two years, 1998 and 1999, only three data points (nine months) pre-intervention
Interventions	FORMAT: PERSUASIVE Management guidelines designed to limit use of cephalosporins by replacing them with piperacillin tazobactam for prophylactic, empiric and definitive treatment indications in Trauma & Burns ICU. In addition a protocol was introduced for diagnosis and treatment of ventilator-associated pneumonia that withdrew antibiotic therapy when broncho-alveolar lavage was negative. Results are presented as run charts for prescribing and VRE in all three ICUs (Figures 3 - 5) DELIVERER: Guidelines written by the Department of Surgery COMPARISON: Pre-intervention period and measurement of outcomes in MICU and SICU. These units did not change their antibiotic policy DESIRED CHANGE: Reduction in established management (reduction in vancomycin use with the aim of reducing VRE infections) TIMING: Before clinical decision-making
Outcomes	PRIMARY: VRE infections per 1000 patient days SECONDARY: MRSA infections, use of vancomycin, third-generation cephalosporins and piperacillin tazobactam per 1000 patient days
Notes	EVIDENCE BASE: NOT DONE (not supported by a single RCT or a systematic review). Previous studies suggest link between cephalosporin use and VRE OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only nine months data pre-intervention so secular/seasonal effects possible. No information about infection control practices before or after the intervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: χ^2 test, uncontrolled before-after with Poisson regression analysis of VRE rates

May 2000 (*Continued*)

Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, objective outcome measure
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Objective outcome measure, VRE infections
Incomplete outcome data addressed (ITS) ?	Low risk	Done, objective outcome measure
Free of selected reporting (ITS) ?	Unclear risk	Not clear, no information about protocol for sampling or testing over study period
Free of other bias (ITS) ?	High risk	NOT DONE **Microbial Outcome Risk of Bias Criteria:** Case definition: DONE clinical isolates of enterococci screened for vancomycin resistance. Planned intervention: NOT DONE for intervention ward (response to increasing VRE in previous two years). However, steady increase not an outbreak and VRE data presented for other wards with no intervention. Other infection control Isolation: NOT DONE. IC practices: NOT DONE No information about isolation or infection control practices before or after the intervention

McElnay 1995

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians from a range of specialties: geriatric, cardiology, general medical, surgical, paediatric, intensive care, ENT, gynaecology and maternity. Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: Number of episodes of care, number of patients, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: All patients receiving antibiotics SETTING: A 370-bed District General Hospital (nonteaching) in the UK
Interventions	FORMAT & DELIVERER:RESTRICTIVE AND PERSUASIVE Restrictive: Antibiotic policy with consultant counter-signature required for restricted drugs Persuasive: Written materials and academic detailing. Antibiotic policy written by Drug

	and Therapeutics Commitee following consultation. Academic detailing: "education of junior medical staff on the rationale behind the antibiotic selection was also carried out by clinical pharmacists" (p208). COMPARISON: A total of 12 months data before the intervention DESIRED CHANGE: reduction in established management (reduced expenditure on antibiotics) TIMING: Immediate, concurrent intervention. Data collected for 12 months after the start of the intervention
Outcomes	PRIMARY: Expenditure on antibiotics SECONDARY: None
Notes	EVIDENCE BASE: the antibiotic policy was developed by the Drug & Therapeutics Committee in consultation with all consultants in the hospital and the final version was approved by the Medical Staff Committee. OTHER: Costing of development and implementation of the antibiotic policy NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	12 months data pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	Antibiotic costs were adjusted to 1989 prices

McGowan 1976

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age, specialty and time since qualification NOT CLEAR. Provides additional data about antibiotic use at four other hospitals but with no baseline data or division into pre- and postintervention periods PARTICIPANTS: All patients in the hospital, number, age, gender and ethnicity NOT CLEAR; 45,000 admissions during study period CLINICAL PROBLEM: requiring antibiotic treatment. SETTING: Single University Hospital in USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE Restrictive: use of target antibiotics required authorization by the ID consultant COMPARISON: Four years before intervention DESIRED CHANGE: Reduction of established management reduction in use of chloramphenicol TIMING: Outcomes measured for four years after the intervention
Outcomes	PRIMARY: Grams of chloramphenicol (thousands) SECONDARY: Data are also presented for other drugs (ampicillin, nafcillin and cloxacillin)
Notes	EVIDENCE BASE: NOT CLEAR OTHER: None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Data over eight years, four years pre- and four years postintervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period

McGowan 1976 (*Continued*)

Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

McLaughlin 2005

Methods	STUDY DESIGN: ITS QUALITY: **Risk of bias: HIGH for first intervention. Second intervention cannot be evaluated at all**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Staff from 12 medical wards PATIENTS: All patients in the wards CLINICAL PROBLEM: Adults requiring IV antibiotic therapy SETTING: Single University hospital in the UK. Weekly data for four weeks pre- and postintervention followed by further four week data collection after repeat of the intervention six months later
Interventions	FORMAT: PERSUASIVE (printed educational materials, educational meetings, reminders and academic detailing). Guidelines introduced at staff meetings ("sepsis and IV to oral antibiotic switch guidelines were launched (by RAS and CM) at three separate staff meetings following completion of the pre intervention phase. The majority of junior doctors responsible for prescribing attended, as did all pharmacists and ward nursing managers"), distribution of guidelines to all staff, reminders via wall posters and 'REFER TO IVOST PROTOCOL' stickers inserted into case notes after 24 hours of IV therapy. Academic detailing: Nurses responsible for administering IV antibiotics were informed of the criteria and rationale for switching from IV to oral antibiotics. The pharmacist discussed specific prescriptions with medical and nursing staff only if requested by prescribers in order to clarify the use of the guidelines. Reinforcement of the guidelines after staff changes six months after introduction with additional staff meetings DELIVERER: Pharmacist COMPARISON: Pre-intervention DESIRED CHANGE: Modification of existing management (faster switch from IV to oral administration of antibiotics) TIMING: Within 24 hours of clinical decision-making
Outcomes	PRIMARY: Appropriateness of timing of IV to oral switch SECONDARY: Appropriateness and duration of IV therapy but no time series data for these outcomes
Notes	EVIDENCE BASE: NOT DONE (not supported by a single RCT or a systematic review) Interventions in other hospitals cited but not RCTs OTHER: Cost of intervention NOT DONE

McLaughlin 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Not done, data were only collected for four weeks before and after the intervention so secular changes could have accounted for any differences
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with χ^2 test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Unclear risk	Not stated
Knowledge of the allocation adequately prevented(ITS)?	High risk	
Free of other bias (ITS) ?	Low risk	

McNulty 1997

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the elderly care unit. Number, age, time since qualification NOT CLEAR PARTICIPANTS: There were 486 episodes of care in the elderly care unit. Age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: All patients in the elderly care unit SETTING: Elderly care unit in a single District General Hospital (nonteaching) in the UK
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Change of antibiotics for treatment of suspected infection to benzylpenicillin, gentamicin and trimethoprim. Restriction of IV cefuroxime and removal of oral cefuroxime from pharmacy stock. Monitoring of antibiotic prescribing by ward pharmacist. COMPARISON: Seven months pre-restriction DESIRED CHANGE: Reduction in established management (reduction in use of target antibiotics with the aim of reducing *C. difficile* infection) TIMING: Single intervention per patient. Outcomes were measured for 16 months and restriction was maintained after the end of the study

Outcomes	PRIMARY: Cases of *Clostridium difficile*-associated diarrhoea (CDAD) per month (ITS data). SECONDARY: monthly cost of cefuroxime (ITS data). Length of stay (LOS) and mortality (UBA data)
Notes	EVIDENCE BASE: Choice of antibiotics for the restriction policy was based on two observational studies of risk factors for CDAD (Anand 1994; Bartram 1995) OTHER: Infection control measures were the same before and after implementation of antibiotic restriction policy. LOS and mortality were similar before (17.2 days, 20.4%) and after (18.9 days, 21.3%) implementation of antibiotic restriction

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only seven months pre-intervention data so secular/seasonal changes possible. Also changes were made to infection control during the intervention phase
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	High risk	**Microbial Outcome Risk of Bias Criteria:** Case definition: DONE *C. difficile* infection, definition unchanged during the study periods. Unplanned intervention: NOT DONE antibiotic restriction was implemented in response to increasing cases of CDAD in the preceding seven months,

		despite increased infection control. Other infection control measures: NOT DONE Changes to environmental cleaning and reminders about hand hygiene implemented three months before the start of intervention

Mercer 1999

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: Number, age, gender and ethnicity of patients NOT CLEAR CLINICAL PROBLEM: Patients receiving ceftriaxone SETTING: A 360-bed community hospital in the USA, teaching status NOT CLEAR
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Removal of 16 antibiotics from stock in the Emergency Room and Operating Room, ID consultant approval required for use of these 16 drugs Persuasive: Written materials and reminder. Antibiotic policy and pneumonia clinical pathway. Reminder placed in the chart of each appropriate patient COMPARISON: 12 months before the intervention were compared with 12 months after DESIRED CHANGE: Reduction in established management (reduction in antibiotic costs) TIMING: The intervention was immediate and patient-specific, requiring authorization for each use of restricted drugs. Follow-up was 12 months after introduction of the restriction
Outcomes	PRIMARY: Cost of antibiotics SECONDARY: None
Notes	EVIDENCE BASE: NOT CLEAR OTHER: Cost of intervention NOT DONE.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Full year before and after
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)

Mercer 1999 (*Continued*)

Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	Antibiotic costs were adjusted to 1995 prices and excluded ancillary or administrative charges

Meyer 1993

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians. Number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: All patients, number, age, gender and ethnicity of patients NOT CLEAR. 432 isolates evaluated CLINICAL PROBLEM: Patients receiving antibiotics SETTING: A 487-bed University hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE Restrictive: Use of ceftazidime required counter-signature of prescription by Infectious Diseases physician. Simultaneous introduction of barrier precautions for colonized and infected patients COMPARISON: A total of 14 months of pre-intervention data DESIRED CHANGE: Reduction of established management (reduction in use of target antibiotics with the aim of reducing colonization with ceftazidime-resistant *Klebsiella pneumoniae*) TIMING: Immediate concurrent intervention. The restriction was maintained and data collected for 11 months
Outcomes	PRIMARY: Incidence of ceftazidime-resistant Klebsiella pneumoniae as the rate per 1000 average daily census. SECONDARY: Use of ceftazidime, imipenem and ceftriaxone reported as number of

	approvals for these drugs and pre-intervention data were incomplete
Notes	EVIDENCE BASE: The study was designed to test the effectiveness of ceftazidime restriction OTHER: Cost of intervention NOT DONE. The authors comment that increased use of imipenem after the intervention was associated with increased imipenem-resistant Acinetobacter infections

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Infection control intervention simultaneous with antibiotic intervention. 14 months pre- and 11 months postintervention so secular change unlikely
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: run chart with no statistical analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period. Criteria for sampling and testing for *C difficile* were unchanged over the study period.
Free of other bias (ITS) ?	High risk	NOT DONE. **Microbial Outcome Risk of Bias Criteria:** Planned intervention: NOT DONE, unplanned intervention. Case definition: DONE Microbial outcome was colonization by surveillance screening. Clinical infection was diagnosed by CDC definition but not used as an outcome. Infection or colonization by case note review. Other infection control measures: NOT DONE Barrier precautions

		were instituted on colonized and infected patients at the same time that ceftazidime restriction was implemented

Micek 2004

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: A total of 290 patients with presumed ventilator-associated pneumonia (VAP) PROVIDERS: Intensive Care Unit (ICU) physicians PATIENTS: Adults (> 18 years) in the ICU CLINICAL PROBLEM: VAP requiring antibiotics SETTING: Single ICU (19 beds) in a US teaching hospital
Interventions	FORMAT: PERSUASIVE Educational outreach (review and recommend change) with written policy. Based on an antibiotic discontinuation policy for VAP with defined clinical and microbiological criteria. Antibiotic treatment was to be discontinued if any one of the following conditions were identified: (1) noninfectious aetiology for the infiltrates was identified not requiring antibiotics (e.g. atelectasis, pulmonary edema); (2) signs and symptoms suggesting active infection had resolved (e.g. temperature < 38. 3°C, circulating leukocyte count < 10,000/L [10 X 10^9/L] or decreased by ≥25% from the peak value, improvement or lack of progression on the chest radiograph, absence of purulent sputum, and a Pao2/FIo2 ratio > 250). All of these criteria had to be met for the antibiotic discontinuation recommendation to be made DELIVERER: Advice from one of two investigators, one a pharmacist and the other an ICU physician COMPARISON: Clinical judgement of ICU physicians DESIRED CHANGE: Reduction in established management (reduction in duration of antibiotics) TIMING: At the point of decision-making. The intervention was in place for 15 months (April 2002 to July 2003)
Outcomes	PRIMARY: Duration of antibiotic therapy SECONDARY: Mortality, length of stay, length of mechanical ventilation, subsequent infections
Notes	EVIDENCE BASE: Previous uncontrolled before-after study (Ibrahim 2001) suggested that clinical guidelines increased appropriate antibiotic treatment for VAP OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Micek 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned" but no details of how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were missing from four (2. 6%) patients in the intervention group and eight (5.4%) in the control group
Selective reporting (reporting bias)	Low risk	Done, outcomes were obtained from routine data systems.
Other bias	High risk	The policy was only implemented at weekends or on holidays when one of the two investigators was available in the hospital
Baseline Outcomes similar?	Unclear risk	No data about duration of therapy before the intervention
Free of contamination?	High risk	Physicians managing patients in the control group would have seen reminders for the intervention group
Baseline characteristics similar?	Low risk	Table 1

Mol 2005

Methods	STUDY DESIGN: ITS QUALITY: **Risk of bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Staff of the 190-bed Department of Internal Medicine (pulmonology, haematology, nephrology, gastroenterology, general internal medicine and ICU) PATIENTS: All patients in the wards CLINICAL PROBLEM: Receiving antibiotic therapy SETTING: Single University hospital in the Netherlands. July 2001 to October 2003. Pre-intervention July 2001 to February 2002; postintervention 1 February 2002 to August 2002; postintervention 2 January 2003 to October 2003
Interventions	FORMAT: PERSUASIVE WITH MARKETING: Specialists and residents were interviewed to determine barriers to following antibiotic guidelines in order to identify the most appropriate intervention to improve prescribing. *First intervention:* guidelines developed from international evidence plus national guide-

	lines adapted to local resistance patterns and fine-tuned through consultation with specialists in the hospital. Guidelines introduced through staff meetings in both book and electronic formats (indexed and searchable version on the hospital intranet). *Second intervention:* academic detailing with individual and group sessions, including feedback of aggregated prescribing data and individual feedback triggered by treatment not in line with guidelines DELIVERER: Feedback (academic detailing) via deliverer NOT CLEAR COMPARISON: Pre-intervention phase DESIRED CHANGE: Increase in established management (increased compliance with guidelines) TIMING: Before clinical decision-making; within one day of clinical decision-making when ciprofloxacin or co-amoxiclav was prescribed
Outcomes	PRIMARY: Overall compliance with guideline SECONDARY: Antibiotic cost and compliance with recommendations for specific drugs
Notes	EVIDENCE BASE: NOT CLEAR for antibiotic guidelines. DONE for academic detailing (one RCT). International evidence, national guidelines, local consultation with target group OTHER: No significant impact of intervention on antimicrobial costs. Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	
Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was increase in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Data collection method was same throughout study
Knowledge of the allocation adequately prevented(ITS)?	High risk	Subjective outcome without blinded assessment
Incomplete outcome data addressed (ITS) ?	Unclear risk	Not stated whether compliance was assessed in all patients
Free of selected reporting (ITS) ?	Unclear risk	Not stated whether compliance was assessed in all patients

Mol 2005 (*Continued*)

