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Antimicrobial Stewardship Programs in Inpatient Settings: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EXECUTIVE SUMMARY

BACKGROUND

It is estimated that in 2009, more than 3 million kilograms of antimicrobials were administered to human patients in the United States. While the life-saving benefits of antimicrobials are indisputable, the consequences of use and misuse must also be considered. Major concerns related to the use of antimicrobials are increasing resistance, higher incidence of *Clostridium difficile (C. difficile)* infection (CDI) and increased healthcare costs (including costs related to adverse events associated with antimicrobial use).

While much of the discussion focuses on overuse, there is also evidence of adverse outcomes associated with inadequate antimicrobial therapy. Antimicrobial stewardship programs (ASPs) are a focused effort by a health care system, a hospital, or a portion of a hospital (e.g., an intensive care unit) to *optimize* the use of antimicrobial agents. The goals of an ASP are to improve patient outcomes, reduce adverse consequences, reduce or prevent an increase in antimicrobial resistance, and deliver cost-effective therapy. The emphasis is on appropriate selection, dosing, route, and duration of antimicrobial therapy.

The purpose of this review is to synthesize the evidence about the effectiveness of antimicrobial stewardship programs implemented in hospital settings. We focus on ASPs including one or more of the following components: prospective audit and feedback, formulary restriction, pre-authorization of prescriptions, guidelines for prescribing and/or modifying therapy, computerized decision support, or laboratory testing. The topic was nominated by Matthew Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, on behalf of the VA Antimicrobial Stewardship Task Force, and is intended to provide a summary of the evidence on inpatient antimicrobial stewardship programs to guide clinical practice and policy within the Veterans Healthcare System. We developed the following key questions with input from a technical expert panel.

Key Question #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

a. Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)
b. Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?

Key Question #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Key Question #3. Does effectiveness vary by: a) hospital setting (rural, urban, academic, VA, non-VA); or b) suspected patient condition?

Key Question #4. What are the harms of inpatient antimicrobial stewardship programs?

Key Question #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

METHODS

An exploratory search identified a 2005 Cochrane review that partially addressed the key questions but was no longer current (search dates 1980 to 2003). We used a search strategy similar to that of the Cochrane review to search MEDLINE (Ovid) through June 2013. We limited the search to studies published from 2000 to the present, in English language, and enrolling human subjects. The full search strategy is presented in Appendix A. Additional citations were identified from systematic reviews, reference lists of retrieved articles, and suggestions made by our technical expert panel members.

Study Selection

Titles, abstracts, and articles were reviewed by investigators and research associates trained in the critical analysis of literature. Full text versions of potentially eligible articles were retrieved for review. We excluded studies done in settings or enrolling patient populations not relevant to the United States; studies not involving an intervention or not involving an intervention of interest (e.g., studies of interventions involving only education were excluded); studies describing an intervention with no assessment of the effects of the intervention; studies not reporting either patient outcomes, prescribing outcomes, microbial outcomes, costs, or harms; studies of antimicrobials for medical or surgical prophylaxis; studies of patients with viral or fungal infection, or tuberculosis; and studies other than randomized controlled trials (RCTs), controlled clinical trials (CCTs), controlled before/after trials (CBAs), or interrupted times series (ITS) with at least three data points before and after implementation of the intervention.

An updated version of the 2005 Cochrane review was released in April 2013 and included studies published through 2009. To avoid duplication, we included in our review only studies meeting the eligibility criteria described above and not included in the most recent version of the Cochrane review.

Data Abstraction

From studies identified as eligible after full-text review, we extracted study characteristics, patient outcomes, prescribing outcomes, microbial outcomes, costs, and harms. We also extracted information on barriers to implementation, sustainability and scalability.

Quality Assessment

We assessed the risk of bias of individual studies using the criteria developed for use in Cochrane Effective Practice and Organization of Care (EPOC) reviews (Appendix B). A study was rated as low risk of bias if each of the individual criteria were scored as low risk, medium risk of bias if one or two criteria were scored as unclear or high risk, and high risk of bias if more than two criteria were scored as unclear or high risk.

Data Synthesis

We constructed evidence tables showing the study characteristics and results for all included studies, organized by intervention category. We created forest plots for outcomes with sufficient data to calculate risk ratios. Due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting among studies for each intervention, we were not able to pool results. We compiled a summary of findings and drew conclusions based on qualitative synthesis of the findings.

Rating the Body of Evidence

We rated overall strength of evidence for our patient outcomes for each intervention category using methods developed by Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program. The strength of the evidence was evaluated based on four domains: 1) risk of bias, 2) consistency, 3) directness, and 4) precision.

Peer Review

A draft version of this report was reviewed by technical experts as well as clinical leadership. Reviewer comments (Appendix C) were addressed and our responses were incorporated in the final report.

RESULTS

We reviewed 6,334 titles and abstracts from the electronic literature search. After applying inclusion/exclusion criteria at the abstract level, 5,775 references were excluded. We retrieved 559 full-text articles for further review and another 539 references were excluded. An additional 15 references were identified from reference lists of recent relevant systematic reviews or were suggested by peer reviewers for a total of 35 included studies. Nine were RCTs (including cluster randomized trials), four were CCTs, two were CBAs, and twenty were ITS studies. We also summarized three systematic reviews relevant to this topic.

We categorized studies initially by primary intervention including 14 studies of audit and feedback programs, 5 studies of formulary restriction and preauthorization programs, 4 studies of guideline implementation with feedback, 4 studies of guideline implementation with no feedback, 4 studies of computerized decision support, and 4 studies of protocol or policy implementation. Within each intervention category, we further described interventions as intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery (31 studies) or intended to decrease unnecessary or excessive prescribing (4 studies).

Most studies were conducted at university affiliated or teaching hospitals. Four studies were performed at community hospitals, three at mixed sites, and two did not specify the hospital type. One study analyzed data from administrative care databases for a Canadian province. We also looked at the site of the intervention with 8 studies conducted in intensive care units (ICUs), 7 studies conducted in medical wards, 12 studies conducted in multiple sites (medical, surgical, ICU), and 1 study in acute care. Seven studies did not report the site.

Seven studies focused on treatment of respiratory illness, 26 included patients with any type of infection, and 1 study included only bloodstream infections. One study did not report infection site.

We also identified two recent systematic reviews and two trials published after those reviews that focused on use of procalcitonin monitoring to guide antimicrobial therapy. All of the individual trials of procalcitonin monitoring that were identified in our original literature search were included in the systematic reviews so we summarized the findings from the existing reviews.

Key Question #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

a. **Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)**
b. **Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?**

Findings from an Existing Systematic Review

The recently updated high quality Cochrane systematic review of 89 studies identified through 2009 (25 RCTs, 3 CCTs, 5 CBAs, and 56 ITS studies) assessed this question focusing mainly on prescribing outcomes. The 56 ITS studies were not included in meta-analyses for outcomes of readmission, mortality, or length of stay due to anticipated high study design heterogeneity versus the RCTs, CCTs and CBAs. Despite the large number of studies included, most did not report on all outcomes (e.g., only 13 of 25 RCTs reported on mortality and only 5 reported on hospital readmissions) or the exact outcome within each category may have varied (e.g., the antimicrobial prescribing outcome could include changes in decision to initiate or stop dose or route of antimicrobial; readmissions were reported as "all-cause" in 1 study and "infection related" in 4 others). The review authors did not state how they identified the single outcome selected from each study for analysis but our independent review suggests that only the primary outcome, identified by the original study author, was included. There was no verification or explanation of whether results would be consistent if the review authors included other outcomes within a category (i.e., clinical, prescribing, microbial, costs). Therefore, summary results for outcomes are based on findings from few studies often in different settings and with variable interventions.

Primary Outcomes

Interventions to increase effective prescribing in patients with any infection had no effect on mortality (k=3) whereas interventions to increase guideline compliance in patients with community acquired pneumonia (k=4) were associated with reduced mortality. Interventions to decrease excessive prescribing had no effect on mortality (k=11) or length of stay (k=6) and were associated with increased hospital readmissions (k=5 with 1 study reporting all-cause readmission and 4 studies reporting infection-related readmission). Five ITS studies (4 with restrictive interventions, 1 with a persuasive intervention) reported on CDI with a median effect of 68.0% reduction in infection.

Secondary Outcomes

Persuasive (k=44) and restrictive (k=25) interventions were associated with improved prescribing outcomes based on median outcome effect sizes (i.e., the percent subjects with an

improvement or change in the antimicrobial selection, dose, route, or duration versus control). In addition, interventions were typically associated with effect size changes in microbial outcomes in the direction of the intended effect. Meta-regression analyses comparing prescribing (k=38) and microbial (k=14) outcomes from studies that were purely persuasive or purely restrictive showed some evidence of a short-term improvement with restrictive interventions that was not sustained. The outcome measures used to assess effectiveness varied across studies. Multifaceted interventions were common but not necessarily more effective than simpler interventions.

Intervention costs and financial savings were reported in 10 studies including 2 studies of prophylactic antimicrobials. In eight of the studies, savings were greater than costs.

Studies at VA Hospitals

The review included 9 studies conducted at VA hospitals and published between 1985 and 2006. Reduced incidence of CDI associated with the stewardship intervention was reported (2 studies). Findings for prescribing and microbial outcomes were mixed. Few clinical outcomes were reported.

Findings from Recent Evidence

The existing systematic review reported mixed results for clinical outcomes and overall improvement in prescribing and microbial outcomes. We focused our review on studies published after 2000 and not included in the prior systematic review or published after the 2009 search date of that review. We summarize findings (Executive Summary Tables 1a and 1b) and report strength of evidence for clinical outcomes (Executive Summary Table 2) according to type of antimicrobial stewardship intervention. Due to small numbers of studies of an intervention reporting each outcome, inconsistency across studies, and overall medium to high risk of bias in included studies, the strength of evidence for all clinical outcomes was rated as low.

Audit and Feedback (k=14)

Among the fourteen studies assessing audit and feedback as the primary stewardship strategy, we found substantial differences in study design, location, and population. Only three were randomized, controlled trials, and the studies were dispersed geographically including Europe, the United Kingdom, Asia, and North and South America.

There were substantial threats to validity, including the possibility of secular trends, contamination within study sites, opportunities for bias in assessment, and the potential for unmeasured or unreported changes in use of antimicrobials not targeted by the interventions.

Few studies reported significant differences in patient-related outcomes, although those that did reported differences that favored the intervention. However, several studies demonstrated reduced antimicrobial use associated with the intervention, whether they targeted specific antimicrobials, or all antimicrobials. In one study usage of the targeted antimicrobials decreased, but overall use was not significantly changed.

Executive Summary Table 1a. Overview of Clinical Outcomes – Antimicrobial Stewardship Interventions for Inpatients

ASP Intervention (# studies)	Mortality	Length of Stay	Readmission	CDI	Summary
Prospective Audit and Feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	**+ 1 study ≈ 9 studies**	**≈ 9 studies**	**+ 1 study ≈ 2 studies**	**p=NR, 1 study**	Audit and feedback showed no association with clinical outcomes.
Formulary Restriction and Preauthorization (1 RCT, 4 ITS)	**≈ 3 studies**	**≈ 2 studies**	NR	**+ 1 study**	Mortality and length of stay were unchanged with formulary restriction and preauthorization. CDI was decreased.
Guidelines with Feedback (2 RCT, 2 ITS)	**≈ 3 studies**	**≈ 3 studies**	NR	**+ 2 studies**	Mortality and length of stay were unchanged. CDI was decreased in two studies following guidelines with feedback intervention.
Guidelines without Feedback (1 CCT, 1 CBA, 2 ITS)	**+ 1 study ≈ 1study - 1 study**	**+ 1 study ≈ 1study - 1 study**	**≈ 1 study**	NR	Inconsistent findings from 3 studies of guidelines implemented without feedback assessing mortality or length of stay. No difference in readmissions.
Computerized Decision Support (1 RCT, 1 CCT, 2 ITS)	**≈ 3 studies**	**+ 1 study ≈ 2 studies**	**≈ 1 study**	**+ 1 study ≈ 1 study**	No differences in mortality or readmissions with computerized decision support versus controls. Mixed results for length of stay and CDI.
Protocols (2 RCT, 2 ITS)	**+ 1 study ≈ 2 studies**	**+ 2 studies ≈ 1 study**	**≈ 1 study**	NR	For protocols, results were mixed for mortality and length of stay. No difference in readmissions.

ASP = antimicrobial stewardship; NR = not reported; CDI = incidence of *C. difficile* infection
CBA = controlled before and after; CCT = controlled clinical trial; ITS = interrupted time series; RCT = randomized controlled trial

+ indicates statistically significant difference favoring antimicrobial stewardship intervention
≈ indicates no statistically significant difference between antimicrobial stewardship intervention and control
- indicates statistically significant difference favoring control

Executive Summary Table 1b. Overview of Prescribing Outcomes – Antimicrobial Stewardship Interventions for Inpatients

ASP Intervention (# studies)	Use	Selection	Timing	Duration	Summary
Prospective Audit and Feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	**Decreased: + 8 studies Appropriate: + 1 study ≈ 1 study**	**+ 1 study ≈ 1 study**	NR	**+ 5 studies**	Prospective audit and feedback showed improvement in prescribing outcomes
Formulary Restriction and Preauthorization (1 RCT, 4 ITS)	**Decreased: + 4 studies**	NR	NR	**+ 1 study**	Formulary restriction and preauthorization were associated with improvement in prescribing outcomes.
Guidelines with Feedback (2 RCT, 2 ITS)	**Decreased: + 1 study Compliant/ appropriate: + 2 studies**	**≈ 1 study**	**+ 1 study**	**≈ 2 studies**	Mixed results were observed for prescribing outcomes with some studies reporting improvements in adherence to guideline recommended treatments and appropriate early initiation of therapy.
Guidelines without Feedback (1 CCT, 1 CBA, 2 ITS)	**Decreased: + 1 study Compliant/ appropriate: + 2 studies ≈ 1 study**	NR	**- 1 study**	**+ 1 study ≈ 1 study**	Improvement in prescribing use but not timing or duration with guidelines implemented without feedback.
Computerized Decision Support (1 RCT, 1 CCT, 2 ITS)	**Decreased: + 1 study ≈ 1 study**	NR	NR	NR	Two studies reported mixed results for antimicrobial use with computerized decision support.
Protocols (2 RCT, 2 ITS)	**Appropriate: ≈ 1 study**	NR	**≈ 1 study**	**+ 2 studies**	No difference in appropriate use or timing but reduced duration of use in studies of ASP protocols.

ASP = antimicrobial stewardship; NR = not reported;
CBA = controlled before and after; CCT = controlled clinical trial; ITS = interrupted time series; RCT = randomized controlled trial

+ indicates statistically significant difference favoring antimicrobial stewardship intervention
≈ indicates no statistically significant difference between antimicrobial stewardship intervention and control
- indicates statistically significant difference favoring control

Executive Summary Table 2. Strength of Evidence for Inpatient Antimicrobial Stewardship Studies, by Clinical Outcome

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
A. Audit and Feedback Studies (k=14)						
Lesprit 2013[1]	RCT	Improve quality of antimicrobial use	Medium	Mortality	NS, RR 0.98 [0.64, 1.50]	Low for Mortality
Camins 2009[2]	RCT	Improve appropriateness	High	Mortality	NS, RR 0.62 [0.30, 1.29]	
Masia 2008[3]	RCT	Decrease targeted antimicrobials	Medium	Mortality	NS, RR 1.12 [0.75, 1.66]	
Weiss 2011[4]	CCT	Improve mortality	High	Mortality	Reduced, OR 0.48 [0.26, 0.88]	
Manuel 2010[5]	CCT	Improve appropriateness	High	Mortality	NS	
Elligsen 2012[6]	ITS	Decrease targeted antimicrobials	Medium	Mortality	NS, 13% pre, 14% post	
Standiford 2012[7]	ITS	Decrease ineffective/excessive	High	Mortality	NS	
Teo 2012[8]	ITS	Improve appropriateness	High	Mortality	NS, 0.44 deaths/100 inpatient days (pre and post)	
Bornard 2011[9]	ITS	Improve quality of antimicrobial use	High	Mortality	NS, RR 0.84 [0.05, 12.99]	
Dunn 2011[10]	CBA	Increase switch rate from IV to oral	High	Mortality	NS	
Lesprit 2013[1]	RCT	Improve quality of antimicrobial use	Medium	Length of stay	NS, 15 days (median) (both groups)	Low for Length of Stay
Camins 2009[2]	RCT	Improve appropriateness	High	Length of stay	NS, 7 days intervention, 8 days control (medians)	
Masia 2008[3]	RCT	Decrease targeted antimicrobials	High	Length of stay	NS, 14 days (median), (both groups)	
Weiss 2011[4]	CCT	Improve mortality	High	Length of stay (ICU)	NS, 4 days intervention, 5 days control, p=0.07	
Manuel 2010[5]	CCT	Improve appropriateness	High	Length of stay	NS	
Elligsen 2012[6]	ITS	Decrease targeted antimicrobials	Medium	Length of stay	NS, 6.9 days (pre and post)	
Standiford 2012[7]	ITS	Decrease ineffective/excessive	High	Length of stay	NS	
Bornard 2011[9]	ITS	Improve quality of antimicrobial use	High	Length of stay	NS, 18 days pre, 19 days post	
Dunn 2011[10]	CBA	Increase switch rate from IV to oral	High	Length of stay	NS	
Lesprit 2013[1]	RCT	Improve quality of antimicrobial use	Medium	Readmission*	Reduced, RR 0.43 [0.23, 0.82]	Low for Readmission
Masia 2008[3]	RCT	Decrease targeted antimicrobials	High	Readmission	NS, RR 1.40 [0.84, 2.33]	
Standiford 2012[7]	ITS	Decrease ineffective/excessive	High	Readmission	NS	
Elligsen 2012[6]	ITS	Decrease targeted antimicrobials	Medium	Incidence of CDI	Significance not reported; 16 cases pre, 11 cases post	Low for Incidence of CDI

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
B. Formulary Restriction and Preauthorization Studies (k=5)						
Rattanaumpawan 2010[11]	RCT	Preauthorization	High	Mortality	NS, RR 1.04 [0.90, 1.20]	Low for Mortality
Peto 2008[12]	ITS	Preauthorization	Medium	Mortality	NS, p=0.44	
Mamdani 2007[13]	ITS	Formulary restriction	Low	Mortality	NS, p=0.62	
Rattanaumpawan 2010[11]	RCT	Preauthorization	High	Length of stay	NS, p=0.80	Low for Length of Stay
Peto 2008[12]	ITS	Preauthorization	Medium	Length of stay	NS, p=0.21	
Aldeyab 2012[14]	ITS	Restriction	High	Incidence of CDI	Reduced *trend* (p=0.008) NS change in *level*	Low for Incidence of CDI
C. Guidelines Implemented with Feedback Studies (k=4)						
Schnoor 2010[15]	RCT	Improve adherence to pneumonia guidelines	High	Mortality	NS	Low for Mortality
Schouten 2007[16]	RCT	Appropriate use	High	Mortality	CAP: NS, RR 0.87 [0.45, 1.66] COPD: NS, RR 1.76 [0.61, 5.08]	
Fowler 2007[17]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Mortality	Rates reported only	
Schnoor 2010[15]	RCT	Improve adherence to pneumonia guidelines	High	Length of stay	NS, RR 0.97 [0.43, 2.17]	Low for Length of Stay
Schouten 2007[16]	RCT	Appropriate use	High	Length of stay	NS, p=0.89	
Fowler 2007[17]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Length of stay	Significance not reported	
Talpaert 2011[18]	ITS	Reduce broad-spectrum antimicrobial use	Medium	Incidence of CDI	Decreased, IRR 0.34 [0.20, 0.58]	Low for Incidence of CDI
Fowler 2007[17]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Incidence of CDI	Decreased, IRR 0.35 [0.17, 0.73]	
D. Guidelines Implemented without Feedback Studies (k=4)						
Goldwater 2001[19]	CCT	Reducing costs without sacrificing patient care	High	Mortality	NS, RR 1.07 [0.63, 1.82]	Low for Mortality
Meyer 2007[20]	ITS	Reduce duration	Medium	Mortality (ICU)	Increased, p<0.05	
Capelastegui 2004[21]	CBA	Appropriateness, timing, duration	High	Mortality	Reduced, OR 1.8 [1.1, 2.9]**	
Goldwater 2001[19]	CCT	Reducing costs without sacrificing patient care	High	Length of stay	Increased, p<0.05	Low for Length of Stay
Meyer 2007[20]	ITS	Reduce duration	Medium	Length of stay	NS	
Capelastegui 2004[21]	CBA	Appropriateness, timing, duration	High	Length of stay	Reduced, p<0.001	
Capelastegui 2004[21]	CBA	Appropriateness, timing, duration	High	Readmission	NS, OR=0.8 [0.3, 2.0]**	Low for Readmission

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
E. Computerized Decision Support Studies (k=4)						
McGregor 2006[22]	RCT	Appropriateness	High	Mortality	NS, RR 1.11 [0.80, 1.53]	Low for Mortality
Barenfanger 2001[23]	CCT	Lower mortality, cost, and duration	High	Mortality	NS, RR 1.12 [0.62, 2.01]	
Nowak 2012[24]	ITS	Appropriateness, cost	High	Mortality	NS Sepsis: RR 0.50 [0.18, 1.38] Pneumonia: RR 0.96 [0.63, 1.47]	
McGregor 2006[22]	RCT	Appropriateness	High	Length of stay	NS, 3.8 days intervention, 4.0 days control (medians)	Low for Length of Stay
Barenfanger 2001[23]	CCT	Lower mortality, cost, and duration	High	Length of stay	Reduced, p=0.035	
Nowak 2012[24]	ITS	Appropriateness, cost	High	Length of stay	NS Sepsis: 7.2 (pre), 7.4 (post) Pneumonia: 5.9 (pre), 5.5 (post)	
Nowak 2012[24]	ITS	Appropriateness, cost	High	Readmission	NS Sepsis: RR 0.83 [0.46, 1.49] Pneumonia: RR 1.02 [0.83, 1.25]	Low for Readmission
Nowak 2012[24]	ITS	Appropriateness, cost	High	Incidence of CDI	Decreased, p=0.018	Low for Incidence of CDI
McGregor 2006[22]	RCT	Appropriateness	High	Incidence of CDI	NS, p=0.49	
F. Miscellaneous (Protocol) Studies (k=4)						
Carratalà 2012[25]	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR 2.01 [0.37, 10.85]	Low for Mortality
Oosterheert 2006[26]	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR 0.63 [0.21, 1.88]	
Pulcini 2011[27]	ITS	Appropriateness	Medium	Mortality	Reduced, p=0.03	
Carratalà 2012[25]	RCT	Evaluate effectiveness of early switch	Medium	Length of stay	Reduced, WMD 2.1 [1.7, 2.7]	Low for Length of Stay
Oosterheert 2006[26]	RCT	Evaluate effectiveness of early switch	Medium	Length of stay	Reduced, WMD 1.9 [0.6, 3.2]	
Pulcini 2011[27]	ITS	Appropriateness	Medium	Length of stay	NS, p=0.99	
Carratalà 2012[25]	RCT	Evaluate effectiveness of early switch	Medium	Readmission	NS, RR 1.21 [0.63, 2.33]	Low for Readmission

RCT = randomized controlled trial; ITS = interrupted time series; CCT = controlled clinical trial; CBA = controlled before and after study; NS = not statistically significant; OR = odds ratio [95% confidence interval]; RR = rate ratio [95% confidence interval]; IRR = incidence rate ratio [95% confidence interval]; HR = hazard ratio [95% confidence interval]; WMD = weighted mean difference; IV = intravenous; CDI = *C. difficile* infection; CAP = community acquired pneumonia; COPD = chronic obstructive pulmonary disease

*This study reported 60 day readmission for relapsing infection; other studies report 30 day readmission for any cause

**In this study, the post-intervention cohort was the reference group; ORs are for the control hospital cohort versus the intervention hospital cohort

Most studies reported information on costs, though data presentation varied markedly from study to study. No study reported on whether the intervention was cost saving, that is whether saving in antimicrobial use and other savings were greater than program costs.

Little information on potential harms of stewardship programs were reported, although among the limited microbiological results reported, there was an increase in one of the assessed antimicrobial-resistant organisms. Furthermore, we found no evidence that clinical outcomes such as mortality, hospital length of stay, or readmissions were increased.

Formulary Restriction and Preauthorization (k=5)

We identified five studies that evaluated restrictive interventions for ASP, three evaluated preauthorization, and two assessed the impact of formulary restriction (i.e., requiring prescribers to provide a reason for fluoroquinolones designated as limited use drugs). The restrictive interventions did not significantly impact overall mortality (three studies) or hospital length of stay (two studies). All four studies reporting antimicrobial use found reductions in use or inappropriate use that favored the restrictive antimicrobial stewardship intervention. In the RCT, antimicrobial costs were lower in the ASP intervention arm but the significance of the difference was not reported.

Guidelines Implemented with Feedback (k=4)

None of the three studies reporting mortality and length of stay found that guidelines implemented with feedback impacted these outcomes in patients with respiratory illnesses or unspecified conditions. Two studies, one enrolling elderly patients in acute care wards, noted decreased CDI when a narrow-spectrum antimicrobial policy was implemented. Three of four studies reported improved antimicrobial use outcomes (adherence to guideline recommended treatment and decreased prescribing of antimicrobials targeted for decreased use). One study reporting antimicrobial timing outcomes reported improvements in the intervention group as did one study reporting selection outcomes. No differences were found in antimicrobial duration. One study reported microbial outcomes and one reported intervention implementation costs.

Guidelines Implemented without Feedback (k=4)

Across studies of guidelines created and implemented for different purposes (conversion from intravenous (IV) to oral therapy, increasing concordant therapy, etc.), results were moderately consistent in finding few differences in mortality or length of hospital stay. Compliance with initiation of recommended treatment typically increased, duration of therapy was 2 to 3 days shorter following the intervention, and costs were significantly reduced.

Computerized Decision Support (k=4)

An RCT comparing computerized alerts to manual review found reduced costs and no difference in mortality, diarrhea, or length of hospital stay. Alerts were directed to the antimicrobial management team rather than treating physicians. With the computerized alerts, the team spent one hour less each day with the greatest time saving in identifying patients who might need an intervention. A CCT comparing a computerized system linking susceptibility testing to pharmacy information to a manual review of test results found no differences in mortality but decreased length of stay, lower total costs, and lower patient care costs with the computerized system. Following introduction of a computerized decision support system to reduce prescribing

of broad-spectrum antimicrobials, susceptibility of *Pseudomonas* to imipenem improved. The addition of software to search medical records and generate reports did not reduce mortality, length of stay, or readmission but reduced CDI. Other changes noted were less clinically significant and, given the large number of comparisons, results should be interpreted with great caution.

Protocols (k=4)

Implementation of protocols for switching from IV to oral therapy, reassessing therapy after three days, or autosubstitution of antimicrobials resulted in mixed findings for mortality (two studies found no difference and one small study reported reduced mortality) and length of stay. Two studies reported shorter length of IV treatment. Another reported no change in the prevalence of inappropriate therapies. The autosubstitution study found improved microbial outcomes as a result of the autosubstitution of ertapenem for ampicillin-sulbactam.

Laboratory Tests (2 systematic reviews, 2 recent RCTs)

Both of the recent systematic reviews found that compared with standard care, the use of procalcitonin to guide antimicrobial therapy (initiation and duration) for patients with acute respiratory infection or ICU patients with any infection significantly reduced antimicrobial use with no change in mortality, length of stay, or treatment failure. Recent trials reported no differences in mortality, mixed results for ICU length of stay, and non-significant findings for prescribing outcomes.

Key Question #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Six studies provided information on intervention components associated with effective antimicrobial stewardship. Consistent and persistent effort from qualified personnel employing effective communication skills and often supported by electronic medical records or computerized decision support systems were central themes through these studies. One study noted that a computerized clinical decision support system was time saving compared with manual chart review and recommendations.

Key Question #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

None of the studies identified in our search for recent evidence were conducted at VA medical centers. Nearly all were conducted in university-affiliated teaching hospitals. Only six studies were conducted in community hospitals and nine in ICUs. Many studies had different focuses, making it difficult to reach any conclusions about differences in effectiveness according to hospital setting or unit (ICU or other unit). Furthermore, because intervention components, study design, patient populations, and targeted infection or antimicrobial use differed across studies with no study directly attempting to replicate previous findings we caution against inferring that any outcome variation was due to hospital setting or unit.

Lung infections were the most frequently reported specific patient condition (seven studies). Results appeared qualitatively similar in these studies compared with the overall findings. Due

to limited information and variability in study design, intervention and patient characteristics we urge caution in trying to assess whether effectiveness varies by suspected patient condition.

Key Question #4. What are the harms of inpatient antimicrobial stewardship programs?

Only two studies reported *possible* harms associated with implementation of antimicrobial stewardship programs. Both were studies with audit and feedback as the primary intervention and reporting of harms was anecdotal. Other "harms" could include statistically significant adverse increases in patient, microbial, or prescribing outcomes due to the ASP intervention. However, reports of possible harms were rare and evidence was of low quality.

Key Question #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

We identified four studies that described implementation barriers. Based on a single survey, barriers to adherence were identified as knowledge, attitude, and external barriers. The authors recommended development of evidence-based guidelines with involvement from representatives from relevant clinical services and opportunity for iterative feedback. Provider attendance at educational sessions was poor and adding audits or continuous quality improvement cycles to the intervention may increase physician compliance. Other suggestions to improve implementation included gaining a better understanding of the local prescribing culture, fostering an environment of appropriate prescribing, and increasing collaboration between infectious diseases physicians and pharmacists.

Several studies reported on resources required. The makeup of an antimicrobial stewardship team, physician and pharmacist time and workload monitoring patients and reviewing prescriptions to make recommendations, frequency of staff training sessions, and costs of personnel and/or equipment were reviewed.

Most reviewed studies were one year or less and did not comment on sustainability. Over a seven year period an audit and feedback program assessed the impact of a preauthorization for use of antimicrobial agents and guidelines for ordering. After study termination, antimicrobial prescriptions increased by 5.2%. The program was discontinued to permit funding for hiring of additional infectious disease physicians. Authors also noted dissatisfaction amongst providers with the preauthorization requirements. No studies commented on scalability.

CONCLUSIONS

Key Findings

- There is low quality evidence that ASPs can improve prescribing and microbial outcomes with reduced costs without significant adverse impact on patient outcomes.
- In the recent literature, the greatest body of evidence is from audit and feedback studies but a systematic review of earlier studies provided evidence of comparable effects for persuasive and restrictive interventions.

- Studies varied in design (with few randomized, controlled trials), population enrolled, hospital setting, intent of the stewardship program, components of the stewardship program, outcomes assessed and length of follow-up making definitive conclusions about successful program elements, type and sustainability difficult. Most studies were done at a single site, often a university-affiliated hospital, limiting conclusions about scalability.
- Although high quality evidence on comparative effectiveness of ASPs would allow for more definitive conclusions and implementation recommendations, the availability of resources to conduct such studies is limited. Because generalizability to other settings is difficult we urge ongoing evaluation and communication with antimicrobial stewardship program leaders to assess whether implementation of these findings results in desired effects at individual institutions or across national healthcare systems.

We found multiple studies providing low quality evidence that ASPs are associated with improvement in antimicrobial prescribing patterns and reductions in antimicrobial resistance and costs without significant negative impact on mortality, hospital length of stay, or 30 day readmission. These conclusions are based on an updated and comprehensive search of the evidence that includes a wide range of study types, populations, interventions, and outcomes.