Free of other bias (ITS) ?	Low risk	The kappa value for the primary outcome measure was 0.71, which is below the level set by EPOC but for the reasons given in the text we feel is adequate for assessment of compliance with an antibiotic guideline. Drug costs were adjusted to April 2001 prices

Naughton 2001

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians (general/family practice); nurses (Registered and Licensed Practical) and physician assistants in 10 Skilled Nursing Facilities (SNF). Number, age and time since qualification NOT CLEAR PARTICIPANTS: There were 350 episodes of care. Number, age, gender and ethnicity not clear CLINICAL PROBLEM: Nursing home-acquired pneumonia (NHAP) SETTING: Ten Skilled Nursing Facilities (SNFs) with a total of 2375 beds in one US city. Mixed reimbursement systems. Nonteaching
Interventions	FORMAT & DELIVERER: PERSUASIVE (printed educational materials, educational meetings, reminders and academic detailing). Written guidelines for NHAP were written with input from physicians working in the SNFs. The guidelines provided specific recommendations for which antibiotics to prescribe, criteria for determining timing of switch to an oral agent after parenteral therapy, and duration of treatment. 19 SNFs received multidisciplinary education about the guidelines: physician-led groups plus reminders (laminated cards and wall mounted posters) plus academic detailing (multiple one-hour nurse-led training to nurses from three shifts in small groups) MARKETING: nurses were given the opportunity to identify barriers to implementation, to develop strategies for addressing those barriers, and to discuss and clarify their role in implementation COMPARISON: Five SNFs assigned to physician-only intervention (physician-led groups and laminated cards but no nurse-led groups) DESIRED CHANGE: Increase in established management (increase in the use of parenteral antibiotics (PA) for patients with severe pneumonia with the aim of reducing mortality) TIMING: Single intervention targeted at providers. Follow-up of outcomes for six months
Outcomes	PRIMARY: Percentage of patients with NHAP who received PA when indicated by the guideline. SECONDARY: Mortality in patients with guideline indication for PA

Notes	EVIDENCE BASE: Criteria for diagnosis and severity assessment of NHAP based on three published papers by the authors: two observational studies and a guideline (references 17, 26, 27). OTHER: No power calculation. No explanation for the much smaller number of cases of NHAP in the intervention SNFs compared with control. Mortality decreased from 54/226 (24%) in the pre-intervention period to 21/116 (18%) postintervention. However, mortality data by intervention and control groups NOT DONE OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Facilities were randomised into a multidisciplinary or a physician only intervention"
Allocation concealment (selection bias)	High risk	Not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Done in follow up
Selective reporting (reporting bias)	Low risk	Outcomes fully reported
Other bias	Unclear risk	Authors acknowledge that indications for parenteral antibiotics were retrospectively abstracted from charts and may not have been consistently recorded at all facilities
Baseline Outcomes similar?	Low risk	Table 2
Free of contamination?	Low risk	Randomization was by nursing home, control homes did not receive the intervention
Baseline characteristics similar?	Unclear risk	"The clinical characteristics of the pre intervention group, including age, sex, activities of daily living (ADL) status, severity of illness, and mortality, did not differ significantly from those of the postintervention group." No details given

Oosterheert 2005

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: A total of 107 patients PROVIDERS: Hospital physicians, number and grade NOT CLEAR PATIENTS: Inpatients with lower respiratory tract infection (LRTI) CLINICAL PROBLEM: Admitted to hospital for treatment of LRTI SETTING: Multicentre: two Dutch hospitals
Interventions	FORMAT: STRUCTURAL Use of rapid detection tests: Polymerase Chain Reaction (PCR) to detect pathogens causing LRTI. The aim was to improve patient care and reduce unnecessary antibiotic use by early identification of patients with viral infections. Test results were reported within 48 hours after samples were obtained "To mimic real-life situations, decisions regarding treatment changes after results of PCR analysis were available were left at the discretion of the physician". "Physicians complied with the hospital guidelines described in the hospital antibiotic formulary." Written antibiotic policy sent to all physicians DELIVERER: Specialist physician (Medical Microbiology) COMPARISON: Conventional diagnostic tests DESIRED CHANGE: Modification of established management (reduction in unnecessary use of antibiotics) TIMING: Results were available 30 (+ 13) hours after sampling. The intervention continued for 18 months (from November 2002 to March 2004)
Outcomes	PRIMARY: Change of antibiotic treatment based on PCR. The study was powered to detect reduction in antibiotic use from 100% to 80% of patients SECONDARY: Mortality Median duration of antibiotic treatment. Cost of hospitalization, all diagnostic and treatment costs
Notes	EVIDENCE BASE: Previous observational studies have suggested that rapid identification of a viral aetiology of LRTI may improve effective patient management OTHER: Cost of intervention DONE. Use of real time PCR increased antibiotic treatment and diagnostic costs by EUR 318 per patient (test cost of EUR 331 only minimally offset by savings in antibiotic cost). No evidence of savings on other diagnostic tests or hospitalization. The total cost per patient for hospitalizations, diagnostic procedures, and treatment was EUR 5117.05 in the intervention group and EUR 4741.30 in the control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated...by means of a computer generated table"
Allocation concealment (selection bias)	High risk	

Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Free of contamination?	Low risk	
Baseline characteristics similar?	High risk	

Patel 1989

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING Single hospital in the UK. Teaching status NOT CLEAR
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change) to promote written formulary disseminated via educational briefings delivered to all junior doctors at induction meetings. Information sheet recommending that co-amoxiclav be restricted for amoxicillin resistant bacteria, distributed to all doctors and reinforced by ward pharmacists through immediate, concurrent, patient-spectric feedback. COMPARISON: data about seven months pre-intervention DESIRED CHANGE: Reduction of established management (reduction in expenditure on oral co-amoxiclav) TIMING: Outcomes were measured during five months after the start of the intervention. The intervention remained in place at the end of the study
Outcomes	PRIMARY: Expenditure on oral co-amoxiclav. SECONDARY: expenditure on other antibiotics (presented as UBA)
Notes	EVIDENCE BASE: The intervention was based on analysis of local microbiology results. OTHER: The intervention was associated with increased expenditure on amoxicillin but expenditure on other antibiotics remained stable or decreased (UBA). Cost of intervention NOT DONE

Patel 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only five months pre-intervention data so secular changes possible
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Paul 2006

Methods	STUDY DESIGN:Cluster-RCT QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: A total of 2326 participants Three sites but wards were unit of randomization PROVIDERS: All physicians in the hospital. Number, age and time since qualification NOT CLEAR PATIENTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Included were (i) patients from whom blood cultures were drawn; (ii) patients prescribed antibiotics (not for prophylaxis); (iii) patients fulfilling criteria for the systemic inflammatory response syndrome; (iv) patients with a focus of infection; (v) patients with shock compatible with septic shock; and (vi) patients with febrile neutropenia

	We excluded HIV-positive patients with a current (suspected or identified) opportunistic disease and/or AIDS-defining illness currently or within the past six months, organ or bone marrow transplant recipients, children < 18 years, suspected travel infections or tuberculosis, and pregnant women. Patients were included only once in the interventional study SETTING: Three university-affiliated primary and tertiary care hospitals in three countries; Israel (six wards of internal medicine, 240 beds); Germany (two gastroenterology, two nephrology, two intensive care wards, 94 beds) and Italy (three infectious disease wards, 90 beds)
Interventions	FORMAT: STRUCTURAL AND PERSUASIVE Structural: Computer decision support system that required substantial adaption to the participating hospitals' existing systems for computerized reporting of laboratory test results and patient administration Persuasive: the decision support system provided advice intended to reduce unnecessary antibiotic use and promote necessary use DELIVERER: TREAT System (computer and decision support system) designed by a multidisciplinary team COMPARISON: Local guidelines DESIRED CHANGE: Modification of established management (improvement in empirical antibiotic treatment) TIMING: At the point of decision-making. Intervention in place for six months, from May to November 2004
Outcomes	PRIMARY: Appropriate antibiotic treatments SECONDARY: Costs, which included the estimated ecological cost of inappropriate antibiotic treatment. Length of stay. 30-day mortality
Notes	EVIDENCE BASE: Performance and safety of TREAT had previously been assessed in non-interventional cohort studies OTHER: Full details of the model for estimation of cost of adverse events including ecological costs are given in Appendix 2 on line Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Wards were randomly allocated...by drawing a random code from a closed opaque box"
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Adjustment of drug costs for changes in prices not necessary because the intervention only lasted six months
Baseline Outcomes similar?	Low risk	
Baseline characteristics similar?	Low risk	

Pear 1994

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital, number, age specialties and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: Single University hospital in the USA with an averaged daily census of 168 patients
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Antibiotic use restricted by a hospital formulary for most staff physicians and house staff that required approval from an ID physician for non-formulary drugs. Use of non-formulary antibiotics required prior approval by ID physician. Intervention was change of clindamycin from formulary to non-formulary (restricted). COMPARISON: A total of 40 months of data before restriction of clindamycin DESIRED CHANGE: Reduction in established management (reduction in use of clindamycin with the aim of reducing *C. difficile* infection) TIMING: Single intervention. Outcomes were measured for 14 months after start of clindamycin restriction and restriction was maintained after the end of the study
Outcomes	PRIMARY: Cases of *Clostridium difficile*-associated diarrhoea (CDAD) per month (ITS data). SECONDARY: Prevalence of clindamycin-resistant *Clostridium difficile*
Notes	EVIDENCE BASE: analysis of association between clindamycin use and cases of CDAD for 19 months before the start of restriction plus six previous observational studies that identified clindamycin as a risk factor for CDAD. OTHER: Infection control measures were identical in the year before and after start of clindamycin restriction. Cost of intervention: NOT DONE

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Low risk	Enough data to account for seasonal variation, and infection control measures did not change over study period
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: run chart with no statistical analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	High risk	Not done, the method of detection of *C difficile* toxin changed from cell culture assay in the first four years of the study to a latex test in the final year (5 months after the start of clindamycin restriction)
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	High risk	Not done, change in method of testing for *C difficile* during the study period (see case definition)
Free of other bias (ITS) ?	High risk	**Microbial Outcome Risk of Bias Criteria** Case definition: NOT DONE Infection: diarrhoea with positive assay for *C. difficile* cytotoxin and antibiotic therapy within the previous 60 days. However, the method of detection of toxin changed from cell culture assay in the first four years of the study to a latex test in the final year (five months after the start of clindamycin restriction). Planned intervention: NOT DONE Response to an outbreak of CDAD starting 12 months before restriction. Other infection control, Isolation & IC practices: DONE Infection control measures were identical in the year before and after start of clindamycin restriction. Hospital staff education and increased availability of gloves and improvement of environmental hygiene were implemented a year before re-

		striction of clindamycin with no apparent impact on the frequency of new cases

Perez 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians, surgeons, paediatricians, obstetricians-gynaecologists and intensivists; level of training, age and time since qualification NOT CLEAR PARTICIPANTS: Adults and children with normal renal function; age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Inappropriate prescribing of antibiotics (specifically in relation to intervals between doses of aminoglycosides and first- and third-generation cephalosporins and timing of surgical prophylaxis) SETTING: University Hospital in Colombia
Interventions	FORMAT: RESTRICTIVE AND PERSUASIVE Restrictive: Compulsory order form for all antibiotics, the pharmacy was instructed to reject prescriptions entered by any different method. The form indicated dosing intervals that were never or rarely indicated due to expected lack of efficacy or increased toxicity. This intervention was specifically intended to reduce inappropriate dosing of three drug groups: aminoglycosides, cephradine/cephalothin and ceftazidime/cefotaxime) Persuasive: written materials, meetings and reminders. Guideline disseminated through lectures in all clinical departments as well as poster reminders. The intervention to promote appropriate dosing for surgical prophylaxis also included a blood pressure cuff for anaesthetists and posters with the logo "Do not forget the antibiotic prophylactic within one hour before surgical incision" DELIVERER: Order form implemented by pharmacists, who rejected any inappropriate prescriptions. Reminders for prophylaxis were posters and messages on blood pressure cuffs. COMPARISON: Number of incorrect prescriptions before and after implementation of the intervention DESIRED CHANGE: Increase established management (reduction in proportion of incorrect prescriptions for antibiotics) TIMING: All new prescriptions for target antibiotics identified daily. A total of 145 weeks of observation (79 - 103 weeks pre-intervention)
Outcomes	PRIMARY: Reduction in incidence of incorrect antibiotic prescriptions (dosing intervals and timing of surgical prophylaxis)
Notes	EVIDENCE BASE: NOT CLEAR OTHER: No data on patient outcome or changes in costs as a result of the intervention are provided. Cost of the intervention NOT DONE

Risk of bias

Perez 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Low risk	> 1 year data pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Done in original paper: ARIMA analysis, selected in preference to segmented regression analysis because of nonlinear outcome data
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Richards 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM** Data analyzed appropriately in original paper: NOT DONE (Kruskal-Wallis test of mean use before-after)
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital, details NOT CLEAR. PARTICIPANTS: All patients except ICU, ER, ID, details NOT CLEAR CLINICAL PROBLEM: Receiving treatment with target antibiotics SETTING: Single University hospital (Royal Melbourne Hospital) in Australia
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE, AMT Restrictive: Cefotaxime was added to hospital's list of restricted antibiotics, removed from stock in general wards and operating theatres. Prescriptions for cefotaxime had to be endorsed with an Antimicrobial Approval Number generated by a web-based form for prescription registration and approval Persuasive: antibiotic policy, meetings, reminder, audit and feedback. The hospital used

	the national antibiotic guidelines. The system was introduced after two months of educational sessions and demonstrations for prescribers, pharmacists and administrators. The computer order form served as a reminder of policy. Prescribing data were fed back to doctors with hospital unit level reports about use of cephalosporins and proportion of use for which approval numbers were obtained. This included review of prescriptions for which the indication 'severe community-acquired pneumonia' was used to justify cephalosporins. "Letters were sent to prescribers who twice or more entered severe pneumonia as the indication when the chest x-ray was formally reported as normal at the time of prescribing." DELIVERER AMT: The programme was devised by a multidisciplinary committee (pharmacists, specialist physician (ID), junior doctor and emergency physician), effectively an AMT. COMPARISON: Eight months pre-intervention DESIRED CHANGE: Reduction in established management (reduction in use of target drugs) TIMING: Single concurrent intervention per patient. Intervention maintained for 15 months
Outcomes	PRIMARY: Use of cefotaxime or ceftriaxone SECONDARY: Use of other antibiotics - gentamicin, benzyl penicillin, carbapenems, piperacillin, ticarcillin and ciprofloxacin
Notes	Notes Concurrent audits showed marked decrease in use for surgical prophylaxis and for respiratory infection without X-ray changes OTHER: Cost of intervention DONE Software cost AUD 6K. Post-intervention audit required 12 person weeks. Increased gentamicin monitoring but cost not quantified.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Unclear risk	Eight months data pre-intervention, 15 months post-, not enough to adjust for seasonal variation
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with Kruskal-Wallis test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period

Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Richardson 2000

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age and time since qualification NOT CLEAR. Three intensive care units, three general medical and one general surgical PARTICIPANTS: A total of 618 episodes of vancomycin use (220 pre- and 398 postintervention). Number of patients, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: Single tertiary care teaching hospital in the USA with 150 acute care and 90 long-term care beds
Interventions	FORMAT & DELIVERER: PERSUASIVE: Educational outreach (review and recommend change) to promote local guideline based on national recommendations (HICCPAC criteria adopted by the Pharmacy and Therapeutics Committee). Reminders delivered to house staff and service chiefs by pharmacists were ineffective. This led to immediate, concurrent review of all vancomycin prescriptions by an ID pharmacist and discussion with house staff of cases that did not meet criteria for appropriate use. COMPARISON: Data about three months in the year before (April, August and January) . DESIRED CHANGE: Reduction of established management (reduction in inappropriate use of vancomycin with the aim of reducing prevalence of VRE infections). TIMING: Outcomes were measured during six one-month periods during a total of 30 months after the start of the intervention. The intervention remained in place at the end of the study
Outcomes	PRIMARY: Percentage of episodes of vancomycin use deemed inappropriate. SECONDARY: impact of intervention on prevalence of infections caused by vancomycin-resistant enterococci NOT CLEAR (data only presented as UBA)
Notes	EVIDENCE BASE: Local guideline based on 1994 CDC guidance about appropriate vancomycin use OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Richardson 2000 (*Continued*)

Intervention independent (ITS) ?	High risk	Data only collected for three months pre- and six months postintervention so secular/ seasonal changes possible
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with t-test.Not done, t-test on means, uncontrolled before-after
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Unclear risk	NOT CLEAR, the reliability of the assessment of appropriate vancomycin use was not reported
Knowledge of the allocation adequately prevented(ITS)?	High risk	Retrospective assessment of appropriateness without concealment of study phase
Incomplete outcome data addressed (ITS) ?	High risk	Assessment of appropriateness from retrospective assessment of all patients treated in one month but only done every four to six months
Free of selected reporting (ITS) ?	Unclear risk	Not clear, data were only collected intermittently
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Saizy-Callaert 2003

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: Single 600-bed University hospital in France
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Use of the most expensive antibiotics required completion of named-patient prescription forms by a senior hospital physician Persuasive: Printed materials, meetings and reminders. Written guideline given to resi-

	dents and all new arrivals during a compulsory training session at the beginning of each semester. Pocket-sized prescribing guide given to all staff COMPARISON: Data for three years after implementation of the programme DESIRED CHANGE: Reduction of established management (reduction in antibiotic expenditure) TIMING: Outcomes analyzed for four years after implementation of the programme, remained in force at the end of the study
Outcomes	PRIMARY: Anti-Infective Expenditure (AIE) per hospital patient SECONDARY: Impact of intervention on percentage of MRSA, extended spectrum beta-lactamase (ESBL) and ceftazidime-resistant *Pseudomonas* spp. NOT CLEAR because data are only provided for the four years after the start of the intervention so microbial data are invalid (inadequate ITS)
Notes	EVIDENCE BASE: Local prescribing guideline was based on "guidelines defined by scientific societies and the public authorities". OTHER: Cost of programme NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Four years data pre and three years data post intervention so enough data to account for seasonal change
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with Fisher's exact test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	High risk	There is no information about change in price of antibiotics over the study period
Free of selected reporting (ITS) ?	Unclear risk	The intervention was targeted at specific antibiotics but no information is provided about their use or cost

Free of other bias (ITS) ?	Unclear risk	No adjustment of antibiotic costs for change in price so change in price of antibiotics (rather than change in use) over the study period may have been responsible for reduction in cost per patient over the study period. No data about number of admissions pre-intervention

Salama 1996

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians. Number, specialties, gender, age and years since qualification NOT CLEAR PARTICIPANTS: Number of episodes, patients, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: All patients requiring antibiotic therapy SETTING: A 465-bed tertiary care university teaching hospital in Canada
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE. Restrictive: Restriction of eight antibiotics via compulsory antibiotic order form plus automatic three-day stop order for all antibiotics plus therapeutic substitution of selected drugs Persuasive: Written materials, meetings, reminders, academic detailing. Clinical antimicrobial guidelines disseminated via newsletters, in-service meetings, wall posters, pocket charts and educational rounds COMPARISON: 13 months pre-intervention DESIRED CHANGE: Reduction in established management (reduction in vancomycin use) TIMING: Intervention at the point of decision-making. Intervention maintained for 29 months
Outcomes	PRIMARY: Vancomycin use SECONDARY: Ceftazidime use (ITS), antibiotic cost as a percentage of total drug cost (ITS) and total antibiotic cost (UBA)
Notes	EVIDENCE BASE: Development and implementation involved physicians, pharmacists, nurses and administrators with approval by the Medical Staff Advisory Committee. OTHER: Total antibiotic costs in the two years pre-intervention were CAD 126,650 and CAD 119,841 versus CAD 108,664 and CAD 80,770 in the two years postintervention. Cost of the programme NOT CLEAR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Salama 1996 (*Continued*)

Intervention independent (ITS) ?	Low risk	> 12 months data pre- and post-intervention, enough to account for seasonal change
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Senn 2004

Methods	STUDY DESIGN: RCT QUALITY: **Risk of bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Residents on medical and surgical wards PATIENTS: All patients in the 77-bed surgical and 101-bed medical units were screened daily for eligibility. Patients were not recruited during weekends. 251 patients were recruited, 126 intervention and 125 control CLINICAL PROBLEM: Adult patients receiving IV antibiotics for three to four days with no modification since starting treatment SETTING: Single 800-bed University hospital in Switzerland. Data collected over five months
Interventions	FORMAT: PERSUASIVE (reminder). The intervention consisted of mailing a printed questionnaire to the resident in charge of patients who were receiving IV antibiotic treatment. This questionnaire asked three questions regarding possible adaptation of antibiotic therapy on day 3 or 4. It was collected 24 hours later. If the resident had not yet completed it at that time, he/she was reminded once to do so. No intervention was made in the control group

	DELIVERER: Mailed questionnaire COMPARISON: Control patients with no intervention made to doctors DESIRED CHANGE: Reduction in established management (reduction in duration of IV therapy) TIMING: Intervention at the point of decision-making (potential modification three to four days after start of antibiotics)
Outcomes	PRIMARY: Modification of IV antibiotic therapy SECONDARY: Time to modification
Notes	EVIDENCE BASE: NOT DONE (not supported by a single RCT or a systematic review). Previous observational studies showed that important new information is usually available for reassessment of antibiotic therapy 72 hours after initiation OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients allocated ....by using a computer generated randomizations list"
Allocation concealment (selection bias)	Low risk	"Concealment of allocation was achieved as the physician in charge of the patient was involved after randomizations"
Blinding (performance bias and detection bias) All outcomes	High risk	"This was a randomised, controlled, open trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcome measure (duration of IV antibiotics) collected on all patients. Only 70% of questionnaires returned for the intervention group, which may account for the intervention effect being lower than expected. However, this did not affect outcome assessment
Selective reporting (reporting bias)	Low risk	Complete primary outcome data
Other bias	Low risk	Complete primary outcome data
Baseline Outcomes similar?	Low risk	Pre-study group, data collected for 2 months before intervention to estimate the magnitude of possible observation bias (Figure 2)

Free of contamination?	Low risk	the pre-intervention group data were comparable to the control group suggesting minimal observation bias
Baseline characteristics similar?	Low risk	Presented in Table 1

Shojania 1998

Methods	STUDY DESIGN: RCT with nested ITS analysis (figures 3 & 4). QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: A total of 396 physicians in seven specialties. Age, gender and time since qualification NOT CLEAR. Nonphysicians (nurses or pharmacists) who were authorized to enter orders that required eventual signing off by physicians were also randomized. PARTICIPANTS: There were 5536 episodes of care in 1798 patients. CLINICAL PROBLEM: Receiving vancomycin treatment SETTING: A 720-bed University hospital in the USA
Interventions	FORMAT & DELIVERER: PERSUASIVE (guideline and reminder). Reminder delivered through computer screen at the time of physician order entry and after 72 hours of therapy. Reminder designed by a multidisciplinary team (AMT) COMPARISON: no reminder. ITS analysis used nine months pre-intervention data. DESIRED CHANGE: Reduction of established management (reduction in use of vancomycin) TIMING: Proximity to clinical decision-making immediate. Two interventions per episode of care. Outcomes were collected for nine months after the start of the intervention
Outcomes	PRIMARY: Initiation and renewal of vancomycin therapy SECONDARY: Duration of vancomycin therapy on a per prescriber basis. Total use of vancomycin in the hospital
Notes	EVIDENCE BASE: Intervention based upon implementation of clinical practice guidelines produced by national/international expert bodies and endorsed by formal consensus process locally. OTHER: Estimated savings of USD 22,500 per year assuming that patients who did not receive vancomycin were treated with cefazolin instead. Cost of intervention: NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The study was a randomised controlled trial"; no details of how randomization sequence was generated

Shojania 1998 (*Continued*)

Allocation concealment (selection bias)	High risk	States "possible that physicians in the control group could learn of the intervention from physicians in the study group"
Blinding (performance bias and detection bias) All outcomes	High risk	Not done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear for primary outcome
Selective reporting (reporting bias)	Low risk	Based on numbers of vancomycin orders
Other bias	Low risk	No issues noted
Baseline Outcomes similar?	Unclear risk	No information about pre-intervention vancomycin use
Free of contamination?	High risk	States "possible that physicians in the control group could learn of the intervention from physicians in the study group"
Baseline characteristics similar?	Low risk	Table 1
Analysed appropriately (ITS) ?	Low risk	Done in original paper, segmented regression analysis

Singh 2000

Methods	STUDY DESIGN: RCT, allocation by patient. QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians on one Intensive Care Unit (ICU). Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: A total of 81 episodes of care in patients with mean age about 65. Number, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Suspected ventilator-associated pneumonia with low clinical pulmonary infection score (CPIS) SETTING: Single nonteaching hospital in the USA.
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Intervention patients received standardized initial therapy (ciprofloxacin IV for three days) with assessment at three days based on CPIS and sputum microbiology. Antibiotic treatment stopped by investigators if CPIS still < 6 at three days. COMPARISON: Choice, number and duration of antibiotics at the discretion of the care providers.

Singh 2000 (*Continued*)

	DESIRED CHANGE: Reduction of established management (reduction in duration of antibiotic treatment) TIMING: Immediate, patient-specific intervention. Patients were followed up until they were discharged from ICU or died. Follow-up cultures were obtained at 7 to 28 days
Outcomes	PRIMARY: Duration of antibiotic treatment SECONDARY: Mortality, length of ICU stay, colonization or infection by antimicrobial-resistant bacteria
Notes	EVIDENCE BASE: CPIS was devised and tested in a previous cohort study (Pugin 1991). OTHER: Total costs of care for patients with CPIS < 6 at three days and no extrapulmonary infections were USD 6484 in the intervention group and USD 16,004 in the standard therapy group. Cost of intervention NOT DONE. The study was terminated prematurely because providers looking after patients in the control group were influenced by the favourable results in the intervention group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized to either the control group or experimental group", no information about how randomization sequence was generated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Page 509: "Because the study was not blinded, physicians and care providers could see the results"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most outcomes are reported for 78 (96%) episodes of care; antimicrobial resistance and super-infection in 74 (91%) of episodes
Selective reporting (reporting bias)	Low risk	No problems found
Other bias	High risk	Case definition for microbial outcome NOT CLEAR: "Follow-up respiratory cultures or cultures from clinical specimens performed 7 to 28 d after initiation of antibiotics were evaluated to assess the emergence of antimicrobial resistance or superinfections. Emergence of resistance was defined as the detection of new antimicrobial resistance pattern in the old or previously isolated organism. Superinfection was de-

Singh 2000 (*Continued*)

		fined as the detection of the following organisms not present at study entry: Acinetobacter species, *Serratia marcescens, Pseudomonas aeruginosa, Stenotrophomonas maltophilia*, Enterobacter species, Citrobacter species, methicillin-resistant *Staphylococcus aureus* (MRSA), Enterococcus species, and Candida species." It is therefore impossible to assess the impact of the intervention on colonization or infection with bacteria resistant to specific antibiotics
Baseline Outcomes similar?	Unclear risk	Not stated, no information about pre-intervention duration of antibiotic treatment
Free of contamination?	Unclear risk	Not stated
Baseline characteristics similar?	Low risk	See Table 1 in study

Sirinavin 1998

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: Single 900-bed University hospital in Thailand with 21,254 to 26,361 admissions per year
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Use of ceftazidime, netilmicin, ciprofloxacin, vancomycin and imipenem restricted through named-patient prescription forms with review of cases of inappropriate prescribing by ID Consultant Persuasive: Meetings, all new residents, medical students and related personnel were orientated about the intervention before starting to work in the hospital COMPARISON: Data for four years pre-restriction. DESIRED CHANGE: Reduction of established management (reduction in cost of antibiotics) TIMING: Outcomes were analyzed for four years after implementation of the restriction. However, staff changes in the final year of the study prevented ID consultant review

Sirinavin 1998 (*Continued*)

Outcomes	PRIMARY: Total restricted drugs cost (million Baht (THB) per 200,000 patient days) SECONDARY: None
Notes	EVIDENCE BASE: The intervention was designed to restrict use of target drugs to documented infections with bacteria resistant to first-line drugs and was endorsed by the Executive Committee of the Hospital. OTHER: Cost of programme NOT DONE. Figure 2 suggests that expenditure increased sharply in the final year of the study when ID consultant review ceased

Risk of bias

Bias	Authors' judgement	Support for judgement
Intervention independent (ITS) ?	Low risk	Four years data pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: run charts with no statistical analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	High risk	NOT DONE, there is no information about change in price of antibiotics over the study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Unclear risk	NOT CLEAR,no adjustment of antibiotic costs for change in price so change in price of antibiotics (rather than change in use) over the study period may have been responsible for some of the change in cost. Data were not adjusted for number of admissions or occupied bed days

Skaer 1993

Methods	STUDY DESIGN: ITS QUALITY: **Risk of bias: LOW (primary outcome only)**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians (numbers not clear) PATIENTS: A total of 51 patients who received imipenem during the postintervention phase; number during the pre-intervention phase, NOT CLEAR CLINICAL PROBLEM: Adult patients receiving imipenem treatment for infection SETTING: A 42-bed nonteaching hospital in the USA. The pre-intervention period was six months (January to June 1991); postintervention period was 18 months (July 1991 to December 1992)
Interventions	FORMAT: PERSUASIVE Educational outreach (review and recommend change). "When diagnostic or laboratory data indicated the appropriateness of initiating an alternative therapeutic regimen (cefazolin or cefuroxime) the clinical pharmacist communicated these findings to the prescribing physician. The conversation and outcome stemming from the presentation were noted in each patient's chart." DELIVERER: Pharmacist COMPARISON: Prescribers of imipenem-cilastatin informed by pharmacist of appropriate, less broad-spectrum alternatives (postintervention phase) vs no intervention (pre-intervention phase) DESIRED CHANGE: Reduction of established management (prescribing of imipenem-cilastatin) TIMING: Intervention implemented after clinical decision-making (once per prescription) between July 1991 and December 1992
Outcomes	PRIMARY: Monthly use of imipenem-cilastatin SECONDARY: Data about length of stay and hospital charges for patients with a primary diagnosis of infection but only in UBA format (aggregate pre- and postintervention)
Notes	EVIDENCE BASE: NOT DONE (not supported by a single RCT or a systematic review). Interventions in other hospitals cited but not RCTs OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Skaer 1993 (*Continued*)

Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	Low risk	
Incomplete outcome data addressed (ITS) ?	Low risk	
Free of selected reporting (ITS) ?	Low risk	
Free of other bias (ITS) ?	Low risk	Yes for primary outcome but fatally flawed (UBA) for secondary outcomes