Improving hospital antimicrobial prescribing in adults through antimicrobial stewardship programs is an important healthcare need. In addition to improving direct clinical outcomes for individual patients (i.e., mortality, length of stay and hospital readmissions), improving hospital antimicrobial prescribing can be considered successful if it has other positive effects that include lower drug and personnel costs and reduced development of hospital antimicrobial resistance even in the absence of measured clinical outcome improvements. Therefore, the use of these "intermediate" measures (prescribing and microbial outcomes) to assess effectiveness may be appropriate in terms of study design and health policy implementation if data provides reasonable reassurance that ASP interventions intended to alter antimicrobial prescribing patterns do not unintentionally result in clinical harms.

We categorized ASP interventions as audit and feedback, formulary restriction and preauthorization, guideline implementation with feedback, guideline implementation without feedback, computerized decision support, protocol or policy, or laboratory testing. These categorizations are consistent with previous research and conceptual frameworks in this area. We recognize that many of these interventions are multifaceted and contain elements of other intervention categories making classification difficult and somewhat subject to interpretation.

Studies were typically low in methodological quality and varied considerably in the study design, populations enrolled, hospital setting, condition or intent of the ASP program, composition and implementation of the intervention, comparison group, and outcomes assessed. This variability along with limited outcome reporting hampers definitive conclusions or recommendations for policy implementation. Furthermore, many programs are multifaceted and results may be unique to a particular intervention component, population, clinical condition or hospital type, unit or setting. Thus generalizability to other settings is difficult. We urge ongoing evaluation to assess whether implementation of these findings results in desired effects at individual institutions or across national healthcare systems.

Our results are generally consistent with a Cochrane review that included studies through 2009

and categorized and analyzed results in a slightly different fashion. Based on our identification of new literature and feedback from our Technical Expert Panel members antimicrobial stewardship is a rapidly developing field with abundant new evidence emerging. Thus ongoing review and assessment is likely needed to provide up-to-date information for practitioners, policymakers, and researchers.

It is not possible based on the evidence to determine if one type of ASP program is more successful than another or whether targeting a program for a specific ASP intent is superior to another approach. Among the recent studies, the greatest body of evidence of effectiveness is for decreasing inappropriate antimicrobial use or increasing appropriate antimicrobial use (Executive Summary Table 1b), especially for prospective audit and feedback interventions. There is also some evidence of the effectiveness of audit and feedback interventions on decreasing duration of antimicrobial use. There is limited evidence of effectiveness based on antimicrobial selection or timing. The Cochrane review reported that the median change in antibiotic prescribing for persuasive interventions included in their review ranged from 3.5% for cluster-RCTs to 42% for interrupted time series (with positive changes in the direction of the intended effect). For restrictive interventions, the range was 17% for CBA studies to 41% for RCTs.

We found very limited data on components of ASPs contributing to success, barriers to implementation, scalability or sustainability or whether results vary by hospital setting (academic, urban, rural) or unit. Reproducibility of specific studies was not done and applicability of reported findings is likely low and requiring replication. Some key components are likely to vary by hospital settings, resources, and needs. Future research is needed to identify the most cost-effective and sustainable programs for individual hospitals and broader health care systems. We recommend ongoing evaluation of any program that is implemented to permit adequate evaluation of effectiveness and harms, assessment and removal of barriers to success, determination of sustainability and cost-effectiveness, and if necessary modification.

ABBREVIATIONS

Abbreviation	Definition
AECB	acute exacerbations of chronic bronchitis
ASP	antimicrobial stewardship program
CAP	community-acquired pneumonia
CBA	controlled before and after study
CCT	controlled clinical trial
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRCT	cluster randomized controlled trial
DDD	defined daily dose
EPOC	Effective Practice and Organization of Care
HAP	hospital-acquired pneumonia
HCAP	healthcare-associated pneumonia

ICU	intensive care unit
ITS	interrupted time series
IV	intravenous
LOS	length of stay
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
OR	odds ratio
PD	patient-days
RCT	randomized controlled trial
RR	risk ratio
VA	Department of Veterans Affairs
VAP	ventilator-associated pneumonia
€	euro, currency used by the Institutions of the European Union
£	pound sterling, currency of the United Kingdom

EVIDENCE REPORT

INTRODUCTION

It is estimated that in 2009, more than 3 million kilograms of antimicrobials were administered to human patients in the United States.[28] While the life-saving benefits of antimicrobials are indisputable, the consequences of use and misuse must also be considered.[29] Unlike any other medication, antimicrobial use influences not only the patient being treated but also the surrounding ecosystem.[30,31] Major concerns related to the use of antimicrobials are increasing microbial resistance, higher incidence of antimicrobial associated *Clostridium difficile (C. difficile)* infection (CDI), other drug related toxicities and increased healthcare costs.[29]

Over the past decade, the number of bacteria identified as resistant to antimicrobials has increased and commonly prescribed antimicrobial treatments are becoming ineffective.[32] A major factor in the emergence of drug-resistant bacteria is bacterial evolution with selective pressure applied via antimicrobial usage including the choice of antimicrobial therapy, the duration of therapy, the route of administration, and the dosage.[33,34] At the patient level, treatment with an antimicrobial increases the risk that the patient will become colonized or infected with a resistant organism.[31,34] At the hospital level, increased use of antimicrobials has increased the prevalence of resistant bacteria in hospitals.[31] Infections due to resistant pathogens, including the epidemic strain of *C. difficile* and Methicillin-resistant *Staphylococcus aureus* (MRSA), are associated with increases in morbidity and mortality.[35-37]

Historically, as new resistance patterns emerged, antimicrobial agents with new targets or new mechanisms of action were developed and became available for use. That approach has slowed dramatically largely due to economic and regulatory factors.[28] Among the suggestions for addressing this delay in the "antibiotic pipeline" are new approaches to funding research and development and a modification of the drug approval process to allow clinical superiority trials.[28]

CDI is concentrated in hospitals and chronic care facilities. The pathogen is widespread in a hospital environment, elderly populations are most vulnerable, and there is high use of fluoroquinolones in those facilities conferring a selective advantage, particularly to the epidemic strain of *C. difficile*.[33,36] Eighty-five percent or more of patients with *C. difficile* associated disease were exposed to antimicrobials in the 28 days before infection.[38,39]

Costs associated with antimicrobial use include not only drug costs but costs associated with adverse events and costs associated with antimicrobial resistance.[30] Several studies have reported over-prescription of antimicrobials in intensive care units (ICUs). Longer courses without clear evidence of infection or courses extending beyond usual durations have no benefits for patients in infectious disease outcomes but substantial harms including increased length of stay, increased adverse effects, and possibly increased mortality when comparing patients treated for 3 or 4 days to those treated for as long as 20 days.[40,41] Increased mortality, increased length of hospital stay, and lost productivity must also be considered.[29] Additionally, an increased risk of death from cardiovascular causes has been reported in patients taking erythromycin[42] or azithromycin.[43] Of emergency department visits for drug-related adverse events, over 19% were due to antimicrobial use with allergic reactions most common.[44]

Inappropriate use of antimicrobials includes prescription of antimicrobials when they are not needed, continuation of antimicrobials when they are no longer needed, prescription of the wrong dose, use of broad-spectrum agents for bacteria susceptible to narrow-spectrum agents, and choice of wrong antimicrobials for an infection.[31] Prescribing decisions made by less-experienced staff members (i.e., interns and residents), pressure to decrease hospital length of stay, and increasingly complex clinical presentation are all potential factors in inappropriate prescribing.[30]

While much of the emphasis is on overuse of antimicrobials, there is evidence of increased mortality associated with inadequate antimicrobial therapy.[45-47] Therefore, in an effort to *optimize* the use of antimicrobial agents in hospitalized settings, antimicrobial stewardship programs have been created.

ANTIMICROBIAL STEWARDSHIP PROGRAMS

An antimicrobial stewardship program (ASP) is a focused effort by a healthcare organization or a portion of an organization (i.e., an intensive care unit) to optimize antimicrobial use for the purposes of improving patient outcomes, reducing adverse consequences (toxicity, selection of pathogenic organisms, or emergence of resistance), and delivering cost-effective therapy.[29,48-50] The emphasis is on appropriate selection, dosing, route, and duration of antimicrobial therapy.[49,50] Despite recognition of the growing problem of antimicrobial resistance, a 2008 survey estimated that only 48% of hospitals in the US had an antimicrobial stewardship program in place.[51]

Proposed strategies for improving antimicrobial stewardship typically involve prospective audit and feedback, formulary restriction, pre-authorization of prescriptions, guidelines for prescribing and/or modifying therapy, and education.[49,52] A comprehensive ASP may include some or all of the following:[30,49,52]

- a multidisciplinary team consisting of infectious disease physicians, clinical pharmacists, clinical microbiologists, information system specialists, infection control specialists, and hospital epidemiologists
- collaboration between the ASP team and hospital infection control and pharmacy and therapeutics committees
- support and collaboration of hospital administrators, medical staff leadership, and local providers
- hospital administrative support for computer systems and other resources to improve decision making, measure and track antimicrobial use, track resistance patterns, and identify hospital-based infections and adverse drug events,
- a microbiology laboratory to provide patient-specific data for optimizing treatment, surveillance of resistant organisms, and molecular-level investigation of outbreaks.

PURPOSE AND SCOPE OF REVIEW

The purpose of this review is to synthesize the evidence about the effectiveness of antimicrobial stewardship programs implemented in hospital settings. The report was nominated by Matthew Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, on behalf

of the VA Antimicrobial Stewardship Task Force, and is intended to provide a summary of the evidence on inpatient antimicrobial stewardship programs to guide clinical practice and policy within the Veterans Healthcare System. We focus on adult hospital inpatients and limit our review to randomized controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs), and interrupted time series (ITS) analyses with data for at least 3 time points before and after the intervention. Our main outcomes of interest were patient-centered outcomes. We also report prescribing outcomes, microbial outcomes, costs, harms of stewardship programs, key intervention components, and barriers to implementation, sustainability, and scalability. In particular, as described above, improvements in antimicrobial prescribing and microbial outcomes and costs can be considered meaningful at a patient, hospital and ecosystem level. Therefore, evidence demonstrating a neutral or lack of untoward effect on clinical outcomes may be sufficient for practice policy implementation. We summarize the findings from a prior Cochrane review that included studies published through 2009[53] and focus on studies published since the time of that review.

METHODS

TOPIC DEVELOPMENT

Our key questions were developed with input from a technical expert panel.

The final key questions are:

Key Question #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

a. Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)
b. Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?

Key Question #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Key Question #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

Key Question #4. What are the harms of inpatient antimicrobial stewardship programs?

Key Question #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

SEARCH STRATEGY

An exploratory search identified a 2005 Cochrane review that partially addressed the key questions but was no longer current (search dates 1980 to 2003).[54] We used a search strategy similar to that of the Cochrane review to search MEDLINE (Ovid) through June 2013. We limited the search to studies published from 2000 to the present, in English language, and enrolling human subjects. Our search included terms for antimicrobial agents (e.g., anti-bacterial agents, anti-infective agents), infection types, and program implementation (e.g., guideline implementation, practice patterns). The full search strategy is presented in Appendix A. Additional citations were identified from systematic reviews, reference lists of retrieved articles, and suggestions made by our technical expert panel members.

STUDY SELECTION

Titles, abstracts, and articles were reviewed by investigators and research associates trained in the critical analysis of literature. During title and abstract review, we excluded studies for the following reasons and identified for full text review any articles that either did not fall into one of these categories or there was uncertainty about eligibility:

1. Study not published in English language,
2. Study done in nursing home (long-term care) setting. Studies were included if done in a mix of hospital or outpatient and nursing home settings if results were presented separately by site,
3. Study not about antimicrobial stewardship,
4. Study of antimicrobials for medical or surgical prophylaxis,
5. Study of patients with viral or fungal infection or tuberculosis,
6. Pediatric study EXCEPT randomized, controlled trials in pediatric settings,
7. Study not involving an intervention or not involving an intervention of interest; we excluded interventions that were *exclusively* provider education (i.e., interventions designed exclusively for enhancing knowledge such as seminars, memos, grand rounds); patient education programs were included; community/public health campaigns were excluded,
8. Description of an intervention with no assessment of the effect of the intervention,
9. Survey of hospitals to establish range of measures used to control or optimize antibiotic prescribing,
10. Study design OTHER THAN randomized, controlled trial, controlled clinical trial, controlled before/after study, or interrupted time series with at least 3 time points before and after implementation of the intervention,
11. No outcomes of interest; outcomes of interest are a) Clinical (e.g., morbidity, mortality, length of stay), b) Drug (e.g., decision to prescribe, appropriateness of selection, dose, route, etc.), Micro (Microbiological – colonization), Cost, Other (process, sustainability, scalability etc.).

We reviewed full text versions of potentially eligible articles and excluded studies that met any of the criteria outlined in items 1 to 11 above. We also added the following exclusion criterion: study done in setting not relevant to medicine in the United States or involving a population or infectious disease not relevant to United States population.

With the recent update of the Cochrane review,[53] we excluded from our review any studies published in the updated version.

DATA ABSTRACTION

From studies identified as eligible after full-text review we extracted the following:

1. Study characteristics – region, intervention, intervention staff (to develop and implement the intervention), resources (i.e., hardware or software used or purchased, staff hired), study design, hospital type, site within hospital (e.g., surgical unit, medical unit, ICU), patients enrolled (number, age), suspected site of infection, suspected organism. We typically categorized ASP interventions using original study author classification. However, we reviewed these classifications with our internal content experts and our Technical Expert Panel Members and stakeholders to ensure general agreement. Within each category we assessed and reportedly separately on specific types of interventions.
2. Patient outcomes – 30-day readmission, mortality, *C. difficile* infection, length of stay, morbidity, adverse effects
3. Antimicrobial prescribing outcomes – timing, use, selection, dose, route, duration

4. Microbial outcomes – institutional resistance and resistance in the study population
5. Costs – healthcare, program, opportunity, drug
6. Harms of stewardship program implementation
7. Other – barriers to implementation, sustainability and scalability of intervention.

From each study, we extracted all data fitting the descriptions of the outcomes in the list above including multiple outcomes, if provided. Our evidence tables (see Appendix), summary tables, and summaries of the evidence report the specific outcome data.

For ITS studies, we report, where provided by study authors, level and trend (or slope) results. Level refers to the change in the value of the outcome measure from pre- to post-intervention. Trend refers to the change between the slope of the line through data points before the intervention and the line through data points after the intervention.

QUALITY ASSESSMENT

We assessed the risk of bias of individual studies using the criteria developed for use in Cochrane Effective Practice and Organization of Care (EPOC) reviews (Appendix B). There are nine criteria for assessing risk of bias for studies with a separate control group (i.e., RCTs, CCTs, and CBA studies) and seven criteria for assessing risk of bias for ITS studies. Each element is scored as high, unclear, or low risk. A study was rated as low risk of bias if each of the individual criteria were scored as low risk, medium risk of bias if one or two criteria were scored as unclear or high risk, and high risk of bias if more than two criteria were scored as unclear or high risk.

Quality of systematic reviews was determined using the measurement tool for assessment of multiple systematic reviews (AMSTAR).[55]

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies, organized by intervention category. We critically analyzed studies to compare their characteristics, methods, and findings. We created forest plots for outcomes with sufficient data to calculate risk ratios. However, due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting among studies for an intervention, the results cannot be meaningfully pooled. Therefore, we compiled a summary of findings for each key question and drew conclusions based on qualitative synthesis of the findings.

RATING THE BODY OF EVIDENCE

We rated overall strength of evidence for our patient outcomes for each intervention category using methods developed by AHRQ and the Effective Health Care Program.[56] The strength of the evidence was evaluated based on four domains: 1) risk of bias (whether the studies for a given outcome or comparison have good internal validity); 2) consistency (the degree of similarity in the effect sizes, i.e., same direction of effect, of the included studies); 3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and 4) precision (degree of certainty surrounding an effect estimate of a given outcome).