Solomon 2001

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: There were 17 Internal Medicine services randomly assigned to intervention (nine services) or control (eight services) with balanced numbers of General Medical, Oncology and Cardiology services. Number of physicians, age and time since qualification NOT CLEAR PARTICIPANTS: A total of 4500 patients admitted during the baseline and study periods of whom 260 patients received 278 unnecessary prescriptions for the target drugs CLINICAL PROBLEM: Patients receiving ceftazidime or levofloxacin. SETTING: Single 697-bed University Hospital in the USA
Interventions	FORMAT & DELIVERER: PERSUASIVE (guideline with academic detailing). Written policy for necessary use distributed to all doctors. Every prescription was reviewed and, if it was unnecessary, the prescriber was contacted by a trained academic detailer (three clinician-educators, two ID physicians and one pharmacist). Encounters were either face-to-face, by telephone or by e-mail. COMPARISON: Randomly assigned control services DESIRED CHANGE: Reduction of established management (reduction in use of ceftazidime and levofloxacin). TIMING: Single intervention per prescription but patients who received more than one new course were entered again. The study continued for 18 weeks and outcomes were measured for 30 days on each patient
Outcomes	PRIMARY: Number of days of unnecessary ceftazidime or levofloxacin SECONDARY: Inpatient mortality, transfer to ICU, LOS and readmission within 30 days of discharge
Notes	EVIDENCE BASE: Effectiveness of academic detailing has been documented in several previous trials in both inpatient and outpatient settings. OTHER: Estimated annual cost of the intervention was USD 21,750. Formal economic

Solomon 2001 (*Continued*)

	analysis was not performed but the institution plans to continue and expand antibiotic counter-detailing Note from Statistician: The study adjusted for some clustering but possibly only in the repeated measures not in the hospitals. Just using the results from table 2 I do not get the P-value that they state in the table using a Unit of analysis error approach. This suggests to me that they are adjusting for "things". I therefore think on balance that it is probably OK to use the results

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Free of contamination?	High risk	
Baseline characteristics similar?	Low risk	

Stevenson 1988

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: LOW**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Receiving antibiotics SETTING: Single University hospital in the UK
Interventions	FORMAT & DELIVERER: PERSUASIVE: nonrestrictive antibiotic prescribing policy implemented by clinical pharmacists. COMPARISON: Ten quarters (30 months) pre-intervention DESIRED CHANGE: Modification of established management (reduction in cost of

	all antibiotics) TIMING: Single intervention. Outcomes were measured for six quarters (18 months) after the start of the intervention
Outcomes	PRIMARY: Expenditure on antibiotics as average cost per patient calculated from total expenditure on antibiotics divided by the number of patients who died or were discharged. Prices were indexed to 1980 SECONDARY: None
Notes	EVIDENCE BASE: NOT CLEAR OTHER: cost of intervention NOT DONE.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Two years data pre- and postintervention, enough to account for seasonal effects
Analysed appropriately (ITS) ?	Low risk	Done in original paper: regression analysis testing for structural break associated with intervention
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, drug costs were adjusted to 1980 prices
Free of other bias (ITS) ?	Low risk	Drug costs were adjusted to 1980 prices and also adjusted for number of discharges or deaths

Suwangool 1991

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the Department of Medicine. Number, age and time since qualification NOT CLEAR PARTICIPANTS: All patients in the Department of Medicine. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: inappropriate antibiotic prescribing SETTING: Single University hospital in Thailand
Interventions	FORMAT: RESTRICTIVE AND PERSUASIVE Restrictive: Written or telephone approval for the use of 'restricted' antibiotics was required from the infectious diseases physicians Persuasive: Antibiotic guidelines for the treatment of patients with common infectious diseases written by a multidisciplinary Antibiotic Management Team (Chairman of the Department of Medicine, ID physicians, three physicians from other specialties and a clinical epidemiologist) DELIVERER: ID physicians and AMT. COMPARISON: six months data pre-intervention DESIRED CHANGE: reduction in established management (reduction in cost of antibiotics) TIMING: Intervention at the point of decision-making; data were collected for 12 months after the start of the intervention
Outcomes	PRIMARY: Cost of antibiotics SECONDARY: None
Notes	EVIDENCE BASE: NOT CLEAR OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	
Analysed appropriately (ITS) ?	Low risk	
Shape of effect pre-specified (ITS) ?	Low risk	
Unlikely to affect data collection (ITS) ?	Low risk	
Knowledge of the allocation adequately prevented(ITS)?	Low risk	
Incomplete outcome data addressed (ITS) ?	Low risk	

Suwangool 1991 (*Continued*)

Free of selected reporting (ITS) ?	Low risk	
Free of other bias (ITS) ?	Unclear risk	No adjustment to antibiotic costs was made for changes in prices during the 18-month study period so changes in cost may have been due to changes in price as well as use

Toltzis 1998

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM for primary outcome (ceftazidime use), FATALLY FLAWED for microbial outcome**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the mixed medical and surgical paediatric ICU. Number, age and time since qualification NOT CLEAR. PARTICIPANTS: All patients in the paediatric ICU. Number, age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: A 16-bed tertiary care paediatric ICU in a University Hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Prohibition of ceftazidime use unless the patient's microbiological results indicated that the drug was necessary for cure. Other third-generation cephalosporins restricted to confirmed or suspected meningitis (Page 1894). Deliverer specialist physician, format NOT CLEAR COMPARISON: Seven months data before the start of the intervention DESIRED CHANGE: Reduction of established management (reduction in use of ceftazidime with the aim of reducing colonization with ceftazidime resistant bacteria) TIMING: Intervention at the time of decision-making. Outcomes were collected for 12 months after the start of the intervention, which remained in place at the end of the study. Each patient was observed until discharged from ICU
Outcomes	PRIMARY: Ceftazidime doses (ITS data) SECONDARY: Impact of intervention on ceftazidime-resistant bacteria NOT CLEAR, only mean data provided before and after (UBA)
Notes	EVIDENCE BASE: The authors had published a previous observational study that reported no association between colonization with ceftazidime-resistant bacteria and exposure to ceftazidime (Toltzis 1997). OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Toltzis 1998 (*Continued*)

Intervention independent (ITS) ?	Unclear risk	NOT CLEAR, data for seven months pre- and 12 months postintervention, not enough to adjust for seasonal variation
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after) with χ^2 test
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	High risk	For secondary outcome, fatally flawed as only uncontrolled before-after data presented

Toltzis 2002

Methods	STUDY DESIGN: CCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians (paediatricians); mixed level of training but age and time since graduation NOT CLEAR PARTICIPANTS: A total of 1062 patients/episodes of care. Mean ages: 35.5 (+/- 4. 7) weeks (intervention) vs 35.4 (+/- 4.7) weeks (control). Gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Neonates with proven or suspected infections caused by gram-negative bacteria SETTING: A 38-bed neonatal intensive care unit in a University hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE: The intervention was a monthly rotation of the antibiotic regimen used for empirical prescribing of patients with proven or suspected gram-negative infections. DELIVERER: Specialist physician, format NOT CLEAR

	COMPARISON: Standard practice (prescribing according to personal preference) DESIRED CHANGE: Modification of established management (rotation of antibiotic use with the aim of reducing colonization with multiresistant bacteria) TIMING: The antibiotic regimen was changed monthly on a rotating schedule. The intervention remained in place for 12 months
Outcomes	PRIMARY: Incidence of colonization with multi-antibiotic-resistant aerobic gram-negative bacilli. SECONDARY: use of rotation antibiotics and total antibiotic use
Notes	EVIDENCE BASE: There is insufficient evidence to support the efficacy of the intervention OTHER: Baseline data are not provided. There was no concealment of allocation (which was based on bed availability). It is not clear if there was protection against contamination. There are no data on patient outcomes other than colonization with antibiotic-resistant aerobic gram-negative bacilli (the choice of antibiotic regimens used in the study group may have exerted an adverse effect on patient outcome compared with the control group) . COST of intervention: NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	CCT monthly rotation of regimens
Allocation concealment (selection bias)	High risk	Not possible with this study design
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible with this study design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated whether screening samples obtained from all patients
Selective reporting (reporting bias)	Unclear risk	Not stated whether screening samples obtained from all patients
Other bias	Unclear risk	NOT CLEAR **Microbial Outcome Risk of Bias Criteria** Case definition: DONE Colonization by screening. "For the purpose of this study, an "antibiotic-resistant Gram-negative organism" was defined as any Gram-negative bacillus resistant to gentamicin, piperacillin-tazobactam, or ceftazidime. Pharyngeal and rectal swab specimens were obtained on all infants every Monday, Wednesday, and Friday". Planned intervention: DONE; Other infection control, Isolation: IC practices:

Toltzis 2002 (*Continued*)

		NOT CLEAR not described but it is reasonable to assume that they were same for intervention and control groups due to the controlled clinical trial design
Baseline Outcomes similar?	Unclear risk	Not stated
Free of contamination?	Unclear risk	Not stated but doctors likely to have been managing patients in more than one study phase
Baseline characteristics similar?	Low risk	Results, paragraph 1

Trenholme 1989

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Age, service, gender and time since qualification NOT CLEAR PARTICIPANTS: A total of 226 patients. Age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Patients with bacteraemia SETTING: single hospital in the USA. University status NOT CLEAR
Interventions	FORMAT & DELIVERER: STRUCTURAL AND PERSUASIVE Structural: Intervention group had rapid processing and reporting of antimicrobial susceptibility tests Persuasive: Intervention and control groups had results reported to physicians by an ID fellow. In the intervention group this was on the same day that the blood culture became positive; in the control group this was on the morning or afternoon of the following day COMPARISON: Routine methods for susceptibility testing. Physicians in both groups were informed of results by an ID fellow. DESIRED CHANGE: Modification of established management (change in antibiotic therapy in response to rapid provision of microbiology test results). TIMING: Immediate concurrent intervention. Patients were enrolled over 11 months. Outcomes were measured within two to three days of randomization
Outcomes	PRIMARY: Changes in therapy in response to recommendations SECONDARY: None
Notes	EVIDENCE BASE: Previous observational studies demonstrated faster test reporting but no previous intervention studies with measurement of impact on clinical practice OTHER: The authors attribute the high rate of noncompliance with recommendations in the control group to reluctance of physicians to change treatment after two or three days in patients with an improving status. Estimate that antibiotic cost saving of USD 6952 occurred in 44 patients who were switched to less expensive therapy and that introduction of rapid testing into routine practice would save about USD 13,000 per

Trenholme 1989 (*Continued*)

	year . The authors say that these savings would exceed the cost of the rapid testing equipment but cost of intervention NOT CLEAR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated; "the organism from the patient was randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated to be blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Table 2 reports primary outcome reported for all 226 patients randomized
Selective reporting (reporting bias)	Low risk	Table 2 reports primary outcome reported for all 226 patients randomized
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Unclear risk	No information about recommendations for changes in therapy before the intervention
Free of contamination?	Unclear risk	Likely to be contamination as doctors managing control patients would receive advice on intervention patients
Baseline characteristics similar?	Unclear risk	No information

Van Kasteren 2005

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: A total of 13 Dutch hospitals and 3813 procedures PROVIDERS: Multidisciplinary teams, number, age and time since qualification NOT CLEAR PATIENTS: Not stated but likely to be 3813 unless > 1 procedure per patient. Age, gender and ethnicity NOT CLEAR CLINICAL PROBLEM: Surgical prophylaxis across four surgical disciplines and covering the following operations: total hip arthroplasty, hemi-arthroplasty, grafting of the

	aorta, femoropopliteal and femorotibial bypass, abdominal and vaginal hysterectomy with or without vaginal repair and various colorectal procedures SETTING: Thirteen Dutch hospitals, University affiliation NOT CLEAR
Interventions	FORMAT: PERSUASIVE, feedback and educational meetings designed to reduce quantity and improve quality of surgical prophylaxis DELIVERER: After the pre-intervention period, every hospital received feedback of its own data on antibiotic prophylaxis. The hospitals' auditing report and the Dutch Working Party on Antibiotic Policy guideline were discussed with surgeons, anaesthetists, pharmacists, microbiologists, nurses and the local antibiotic policy committee. The Surgical Prophylaxis and Surveillance project study group formulated recommendations for local improvement in each hospital and discussed them with the participants. In addition, educational meetings were organized for medical specialists and nurses. Depending on the results of the audit, the intervention focused on modification of the local guidelines, guideline adherence or both COMPARISON: Pre-intervention periods DESIRED CHANGE: Reduction in established management (reduction in total use of antibiotics by reducing duration of prophylactic antibiotics) TIMING: Education with feedback of baseline data before clinical decision-making. The day of the first feedback was considered as the start of the intervention period in each hospital.The intervention period varied between two and nine months, median six months depending on the time needed to achieve approval on updated guidelines. All hospitals had at least six months pre-intervention data and only six months data were used for all hospitals in the analysis. The postintervention period was six months
Outcomes	PRIMARY: Antibiotic use as DDDs SECONDARY: Costs of antibiotics and surgical site infections (SSI)
Notes	EVIDENCE BASE: National policy guideline; evidence level not stated OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	High risk	Only six months pre- and postintervention data and the model was not adjusted for seasonal trends
Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period

Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period. Change in price unlikely to be a problem because only six months data pre- and postintervention

Walker 1998

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Physicians, number, level of training, clinical specialty, age and time since graduation NOT CLEAR PARTICIPANTS: A total of 50 participants. Mean ages: 69 +/- 17.8 years (intervention group), 65.7 +/- 16.1 years (control); gender: 20 women, 5 men (intervention), 16 women, 9 men (control); ethnicity: NOT CLEAR CLINICAL PROBLEM: Excessive duration of IV antibiotic therapy of patients with community-acquired pneumonia SETTING: One 498-bed community hospital in the USA
Interventions	FORMAT: PERSUASIVE: Educational outreach (review and recommend change). A written recommendation to change from IV ceftriaxone to an oral regimen was placed in each patient's prescription chart by the pharmacist. Direct contact with prescribers was not possible "because the medical staff in community hospitals have a large variation in the hours in which they make rounds" and " "the physician is frequently busy, phone calls usually involve multiple pharmacists". DELIVERER: Pharmacist COMPARISON: Standard practice (no intervention) DESIRED CHANGE: Modification of established management (increase in number of patients switched to oral therapy) TIMING: More than 48 hours after IV ceftriaxone had been started. The intervention remained in place for 12 months
Outcomes	PRIMARY: Number of patients changed to oral antibiotic therapy SECONDARY: Number of readmissions overall and number of readmissions for pneumonia

Walker 1998 (*Continued*)

Notes	EVIDENCE BASE: DONE; the efficacy of the intervention is supported by at least two RCTs. OTHER: As there was no power calculation and as the number of patients in each group (25) was small, the study may have been underpowered and/or may have been designed to show only equivalence. As the patients, not the physicians, were randomized, the same physicians managed patients in both groups and there is evidence of a learning effect. Clinical outcome was evaluated only in terms of the number of patients who were readmitted Cost of the intervention: NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A list of random numbers was generated from Sigmastat version 1.0 statistical software"
Allocation concealment (selection bias)	Unclear risk	Not stated but open label so unlikely to be concealed
Blinding (performance bias and detection bias) All outcomes	High risk	"Open label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems found
Selective reporting (reporting bias)	Low risk	No problems found
Other bias	Low risk	No other apparent biases found
Baseline Outcomes similar?	Unclear risk	Not stated
Free of contamination?	Unclear risk	Not stated
Baseline characteristics similar?	Low risk	See Table 1 in paper

Weinberg 2001

Methods	STUDY DESIGN: Controlled ITS QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: A total of 8950 caesarean (C-) sections (calculated from Table 1) in low-income women, age and ethnicity NOT CLEAR PROVIDERS: Teams at participating hospitals. Number, age and time since qualification NOT CLEAR