PEER REVIEW

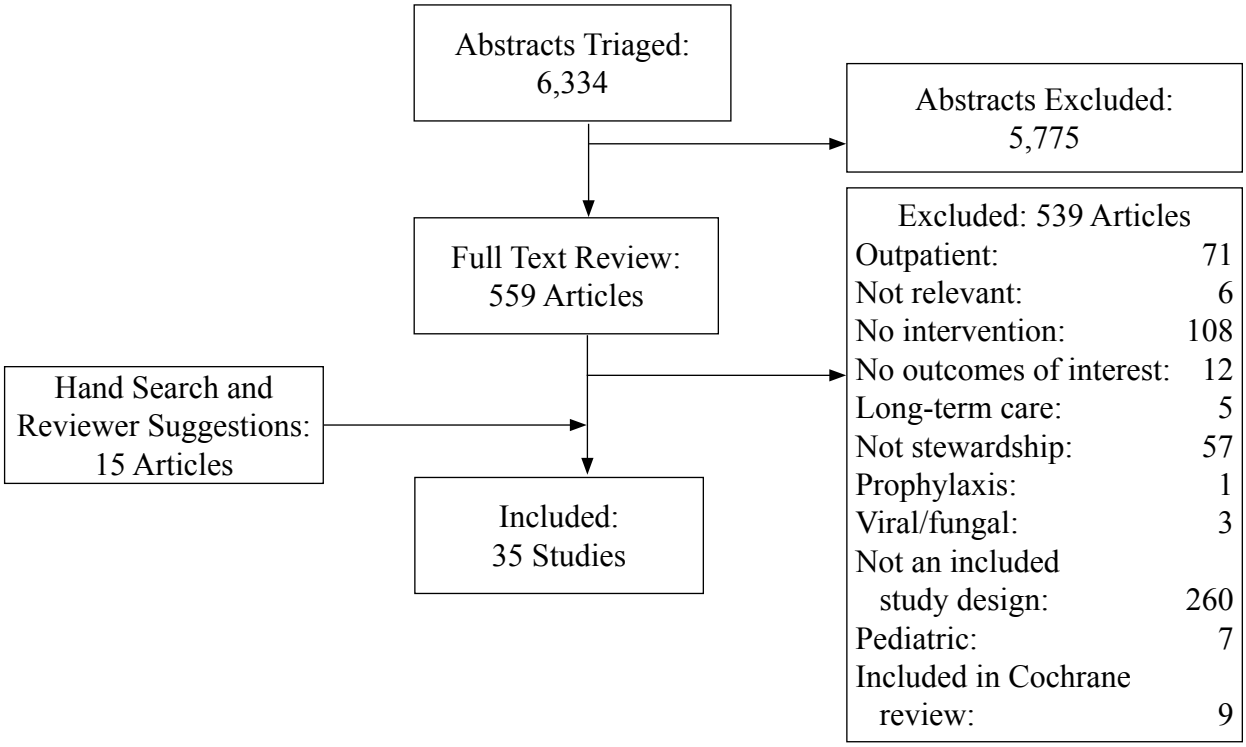
A draft version of this report was reviewed by technical experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix C.

RESULTS

LITERATURE FLOW

We reviewed 6,334 titles and abstracts from the electronic literature search. After applying inclusion/exclusion criteria at the abstract level, 5,775 references were excluded. We retrieved 559 full-text articles for further review and another 539 references were excluded. An additional 15 references were identified from reference lists of recent relevant systematic reviews or were suggested by peer reviewers for a total of 35 included studies. We grouped the studies by key question, type of intervention, hospital site, and clinical condition. Figure 1 details the exclusion process. We also summarized the results from three recent systematic reviews.

Figure 1. Literature Flow Diagram



KEY QUESTION #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

a. **Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)**
b. **Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?**

Existing Systematic Review

A high quality Cochrane review of interventions to improve antimicrobial prescribing for hospital inpatients was originally published in 2005 and included studies published to November 2003.[54] The review was recently updated to include studies published through December 2006 or listed in the Cochrane Effective Practice and Organization of Care (EPOC) Registry through 2009.[53] Interventions were categorized as persuasive, restrictive, or structural. Persuasive interventions focused on education and included distribution of educational materials, educational meetings, local consensus processes, local opinion leaders, verbal, paper, or electronic reminders, audit and feedback and educational outreach (including academic detailing and review and recommend change). Restrictive interventions included order forms, expert approval, removal of restricted antimicrobials, and substitution. Structural interventions included conversion from paper to electronic records, rapid laboratory testing, computerized decision support, and quality monitoring mechanisms. The aim of the intervention was described as either reducing the amount of antimicrobials prescribed where excessive or increasing effective treatment by increasing amount prescribed or improving the timing of antimicrobial administration.

Outcomes reported in the Cochrane review were antimicrobial prescribing (i.e., the decision to prescribe an antimicrobial and the choice of drug, dosage, route, or duration), clinical outcomes (mortality, length of hospital stay), microbial outcomes (colonization or infection with *C. difficile* or antimicrobial-resistant bacteria), and financial outcomes.

The updated review included 89 studies – 25 RCTs, 3 CCTs, 5 CBAs, and 56 ITS studies. The interventions were classified as persuasive in 44 studies, restrictive in 22 studies, both persuasive and restrictive in 15 studies, structural in 2 studies, and both structural and persuasive in 6 studies. There were 95 interventions in the 89 studies, 79 of which were categorized as intended to decrease unnecessary antimicrobial prescribing, 11 categorized as intended to increase effective antimicrobial prescribing, and 5 categorized as intended to reduce inappropriate prescribing but unclear whether the aim was to reduce excessive prescribing or reduce ineffective prescribing. The studies were conducted in North America (52 studies), Europe (29), the Far East (3), South America (3), and Australia (2). Seven studies were based in neonatal or pediatric settings and eight studies were focused on prophylactic antimicrobials. Meta-analyses were performed for selected pre-identified comparisons. However, the number of studies reporting individual outcomes was often limited (for example only 13 of 25 RCTs reported on mortality and only 5 reported on hospital readmissions) or the exact outcome within each category may have varied (e.g., antimicrobial prescribing outcome could include changes in decision to initiate or stop, dose or route of antimicrobial). The review authors did not state how they identified the single outcome selected from each study for analysis but our independent review suggests that only the primary outcome, identified by the original study author, was included. There was no verification or explanation of whether results would be consistent if the review authors included other outcomes within a category (i.e., clinical, prescribing, microbial, costs). Therefore, summary results for outcomes are based on findings from few studies often in different settings and with variable interventions. Selective outcome reporting bias and selective analysis reporting bias have not been adequately addressed.

Primary Outcomes – Clinical

Several clinical outcomes were analyzed using meta-analysis (Table 1). ITS studies were not included in the meta-analyses due to anticipated high heterogeneity versus the RCT, CCT, and CBA studies.

Table 1. Clinical Outcomes by Intervention Aim (from Davey et al., 2013)[53]

Intervention Aim	Outcome	Risk Ratio [95% Confidence Interval] except as noted	I^2	Study designs, number of participants (n)
Increase effective prescribing	Mortality	0.92 [0.69, 1.22]	72%	2 RCTs, 1 CCT, n=1,484
Increase guideline compliance (CAP)	Mortality	0.89 [0.82, 0.97]	0%	1 RCT, 3 CBAs; n=22,526
Decrease excessive prescribing	Mortality	0.92 [0.81, 1.06]	0%	7 RCTs, 3 cluster RCTs, 1 cluster CCT; n=9,817
Decrease excessive prescribing	Length of stay	Mean difference (days) -0.04 [-0.34, 0.25]	63%	4 RCTs, 2 cluster RCTs; n=8,071
Decrease excessive prescribing	Readmission (all-cause or infection-related)	1.26 [1.02, 1.57]	9%	4 RCTs, 1 cluster RCT; n=5,856

I^2 = test for heterogeneity; RCT = randomized controlled trial; CBA = controlled before and after trial; CCT = controlled clinical trial

Interventions intended to increase effective prescribing did not significantly affect mortality (RR=0.92 [95% CI 0.69, 1.22]; k=3). One trial was a persuasive intervention for blood stream infections; two involved rapid laboratory tests for multiple infection sites. Each study was conducted in a single hospital.

Interventions intended to increase effective prescribing by increasing guideline compliance in patients with pneumonia reduced mortality (RR=0.89 [95% CI 0.82, 0.97]; k=4). The number of participants was high primarily due to the large control group of one trial. All interventions were persuasive. One study was conducted in multiple nursing homes, the remaining three studies were conducted in multiple hospitals.

Based on meta-analysis of 10 RCTs and 1 CCT, interventions intended to decrease excessive prescribing did not affect mortality (RR=0.92 [95% CI 0.81, 1.06]). Each of the trials included a persuasive component; three trials also involved a structural intervention. One study was conducted in neonatal wards. Of the remaining 10 studies, 5 enrolled patients with respiratory infections and 5 did not specify an infection site. Eight studies were conducted in a single hospital.

Six of the studies reported length of stay and found no significant difference (mean difference -0.04 [95% CI -0.34, 0.25] days). The analysis included the three trials with structural and persuasive components. Four trials enrolled patients with respiratory infections, and five trials were conducted in a single hospital. Five studies reported readmission. One study reported total readmissions (RR=3.00 [95% CI 1.18, 7.64]) while 4 studies reported infection-related readmissions (RR=1.33 [95% CI 0.31, 5.66]). The combined result was a significant increase in overall readmissions (RR=1.26 [95% CI 1.02, 1.57]). Two of the five studies enrolled patients with respiratory infections; three of the five studies were conducted in a single hospital.

Five ITS studies reported on CDI. The four studies reporting incidence data at one month post-intervention reported reductions in incidence ranging from 15% to 65%. Three of the studies also reported data at twelve months with reductions in incidence ranging from 77% to 85% in absolute terms. The fifth study reported prevalence with a reduction of 52% at 12 months post-intervention.

Secondary Outcomes – Prescribing, Microbial, Costs, Harms

Effect sizes were calculated to allow determination of a median effect encompassing the different prescribing outcomes reported (i.e., "any prescribing outcome" included decreased antimicrobial use, decreased frequency, increased appropriate use, etc.). It was not stated if other prescribing outcomes were reported by the original study authors, if review of original results varied by outcome definition, or what justification original authors had for using different outcomes as their primary outcome. It is not possible to assess the pooled effect on individual prescribing outcomes or which specific outcome is dominating the results. With those limitations in mind we describe the findings below. Positive numbers represent a percent change in the intended direction and are considered an absolute pooled percentage difference of the individuals achieving such an outcome in the intervention group minus the control. Median changes were calculated by intervention type and by study design (Table 2). The authors noted that clinical heterogeneity was high due to variations in the clinical outcomes, patient and provider populations, study methodologies, the features of the interventions, and the different settings in which the interventions were applied. Many of the studies included more than one intervention component.

Table 2. Median Change* in Antimicrobial Prescribing by Intervention Type and Study Design (from Davey et al., 2013)[53]

Intervention Type	RCT	CRCT	CBA	ITS	CITS
Persuasive	24.7%	3.5%	17.7%	42.3%	31.6%
Dissemination of educational materials		-3.1% (k=1)#	16.1% (k=2)	10.6% (k=2)	42.5% (k=1)
Reminders	27.4% (k=3)#			20.0% (k=5)#	
Audit and feedback		3.5% (k=1)#	7.5% (k=2)	32.7% (k=4)#^	24.3% (k=2)
Educational outreach‡	25.0% (k=10 including 1 CRCT)†		20% (k=1)#	46.3% (k=10)	
Restrictive	40.5%		17.1%	34.7%	
Compulsory order forms				7.3% (k=5)#	
Expert approval‡			-2.8% (k=1)	24.1% (k=7)	
Removal by restriction			37.0% (k=1)	60.7% (k=7)#^	
Review and make change	40.5% (k=2)			94.3% (k=2)	
Structural	13.3% (k=6)^	23.6% (k=2)			

RCT = randomized controlled trial; CRCT = cluster randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after study; ITS = interrupted time series; CITS = controlled interrupted time series; k = number of studies

*Positive change is a change in the direction of the intended change

#Includes at least 1 trial of prophylactic antimicrobials

^Includes at least 1 trial from neonatal or pediatric setting

‡One additional study of this intervention type was not included in calculation of median change

†Includes one study from nursing home setting

A subsequent meta-regression included only studies that were purely persuasive or purely restrictive. All were ITS studies. Thirty-eight studies reported prescribing outcomes. Persuasive and restrictive interventions had a similar effect on "any prescribing outcome" at 6, 12, and 24 months post-intervention.

Effect sizes were also determined for "any microbial outcome" (reported in 21 studies). Nine studies (7 ITS, 2 CCT) reported colonization (3 studies) or infection (6 studies) with antibiotic-resistant *gram-negative* bacteria. Of the seven ITS studies, five reported incidence at one month post-intervention with reductions ranging from 36% to 92%. Only one of the studies also reported incidence at 12 months with a change in reduction from 36% at one month to 29% at twelve months. Two ITS studies reported prevalence with a reduction in colonization of 23% at one month in one study and a reduction in infection of 41% in the other study. In one cluster CCT from a neonatal intensive care unit, a 68% reduction in days of colonization with resistant bacteria at six month post-intervention was reported. An effect opposite from the intended effect was observed in a CCT from a neonatal intensive care unit (increased incidence of 39.0%). Seven studies (6 ITS, 1 CBA) reported colonization (1 study) or infection (6 studies) with antibiotic-resistant *gram-positive* bacteria. Outcomes varied in the studies. In the ITS studies, one study reported an outcome at 1 month (a 25% effect in the intended direction), two studies reported outcomes at 6 months (21% and 87% effects in the intended direction), three studies reported outcomes at 12 months (a 2% effect in the opposite direction and 38% and 100% effects in the intended direction), and three studies reported outcomes at 24 months (a 10% effect in the opposite direction and 23% and 50% effects in the intended direction). The CBA study reported a 13.2% difference in VRE infection favoring the intervention ($p<0.001$). A meta-regression of 14 ITS studies that were purely persuasive or purely restrictive found that persuasive and restrictive interventions had a similar effect on microbial outcomes at 12 and 24 months post-intervention.

Data on both intervention costs and financial savings were reported in 10 studies (including 2 studies of prophylactic antimicrobials). In eight of the studies, savings were greater than costs.

Studies from VA Hospitals

The review cited 9 studies (2 RCTs, 7 ITS) conducted at VA hospitals between 1985 and 2006. Seven were assessed as high risk of bias and 2 as medium risk of bias. Three were categorized as persuasive and six as restrictive interventions. One enrolled patients in the ICU with VAP, the others enrolled patients with any infection.

By our definition of outcome categories, the primary outcome was a clinical outcome in three studies (two reporting CDI incidence and one reporting length of stay) although the length of stay data were not provided in the review. Two studies reporting CDI, both ITS studies with restrictive interventions and enrolling all hospitalized patients, found decreased incidence of CDI (-53% [95% CI -3%, -102%] and -65% [95% CI -48%, -81%] at 1 month, -79% [95% CI -34%, -124%] and -77% [95% CI -60%, -94%] at 12 months). One RCT reported a clinical outcome as a secondary outcome finding a non-significant decrease in mortality (13% intervention, 31% control; RR=0.41 [95% CI 0.16, 1.05]).

In three studies, the primary outcome was a prescribing outcome. Results were mixed with one ITS reporting a non-significant decrease in orders for vancomycin that were deemed inappropriate, one RCT reporting a significant decrease in the percentage of patients receiving antimicrobials for more than three days, and one ITS reporting a decrease in slope but not level for use of levofloxacin.

In the remaining three studies, the primary outcome was microbial. A significant decrease

in colonization or infection with gram-negative bacteria at one month post-intervention was reported in one ITS study but the decrease was non-significant by six months. Another ITS study reported a reduction in incidence of ceftazidime-resistant *Klebsiella pneumonia*, MRSA, and cefotaxime-resistant *Acinetobacter* species. A third ITS study reported a significant decrease in MRSA infections at 6 months.

Conclusions

Overall, interventions to increase effective prescribing had no effect on mortality whereas interventions to increase guideline compliance were associated with a reduction in mortality. Interventions to decrease excessive prescribing had no effect on mortality or length of stay but led to an increase in hospital readmissions. Persuasive and restrictive interventions were similarly effective in improving prescribing outcomes based on median effect sizes across "any prescribing" outcome. There was some evidence of a short-term improvement with restrictive interventions but the benefit was not sustained. A similar pattern was observed for microbial outcomes. Multifaceted interventions were common but not necessarily more effective than simpler interventions. The authors commented on the lack of comparative effectiveness research, incomplete outcome reporting, and the high risk of bias associated with many studies.

Recent Evidence

We identified 35 studies that were not included in the updated Cochrane review. Nine were RCTs (including cluster randomized trials), four were CCTs, two were CBAs, and twenty were ITS studies.

We categorized studies initially by primary intervention including 14 studies of audit and feedback programs,[1-10,57-60] 5 studies of formulary restriction and preauthorization programs,[11-14,61] 4 studies of guideline implementation with feedback,[15-18] 4 studies of guideline implementation with no feedback,[19-21,62] 4 studies of computerized decision support,[22-24,63] and 4 studies of protocol or policy implementation.[25-27,64] We summarize systematic reviews and recent evidence from studies of the use of laboratory tests to guide prescribing decisions. Within each of our primary intervention categories, we described interventions as intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery (31 studies) or intended to decrease unnecessary or excessive prescribing (4 studies).

Within the framework of the Cochrane review,[53] interventions we categorized as audit and feedback, guidelines with feedback, and guidelines without feedback would be considered persuasive interventions, formulary restriction and preauthorization and protocol interventions would be considered restrictive interventions, and computerized decision support and laboratory tests would be conserved structural interventions.

Most studies were conducted at university-affiliated or teaching hospitals. Six studies were performed at community hospitals[6,8,14,18,19,58] and two did not specify the hospital type.[15,16] One study analyzed data from administrative care databases for a Canadian province.[13] We also looked at the site of the intervention with 8 studies conducted in intensive care units (ICUs),[4,6,9,12,20,27,62,63] 7 studies conducted in medical wards,[2,5,10,16,26,59,60] 12 studies conducted in multiple sites (medical, surgical, ICU),[1,3,7,8,11,14,18,22,24,57,58,61] and 1 study in acute care.[17] Seven studies did not report the site.[13,15,19,21,23,25,64]

Seven studies focused on treatment of respiratory illness,[15,16,21,24,25,26,62] 26 included patients with any type of infection,[1-11,13,14,17-20,22,23,27,57,58,60,61,63,64] and one study included only bloodstream infections.[12] One study did not report infection site.[59]

We also identified two recent systematic reviews of studies on the use of laboratory testing, specifically procalcitonin, to monitor bacterial infection.[66,67] We summarize the findings of those reviews and two RCTs published after the systematic reviews[67,68] under Laboratory Tests, below.

Table 1a provides an overview of the clinical outcomes by intervention category; prescribing outcomes are presented in Table 1b. We constructed forest plots with RCTs or CCTs that reported risk ratios for mortality (Figure 2) or appropriate prescribing (Figure 3), or reported data that allowed us to calculate the risk ratios. Due to heterogeneity of interventions and populations, results were not pooled. Despite the large number of included studies there was limited outcome reporting. For example, of the 14 audit and feedback studies only 10 reported on mortality, 8 reported on length of stay, 3 on readmissions, and 1 on CDI. Furthermore, while we present forest plots for RCTs and CCTs providing sufficient information, much of the reported evidence is from ITS studies (20 of the 35 included studies) and therefore not suitable for inclusion on forest plots. For appropriate prescribing, only 4 of 12 included RCTs and CCTs provided data in a fashion that permitted creation of forest plots. Because selective outcome reporting and presentation can result in misleading and biased findings we urge caution in drawing definitive conclusions based on reliance of data presented only in a forest plot or even some of the outcomes provided in tables.

Table 3a. Overview of Clinical Outcomes – Antimicrobial Stewardship Interventions for Inpatients

ASP Intervention (# studies)	Mortality	Length of Stay	Readmission	CDI	Summary
Prospective Audit and Feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	**+ 1 study ≈ 9 studies**	**≈ 9 studies**	**+ 1 study ≈ 2 studies**	**p=NR, 1 study**	Audit and feedback showed no association with clinical outcomes.
Formulary Restriction and Preauthorization (1 RCT, 4 ITS)	**≈ 3 studies**	**≈ 2 studies**	NR	**+ 1 study**	Mortality and length of stay were unchanged with formulary restriction and preauthorization. CDI was decreased.
Guidelines with Feedback (2 RCT, 2 ITS)	**≈ 3 studies**	**≈ 3 studies**	NR	**+ 2 studies**	Mortality and length of stay were unchanged. CDI was decreased in two studies following guidelines with feedback intervention.
Guidelines without Feedback (1 CCT, 1 CBA, 2 ITS)	**+ 1 study ≈ 1study - 1 study**	**+ 1 study ≈ 1study - 1 study**	**≈ 1 study**	NR	Inconsistent findings from 3 studies of guidelines implemented without feedback assessing mortality or length of stay. No difference in readmissions.
Computerized Decision Support (1 RCT, 1 CCT, 2 ITS)	**≈ 3 studies**	**+ 1 study ≈ 2 studies**	**≈ 1 study**	**+ 1 study ≈ 1 study**	No differences in mortality or readmissions with computerized decision support versus controls. Mixed results for length of stay and CDI.
Protocols (2 RCT, 2 ITS)	**+ 1 study ≈ 2 studies**	**+ 2 studies ≈ 1 study**	**≈ 1 study**	NR	For protocols, results were mixed for mortality and length of stay. No difference in readmissions.

ASP = antimicrobial stewardship; NR = not reported; CDI = incidence of *C. difficile* infection
CBA = controlled before and after; CCT = controlled clinical trial; ITS = interrupted time series; RCT = randomized controlled trial

+ indicates statistically significant difference favoring antimicrobial stewardship intervention
≈ indicates no statistically significant difference between antimicrobial stewardship intervention and control
- indicates statistically significant difference favoring control

Table 3b. Overview of Prescribing Outcomes – Antimicrobial Stewardship Interventions for Inpatients

ASP Intervention (# studies)	Use	Selection	Timing	Duration	Summary
Prospective Audit and Feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	**Decreased: + 8 studies Appropriate: + 1 study ≈ 1 study**	**+ 1 study ≈ 1 study**	NR	**+ 5 studies**	Prospective audit and feedback showed improvement in prescribing outcomes
Formulary Restriction and Preauthorization (1 RCT, 4 ITS)	**Decreased: + 4 studies**	NR	NR	**+ 1 study**	Formulary restriction and preauthorization were associated with improvement in prescribing outcomes.
Guidelines with Feedback (2 RCT, 2 ITS)	**Decreased: + 1 study Compliant/ appropriate: + 2 studies**	**≈ 1 study**	**+ 1 study**	**≈ 2 studies**	Mixed results were observed for prescribing outcomes with some studies reporting improvements in adherence to guideline recommended treatments and appropriate early initiation of therapy.
Guidelines without Feedback (1 CCT, 1 CBA, 2 ITS)	**Decreased: + 1 study Compliant/ appropriate: + 2 studies ≈ 1 study**	NR	**- 1 study**	**+ 1 study ≈ 1 study**	Improvement in prescribing use but not timing or duration with guidelines implemented without feedback.
Computerized Decision Support (1 RCT, 1 CCT, 2 ITS)	**Decreased: + 1 study ≈ 1 study**	NR	NR	NR	Two studies reported mixed results for antimicrobial use with computerized decision support.
Protocols (2 RCT, 2 ITS)	**Appropriate: ≈ 1 study**	NR	**≈ 1 study**	**+ 2 studies**	No difference in appropriate use or timing but reduced duration of use in studies of ASP protocols.

ASP = antimicrobial stewardship; NR = not reported;
CBA = controlled before and after; CCT = controlled clinical trial; ITS = interrupted time series; RCT = randomized controlled trial

+ indicates statistically significant difference favoring antimicrobial stewardship intervention
≈ indicates no statistically significant difference between antimicrobial stewardship intervention and control
- indicates statistically significant difference favoring control

Figure 2. Mortality Outcome Reported in Randomized or Controlled Clinical Trials (k=12)
(NB Our review included 20 ITS studies that did not present data in a format suitable for inclusion on a forest plot. Therefore the figure below provides only a subset of all included data.)

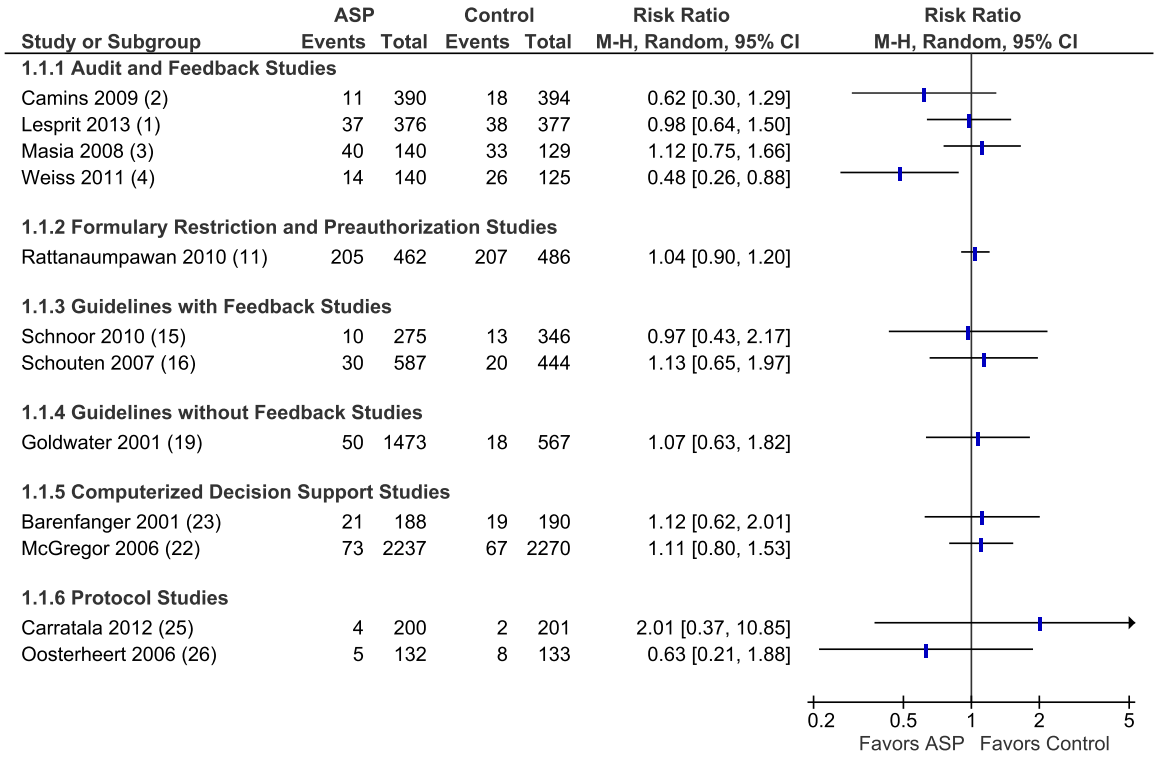
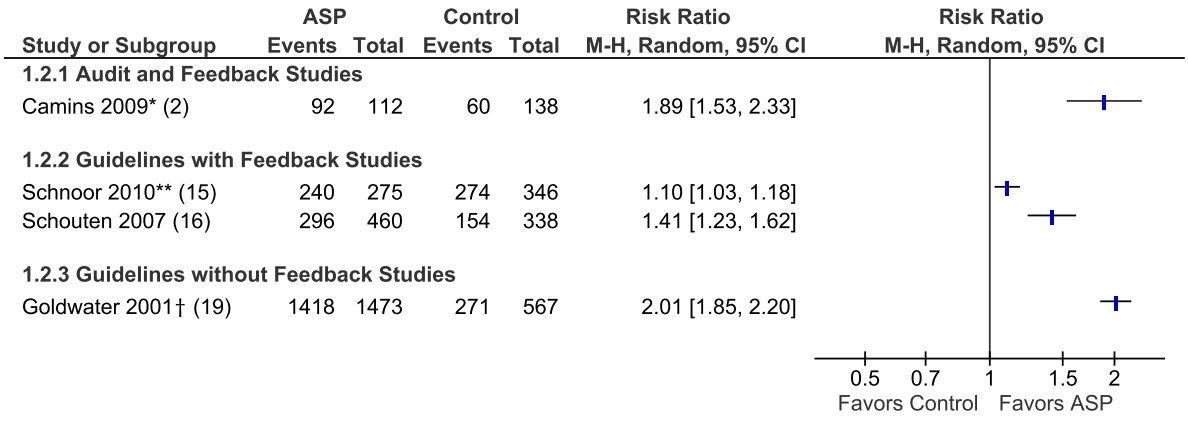


Figure 3. Appropriate Antimicrobial Use Outcome Reported in Randomized or Controlled Clinical Trials (k=4) (NB Many RCTs/CCTs did not report on appropriate antimicrobial use, definitions of use varied across and within studies, and some studies did not provide sufficient information to create forest plots. Furthermore, our review included 20 ITS studies that did not present data in a format suitable for inclusion on a forest plot. Therefore the figure below is a subset of all included data.)



* Definitive use
** Estimated from odds ratio (adjusted)
† Replacement of ciprofloxacin with levofloxacin (number of patients)

Audit and Feedback (k=14)

Key Findings

- ***Patient Outcomes:*** Mortality was reported in ten studies with no differences observed between intervention and control groups or pre- to post-intervention in nine studies. No differences were reported for length of stay (reported in nine studies) or 30-day readmission (reported in two studies); 60-day readmission for relapsing infection was reduced in one study. One study reported fewer *C. difficile* infections following the intervention. Two studies reported adverse events, specifically the need to re-initiate intravenous (IV) antimicrobials in a small number of subjects.
- ***Prescribing Outcomes:*** Audit and feedback programs were found to decrease use of targeted antimicrobials (reported in seven studies) and decrease excessive use (measured in one study). Results for increasing appropriate use (reported in two studies) were mixed. Five studies reported improvement in duration of therapy (including duration of inappropriate therapy, time to modification of therapy, duration of targeted therapy, and hours of IV therapy) following the intervention. One study reported improvements in antimicrobial selection post-intervention while one study reported mixed results for targeted antimicrobials.
- ***Microbial Outcomes:*** Two studies reported decreased rates of selected antimicrobial-resistant bacteria following implementation of an antimicrobial stewardship program, but in one of these the incidence of another antimicrobial-resistant organism increased. In another study, no differences in antimicrobial resistance trends were reported for five pathogens but the measure is unclear. One study reported increased gram-negative susceptibility to one antimicrobial but no change in susceptibility to five others. Another study reported no difference between intervention and control groups in secondary infections or colonization.
- ***Cost Outcomes:*** Nine reported cost outcomes with all reporting decreased drug costs or decreased costs to patients and/or insurers.
- ***Limitations:*** There were substantial threats to validity, including the possibility of secular trends, opportunities for contamination within study sites, opportunities for bias in assessment, and the potential for unmeasured or unreported changes in use of antimicrobials not targeted by the interventions. Studies were not designed with adequate power to measure impacts of the interventions on patient outcomes.

Characteristics of Studies

We categorized interventions as audit and feedback if, following review of the prescription, feedback on an individual patient basis was provided within 24 hours of the review and was provided directly to the prescriber (either written or verbally). Fourteen studies met inclusion criteria. Eight were ITS studies,[6-9,57-60] three were RCTs,[1-3] two were CCTs,[4,5] and one was a CBA.[10] Four studies were conducted in North America,[2,4,6,7] one in the United Kingdom, [58] five in Europe,[1,3,5,9,10] three in the Asia Pacific region,[8,57,60] and one in South America.[59]

One study was low risk of bias[60] and four were medium risk of bias.[1,3,6,58] The remaining nine studies were considered to be high risk of bias.