	PATIENTS: Low-income women needing C-Section CLINICAL PROBLEM: Infection after C-Section SETTING: Colombia. Two non-profit hospitals over two years (1996 to 1998)
Interventions	FORMAT: PERSUASIVE Multifaceted intervention based on the Nolan model for improvement. Included team meetings, defining shared goals, constructing care pathways, identifying barriers to change in practice, measures for improvement and feedback. Aim was to reduce infection rates after C-section using systems to improve prescribing of prophylactic antibiotics. Feedback was in the form of run charts for the two key process measures (secondary outcomes) with data collected and displayed by the clinical teams DELIVERER: Obstetric teams, doctors and nurses COMPARISON: Physician choice about antibiotic and timing DESIRED CHANGE: Reduce infection after C-Section TIMING: Before clinical decision-making; the intervention was continued for two years
Outcomes	PRIMARY: Surgical site infection (SSI) rate per 100 C-sections SECONDARY: Percentage of women who received prophylaxis; percentage who received prophylaxis within one hour
Notes	EVIDENCE BASE: DONE: Two-day workshop to summarize literature OTHER: Number of cases lower in Hospital A than B. Also timings dissimilar. Planned intervention: DONE; Case definition: clinical infection by CDC definition. Full details of surveillance given with validation by second observer at both hospitals. No information about isolation or other infection control processes Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	Data collection method was the same pre- and postintervention
Analysed appropriately (ITS) ?	Low risk	Done in original paper: segmented regression analysis
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Data collection method was the same pre- and postintervention
Knowledge of the allocation adequately prevented(ITS)?	High risk	Data collectors were not blinded
Incomplete outcome data addressed (ITS) ?	Unclear risk	Not stated whether SSI was evaluated in all patients

Weinberg 2001 (*Continued*)

Free of selected reporting (ITS) ?	Unclear risk	Not stated whether SSI was evaluated in all patients
Free of other bias (ITS) ?	High risk	Information about other infection control measures not given

Wilson 1991

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: Medium**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians; number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: Number and characteristics of patients and episodes NOT CLEAR CLINICAL PROBLEM: Patients receiving amoxicillin or pivampicillin SETTING: Three hospitals in Nottingham UK, University status NOT CLEAR
Interventions	FORMAT & DELIVERER: PERSUASIVE: newsletter prepared by pharmacists and distributed to all prescribers. Method of distribution or reinforcement (e.g. by clinical pharmacists or by inclusion in antibiotic policies) NOT CLEAR COMPARISON: Five months before introduction of the newsletter DESIRED CHANGE: Modification of established management (decreased use of amoxicillin with substitution by pivampicillin) TIMING: Frequency of distribution and reinforcement of the newsletter NOT CLEAR. Effect of intervention measured for 26 months after the newsletter was first issued
Outcomes	PRIMARY: Use of amoxicillin and pivampicillin. SECONDARY: None
Notes	EVIDENCE BASE: NOT CLEAR OTHER: Cost of the intervention and effect on antibiotic costs NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Unclear risk	NOT CLEAR, only five months pre-intervention data. Even with 26 months postintervention data could still be secular changes
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: run chart with no statistical analysis

Wilson 1991 (*Continued*)

Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Woodward 1987

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All clinical services at a large teaching hospital. Number, level of training, age and time since graduation NOT CLEAR PARTICIPANTS: Number and characteristics of patients and episodes NOT CLEAR except for bacteraemia: 322 patients (164 pre- and 158 post-study) CLINICAL PROBLEM: Inpatient prescribing of all antibiotics SETTING: A 1208-bed teaching hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE AND PERSUASIVE Restrictive: Antibiotic use regulated by placing drugs in one of three categories. 'Restricted' (only initiated after approval by Infectious Diseases Division); 'Controlled' (automatic stop order after 72 hours unless approved by ID Division) and 'Unrestricted'. For 'Restricted' and 'Controlled' approval was obtained by telephone consultation, 24 hours per day Persuasive: meetings; members of the ID Divsion taught sessions on antibiotic use for the house and attending staff at the hospital (p 818) COMPARISON: Pre-study data (25 months). DESIRED CHANGE: Decrease in established management (decrease in antibiotic expenditure) TIMING: Single intervention per patient. Data collected for 17 months after intervention introduced

Woodward 1987 (*Continued*)

Outcomes	PRIMARY: Total antibiotic costs SECONDARY: Appropriateness of antibiotic treatment for bacteraemia. The paper reports "At the hospital level, the antibiotic controls did not result in increased patient mortality or length of stay", but no data are provided to support this claim.
Notes	EVIDENCE BASE: Programme devised by the Pharmacy and Therapeutics Committee, discussed with the chairmen of all the clinical services; eventually approved by all clinical services and by a Hospital Society, representing all of the practising physicians on staff. Appropriateness of antibiotic treatment of bacteraemia was evaluated by modification of a published method (Kunin 1973). OTHER: Programme required 76 hours per month from pharmacists, 24 hours per month from ID fellows and 10 hours for ID faculty. These hours were absorbed within the working days of each person

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Low risk	25 months pre- and 17 months postintervention data
Analysed appropriately (ITS) ?	Low risk	Done in original paper: ordinary least squares regression analysis adjusting for pre-existing time trends, Re-analysis with segmented regression performed for the purposes of comparison of effect size with other studies in the review
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention
Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Unclear risk	The abstract states that "Even after some cost increases (not significant) in new and other antibiotics, the program saved

		$1.33 per antibiotic day" but it is not clear whether the analysis was adjusted for changes in the price of antibiotics during the 3½ year study period

Wyatt 1998

Methods	STUDY DESIGN: Cluster-RCT QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: A total of 25 hospitals, 13 control and 12 intervention, targeting two providers (lead obstetrician and senior midwife manager) in each hospital PARTICIPANTS: There were1318 episodes of care in 1318 patients CLINICAL PROBLEM: Caesarean section SETTING: A total of 25 district general (nonteaching) hospitals with more than 1500 deliveries per year in two regions in the UK, forming 15% of all English obstetric units
Interventions	FORMAT & DELIVERER: PERSUASIVE (educational meeting). Single informal 1½ to three-hour visit by a single obstetrician targeted at lead obstetrician and midwife on the labour ward in 12 hospitals, with feedback about quality of existing guidelines in comparison with evidence from Cochrane reviews MARKETING: In two separate studies the investigators surveyed all UK teaching hospitals and a random sample of obstetric units in district general hospitals to identify potential local barriers to change COMPARISON: Thirteen control hospitals with no intervention DESIRED CHANGE: Increase in established management (increase in use of antibiotic prophylaxis for C-section). This was one of four targets; the other three did not involve antibiotics (rates of perineal suturing with polyglycolic acid, ventouse delivery and steroids in preterm delivery) TIMING: Single intervention before the point of decision=making; follow-up for nine months after the intervention
Outcomes	PRIMARY: Percentage of caesarean sections that received antibiotic prophylaxis
Notes	EVIDENCE BASE: Systematic reviews published in *The Cochrane Library*. OTHER: The intervention was only associated with a significant change in comparison with control for one of the four targets (ventouse usage). Use of polyglycolic acid sutures increased similarly at intervention and control hospitals and use of steroids in pre-term labour did not increase at either control or intervention hospitals. Authors identified a ceiling effect ("hard to improve on baseline rates for clinical practices of 60% to 80%") . Fixed cost of preparing the video was GBP 5000. Variable costs per visit GBP 445 (travel GBP 25, hotel GBP 60, staff time GBP 330) Overall mean cost per visit GBP 860, (1995 costs)

Risk of bias

Wyatt 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Obstetric units were allocated to intervention or control group by the toss of a coin
Allocation concealment (selection bias)	Low risk	To eliminate bias during data collection at follow-up by a second research midwife, and to allow blinded assessment of guideline quality, the allocation was concealed from everyone except JCW, DGA, RJ, and the first research midwife
Blinding (performance bias and detection bias) All outcomes	Low risk	To eliminate bias during data collection at follow-up by a second research midwife, and to allow blinded assessment of guideline quality, the allocation was concealed from everyone except JCW, DGA, RJ, and the first research midwife
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No unit was excluded after randomisation, all intervention units participated in the visits, and data on clinical practices were available for all units, although smaller numbers of case notes were obtainable than planned for steroid usage"
Selective reporting (reporting bias)	Low risk	See above
Other bias	Low risk	"To reduce the impact of ceiling effects, the proportion of cases in which clinicians failed to carry out each clinical practice was recorded for each obstetric unit at baseline and follow up, and then baseline to follow up ratios were computed to yield the risk ratio for failure to implement each practice in each unit."
Baseline Outcomes similar?	Unclear risk	"Accurate baseline figures for the rates and variability of the four marker clinical practices were not available"
Free of contamination?	Low risk	Randomization by units, which were located in different hospitals
Baseline characteristics similar?	Low risk	"Despite randomisation there were baseline differences in two of the four clinical practices" (use of ventouse and use of polyglycolic acid sutures). "There were no other baseline differences." (includes antibiotic

		prophylaxis)

Young 1985

Methods	STUDY DESIGN: ITS QUALITY: **Risk of Bias: MEDIUM**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: All physicians in the hospital. Number, age, specialty and time since qualification NOT CLEAR PARTICIPANTS: All patients in the hospital. Number, age, gender and ethnicity NOT CLEAR. 13,800 isolates assessed CLINICAL PROBLEM: Patients requiring antibiotic treatment SETTING: A 1060-bed tertiary care University Hospital in the USA
Interventions	FORMAT & DELIVERER: RESTRICTIVE: Substitution of amikacin for gentamicin. Use of gentamicin required approval from the Infectious Diseases Division COMPARISON: Three months data before the start of restriction and 22 months data after the end of restriction. DESIRED CHANGE: Modification of established management (substitution of gentamicin with amikacin) TIMING: Outcomes were collected for 15 months after the start of the intervention and for an additional 22 months after the restriction was removed
Outcomes	PRIMARY: Gentamicin usage as a percentage of total aminoglycoside usage (ITS data) SECONDARY: Impact of intervention on gentamicin-resistant bacteria NOT CLEAR, only provides UBA data of prevalence (percentage of total isolates) of gentamicin-resistant bacteria
Notes	EVIDENCE BASE: Previous published studies have shown reduction in gentamicin resistance associated with change from gentamicin to amikacin. OTHER: Cost of intervention NOT DONE

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Intervention independent (ITS) ?	Unclear risk	Three months data before, 15 months during and 22 months after the restriction. Not enough data to adjust for seasonal variation
Analysed appropriately (ITS) ?	Low risk	Re-analyzed. Not done in original paper: comparison of means (uncontrolled before-after)
Shape of effect pre-specified (ITS) ?	Low risk	Done, intended effect was decrease in primary outcome and point of analysis was point of intervention

Unlikely to affect data collection (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Knowledge of the allocation adequately prevented(ITS)?	Low risk	Done, data were from routine systems and unlikely to change over study period
Incomplete outcome data addressed (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of selected reporting (ITS) ?	Low risk	Done, data were from routine systems and unlikely to change over study period
Free of other bias (ITS) ?	Low risk	No other apparent biases found

Zanetti 2003

Methods	STUDY DESIGN: RCT QUALITY: **Risk of Bias: HIGH**
Participants	NUMBER & CHARACTERISTICS: PROVIDERS: Surgical team PARTICIPANTS: A total of 331 patients were randomized CLINICAL PROBLEM: Undergoing cardiac surgery that lasted more than four hours after the pre-operative administration of cefazolin SETTING: Single University Hospital in the USA
Interventions	FORMAT: PERSUASIVE: reminder (automated intra-operative alert) and guideline DELIVERER: An audible and visual reminder on the operating room computer console generated by the operating room computer for patients whose procedure lasted more than 225 minutes after the administration of a first pre-operative dose of antibiotic. This time of activation was chosen because the guidelines in force in the hospital recommended cefazolin as prophylaxis for cardiac surgery and suggested intra-operative re-dosing intervals of 240 minutes for this antibiotic. "Simultaneous with the alarm, a message was displayed on the same computer console. This message cited hospital guidelines on intraoperative re dosing of antibiotics, and asked whether the surgical team was considering re dosing. A reply was required to clear the display for any other use. If the response indicated that re dosing of prophylaxis was planned, a new audible alert and screen appeared 30 minutes later, asking whether re dosing had actually been performed. We did not attempt to document the circulation of the information provided by the reminder system within the surgical team". Reminder was designed by a multidisciplinary team (AMT) COMPARISON: Patients randomized to a no-intervention control group plus 480 patients from the six months before the study period. DESIRED CHANGE: Increase in established management (administration of additional doses of antibiotic prophylaxis for prolonged operations) TIMING: Immediate, concurrent, patient-specific. Patients were enrolled over three

Zanetti 2003 (*Continued*)

	months
Outcomes	PRIMARY: Percentage of patients who received additional intra-operative antibiotics SECONDARY: Wound infection rate.
Notes	EVIDENCE BASE: an observational study by the same authors showed that intra-operative administration was associated with lower wound infection rate. OTHER: One patient in the intervention arm received intra-operative antibiotics unnecessarily due to a computer error. Cost of intervention DONE, the intervention had minimal cost because it used an existing operating room management system to deliver the reminder This study had high risk of bias towards the null because of contamination and inability to conceal allocation. The results demonstrate the importance of having baseline data about outcomes in RCTs of professional behaviour change

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Baseline Outcomes similar?	High risk	
Free of contamination?	High risk	
Baseline characteristics similar?	Low risk	

Abbreviations

<: less than; h: hour(s); AB: antibiotic; AMT: multidisciplinary antibiotic review team; ARIMA: autoregressive integrated moving average; CAP: community-acquired pneumonia; CBA: controlled before-after; CCT: controlled clinical trial; CDAD: *Clostridium difficile*-associated diarrhoea; CDC: Centers for Disease Control and prevention; CDI: *Clostridium difficile* infection; CI: confidence interval; CPIS: clinical pulmonary infection score; CRP: c-reactive protein; C-section: caesarean- section; CXR: chest x-ray; DDD: defined daily dose; ER: emergency room; ESBL: extended spectrum beta-lactamase; FTE: full time equivalent; GRE: glycopeptide-resistant enterococci; IC: infectious control; ICU: intense care unit; ID: infectious diseases; IHC: Intermountain Health Care; IL-

8: interleukin-8; ITS: interrupted time series; IQR: interquartile range; IV: intravenous; LOS: length of stay; MRSA: methicillin-resistant Staphylococcus aureus; LRTI: lower respiratory tract infection; MICU: medical intensive care unit; NHAP: nursing home-acquired pneumonia; OR: odds ratio; PA: parenteral antibiotics; PCR: polymerase chain reaction; RCT: randomized controlled trial; RCOG: Royal College of Obstetricians and Gynaecologists; SD: standard deviation; SE: standard error; SHRA: Society of Healthcare Epidemiologists of America; SICU: surgical intensive care unit; SNF: skilled nursing facilities; SSI: surgical site infection; TREAT: computerized decision support system for antibiotic treatment; UBA: uncontrolled before-after; VAP: ventilator-associated pneumonia; VRE: vancomycin-resistant enterococci; UBA: uncontrolled before-after; UK: United Kingdom; USA: United States of America.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahronheim 2000	RCT with no relevant data. Antibiotics were only part of a complex care plan for 6% of patients in the Intervention group and the outcome data do not provide data about the effect of the intervention on antibiotic prescribing
Bruno-Murtha 2005	ITS of antibiotic cycling with no interpretable data because there are no pre-cycling data. Only provides data for four phases of cycling
Burke 1997	ITS with no interpretable data. Two different interventions (education, then restriction via order form) with three points before the education intervention and three after, but the restriction intervention started after the fourth point
Cook 2006	ITS with no interpretable data because no clearly defined point in time at which the intervention started
Crist 1987	CCT with no interpretable data. Unacceptable allocation bias ("the allocation of a patient to a particular group was determined by the attending physician")
Dellinger 2005	ITS with no interpretable data because no clearly defined point in time at which the intervention started. Only four data points for antibiotic use and the intervention included multiple components in addition to antibiotic use, so even if an intervention effect could be calculated reliably it could not be attributed to change in antibiotic prescribing
Destache 1990	RCT with no interpretable data because of incomplete and selective reporting of outcome data. The primary outcome measure was length of stay, but 32% of the intervention group were excluded because they had prolonged length of stay
Ehrenkranz 1992	RCTwith no interpretable data. Only report data for patients whose physicians followed recommendations
Ehrenkranz 1993	RCTwith no interpretable data. Only report data for patients whose physicians followed recommendations
Evans 1994	CCT with no interpretable data. The first part compared the drugs that the Antibiotic Consultant programme recommended with the drugs actually prescribed by physicians. Data from the second part are presented in an uninterpretable format, with the denominator as cultures, not patients or physicians
Gerding 1991	ITS with no interpretable data. Describes ten years of experience with aminoglycoside cycling but the intervention periods cannot be mapped onto the outcome data about prescribing or resistance

(*Continued*)

Hampson 1988	Secondary publication for Stevenson 1988
Kolar 1999	ITS with no interpretable data due to inadequate control for the effect of other interventions (infection control measures; see detailed critique by Monnet in Vol 21 No 1 pages 7-8)
Lan 2003	ITS with unacceptable missing data and inappropriate statistical analysis. There are three monthly data points pre-intervention, then a gap in colonization data for three months at the start of the intervention period followed by three monthly data points from months four to six of the intervention phase
Lee 2004	ITS with no interpretable data. There were no isolates of ESBL-*Klebsiella pneumoniae* in the last three months of the intervention phase but no data are provided about the number of specimens screened. Appropriate statistical analysis in original paper not done (averages pre- and postintervention with χ^2 and Fisher's exact test). Re-analysis not possible because there are only two reliable data points in the postintervention phase
MacCosbe 1985	RCT with no interpretable data. Only 29% of randomized doctors were followed up and recommendations were only made in 6% of the intervention group
Marrie 2000	Cluster-RCT with no relevant data. Antibiotic prescribing was only one component of a care pathway, results for impact on antibiotic prescribing and its contribution to outcome not reported separately
Martin 2005	ITS with no interpretable data. No antibiotic data pre-intervention, only data about MRSA but this is uninterpretable without information about pre-intervention antibiotic prescribing
McGowan 1974	Secondary publication to McGowan 1976
McGregor 2006	RCT with no interpretable data. Statistical analysis of primary outcome measure (antibiotic costs) not done and re-analysis not possible from the data presented
Palmer 2000	Secondary publication to Marrie 2000.
Pastel 1992	CCT in one hospital, no interpretable data because no protection against contamination and unreliable primary outcome measure
Ronning 1998	RCT with no relevant data. Not primarily an intervention on antibiotic therapy, compared stroke unit versus general medical ward
Sanazaro 1978	CCT with no relevant data. Antibiotic prescribing was only one of three components of a care pathway, results for impact on antibiotic prescribing and its contribution to outcome not reported separately
Thomas 2002	CBA in 64 hospitals, no interpretable data because no clear point in time for the intervention
Tiley 2003	ITS with no interpretable data. Multiple interventions are described without clear definition of intervention points
Tsiata 2001	RCT in a single hospital, fatally flawed because these are provider interventions but allocation was by patient randomization. The unequal numbers of patients in each group (134 Group A, 141 Group B and 105 Group C) and the differences in baseline characteristics indicate unacceptable allocation bias

(*Continued*)

Van Loon 2005	ITS with no interpretable data about the impact of antibiotic cycling on resistance because there are no pre-cycling data
Wahlstrom 2003	RCT with no relevant data. Antibiotics included in the indicators for treatment of hospitalized cases of pneumonia (compliance with policy, dose and duration) and diarrhoea (no use of antibiotics without bacterial identification) but no separate data are presented for these outcomes. The only data provided are mean scores on a single composite indicator for each condition

Abbreviations

CBA: controlled before-after; CCT: controlled clinical trial; ESBL: extended-spectrum beta-lactamase; ITS: interrupted time series; MRSA: methicillin-resistant Staphylococcus aureus; RCT: randomized controlled trial.

DATA AND ANALYSES

Comparison 1. Intended clinical outcomes, interventions intended to increase effective prescribing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality, interventions intended to increase appropriate antimicrobial therapy, all infections	3	1484	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.22]
2 Mortality, interventions intended to increase antibiotic guideline compliance for pneumonia	4	22526	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.82, 0.97]

Comparison 2. Clinical outcomes, interventions intended to decrease excessive prescribing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality, interventions intended to decrease excessive prescribing	11	9817	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.06]
2 Readmission, interventions intended to decrease excessive prescribing	5	5856	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.02, 1.57]
3 Length of stay, interventions intended to decrease excessive prescribing	6	8071	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.34, 0.25]

ADDITIONAL TABLES

Table 1. Impact on antibiotic use of persuasive interventions that used dissemination of printed educational materials or educational meetings as the main intervention.

Study	Sites	Design	Intended effect	Intervention	Impact on antibiotic use
Fridkin 2002 (intervention 4)	50	CBA	Decrease use of vancomycin	National guideline on vancomycin use disseminated by ICU-specific education in-service sessions on appropriate vancomcyin use	Decrease in vancomycin use by 35%, P = 0.01

Table 1. Impact on antibiotic use of persuasive interventions that used dissemination of printed educational materials or educational meetings as the main intervention. (*Continued*)

Fridkin 2002 (intervention 1)	50	CBA	Decrease use of vancomycin	National guideline on vancomycin use disseminated by newsletter or mail	Increase in vancomycin use by +2.8% after the intervention, P = 0.34
May 2000	1	CITS	Decrease use of vancomycin	Written care pathways for antibiotic choice and for duration of treatment disseminated by ICU staff	Decrease in vancomycin use by 42.5% (95% CI -102.0 to +17.0), P = 0.191
Stevenson 1988	1	ITS	Decrease cost of antibiotics	Writen antibiotic prescribing policy about prophylaxis and empiric treatment disseminated by pharmacists	Decrease in antibiotic cost per patient at 12 months by 50.1% (95% CI -26.5% to -73.7%)
Wyatt 1998	25	Cluster- RCT	Increase in women receiving prophylactic antibiotics for Caesarean section	Single educational visit by a single obstetrician targeted at lead obstetrician and midwife on the labour ward in 12 hospitals, with feedback about quality of existing guidelines in comparison with evidence from Cochrane reviews. Intervention informed by previous study about barriers to change	Postintervention absolute difference was 3.1% fewer women receiving prophylaxis in the intervention arm (95% CI -10.1% to +4.0%)
Wilson 1991	3	ITS	Decrease use of amoxicillin	Newsletter prepared by pharmacists and distributed to all prescribers	Increase in amoxicillin use by 28.9% (95% CI -43.8% to +101.7%, P > 0.1 for change in level and slope)

Studies are in alphabetical order of study.

Abbreviations

>: greater than; CBA: controlled before-and-after; CI: confidence interval; CITS: controlled interrupted time series; ICU: intensive care unit; ITS: interrupted time series; RCT: randomized controlled trial.

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component

Study	Sites	Design	Main intervention	Other components			Intended effect	Method of review	Impact on antibiotic use
				Education materials/ meet-	Reminder	Other			

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component (*Continued*)

				ings					
Abramowitz 1982	1	ITS	Review and recommend change	Yes	No	Yes	Decrease in use of cefoxitin and cefamandole	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect one month was a 42.3% decrease (95% CI -0.1 to -84.4)
Adachi 1997	1	ITS	Review and recommend change	Yes	Vancomycin order sheet	No	Decrease in use and cost of vancomycin	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect at 12 months was a 84.3% decrease (95% CI -31.4 to -137.2), change in level P = 0.037, change in slope P = 0.028
Ansari 2003	1	ITS	Review and recommend change	Yes	No	No	Decrease in use and cost of Alert Antibiotics	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect at two years was 24.0% reduction in cost (95% CI -13.9 to -34.1), change in level P = 0.2, change in slope P < 0.001
Bailey 1997	2	RCT	Review and recommend change	No	No	No	Decrease in duration of IV antibiotics	Immediate, concurrent, patient-specific by clinical pharmacist	Difference (control - intervention) in mean IV antibiotic days 9.8%, 95% CI -27.2 to +7.6%, P > 0.1

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component (*Continued*)

Bouza 2004	1	RCT	Review and recommend change	No	No	No	Increase in percentage of days of adequate antibiotic treatment	Written recommendation in case notes vs written recommendation plus direct conversation with the physician	Both interventions were associated with 25% absolute increase in proportion of adequate days, P < 0.001
Dranitsaris 2001	2	RCT	Review and recommend change	Yes	No	No	Decrease in use of cefotaxime	Immediate, concurrent, patient-specific by clinical pharmacist	Intervention was associated with 6% reduction in mean duration of therapy: 4.3 days intervention vs 4.6 days control (P = 0.28)
Fine 2003	7	Cluster-RCT	Review and recommend change	Yes	In case notes	No	Decrease in duration of IV antibiotics and length of stay	Concurrent, patient-specific but timing not clear (nurse contacted doctor and offered to take a verbal order to switch)	Intervention associated with 25% reduction in duration of IV. Hazard ratio 1.23 (95% CI 1.00 to 1.52; P = 0.06)
Fraser 1997	1	RCT	Review and recommend change	No	Yes, placed in case notes	No	Reduction in cost of antibiotics	Concurrent, patient-specific by ID fellow or pharmacist	Per patient antibiotic charges reduced by 24.3%, P = 0.05.

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component (*Continued*)

Gums 1999	1	RCT	Review and recommend change	No	In case notes	No	Reduction in inappropriate antibiotic use intended to reduce length of stay	Immediate, concurrent, patient-specific by a member of the AMT	22.6% reduction in antibiotic cost, P = 0.038
Hess 1990	1	ITS	Review and recommend change	Yes	No	No	Reduction in dosing of cefazolin at < eight-hour intervals	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect at one month 42.6% reduction (95% CI -29.0 to -56.2), change in level P = 0.009, change in slope P = 0.829
Landgren 1988	12	CBA	Academic detailing	Yes	Wall posters	No	Reduction in duration of surgical prophylaxis	Visit to practitioners by project pharmacist	Increase in antibiotics for < 24 hours by 20% in study vs control, P = 0.04
Lee 1995	1	ITS	Review and recommend change	Yes	Letter to departments	No	Reduction in ceftriaxone use	Immediate, concurrent, patient-specific by multidisciplinary AMT	Net effect at one month was 68.3% reduction in ceftriaxone use (95% CI -36.6 to -100.1), change in level P = 0.004, change in slope P = 0.453
McLaughlin 2005	1	ITS	Academic detailing	Yes	Sticker in notes, wall posters	No	Reduction in du-	The pharmacist	Increase in appropriate

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component (*Continued*)

							ration of IV antibiotics	informed nurses responsible for administering IV antibiotics of the criteria and rationale for switching from IV to oral antibiotics	switching of IV to oral route by 48.7%, change in level P = 0.15, change in slope (P = 0.474)
Micek 2004	1	RCT	Review and recommend change	Yes	No	No	Reduction in duration of treatment for ventilator-associated pneumonia	Immediate, concurrent, patient-specific by multidisplinary AMT	Duration of antibiotics 25% shorter in the intervention group, P = 0.001
Mol 2005	1	ITS	Academic detailing	Yes	No	Marketing	Increase in compliance with hospital antibiotic policy, intended to reduce drug costs	Group and individual, triggered by non-compliant prescribing. Frequency and reach not clear	Addition of academic detailing to audit and feedback associated with 12.5% increase in compliance but not statistically significant (95% CI -3% to +28%)
Naughton 2001	10	RCT	Academic detailing	Yes	Laminated card	Marketing	Increase in use of IV antibiotics for nursing home-acquired pneumonia	Multiple 1-hour nurse-led training to nurses from three shifts in small groups	Postintervention difference of 13% in appropriate use of IV antibiotics but P = 0.13 in multi-

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component (*Continued*)

									variate analysis
Patel 1989	1	ITS	Review and recommend change	Yes	Information sheet	No	Reduction in expenditure on co-amoxiclav	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect at one month was reduction in co-amoxiclav cost by 43.8% (95% CI -25.9 to -61.8) , change in level P = 0.002, change in slope P = 0.248
Richardson 2000	1	ITS	Review and recommend change	Yes	No	No	Reduction in inappropriate vancomycin use	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect was 50.6% reduction in inappropriate vancomycin use (95% CI +1.9 to -103.1) , change in level P = 0.131, change in slope P = 0.546
Skaer 1992	1	ITS	Review and recommend change	No	No	No	Reduction in use of imipenem-cilastatin	Immediate, concurrent, patient-specific by clinical pharmacist	Net effect at six months was reduction by 52.7% (95% CI -153.4 to +48.0) , change in level P = 0.181) , no change in slope
Solomon 2001	1	RCT	Review and recommend	Yes	No	No	Decrease in use of ceftazidime	Immediate, concurrent, pa-	Risk of receiving a day of un-

Table 2. Impact on antibiotic use of persuasive interventions that used educational outreach as the main component (*Continued*)

			change				and levofloxacin	tient-specific by clinician-educators, ID physicians or pharmacist	necessary treatment with target drugs reduced by 41% (P < 0.001 multivariate analysis)
Walker 1998	1	RCT	Review and recommend change	No	No	No	Reduction in use of IV antibiotics	Concurrent, patient-specific: written recommendation placed in each patient's prescription record by clinical pharmacist	52% absolute difference between intervention and control, OR 13.04 (95% CI 3.04 to 55.95), P < 0.001

Studies are in alphabetical order of study.

Abbreviations

>: greater than; <: less than; AMT: multidisciplinary antibiotic review team; CI: confidence interval; h: hour(s); ID: infectious diseases; ITS: interrupted time series; IV: intravenous; RCT: randomized controlled trial.

Table 3. Impact on antibiotic use of restrictive interventions that used restriction by removal as the main component

Study	Sites	Design	Stop order	Educational materials or meetings	Reminder	Other	Multifaceted	Intended effect	Impact on antibiotic use
Bradley 1999	1	ITS	No	No	No	None	No	Reduction in GRE through restriction of ceftazidime	Net effect at one month was 60.7% reduction (95% CI -150. 6 to +29.3) , change in level P = 0.228, change in slope P = 0.439

Table 3. Impact on antibiotic use of restrictive interventions that used restriction by removal as the main component (*Continued*)

Everitt 1990	1	ITS	No	Yes	Yes, on prescription	None	Yes	Reduction in use of cefoxitin for surgical prophylaxis	Net effect at one month was 34.7% reduction (95% CI +2.8% to -72.2%), change in level P = 0.08, change in slope P = 0.896
Fridkin 2002 (Intervention 5)	50	CBA	No	Yes	No	None	Yes	Reduction in VRE through reduced use of vancomycin	Removal of vancomycin for cardiac surgery prophylaxis associated with 37% decrease in vancomycin use (P < 0.01)
Inaraja 1986	1	ITS	No	No	No	Educational outreach (pharmacy review)	Yes	Reduction in use and cost of cephalosporin	Net effect at one month 31.4% decrease (95% CI +0.2 to -63.1), change in level P = 0.093, change in slope P = 0.316
McNulty 1997	1	ITS	No	Yes	No	None	Yes	Reduction in use of cefuroxime to reduce *C. difficile* infection	Transient effect : net effect at one month was reduction by 75.4% (95% CI -20.4 to -130.5) dimin-

Table 3. Impact on antibiotic use of restrictive interventions that used restriction by removal as the main component (*Continued*)

									ishing by six months to 59.6% decrease (95% CI +103.7 to -222.8), change in level P = 0.015, change slope P = 0.187
Mercer 1999	1	ITS	Yes	Yes	Yes, in case notes	None	Yes	Reduction in cost of antibiotics	Net effect at six months 16.7% decrease (95% CI -37.7 to +4.3), change in level P = 0.07, change in slope P= 0.9
Richards 2003	1	ITS	No	Yes	Yes, computer order form	Audit and feedback	Yes	Audit and feedback	Sustained effect: net effect at one month was -75.9% reduction (95% CI -56.1 to -95.6) sustained to 12 months -63.7% reduction (95% CI -16.1 to -111.2), change in level P < 0.001, change in slope P = 0.948
Toltzis 1998	1	ITS	No	No	No	None	No	Reduction in use of cef-	Sustained effect: net

Table 3. Impact on antibiotic use of restrictive interventions that used restriction by removal as the main component (*Continued*)

								tazidime	effect at one month 96. 5% reduction (95% CI -71.6 to -121.3) sustained at six months (96. 1% reduction, CI -64. 7 to -127.5) , change in level P < 0. 001, change in slope P = 0.012

Studies are in alphabetical order of study.