In 13 studies, the aim of the intervention was to alter antimicrobial timing, drug selection, tailoring, and route of delivery.[1-6,8-10,57-60] In one study, the aim was to decrease unnecessary or excessive prescribing.[7]

All studies were audit and feedback[30,49] involving a pharmacist or physician who reviewed the management of individual cases in real time and provided advice to clinicians during a course of antimicrobial therapy. Audit and feedback was performed by some combination of clinical pharmacists and physicians in seven studies;[2,3,6-8,57,59] a clinical pharmacist, physician, and clinical microbiologist in one study;[60] clinical pharmacists in one study;[10] a clinical microbiologist in one study;[58] an infectious disease physician alone in three studies;[1,5,9] and a resident physician in one study.[4] Most studies involved multifaceted interventions. In nine studies, the providers had access to institutional guidelines on antimicrobial use.[1,2,3,7,8,10,57,58,60] In three studies, provider education was offered.[1,9,58] In one study, the targeted antimicrobials would only be provided after approval by the infectious disease service.[7] In another study, providers were asked to run through a daily checklist which included a statement about adjustments to antimicrobial use.[4]

Thirteen of the fourteen studies were conducted in urban hospitals, most of which were University-affiliated teaching hospitals. The sole exception was conducted in a rural community hospital.[58] In six studies, the interventions were carried out on general medical wards, or a mixture of medical, surgical, and step-down (telemetry) wards.[1-3,5,8,10,] In three studies,[4,6,9] the intervention was implemented in an Intensive Care Unit (ICU), whereas in three studies,[7,57,58] it was implemented in both ICUs and general medical wards. One study was implemented in a medical oncology unit,[60] one in general surgery, renal medicine, and endocrinology departments,[8] and another was implemented on the medical wards of a cardiology hospital.[59]

The unit of analysis differed among included studies. Seven used aggregate data from the entire study population.[6,7,8,57-60] Seven used data on individual patients or antimicrobial prescriptions.[1-5,9,10] One study specified that since the unit of analysis was the prescription, individual subjects could be enrolled multiple times.[3] However, since this study randomly assigned prescription courses to intervention versus control, it is not clear how they dealt with situations in which the same subject was associated with prescriptions in both the intervention and control groups.

Thirteen studies included patients with all sites of infection; two did not report site. Six studies reported specific sites with respiratory tract, urinary tract, gastrointestinal, and skin/soft tissue infections the most common.[1-4,9,10] In six studies that reported patient characteristics, mean or median age ranged from 54 to 69 years and between 45% and 65% were male.[2-5,10,57]

Reported outcomes are depicted in Table 4. Detailed results are presented in Appendix D, Tables 1 to 8.

Table 4. Audit and Feedback Interventions: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Cairns 2013[57]		X			
Lesprit 2013[1]	X	X	X	X	
Elligsen 2012[6]	X	X	X	X	
Magedanz 2012[59]		X	X	X	
Standiford 2012[7]	X	X		X	
Teo 2012[8]	X	X		X	
Weiss 2011[4]	X				
Yeo 2012[60]	X	X	X	X	X
Bornard 2011[9]	X	X			
Dunn 2011[10]	X	X		X	
Manuel 2010[5]	X	X		X	
Camins 2009[2]	X	X			
Liebowitz 2008[58]		X	X		
Masia 2008[3]	X	X		X	X

Patient Outcomes

Of the 13 studies that aimed to alter antimicrobial timing, drug selection, tailoring, or route of delivery, 10 reported patient-specific outcomes. Nine included mortality data[1-6,8-10] with only one study reporting a significant difference in mortality between intervention and control groups or pre- and post-intervention periods. This study was a CCT of prompting during daily rounds. ICU physicians were prompted to consider six parameters of care, one of which was empirical antimicrobial utilization.[4] This intervention was associated with reduced risk-adjusted odds of death (OR=0.48 [95% CI 0.26, 0.88]) in the intervention group compared with the control (no prompting) group. A subsequent exploratory analysis including all patients who received empiric antimicrobials also found reduced mortality in the prompting group (OR=0.41 [95% CI 0.18 to 0.92]). When empiric antimicrobial duration was added to mortality models, the adjusted OR for the intervention was attenuated from 0.41 to 0.50, suggesting that shorter duration of empiric antimicrobials explained 15.2% of the overall benefit of prompting.[69]

Nine studies reported length of stay with no significant differences between intervention and control groups or pre- and post-intervention periods.[1-6,8-10]

Two studies reported 30-day readmission with no difference between intervention and control groups in a randomized trial (21% intervention, 15% control, p=0.22)[3] and no difference between whether the intervention was accepted or rejected during the post-intervention phase of an interrupted time series (33% vs. 25%, p=0.10).[8] A third study, a randomized trial, reported a significant difference in 60-day readmission for relapsing infection (3.4% intervention, 7.9% control, p=0.01).[1]

One study reported a 31% decrease in *C. difficile* infections post intervention.[6] By comparison, a 33% increase was noted in non-study wards at the same hospital.

Adverse events were reported in two studies. In the ITS study conducted on the oncology wards, it was reported that following acceptance of the antimicrobial stewardship recommendations, there were 32/580 cases (5.5%) in which patients deteriorated. In 24 of those cases, deterioration was wholly or partially attributed to progression of malignancy. Two patients were subsequently placed back on broad-spectrum antimicrobials despite negative bacterial cultures and improved to the point of discharge. Four patients deteriorated despite escalation of antimicrobial therapy, and two patients deteriorated due to new-onset fungal infection.[60] In the CBA study of application of criteria for switching from IV to oral therapy, during the intervention phase, one patient each in both the intervention and control groups required reinstatement of IV therapy.[10]

In the study that aimed to reduce ineffective or excessive treatment, no differences in mortality, length of stay, or 30-day readmissions were observed across the 10 year study period.[7] CDI rates and adverse events were not reported.

Results for individual studies and strength of evidence for patient outcomes across all audit and feedback studies regardless of the intended purpose of the intervention are presented in Table 5.

Table 5. Strength of Evidence for Audit and Feedback Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Lesprit 2013[1]	RCT	Improve quality of antimicrobial use	Medium	Mortality	NS, RR 0.98 [0.64, 1.50]	Low for Mortality
Camins 2009[2]	RCT	Improve appropriateness	High	Mortality	NS, RR 0.62 [0.30, 1.29]	
Masia 2008[3]	RCT	Decrease targeted antimicrobials	Medium	Mortality	NS, RR 1.12 [0.75, 1.66]	
Weiss 2011[4]	CCT	Improve mortality	High	Mortality	Reduced, OR 0.48 [0.26, 0.88]	
Manuel 2010[5]	CCT	Improve appropriateness	High	Mortality	NS	
Elligsen 2012[6]	ITS	Decrease targeted antimicrobials	Medium	Mortality	NS, 13% pre, 14% post	
Standiford 2012[7]	ITS	Decrease ineffective/excessive	High	Mortality	NS	
Teo 2012[8]	ITS	Improve appropriateness	High	Mortality	NS, 0.44 deaths/100 inpatient days (pre and post)	
Bornard 2011[9]	ITS	Improve quality of antimicrobial use	High	Mortality	NS, RR 0.84 [0.05, 12.99]	
Dunn 2011[10]	CBA	Increase switch rate from IV to oral	High	Mortality	NS	
Lesprit 2013[1]	RCT	Improve quality of antimicrobial use	Medium	Length of stay	NS, 15 days (median) (both groups)	Low for Length of Stay
Camins 2009[2]	RCT	Improve appropriateness	High	Length of stay	NS, 7 days intervention, 8 days control (medians)	
Masia 2008[3]	RCT	Decrease targeted antimicrobials	High	Length of stay	NS, 14 days (median) (both groups)	
Weiss 2011[4]	CCT	Improve mortality	High	Length of stay (ICU)	NS, 4 days intervention, 5 days control, p=0.07	
Manuel 2010[5]	CCT	Improve appropriateness	High	Length of stay	NS	
Elligsen 2012[6]	ITS	Decrease targeted antimicrobials	Medium	Length of stay	NS, 6.9 days (pre and post)	
Standiford 2012[7]	ITS	Decrease ineffective/excessive	High	Length of stay	NS	
Bornard 2011[9]	ITS	Improve quality of antimicrobial use	High	Length of stay	NS, 18 days pre, 19 days post	
Dunn 2011[10]	CBA	Increase switch rate from IV to oral	High	Length of stay	NS	
Lesprit 2013[1]	RCT	Improve quality of antimicrobial use	Medium	Readmission*	Reduced, RR 0.43 [0.23, 0.82]	Low for Readmission
Masia 2008[3]	RCT	Decrease targeted antimicrobials	High	Readmission	NS, RR 1.40 [0.84, 2.33]	
Standiford 2012[7]	ITS	Decrease ineffective/excessive	High	Readmission	NS	
Elligsen 2012[6]	ITS	Decrease targeted antimicrobials	Medium	Incidence of CDI	Significance not reported; 16 cases pre, 11 cases post	Low for Incidence of CDI

RCT = randomized controlled trial; CCT = controlled clinical trial; ITS = interrupted time series; CBA = controlled before and after study; NS = not statistically significant; RR = rate ratio [95% confidence interval]; OR = odds ratio [95% confidence interval]; IV = intravenous

*This study reported 60 day readmission for relapsing infection; other studies report 30 day readmission for any cause

Prescribing Outcomes

Antimicrobial Use

Among the 13 studies of interventions intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery, 9 reported antimicrobial use outcomes. One randomized study found a significant increase in initial (less than 72 hours) use that was considered "appropriate" in the intervention arm versus control (78% vs. 58%, RR=1.35 [1.22, 1.49], p<0.001). A significant increase in appropriate end antimicrobial use (the final choice of antimicrobial regimen) was also noted in the intervention arm (94% vs. 70%, RR=1.34 [1.25, 1.43], p<0.001).[2] However, an interrupted time series reported that changes in level and trend for appropriate therapies were non-significant.[9]

Three studies, all interrupted time series with the focus of the stewardship program on specific antimicrobials, found evidence of a substantial decrease in use of audited antimicrobials associated with the intervention. In one recent study there was a significant decrease in the level of consumption of audited antimicrobials but no change in the level of total antimicrobials. The change in the trend for use of targeted antimicrobials was not significant.[8] In another study, the mean amounts of antimicrobials prescribed increased between the pre-evaluation and intervention periods, but the trend for prescriptions decreased during the intervention period, moving from stable to a significant decrease (p=0.001). [60] The third study reported a decrease in mean monthly consumption from 48.9 DDD/100 patient-days during the baseline period to 36.9 DDD/100 patient-days during the full implementation of the stewardship program (p=0.001).[59]

Several studies were focused on reducing use of broad-spectrum antimicrobials. A randomized trial of an intervention to decrease use of specific antimicrobials by comparing antimicrobial use to institutional guidelines for selected conditions, found median total consumption of targeted antimicrobials was 8 DDD per patient in the intervention group and 10 DDD per patient in the control group (p=0.04).[3] However, there was a corresponding increase in antimicrobials that were not a focus of their intervention, and overall antimicrobial use and the costs of antimicrobials dispensed were similar in intervention and control groups.[3] The authors concluded that the impact of the intervention was "limited." Two interrupted time series reported significant decreases in use (level) of broad-spectrum antimicrobials both in the ICU[6,57] and general wards.[57] Changes in trend were less consistent with one study reporting a significant change in trend in the ICU but not in the general wards[57] and the other study reporting a non-significant trend in the ICU.[6]

Dunn reported an increase in the percentage of courses switched from IV to oral antimicrobial therapy on the appropriate day after the intervention (72% vs. 51%, p=0.02).[10]

In the study that aimed to decrease unnecessary or excessive prescribing, total antimicrobial use decreased from 1,512 DDD/1000 patient-days in 2004 to 1,073 DDD/1000 patient-days in 2008 (29%, p=0.14).[7] The antimicrobial stewardship program began in 2002 but defined daily dose data were not available until 2004. Significant decreases from 2004 to 2008 were also observed for use of antibacterial, antifungal, and antiviral agents.

Duration

Each of the five studies that reported on duration of antimicrobial therapy[1-3,5,10] observed a significant decrease associated with the intervention.

One study required that a single infectious disease physician review all prescriptions for any of the 15 selected intermediate or broad spectrum antimicrobials. Median days of total antimicrobial, broad-spectrum, and IV use decreased post-intervention while oral consumption increased.[1] Another study, evaluating the use of an antimicrobial utilization team to improve appropriate prescribing, reported shorter days of inappropriate antimicrobial use in the intervention group (median of 2 days vs. 5 days, $p<0.001$).[2] A study of reassessment of IV therapy after 3 days reported shorter time to therapy modification in the intervention group (3.9 days vs. 5.0 days, $p=0.007$).[5] Masia reported median days receiving three targeted antimicrobials was significantly shorter in the intervention group (4 vs. 6 days, $p=0.002$).[3] An intervention to encourage IV to oral switch reported fewer hours of IV treatment (median of 72 hours in the intervention group vs. 96 hours in the control group, $p=0.02$).[10]

Selection

Two studies assessed the effect of the intervention on drug selection. In one study, overall antimicrobial use decreased during the intervention phase.[59] There was a significant increase in the use of drugs that were encouraged (i.e., penicillins: $p=0.03$ for level, $p=0.007$ for trend), whereas the use of drugs that were discouraged significantly decreased (i.e., fluoroquinolones: $p=0.004$ for level and for trend).

In the second study, following implementation of an intervention discouraging use of ciprofloxacin and second- and third-generation cephalosporins, third-generation cephalosporin use decreased both hospital-wide (36 DDD/1000 occupied bed-days to 9 DDD/1000 occupied bed-days) and in the intensive care unit (29 DDD/1000 occupied bed-days to 1 DDD/1000 occupied bed-days,).[58] For ITS regression analysis, the change in level was significant both hospital wide ($p<0.001$) and in the ICU ($p<0.001$) while the change in trend was significant only for the hospital-wide data ($p=0.003$). Ciprofloxacin use hospital-wide decreased (12 DDD/1000 occupied bed-days to 1 DDD/1000 occupied bed-days) but the changes in level ($p=0.09$) and trend were not significant ($p=0.14$). Ciprofloxacin use decreased in intensive care units (57 DDD/1000 occupied bed-days to 8 DDD/1000 occupied bed-days) with a significant change in level ($p=0.014$) but not trend ($p=0.95$).

Microbial Outcomes

Five studies reported microbial outcomes. All were studies that aimed to alter antimicrobial timing, selection, tailoring, or route of delivery.

In a recent randomized, controlled trial focused on improving quality of antimicrobial use, an infectious disease physician reviewed and made recommendations, if appropriate, for new prescriptions for any of 15 targeted intermediate or broad spectrum antimicrobials ordered for patients in the intervention group.[1] Rates of secondary infection or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or extended spectrum B-lactamase-producing Enterobacteriaceae (ESBLE) did not differ significantly between the intervention or control

groups during the 6 months following randomization (MRSA 2.9% intervention, 2.6% control, p=0.82; ESBLE 3.2% intervention, 4.5% control, p=0.34).

In another study, the focus was on decreasing the incidence of infections caused by MRSA.[58] The intervention involved a clinical microbiologist rounding with inpatient teams. A major goal of the study was to decrease use of broad-spectrum cephalosporins and ciprofloxacin. The rate of MRSA bacteremia decreased by 63% (p<0.001) after the intervention was implemented. There was no significant change in the methicillin-susceptible *S. aureus* (MSSA) bacteremia rate or the rate of MRSA colonization.

A third study looked at resistance trends before and after implementation of a multidisciplinary stewardship program.[60] The analysis included the five most commonly cultured nosocomial pathogens identified in area hospitals. Data were reported as incidence density per 1000 inpatient days but no further information was provided on the measure. No significant differences were noted for trends over the study period. There was a significant decrease (p=0.017) in the mean incidence-density for MRSA during the intervention period but differences in the means for the other four pathogens were not significant.