Abbreviations

<: less than; CBA: controlled before and after; CI: confidence interval; ITS: interrupted time series; VRE: vancomycin-resistant enterococci.

Table 4. Impact on antibiotic use of persuasive interventions that used reminders as the main component

Study	Sites	Design	Other components		Intended effect	Reminder format	Impact on antibiotic use
			Education materials/ meetings	Other			
Avorn 1988	1	ITS	Yes	Antibiotic order form	Reduce frequency of dosing of target antibiotics	Written "unadvertisements" mailed to all physicians and posters displayed on wards	At 12 months 54. 0 % reduction in inappropriate dosing of cefazolin (95% CI from -7.5% to -100%) with greater impact on clindamycin and metronidazole, change in slope P = 0.128, change in level P = 0.067
Halm 2004	4	ITS	Yes	Patient education sheets	Increase in percentage of patients who re-	Pocket, printed card plus order sheets (printed in	Combined effect at one month after interven-

Table 4. Impact on antibiotic use of persuasive interventions that used reminders as the main component (*Continued*)

					ceived appropriate antibiotics for CAP	two hospitals and computerized in two hospitals)	tion 12.7% increase (95% CI -0.3% to +25.6%) Change in level P = 0.115; change in slope P = 0.334
Hulgan 2004	1	ITS	No	None	Increase oral quinolone use	Computer decision support system delivered as part of an existing ordering system	Absolute increase in oral quinolone orders of +5.6% (95% CI 2.8 to 8.4%), P < 0.001 from a baseline of 55% oral orders (10% relative increase)
Madaras-Kelly 2006	1	ITS	Yes	Feedback about MRSA rates	Reduce use of levofloxacin and reverse increase in MRSA	Computer-generated reminder about hospital policy at the point of prescribing by physicians	Levofloxacin use decreased by 50% (from 115.8 to 57.5 DDD per 1000 patient days), change in slope P = 0.009, change in level P = 0.468
Perez 2003 (intervention 1)	1	ITS	Yes	None	Increase in percentage of patients who received surgical prophylaxis within one hour of incision	Posters and blood pressure cuffs for anaesthetists with a logo reminding them to administer prophylaxis within one hour	Increase in appropriate administration by 20% (ARIMA analysis P = 0.004)
Senn 2004	1	RCT	Yes	None	Reduce duration of IV antibiotic therapy	Questionnaire mailed to residents responsible for each patient who was receiving IV antibiotics	Adjusted hazard for switching IV therapy with intervention was 1.28 (CI 0.99 to 1.67, P = 0.06), which corresponds to a 14% shortening of the days of IV therapy
Shojania 1998	1	RCT	Yes	None	Reduce use of vancomycin	Computer-generated reminder	28% fewer patients re-

Table 4. Impact on antibiotic use of persuasive interventions that used reminders as the main component (*Continued*)

						about hospital policy at the point of prescribing by physicians and three days after start of treatment	ceived vancomycin in intervention group (P = 0.02) and duration of vancomycin therapy 36% less in intervention group (26.5 days vs. 41.2 days per physician, P = 0.05)
Zanetti 2003	1	RCT	Yes	None	Increase in percentage of patients who received additional intra-operative doses of prophylactic antibiotics	Audible and visible computer-generated reminder about hospital guideline for patients with prolonged operations	Intra-operative antibiotics were administered to 68% intervention patients vs 40% randomized controls. In a multivariate analysis there were two predictors of intra-operative redosing: the intervention (OR 3.31, 95% CI 1.97 to 5.56, P < 0.001) and duration of operation (OR 1.62, 95% CI 1.30 to 2.03, P < 0.001)

Studies are in alphabetical order of study.

Abbreviations

<: less than; ARIMA: autoregressive integrated moving average; CAP: community acquired pneumonia; CI: confidence interval; DDD: defined daily dose; ITS: interrupted time series; IV: intravenous; MRSA: methicillin-resistant Staphylococcus aureus; OR: odds ratio; RCT: randomized controlled trial

Table 5. Impact on antibiotic use of restrictive interventions that used a compulsory order form as the main component

Study	Sites	Design	Stop order	Persuasive components			Intended effect	Impact on antibiotic use
				Education materials/ meetings	Reminder	Other		

Table 5. Impact on antibiotic use of restrictive interventions that used a compulsory order form as the main component (*Continued*)

Belliveau 1996	1	ITS	Yes	Yes	Posters and letter from chair of Medical Executive Committee	Academic detailing	Reduction in use of vancomycin	Transiently effective: net effect at one month 18.1% decrease (95% CI -35.5 to -0.7). However, net effect at six months was 5.4% increase (95% CI -21.1 to +31.8%) and by 12 months 47.2% increase (95% CI -2.1 to +96.6)
Perez 2003 (intervention 2)	1	ITS	No	Yes	Posters	None	Reduction in inappropriate dosing interval for three drug groups,	ARIMA analysis revealed variable effect on incorrect prescription by drug group: 47% reduction for aminoglycosides (P < 0.001), 7.3% reduction for ceftazidime /cefotaxime (P = 0.03). No significant change for cephradine and cephalothin
Salama 1996	1	ITS	Yes	Yes	Posters and pocket charts	Academic detailing	Reduction in use of eight target drugs	At 12 months there was a 28.2% reduction in antibiotic cost, change in level P = 0.943, change in slope P < 0.01

Table 5. Impact on antibiotic use of restrictive interventions that used a compulsory order form as the main component (*Continued*)

Saizy-Callaert 2003	1	ITS	No	Yes	Pocket-sized prescribing guide	None	Reduction in expenditure on antibiotics	Net effect at one year 0.1% increase (95% CI -7.3 to +7.5), change in level P = 0.981, change in slope P = 0.3.
Sirinavin 1998	1	ITS	No	Yes	No	None	Reduction in cost of antibiotics	Net effect at 12 months 45.9% decrease (95% CI -33.0 to -58.8), change in level P = 0.006, change in slope P = 0.006

Studies are in alphabetical order of study.

Abbreviations

ARIMA: autoregressive integrated moving average; CI: confidence interval; ITS: interrupted time series.

Table 6. Impact on antibiotic use of persuasive interventions that used audit and feedback as the main component.

Study	Sites	Design	Other components		Intended effect	Feedback information	Dissemination of feedback information	Impact on antibiotic use
			Education materials/ meetings	Other				
Barlow 2007	2	CITS	Yes	Reminder	Increase timely, appropriate treatment for patients with CAP	Aggregated, unit- level data	Written feedback every six weeks	Mean 17% increase in timely, appropriate treatment (95% CI +1% to +32%)
Berild 2001	1	ITS	Yes	No	Decrease in antibiotic cost through decrease in total antibiotic use and in use of five specific groups of an-	Aggregated data from point prevalence surveys	Oral and written feedback every three months.	By 12 months postintervention cost decreased by 30.7% (95% CI -26.1 to -35.4)

Table 6. Impact on antibiotic use of persuasive interventions that used audit and feedback as the main component. (*Continued*)

					tibiotics			
Chu 2003	36	CBA	Yes	No	Increase in four quality indicators for CAP, including timely treatment	Aggregated data with benchmarking data from other hospitals	Single feedback at the start of the intervention phase disseminated at scheduled, medical staff meetings	Absolute 17.7% difference (intervention-control) in timely antibiotics postintervention, P < 0.05
Foy 2004	26	Cluster-RCT	Yes	No	Increase in five quality indicators for termination of pregnancy, including prophylactic antibiotics	Aggregated data about compliance with all five indicators	Single at start of intervention, verbal feedback with discussion of barriers to change and potential solutions	Small (3.5%) difference between intervention and control but note ceiling effect
Fridkin 2002 (intervention 2)	50	CBA	Yes	No	Reduce use of vancomycin in the ICU	Aggregated data about use of vancomycin at the hospital level	Frequency and method of distribution not clear	2.8% increase in vancomycin use, P = 0.62
Mol 2005 (intervention 1)	1	ITS	Yes	Marketing	Increase in compliance with hospital antibiotic policy, intended to reduce drug costs	Aggregated data about compliance with the antibiotic policy	Frequency and method of distribution not clear	By one month postintervention policy compliance increased by 15.5% (95% CI +8% to +23%, P < 0.001)
Kumana 2001	1	ITS	Yes	Reminder	Reduce use of vancomycin in the hospital	Memo about errant prescribing of glycopeptides signed by a consultant physician or microbiologist	Memo sent on the same day to the prescriber and to the supervising medical officer	By six months postintervention vancomycin use decreased by 39% (95% CI -16% to -61%, P < 0.05)

Table 6. Impact on antibiotic use of persuasive interventions that used audit and feedback as the main component. (*Continued*)

Van Kasteren 2005	13	ITS	Yes	No	Reduce duration of surgical prophylaxis and total antibiotic use for prophylaxis	Aggregated pre-intervention data about compliance with guideline on duration of surgical prophylaxis	Single feedback at the start of the intervention phase disseminated at multidisciplinary meetings	By six months antibiotic use decreased by 34.7% (95% CI -13.3% to -56.1%, P = 0.01)
Weinberg 2001	2	CITS	Yes	Marketing	Increase in percentage of women who received timely antibiotic prophylaxis for Caesarean section	Teams monitored the effects of changes to practice on the process measures,	Frequency and method of dissemination not clear.	Increase in the percentage who received antibiotics by 31.6% (95% CI 30.0 to 34.2, P < 0.001)

Studies are in alphabetical order of study.

Abbreviations

<: less than; CAP: community-acquired pneumonia; CBA: controlled before-after; CI: confidence interval; CITS: controlled interrupted time series; ICU: intensive care unit; ITS: interrupted time series; RCT: randomized controlled trial

Table 7. Impact on antibiotic use of restrictive interventions that used expert approval as the main component.

Study	Hospitals	Design	Stop order	Educational materials or meetings	Reminder	Other	Multifaceted	Intended effect	Impact on antibiotic use
Fridkin 2002 (intervention 3)	50	CBA	No	Yes	No	None	Yes	Reduction in VRE through reduced use of vancomycin	Hospital-wide prior approval for vancomycin use was associated with 2.8% increase in vancomycin use (P = 0.25)
Huber 1982	1	ITS	No	No	No	None	No	Reduction in use of	Net effect at 12

Table 7. Impact on antibiotic use of restrictive interventions that used expert approval as the main component. (*Continued*)

								cephalexin	months reduction by -69.7% (95% CI -25. 8 to -113.6), change in level P = 0. 053, change in slope P = 0. 037
Lautenbach 2003	1	ITS	No	No	No	None	No	Reduction in use of vancomycin	Net effect at 12 months 19. 6% decrease (95% CI +44.3 to -83. 5), change in level P = 0.6, change in slope P = 0.7
McElnay 1995	1	ITS	No	Yes	No	Academic detailing	Yes	Reduction in cost by reducing target drugs	Transient effect: net effect at one month 24. 3% reduction (95% CI -55.4 to +6.6) diminishing to 8.9% reduction at six months (95% CI -47. 0 to +29.1), change in level P = 0. 141, change in slope P = 0. 259

Table 7. Impact on antibiotic use of restrictive interventions that used expert approval as the main component. (*Continued*)

McGowan 1976	1	ITS	No	No	No	None	No	Reduction in use of chloramphenicol	Net effect at 12 months 82.8% decrease (95% CI -61.6 to -104.0), change in level P = 0.007, change in slope P = 0.398
Suwangool 1991	1	ITS	No	Yes	No	None	Yes	Reduction in cost of antibiotics	Net effect at six months was 24.1% reduction in antibiotic cost, change in level P = 0.054, change in slope P = 0.07
Woodward 1987	1	ITS	Yes	Yes	No	None	Yes	Reduction in cost of antibiotics	Net effect at six months was a reduction by 7.6% (95% CI -1.2% to -13.9%), change in level P = 0.026, change in slope P = 0.928
Young 1985	1	ITS	No	No	No	None	No	Reduction in cost of antibiotics	Net effect at 12 months was reduction

Table 7. Impact on antibiotic use of restrictive interventions that used expert approval as the main component. (*Continued*)

									by 127.2% (95% CI -35. 6 to -218.8) , change in level P = 0. 003, change in slope P = 0. 466

Studies are in alphabetical order of study.

Abbreviations

CBA: controlled before and after; CI: confidence interval; ITS: interrupted time series; VRE: vancomycin-resistant enterococci.

Table 8. Impact on antibiotic use of restrictive interventions with review and make change as the main intervention.

Study	Sites	Design	Stop order	Educational materials or meetings	Reminder	Other	Multifaceted	Intended effect	Impact on antibiotic use
Borer 2004	1	RCT	No	No	No	None	No	Increase in appropriate antibiotic treatment	Appropriate antibiotic treatment 55% for intervention vs 43% control (12% absolute, 28% relative increase)
Bunz 1990	1	ITS	No	Yes	Memo to head nurses	None	Yes	Decrease in percentage of metronidazole prescriptions dosed < 12-hourly	Net effect at one month 95.2% reduction (95% CI -78.5 to -111. 9), change in level P < 0. 0001, change in slope P = 0. 45
Gupta 1989	1	ITS	No	Yes	Memo to head nurses	None	Yes	Decrease in percentage of cefa-	Net effect at one month 93.4% reduction (95% CI

Table 8. Impact on antibiotic use of restrictive interventions with review and make change as the main intervention. (*Continued*)

								zolin prescriptions dosed < eight-hourly	-81.4 to -105.3), change in level P < 0.0001, change in slope P = 0.52
Singh 2000	1	RCT	No	No	No	None	No	Decrease in percentage of patients with low risk of pneumonia treated for > three days	Intervention reduced percentage of patients receiving antibiotics for > three days to 28% vs 97% control (69% absolute decrease), P < 0.05

Studies are in alphabetical order of study.

Abbreviations

>: greater than; <: less than; CI: confidence interval; ITS: interrupted time series; RCT: randomized controlled trial.

Table 9. Impact on antibiotic use of structural interventions that aimed to decrease use of target antibiotics

Study	Sites	Design	Structural change	Educational resources or meetings	Reminders	Educational outreach	Multifaceted	Intended effect	Impact on antibiotic use
Bruins 2005	1	RCT	Rapid processing of microbiology tests	No	No	Yes	Yes	Increase in percentage of patients who received appropriate treatment in first 48 hours	Increase by 13% in appropriate antibiotic treatment (64% intervention vs 51% control, P = 0.078). Addition of same-day written report had no additional effect

Table 9. Impact on antibiotic use of structural interventions that aimed to decrease use of target antibiotics (*Continued*)

Christ-Crain 2004	1	Cluster-RCT	Inflammatory marker test (procalcitonin)	Yes	Yes	No	Yes	Decrease in percentage of patients treated with antibiotics for lower respiratory tract infection with no change in clinical outcome	Absolute reduction in antibiotic prescribing 38.8% (95% CI -27.8 to -49.9), adjusted relative risk of antibiotic exposure 0.49 (CI 0.44 to 0.55, P < 0.001)
Christ-Crain 2006	1	RCT	Inflammatory marker test (procalcitonin)	Yes	Yes	No	Yes	Decrease in percentage of patients treated with antibiotics for community acquired-pneumonia with no change in clinical outcome	Absolute reduction in antibiotic prescribing 13.9% (95% CI -7.9 to -19.9), adjusted relative risk, 0.52; 95% CI 0.48 to 0.55; P < 0.001
Doern 1994	1	RCT	Rapid processing of microbiology tests	No	Yes	No	Yes	Increase in percentage of patients whose empiric therapy was changed because of microbiology test results	Absolute increase in appropriate antibiotic treatment 5.9%, (95% CI -2.7% to +14.6%, P = 0.18)
Franz 2004	8	RCT	Inflammatory marker test (interleukin)	Yes	No	No	Yes	Decrease in percentage of newborn infants who	Absolute reduction in antibiotic pre-

Table 9. Impact on antibiotic use of structural interventions that aimed to decrease use of target antibiotics (*Continued*)

								received empiric antibiotics without increase in the percentage of initially missed infections	scribing 13.5% (95% CI -8.1% to -18.8%, P < 0.001)
Oosterheert 2005	2	RCT	PCR test for viruses and atypical bacteria	Yes	No	No	Yes	Decrease in percentage of patients that completed a full course of antibiotic treatment for lower respiratory tract infection	The absolute increase in the number of patients who stopped treatment early (2/55 vs 0/52) was 3.6% (95% CI, -1.3% to +8.6%, P = 0.15)
Paul 2006	3	Cluster RCT	Computerized decision support system	Yes	Yes	No	Yes	Decrease in percentage of paients receiving inappropriate empiric antibiotic treatment for suspected bacterial infection	Absolute difference in risk of inappropriate treatment 8.3%, (95% CI 0.6 to 15.9)
Trenholme 1989	1	RCT	Rapid processing of microbiology tests	No	No	Yes	Yes	Increase in the percentage of patients with change to empiric antibiotic	Absolute increase in changes in antibiotic treatment 33.9% (95% CI

Table 9. Impact on antibiotic use of structural interventions that aimed to decrease use of target antibiotics (*Continued*)

								treatment made because of microbiology test results	22.0 to 45.9)

Studies are in alphabetical order of study.

Abbreviations

<: less than; CI: confidence interval; h: hour(s); PCR: polymerase chain reaction; RCT: randomized controlled trial.

Table 10. Impact of interventions on colonization or infection with *C difficile*.

Study	Design	Antimicrobial target	Microbial outcome	Impact on prescribing	1 month	6 months	12 months	24 months	Microbial Risk of Bias
Carling 2003	ITS	Cephalospor aztreonam, fluoroquinolones, or imipenem	*C difficile* infection	No reliable data	No data	No data	-52% (-41% to -63%)	-63% (-52% to -74%)	Low
Climo 1998	ITS	Clindamycin	*C difficile* infection	No reliable data	-65% (-48% to -81%)	No data	-77% (-60% to -94%)	No data	Medium: Unplanned
Khan 2003	ITS	Ceftriaxone removed	*C difficile* infection	No reliable data	-15% (-60% to +30%)	No data	No data	No data	Low
McNulty 1997	ITS	Cefuroxime	*C difficile* infection	75% reduction (Results Table 7)	-50% (-110% to +10%)	-70% (-157% to +16%))	-85% (-198% to +27%)	No data	High: Unplanned IC changed
Pear 1994	ITS	Clindamycin	*C difficile* infection	No reliable data	-53% (-3% to -102%	-68% (-30% to -107%)	-79% (-34% to -124%)	No data	High: Unplanned Lab method changed

Studies are in alphabetical order of study.

Abbreviations

IC: infectious control; ITS: interrupted time series

Table 11. Impact of interventions on colonization or infection with antibiotic-resistant gram-negative bacteria

Study	Design	Antimicrobial target	Microbial outcome	Impact on prescribing	1 month	6 months	12 months	24 months	Microbial Risk of Bias
Calil 2001	ITS	3G cephalospirii	Infections	No reliable data	-92% (-77% to -108%)	No data	No data	No data	Medium: Unplanned
Carling 2003	ITS	3G cephalospori aztreonam, IV fluoroquinolones, imipenem	Infections, ceftazidime R	No reliable data	No data	No data	-41% (-14% to -69%)	-53% (-22% to -83%)	Low
de Champs 1994	ITS	Gentamicin	Infections, gentamicin R	No reliable data	-91% (-58% to -123%)	-96% (-60% to -132%)	No data	No data	High: Unplanned; Unreliable CD
de Man 2000	Cluster-CCT	Cefotaxime	Colonization, cefotaxime or tobramycin R	No reliable data	No data	68% reduction in days of colonization with resistant bacteria (CI only for relative risk)	No data	No data	Low
Gerding 1985	ITS	Cycling gentamicin, amikacin	Infections, gentamicin R	No reliable data	-42% (-6% to -78%)	-33% (-78% to +11%)	No data	No data	Medium: IC not described
Landman 1999	ITS	3G cephalospori imipenem	Intended ceftazidime R infections	No reliable data	-36% (-90% to +19%)	-35% (-92% to +22%)	-29% (-89% to +31%)	No data	Medium: IC change
Leverstein 2001	ITS	Gentamicin	Colonization, Gentamicin R	No reliable data	-23% (-63% to +16%)	-25% (-383% to +332%)	No data	No data	High: Unplanned; IC change

Table 11. Impact of interventions on colonization or infection with antibiotic-resistant gram-negative bacteria (*Continued*)

Meyer 1993	ITS	Ceftazidime	Infections, ceftazidime R	No reliable data	-55% (-31% to -79%)	-80% (-56% to -105%)	No data	No data	High: Unplanned; IC changed
Toltzis 2002	CCT	Cycling gentamicin, ceftazidime, piperacillin-tazobactam	Colonization, R to any of the target drugs	No reliable data	+39% (effect opposite to intended, no CI)	No data	No data	No data	Medium: IC not described

Studies are in alphabetical order of study.

Abbreviations

CCT: controlled clinical trial; CD: case definition; CI: confidence interval; IC: infectious control; ITS: interrupted time series; IV: intravenous.

Table 12. Impact of interventions on colonization or infection with antibiotic-resistant gram-positive bacteria

Study	Design	Antimicrobial target	Microbial outcome	Impact on prescribing	1 month	6 months	12 months	24 months	Microbial Risk of Bias
Bradley 1999	ITS	Ceftazidime	VRE colonization	60.7% reduction (Results Table 7)	-25% (P < 0.001 log rank test, no CI)	No data	No data	No data	Low
Carling 2003	ITS	3G cephalosporin aztreonam, IV fluoroquinolones, imipenem	MRSA infections,	No reliable data	No data	No data	+2% (-34% to +40%)	+10% (-38% to +59%)	Low
Charbonneau 2006	ITS	Fluoroquinolones	MRSA infections,	No reliable data	No data	No data	No data	-23% OR 0.82 (95% CI 0.68 to 0.99) vs pre-intervention	Low
Fridkin 2002	CBA	Vancomycin	VRE infections	35 - 37% reduction	No data	No data	No data	Absolute dif-	Medium: IC not de-

Table 12. Impact of interventions on colonization or infection with antibiotic-resistant gram-positive bacteria (*Continued*)

				(Results Tables 1 and 7)				ference 13.2% lower VRE for intervention vs control, P < 0.001, no CI	scribed
Lautenbach 2003	ITS	Vancomycin	VRE infections	19.6% reduction (Results Table 6)	No data	No data	-38% (-4% to -73%)	-50% (-12% to -89%)	High: Unplanned with only three pre-intervention data points
Madaras-Kelly 2006	ITS	Levofloxacin	MRSA infections,	50% reduction (Results Table 2)	No data	-21% (-5% to -36%)	No data	No data	Medium: IC changed
May 2000	ITS	Vancomycin	VRE infections	42.5% reduction (Results Table 1)	No data	-87% (-21% to -153%)	-100% (-7% to -210%)	No data	High: Unplanned; IC not described

Studies are in alphabetical order of study.

Abbreviations

CBA: controlled before-and-after; CI: confidence interval; IC: infectious control; ITS: interrupted time series; IV: intravenous; MRSA: methicillin-resistant Staphylococcus aureus; OR: odds ratio; VRE: vancomycin-resistant enterococci.

Table 13. Information from studies that provide data about intervention costs and savings.

Study	Intervention Cost	Savings or Costs Achieved by Intervention
Abramowitz 1982	80 hours of clinical pharmacists' time per month (2.5 hours per week by eight pharmacists) USD 16,000 per year at 1982 prices.	Our segmented regression analysis showed a sudden change in level of -USD 23,913 (P = 0.078) and a nonsignificant change in slope by USD 1423 per year (P = 0.684). This estimate of savings was substantially lower than the authors' estimate of USD 156,756 per year, which was based on an uncontrolled before-and-after analysis
Ansari 2003	The cost of the first year of the intervention, which included setting up the programmes for extraction, formatting and analysis was GBP 15,143 and the cost of running the intervention in the second year was GBP	The most conservative estimate of the reduction in cost of Alert Antibiotics was GBP 133,296 (the lower boundary of the 95% CI for change in slope after the intervention, GBP 5554 per month times 24 months)

Table 13. Information from studies that provide data about intervention costs and savings. (*Continued*)

	4990 (full details of intervention costs are in Table 3 of the paper). The total cost of the intervention (GBP 20,133) over the two years was GBP 20,133	. However, assuming that the cost of Alert Antibiotics would have continued to increase without the intervention, the cost of Alert Antibiotics was estimated to have decreased by an average of GBP 23,852 per month (95% CI GBP 18,154 to GBP 29,549, P < 0.0001)
Bailey 1997	Labour costs (pharmacists' time) were estimated to be USD 15,000 per year at Hospital A and USD 7000 per year at Hospital B at 1997 prices	Extrapolating the average postrandomization costs to 200 patients per year at Hospital A, the estimated annual saving was USD 1600 per year (95% CI USD 3100 to USD 6300) Extrapolating the average postrandomization costs to 100 patients per year at Hospital B, the estimated annual saving was USD 4200 per year (95% CI USD 700 to USD 9000)
Christ-Crain 2006	In the procalcitonin group, the marker was measured 529 times (151 on admission, 21 at follow-up after 6 to 24 hours, 139 on Day 4, 128 on Day 6, and 90 on Day 8), thus 3.5 times per patient. The use of procalcitonin for antibiotic stewardship in CAP would become cost saving below USD 25 per analysis	Median costs of antibiotics in the procalcitonin group were USD 100 per patient, as compared with USD 190 per patient in the control group (Table 3 of the paper)
Gums 1999	For the 125 patients in the Intervention group, the time required was 15.6 hours (7.5 minutes per patient) for Infectious Diseases physician consults and 10.4 hours (5 minutes per patient) for Microbiology consults, adding up to a total of USD 1092 at 1999 prices, or USD 8.74 per patient. Pharmacist time was 3.5 days per week or approximately USD 21,000 per year	The difference in median antibiotic costs was -USD 605 per patient (CI -USD 548 to -USD662) so that savings greatly exceeded costs
Landgren 1988	The total cost of both campaigns, including the audits and analysis of results was AUD 71,950	The estimated annual saving was AUD 69,434 for the first intervention and AUD 55,636 for the second intervention
Oosterheert 2005	Use of real time PCR increased antibiotic treatment and diagnostic costs by EUR 318 per patient (test cost of EUR 331 only minimally offset by savings in antibiotic cost)	No evidence of savings on other diagnostic tests or hospitalizations. The total cost per patient for hospitalizations, diagnostic procedures, and treatment was EUR 5117.05 in the intervention group and EUR 4741.30 in the control group
Solomon 2001	Estimated annual cost of the intervention was USD 21,750.	Formal economic analysis was not performed but the institution "plans to continue and expand antibiotic counter-dealing."
Woodward 1987	The expenses incurred in setting up the programme (computer costs and consultant time) were paid by the hospital but details are not provided Programme required 76 hours per month from phar-	Our segmented regression analysis shows that at 12 months the intervention was associated with 7.6% reduction in the average cost of antibiotics per patient (95% CI -1.2 to -13.9%)

Table 13. Information from studies that provide data about intervention costs and savings. (*Continued*)

	macists, 24 hours per month from ID fellows and 10 hours for ID faculty. These hours were "absorbed within the working days of each person" and were not costed	
Wyatt 1998	Fixed cost of preparing the video was GBP 5000. Variable cost per visit GBP 445 (travel GBP 25, hotel GBP 60, staff time GBP 330). Overall mean cost per visit GBP 860, at 1995 prices	The intervention had no significant impact on practice.

Abbreviations
<: less than; CAP: community acquired pneumonia; CI: confidence interval; h: hour(s); ID: infectious diseases; PCR: polymerase chain reaction.

WHAT'S NEW

Last assessed as up-to-date: 3 February 2009.

Date	Event	Description
1 May 2013	Amended	Minor edits, correction to excluded study reference

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 3, 2005

Date	Event	Description
26 February 2013	New citation required and conclusions have changed	New search, 89 new studies found.
26 February 2013	New search has been performed	New search, 89 studies found.
12 February 2009	Amended	Minor edits, tables modified
29 July 2008	Amended	Converted to new review format.
28 July 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Erwin Brown (Medical Microbiologist): Chairman of Joint BSAC and Healthcare Infection Society (HIS) Working Party on Optimising Antibiotic Prescribing in Hospitals, initiated the review; designed and conducted the literature search; handsearched bibliographies of individual papers for additional references; reviewed all papers to identify those that reported the results of an intervention to change antibiotic prescribing; contributed to EPOC check sheets and data extraction.

Peter Davey (Clinical Pharmacologist): wrote the protocol; assisted with the literature search; reviewed all intervention studies for quality using EPOC methodology; re-analyzed data from included CBA, CCT and RCT studies; member of the writing group responsible for the first draft of the review and for final decisions about included studies; contributed to EPOC check sheets and data extraction.

Craig Ramsay (Statistician): re-analyzed all of the ITS studies that did not include regression methods in the original paper; member of the writing group responsible for the first draft of the review and for final decisions about included studies; contributed to EPOC check sheets and data extraction.

Phil Wiffen (Clinical Pharmacist, Director of Operation and Training at the UK Cochrane Centre): designed the Included Studies Table; advised on risk of bias; presentation of results; transferred review text, tables and figures to Review Manager 5; member of the writing group responsible for the first draft of the review and for final decisions about included studies; contributed to EPOC check sheets and data extraction.

Ian Gould (Microbiologist), Lynda Fenelon (Microbiologist), Alison Holmes (Hospital Epidemiologist) and Mark Wilcox (Microbiologist) are members of the BSAC/HIS Working Party; were involved in the design of the protocol; participated in the review of excluded and included studies; completed EPOC check sheets and extracted data from included studies; assessed microbial risk of bias; attended regular meetings of the Working Party and commented on the final draft of the review.

Esmita Charani (Pharmacist) participated in the review of social marketing study by adapting the EPOC definition of marketing, reviewing the relevant studies and writing additional text for the Results and Discussion sections.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Aberdeen Royal Infirmary, Aberdeen, Scotland, UK.
- Emory University, Atlanta, Georgia, USA.
- Frenchay Hospital, Bristol, England, UK.
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- St Vincent's University Hospital, Dublin, Ireland.
- Tel Hashomer Hospital, Tel Aviv, Israel.
- University of Dundee, Dundee, Scotland, UK.
- University of Nottingham, Nottingham, England, UK.
- Vale of Leven Hospital, Alexandria, Scotland, UK.
- UK Cochrane Centre, UK.

External sources

- British Society for Antimicrobial Chemotherapy, UK.
- Hospital Infection Society, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Drug Resistance, Bacterial; *Physician's Practice Patterns; Anti-Bacterial Agents [adverse effects; *therapeutic use]; Bacterial Infections [*drug therapy; prevention & control]; Cross Infection [*drug therapy; prevention & control]; Inpatients; Randomized Controlled Trials as Topic

MeSH check words

Humans