The focus of the fourth study was on appropriate prescribing of targeted antimicrobials but infection rates were reported for several antimicrobial-resistant bacteria.[59] The study included three phases: 1) baseline, 2) audit and feedback by an infectious disease physician, and 3) audit and feedback by both the physician and a clinical pharmacist. The authors did not provide a definition for the reported rates (e.g., rates of isolates identified in the microbiology laboratory, or rates of resistant bacteria associated with infectious diseases in patients). However, there were significant increases in ceftazidime-resistant *Klebsiella* spp. (from 12% and 16% in stages 1 and 2, to 42% in stage 3; p<0.001) and ceftazidime-resistant *Pseudomonas* spp. (4% and 3% in stages 1 and 2, and 14% in stage 3; p=0.005). The rate of carbapenem-resistant *Pseudomonas* spp. decreased from 6% and 7% in stages 2 and 3, to 1% in stage 3 (p=0.01). The rate of ceftazidime-resistant *Klebsiella* spp. was significantly correlated with the increase in total cephalosporin use (r=0.239; p=0.04).

The final study, an interrupted time series study targeting broad spectrum antimicrobial use in the ICU, involved review of prescriptions by an antimicrobial stewardship pharmacist, an infectious disease pharmacist, and an infectious disease physician.[6] The authors reported a significant increase in gram-negative susceptibility to meropenem during the post-intervention phase (83.4% vs. 78.2% prior to the intervention, p=0.03). There was no change in susceptibility to ceftriaxone, piperacillin-tazobactam, ciprofloxacin, or ceftazidime.

Costs

Eight studies were intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery reported cost data.[1,3,5,6,8,10,59,60] All found that their interventions were associated with decreased costs. The magnitude of the cost-savings varied.

Most reported drug costs. In a randomized trial, drug costs for the study period (24 weeks) were €4,670 lower in the intervention group.[1] Another trial reported a €6.41 per patient decrease in antimicrobial costs in the intervention group versus a €1.69 reduction in the control group (p value not reported).[10] A third trial reported a difference in antimicrobial cost of €2,657 per 1,000

patient days between intervention and control groups (IRR=0.87 [0.87, 0.88]).[5] Another trial reported a small but not significant reduction in median drug costs in the intervention group (€100 vs. €118.5).[3]

Among the interrupted time series studies, Magedanz reported that mean monthly hospital antimicrobial costs in their hospital dropped from $30,728 to $9,624 from stage 1 to 3 of their intervention.[59] Another study reported a $95,000 per year decrease in antimicrobial costs.[6] A third study reported a savings of $198,575 due to decreased consumption of audited antimicrobials.[8] The authors noted that savings to patients were $91,194. Another study reported in the Discussion section that aggregate costs to patients and/or insurers averaged $3,758 less per month, but details of the analysis were lacking.[60]

One study reported program costs. The estimated cost of the intervention was €2,147 over 24 weeks (including review of antimicrobial prescriptions and ward visits by the infectious disease physician).[1]

One study that was intended to decrease unnecessary or excessive prescribing reported that switching from IV to oral therapy, where appropriate, resulted in a cost savings of $179, 285 during the first year of the program. The total reduction in antimicrobial cost during the first year of the program was $1,284,357.[7] The authors also reported a significant reduction in total antimicrobial costs per 1,000 patient days over the duration of the stewardship program (from $44,181 to $23,933, p=0.04), which translated to a savings of $2,949,705 during the first 3 years of the program.

Formulary Restriction and Preauthorization (k=5)

Key Findings

- ***Patient Outcomes:*** Formulary restriction and preauthorization interventions were associated with no change in mortality or length of stay. In one study, CDI incidence was reduced post-intervention.
- ***Prescribing Outcomes:*** Four studies reported decreased use post-intervention. Dose and duration of antimicrobial treatment were lower in the intervention group in one study.
- ***Microbial Outcomes:*** One study of ciprofloxacin restriction reported decreases in the percentage and rate of carbapenem- and ciprofloxacin-resistant *P. aeruginosa* isolates.
- ***Cost Outcomes***: One study reported cost outcomes with lower drug costs in the intervention group.

Characteristics of Studies

We identified five studies assessing formulary restriction or restricted authorization to prescribe antimicrobials.[11-14,61] One was an RCT[11] and the remainder were ITS studies. Three studies focused on altering antimicrobial timing, drug selection, tailoring, or route of delivery[13,14,61] while two were aimed at reducing unnecessary or excessive prescribing.[11,12] The risk of bias was high for the RCT[11] and two of the ITS studies,[14,61] medium for one of the ITS studies,[12] and low for the remaining ITS study.[13] Two of the studies were conducted in North America,[13,61] two in Europe or the United Kingdom,[12,14] and one in the Pacific region.[11] One study was conducted in the ICU of a university-affiliated hospital and enrolled patients with bloodstream infections.[12]

Three studies enrolled patients with any infection from either all wards (including ICU wards)[14,61] or medical/surgical wards.[11] Two studies were conducted at university-affiliated or teaching hospitals[11,61] and one at a community hospital.[14] One study analyzed data from administrative healthcare databases covering individuals age 65 and older who were hospitalized.[13] Of the studies done in hospital settings, one involved an antimicrobial stewardship team,[14] two involved physicians and pharmacists,[11,61] and one involved physicians only.[12] The interventions typically involved multiple stewardship components. Three studies incorporated elements of case review with feedback[11,14,61] and two reported increased availability of either infectious disease physician consultation or pharmacy services.[12,14]

Two studies reported patient characteristics. Mean ages ranged from 57 to 63 years[11,12] and 53% were male.[11]

Reported outcomes are depicted in Table 6. Detailed findings are presented in Appendix D, Tables 9 to 16.

Table 6. Formulary Restriction and Preauthorization Interventions: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Aldeyab 2012[14]	X	X			
Lewis 2012[61]		X	X		
Peto 2008[12]	X	X			
Mamdani 2007[13]	X	X			
Rattanaumpawan 2010[11]	X	X		X	

Patient Outcomes

Four of the studies reported patient outcomes.[11-14] The formulary restriction ITS study reported no significant difference in mortality rates following implementation of a fluoroquinolone restriction policy (values not reported, p=0.62).[13] The restricted authorization ITS study found no significant differences in ICU mortality (64.3 deaths per 1000 patients after implementation versus 66.2 deaths per 1000 patients before implementation) or mean length of stay (2.4 days after implementation versus 2.6 days before implementation).[12] The single-site RCT found no significant difference between the authorization and no-authorization groups in the number of deaths occurring during hospitalization (44% vs. 43%, p=0.58), mean length of hospital stay (30.4 vs. 30.7 days, p=0.80), or death due to infection (29% vs. 35%, p=0.05).[11] In addition, there were no significant differences in the incidence of adverse events, including antimicrobial allergy (2% vs. 7%, p=0.10) and antimicrobial-associated diarrhea (25% vs. 18%, p=0.21).[11] The ITS study of an intervention to reduce high-risk antimicrobial use reported a significant trend for reduced CDI post-intervention.[14]

Strength of evidence for the patient outcomes is presented in Table 7.

Table 7. Strength of Evidence for Formulary Restriction and Preauthorization Interventions, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Rattanaumpawan 2010[11]	RCT	Preauthorization	High	Mortality	NS, RR 1.04 [0.90, 1.20]	Low for Mortality
Peto 2008[12]	ITS	Preauthorization	Medium	Mortality	NS, 64.3/1000 pts (after) vs. 66.2/1000 pts (before) (p=0.44)	
Mamdani 2007[13]	ITS	Formulary restriction	Low	Mortality	NS (p=0.62)	
Rattanaumpawan 2010[11]	RCT	Preauthorization	High	Length of stay	NS (p=0.80)	Low for Length of Stay
Peto 2008[12]	ITS	Preauthorization	Medium	Length of stay	NS, 2.4 days (after) vs. 2.6 days (before) (p=0.44)	
Aldeyab 2012[14]	ITS	Restriction	High	Incidence of CDI	Reduced trend (p=0.008) NS change in level	Low for Incidence of CDI

RCT = randomized controlled trial; ITS = interrupted time series; NS = not statistically significant; RR = rate ratio [95% confidence interval]

Prescribing Outcomes

Antimicrobial Use

Four studies reported antimicrobial use with each study finding decreased use following the intervention.[12-14,61] The ITS analysis of bloodstream infections reported that estimated mean antimicrobial consumption decreased from 162.9 DDD per 100 patient-days to 101.3 DDD per 100 patient-days. Prior to the intervention, the prescription rate had been rising (slope=1.31). After the intervention, not only did the level decrease (an estimated drop of 84.6 DDD per 100 patient-days) but the post-intervention slope was -0.18 (an estimated mean change in the slope of -1.5 (95% CI -0.16 to -2.83) DDD per 100 patient-days). The decrease was associated with a significant reduction in the use of fluoroquinolones, aminoglycosides, metronidazole, and carbapenems.[12]

One ITS study reported decreased level of use of high-risk antimicrobials as well as total antimicrobials with a restrictive intervention supplemented tine guidelines and weekly audit and feedback.[14] Another restrictive study (also supplemented with audit and feedback) found decreased trend in use of ciprofloxacin).[61]

The large Canadian, population-based ITS analysis found a significant decrease in overall fluoroquinolone prescription rates following implementation of a fluoroquinolone restriction policy, with an immediate drop to approximately 70 percent of the expected rate ($p<0.01$).[13] Within one year of implementation, the fluoroquinolone prescription rate began to rise again but the changes were not statistically significant. Specifically, ciprofloxacin use decreased to approximately 40% of the expected use rate in the months following implementation and remained significantly lower than expected during the one-year follow-up period. The actual use rate was 17.1 prescriptions per 1000 elderly persons per quarter compared with a predicted 43.6 prescriptions per 1000 elderly persons per quarter ($p<0.01$). Increased norfloxacin use was observed after implementation of the restriction policy ($p<0.01$). No significant changes in use were observed for cephalosporins, macrolides, penicillins, or tetracyclines. Use of sulfonamides and urinary anti-infectives (mainly nitrofurantoin and trimethoprim) was significantly higher within one year of the implementation of the restriction policy (all $p\leq0.01$). Authors did not report for what conditions fluoroquinolones were prescribed prior to the intervention. The restriction policy did restrict ciprofloxacin and ofloxacin to "limited use" for urinary tract infection. Hospitalization for urinary tract infections increased in the year after policy implementation (approximately 8% higher than predicted; $p<0.01$) while overall, infection-related hospitalizations were unchanged.

Dose

The RCT from Thailand reported that antimicrobial authorization significantly reduced doses of the targeted antimicrobials (piperacillin/tazobactam, imipenem, and meropenem) when compared with the no-authorization group (p values not reported).[11] The DDDs of all antimicrobials and targeted antimicrobials per episode were 21.0 and 5.8, respectively, in the authorization group compared with 26.2 and 7.2 in the no-authorization group. The investigators noted that 22% of prescriptions in the authorization group were changed to other antimicrobials (not recommended by the infectious diseases physicians).

Duration

The RCT from Thailand reported that treatment durations with all antimicrobials and treatment targeted antimicrobials were significantly shorter in the intervention group.[11]

Microbial Outcomes

Lewis reported significant decreases in the percentage and rate of carbapenem- and ciprofloxacin-resistant *P. aeruginosa* isolates following an intervention to restrict ciprofloxacin.[61] Although carbapeneum use increased, no changes were observed in the susceptibilities of nosocomial Enterobacteriaciae or *A. baumannii* to carbapenems.

Costs

Rattanaumpawan estimated that the annual antimicrobial cost savings from drug use evaluation and authorization for all prescriptions of the targeted antimicrobials would be $862,704.[11]

Guidelines Implemented with Feedback (k=4)

Key Findings

- ***Patient Outcomes:*** Mortality and length of stay were unchanged following implementation of guidelines for management of respiratory illnesses (2 studies) or to reduce broad-spectrum antimicrobial prescribing (1 study). Incidence of CDI was significantly reduced following the intervention (2 studies).
- ***Prescribing Outcomes:*** Implementation of guidelines with feedback was found to significantly decrease use, improve appropriate/compliant prescribing, improve selection, and improve timing. Duration of antimicrobial use was unchanged.
- ***Microbial Outcomes:*** No studies reported microbial outcomes.
- ***Cost Outcomes***: No studies reported cost outcomes.

Characteristics of Studies

Four studies implemented guidelines and provided feedback for guideline users. All reported interventions to alter antimicrobial timing, drug selection, tailoring, or route of delivery. Studies included an RCT evaluating a guideline for treatment of adults with CAP,[15] a cluster RCT evaluating a guideline on antimicrobial use for patients with lower respiratory tract infection,[16] and two ITS studies of guidelines to encourage narrow spectrum antimicrobial use for any infection site.[17,18] All studies were done in Europe[15,16] or the UK.[17,18] Two studies were rated as high risk of bias[15,16] and two were rated as medium risk.[17,18] The two studies of patients with respiratory infections were conducted at multiple hospital sites.[15,16] In one study, the intervention involved a "local organizing committee" consisting of physicians, pharmacists, microbiologists, pulmonologists, and quality improvement officers.[16] The second study did not provided detail on the intervention staff.[15] The two studies of interventions to reduce the risks from broad spectrum antimicrobials were each conducted in one hospital.[17,18] One reported involvement of a "team" (microbiologist and pharmacist)[18] while the other did not provide information about intervention staffing.[18] Three studies incorporated provider education in the intervention[15,16,18] and one included ward rounds by the antimicrobial stewardship team.[18]

One study enrolled patients who were 80 years and older.[17] Two studies reported patient characteristics with mean ages ranging from 56 to 70 years and between 46% and 53% male.[15,16]

Reported outcomes are depicted in Table 8. Detailed findings are presented in Appendix D, Tables 17 to 22.

Table 8. Guidelines with Feedback Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Talpaert 2011[18]	X	X			
Schnoor 2010[15]	X	X			
Schouten 2007[16]	X	X			
Fowler 2007[17]	X	X			

Patient Outcomes

In the RCT of an intervention to improve quality of care for patients with CAP, no significant differences were observed in length of hospital stay or all-cause and CAP-related mortality between intervention and control sites but results were not reported by initial treatment location (inpatient or outpatient) and p values were not reported for post-intervention differences.[15] Overall, post-intervention length of stay was approximately 10 days in the intervention group and 11 days in the control group; thirty-day overall mortality was 3.6% in the intervention group and 3.8% in the control group; and CAP-related mortality was 2.9% in the intervention group and 0.5% in the control group. None of the differences was significant.

In the cluster RCT of an intervention to improve quality of antimicrobial use for lower respiratory tract infections, post-intervention hospital mortality did not differ whether the patients were treated in intervention or control hospitals for either CAP (7.2% intervention vs. 8.7% control, p=0.58) or acute exacerbation of chronic bronchitis/chronic obstructive pulmonary disease (AECB/COPD) (4.3% intervention vs. 2.6% control, p=0.35). Hospital length of stay also did not differ (CAP: 8.0 days intervention vs. 10.0 days control, p=0.47; AECB/COPD: 11.5 days intervention vs. 11.4 days control, p=0.89).[16]

In an ITS study evaluating a guideline emphasizing narrow-spectrum antimicrobials, there was a significant decrease in monthly counts of CDI (IRR=0.35 [0.17, 0.73], p=0.0009) following the intervention but not in new cases of MRSA (IRR=0.79 [0.49, 1.28], p=0.32).[17] MRSA count data were collected as a control outcome since levels were not expected to change as a result of the intervention. Mortality and length of stay were reported to "fluctuate randomly" (range 4.7% to 21.0%). Pre- and post-intervention means were reported to be unchanged although it is unclear whether ITS analysis methods were used.

In the second ITS study, the only reported clinical outcome was CDI. Following introduction of a guideline to reduce use of broad-spectrum antimicrobials, there was a decreased incidence of CDI (IRR=0.34 [0.20, 0.58]).[18]

Strength of evidence for these outcomes is presented in Table 9.

Table 9. Strength of Evidence for Guidelines with Feedback Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Schnoor 2010[15]	RCT	Improve adherence to pneumonia guidelines	High	Mortality	NS, RR 0.97 [0.43, 2.17]	Low for Mortality
Schouten 2007[16]	RCT	Appropriate use	High	Mortality	CAP: NS, RR 0.87 [0.45, 1.66] COPD: NS, RR 1.76 [0.61, 5.08]	
Fowler 2007[17]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Mortality	Rates reported only	
Schnoor 2010[15]	RCT	Improve adherence to pneumonia guidelines	High	Length of stay	NS	Low for Length of Stay
Schouten 2007[16]	RCT	Appropriate use	High	Length of stay	NS, p=0.89	
Fowler 2007[17]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Length of stay	Significance not reported	
Talpaert 2011[18]	ITS	Reduce broad-spectrum antimicrobial use	Medium	Incidence of CDI	Decreased, IRR 0.34 [0.20, 0.58]	Low for Incidence of CDI
Fowler 2007[17]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Incidence of CDI	Decreased, IRR 0.35 [0.17, 0.73]	

RCT = randomized controlled trial; ITS = interrupted time series; NS = not statistically significant; RR = rate ratio [95% confidence interval]; CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; CDI = *C. difficile* infection; IRR = incidence rate ratio

Prescribing Outcomes

Antimicrobial Use

The RCT reported adherence to guidelines for management of inpatients with CAP. Adherence to recommendations for initial treatment increased at the intervention sites (5.6%) and decreased at the control sites (-5.5%). Post-intervention, the difference between sites was significant (66% intervention vs. 53% control, p=0.016). The adjusted odds of patients receiving appropriate antimicrobial treatment in the intervention group was 1.8 [95% CI 1.1, 2.8].[15]

In the cluster RCT, guideline concordance for treatment of CAP, AECB, or COPD improved in intervention hospitals more than in control hospitals (OR=2.63 [1.57, 4.42], p=0.0003).[16] For patients with either CAP, AECB, or COPD, there was no difference in the change in switching from IV to oral therapy in accordance with existing criteria from before to after in the intervention or control sites (OR=1.20 [0.02, 76.51], p=0.931).

In the ITS, for the antimicrobials targeted for decreased use (cephalosporins and amoxicillin/clavulanate), significant reductions in use were observed as indicated by significant changes in level (p=0.015 for sudden change in level) and trend (p=0.03 for long term linear trend).[17] Results were less consistent for narrow-spectrum antimicrobials targeted for increased use. There was a significant change in the level of amoxicillin use post-intervention (p=0.001 for sudden change in level) and a significant change in trend for benzyl penicillin (p=0.012 for long term linear trend). No significant differences in level or trend were observed for trimethoprim or other (untargeted) antimicrobials.

Timing

In the cluster RCT, patients with CAP were significantly more likely to receive timely antimicrobials in intervention sites than at control sites antimicrobial (OR=3.59 [1.02, 12.6], p=0.046).[16]

Selection

In the cluster RCT, among patients with CAP, AECB, or COPD, no significant difference was observed in "streamlining" (i.e., changing from broad-spectrum therapy to pathogen-directed therapy) (OR=1.94 [0.34, 11.03], p=0.456) although few patients were eligible.[16]

Duration

The RCT reported adherence to recommendations for duration of treatment of CAP for inpatients increased at the intervention sites (from 47% to 52%) and decreased at the control sites (from 57% to 54%) but the difference between sites post-intervention was not significant.[15]

In the cluster RCT, for patients with either AECB or COPD, there was no difference in the change in patients receiving optimal duration of antimicrobial therapy (5 to 7 days) (OR=2.22 [0.96, 5.12], p=0.62). The odds ratio was adjusted for clustering of patients relative to providers and hospitals.[16]

Microbial Outcomes

No studies reported microbial outcomes.

Costs

No studies reported cost outcomes.

Guidelines Implemented without Feedback (k=4)

Key Findings

- ***Patient Outcomes:*** Three studies of guideline implementation without feedback yielded inconsistent results for mortality and length of stay. One study in a neurosurgical ICU reported higher ICU mortality in the intervention group while two non-ICU studies reported either no difference or reduced mortality in the intervention group. One study in community and rehabilitation hospitals reported longer length of stay for patients in the intervention group while the ICU study reported no difference and a non-ICU study reported shorter length of stay post-intervention.
- ***Prescribing Outcomes:*** Improvements in use and/or appropriate use and compliance were noted in three of the four studies with no difference in the fourth study. Treatment duration was shorter in one study and unchanged in a second study. One study reported on timing with significantly fewer patients receiving antimicrobials within 8 hours in the intervention group.
- ***Microbial Outcomes:*** One study reported a decrease in the MRSA resistance proportion post-intervention.
- ***Cost Outcomes***: Two studies reported significantly lower drug costs following the intervention.

Characteristics of Studies

Four studies reported on development and implementation of guidelines. Two focused on interventions to alter antimicrobial timing, drug selection, tailoring, or route of delivery[21,62] and two were interventions to decrease unnecessary or excessive prescribing.[19,20] Two studies were considered high risk of bias[19,21] and two medium risk of bias.[20,62] Two studies were conducted in the United States[19,62] and two in Europe.[20,21]

All but one of the studies[19] was conducted in a university-affiliated hospital. Two enrolled patients in the ICU;[20,62] the other two studies were either unclear or did not report the site of the intervention. An antimicrobial team was involved in both of the ICU studies.[20,62] In one study, a physician and pharmacist were involved[19] while the fourth study did not specify. Three studies reported patient characteristics with mean age of participants ranging from 58 to 71 years and between 43% and 65% male.[19,20,62]

Table 10 shows outcomes reported in studies of guidelines without feedback. Detailed results are presented in Appendix D, Tables 23 to 30.

Table 10. Guidelines without Feedback Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Mangino 2011[62]		X			
Meyer 2007[20]	X	X	X	X	
Capelastegui 2004[21]	X	X			
Goldwater 2001[19]	X	X		X	

Patient Outcomes

The CBA study of guidelines for conversion from IV to oral therapy reported patient outcomes. Post-intervention adjusted mortality was significantly higher in the control cohort (OR=1.8 [1.1, 2.9]) than in the intervention cohort. The analysis was adjusted for pneumonia severity, multilobar involvement, COPD, and antimicrobial administration before hospital admission.[21] Readmission did not differ between groups. The post-intervention adjusted length of stay in the intervention cohort (4.7 days) was significantly shorter than in control cohort (7.6 days) ($p<0.001$).[21]

The ITS aimed at reducing duration of treatment reported an *increased* number of deaths in the ICU after the intervention (6.9% vs. 4.1%, $p<0.001$).[20] Length of stay did not differ (mean of 3.1 days both before and after the intervention). It was noted that these findings are based on a before-after analysis rather than an ITS analysis. There was some evidence (notably increased use of ventilators, central venous catheters, and urinary catheters) to suggest that the severity of disease increased from the pre-intervention to the post-intervention period.

The study comparing guidelines for therapeutic interchange with standard education found no significant difference in mortality (3.4% therapeutic interchange vs. 3.2% educational tools; p value not reported) or total adverse events (0.7% therapeutic interchange, 1.6% standard educational tools).[19] However, length of hospital stay was significantly *longer* in the therapeutic interchange hospitals (12.1 days vs. 10.5 days, p value not reported) which the authors suggested may be due to the long-term rehabilitation beds at one of the therapeutic interchange hospitals. Total adverse events did not differ between hospital groups.

Table 11 presents strength of evidence for these outcomes.

Table 11. Strength of Evidence for Guidelines without Feedback Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Goldwater 2001[19]	CCT	Reducing costs without sacrificing patient care	High	Mortality	NS, RR 1.07 [0.63, 1.82]	Low for Mortality
Meyer 2007[20]	ITS	Reduce duration	Medium	Mortality	Increased, p<0.05	
Capelastegui 2004[21]	CBA	Appropriateness, timing, duration	High	Mortality	Reduced, OR 1.8 [1.1, 2.9]*	
Goldwater 2001[19]	CCT	Reducing costs without sacrificing patient care	High	Length of stay	Increased, p<0.05	Low for Length of Stay
Meyer 2007[20]	ITS	Reduce duration	Medium	Length of stay	NS	
Capelastegui 2004[21]	CBA	Appropriateness, timing, duration	High	Length of stay	Reduced, p<0.001	
Capelastegui 2004[21]	CBA	Appropriateness, timing, duration	High	Readmission	NS, OR=0.8 [0.3, 2.0]**	Low for Readmission

CCT = controlled clinical trial; ITS = interrupted time series; CBA = controlled before and after study; NS = not statistically significant; RR = rate ratio [95% confidence interval; OR = odds ratio

*In this study, the post-intervention cohort was the reference group; ORs are for the control hospital cohort versus the intervention hospital cohort

Prescribing Outcomes

Use

In the ITS study of management of patients with HAP, VAP, and HCAP, from pre-implementation to post-implementation of locally-customized treatment guidelines, there were no differences in compliance with de-escalation of therapy after 3 days of therapy where clinically appropriate (56/173 [32%] vs. 36/96 [38%], p=0.40). Use of empiric antimicrobials was more likely to be compliant with ATS/IDSA guidelines during the post-implementation period (79/257 [31%] vs. 66/151 [44%], p=0.01), an effect that was sustained over 3 quarterly intervals (p=0.0008).[62]

In the CBA study of conversion from IV to oral therapy, there was no significant difference in receipt of appropriate antimicrobial therapy between the post-intervention group and the post-intervention control group (OR=1.1 [0.7, 1.7]). There was a significant improvement from pre- to post-intervention at the intervention site.[21]

An ITS study of a guideline focused on reducing duration of antimicrobial therapy for ICU patients with pneumonia reported a significant decrease in total antimicrobial use. The DDD/1000 pd decreased from 949.8 to 626.7, a change of 323.1 DDD/1000 pd (95% CI -444.5, -201.6).[20] Significant decreases in use were observed for second-generation cephalosporins, imidazoles, penicillins with B-lactamase inhibitor, and glycopeptides.

In the CCT comparing therapeutic interchange to standard educational tools for the purpose of switching from ciprofloxacin to levofloxacin, use of levofloxacin was higher in the therapeutic interchange hospitals with 97% of patients receiving levofloxacin compared with 48% in the standard educational tools hospitals (p<0.001).[19]

Duration

The CBA study of guidelines for conversion from IV to oral therapy reported a significant reduction in duration of IV therapy with an adjusted mean of 2.6 days in the post-intervention cohort, 3.9 days in the pre-intervention cohort (p<0.001), 5.2 days in the pre-intervention control cohort, and 5.3 days in the post-intervention control cohort. Similar differences were observed for overall duration of antimicrobial therapy.[21]

In a study of therapeutic interchange versus standard educational tools to encourage a change in prescribing pattern, the duration of fluoroquinolone use did not differ significantly between the hospital sites.[19]

Timing

In the controlled before and after study of guidelines for conversion from IV to oral therapy in patients with CAP, patients in the intervention cohort were significantly less likely than those in the pre- or post-intervention control cohorts to receive antimicrobials within 8 hours after presentation. There was a significant improvement from pre- to post-intervention at the intervention site.[21]

Microbial Outcomes

The ITS study of the effects of a guideline on reducing duration of therapy reported a significant decrease in the antimicrobial resistance proportion of MRSA from the ICU following the intervention (8.4% to 2.9%, $p<0.05$).[20] Changes for other pathogens were not significant.

Costs

Goldwater reported cost outcomes in the study comparing therapeutic interchange with standard educational tools.[19] Mean drug costs per patient were significantly lower in the therapeutic interchange hospitals ($79.80 vs. $114.50, $p<0.001$). The cost savings associated with replacement of ciprofloxacin with levofloxacin were $60.10 per patient in the therapeutic interchange hospitals and $37.30 per patient in the educational tools hospitals.

Implementation of a guideline aimed at reducing duration of antimicrobial therapy in ICU patients with pneumonia significantly reduced total antimicrobial costs per 1000 patient days.[20] The change in level was -5.86 €/pd (95% CI -8.66, -3.05).

Computerized Decision Support (k=4)

Key Findings

- ***Patient Outcomes:*** Three studies of computerized systems to identify cases for possible intervention or link susceptibility test results to pharmacy orders found no significant effect on mortality. One study of a system linking laboratory results and pharmacy orders found a shorter length of stay in the intervention group but two studies of systems for case identification found no differences. Readmission rates were unchanged following implementation of a system to identify cases for intervention. Incidence of CDI was decreased in one study of a computerized case identification system but unchanged in a second study.
- ***Prescribing Outcomes:*** Two studies of systems to identify cases for possible intervention reported decreased use of broad-spectrum antimicrobials with no change in recommended antimicrobials.
- ***Microbial Outcomes:*** A computerized decision support system aimed at reducing broad-spectrum antimicrobial use improved susceptibility of ICU Gram-negative isolates.
- ***Cost Outcomes*****:** Computerized systems to identify cases were found to reduce costs although only one of three studies reported a significant change.

Characteristics of Studies

Four studies implemented computerized support systems.[22-24,63] All of the interventions were designed to alter antimicrobial timing, drug selection, tailoring, or route of delivery. Three studies were of high risk of bias[22-24] and one of medium risk of bias.[6] The studies were conducted in university-affiliated hospitals in the United States,[22,23] a community teaching hospital in the United States,[24] or the ICU of a teaching hospital in Australia[63] and generally enrolled all inpatients. Two of the four studies reported multifaceted interventions including education, guidelines, and microbiologist consults.[23,24]

In one RCT, the goal was to optimize patient therapy and minimize inappropriate or inadequate use.[22] All patients received the control (standard care) protocol in which the pharmacist manually

created a list of patients receiving one of 23 restricted antimicrobials over the past 24 to 48 hours. The antimicrobial team reviewed the charts of those patients and recommended changes to therapy, if necessary. In the intervention group, a Web-based clinical decision support system generated alerts based on a patient's antimicrobial use and laboratory results. The antimicrobial team would access the alerts, review the patient's information (laboratory results, medications, and admission, discharge, and transfer data), and enter recommendations for change, if needed. Alerts were generated for control patients but the antimicrobial team was blinded from receiving them. Patients and treating physicians were not aware of which group the patient was randomized to. Data were reported for 4,507 patients (2,237 intervention, 2,270 control). Mean age was 50 years and 53% were female. Alerts were generated for 570 (26%) of the intervention arm patients; the team intervened on 359 (16%) patients. The team intervened on 180 (8%) of the patients in the control arm.

A CCT was designed to study the effect of a computerized system for linking microbiological data to pharmacies and alerting pharmacists to potential interventions to prevent inappropriate antimicrobial therapy.[23] The trial was discontinued early due to the observed benefits of the computerized system. In the control group, a pharmacist manually retrieved results of all antimicrobial susceptibility testing (AST) from the microbiology department, reviewed a patient's antimicrobial regimen and test results, and intervened, if necessary, by either written or verbal communication with the treating physician. In the study group, a computer program linked test results and pharmacy information and alerted pharmacists to potential treatment changes. In this group, pharmacists also received education about microbiologic topics and it is not possible to determine whether outcomes were due to the computerized support or the education session.

An ITS study was designed to assess the clinical and economic effects of reports generated by "data-mining software."[24] The study included patients with either pneumonia or intraabdominal sepsis. The reports included patient demographics, laboratory values, medications, and selected medical history gathered from the electronic medical record. The reports also provided recommendations for choice of antimicrobial therapy and de-escalation of therapy. Reports were reviewed by an antimicrobial stewardship pharmacist. If a patient was considered to be receiving inappropriate treatment, the case was reviewed with an infectious disease physician and written recommendations were providers. It was noted that the hospital already had in place a provider education program, antimicrobial prescribing pathways, a protocol for conversion from IV to oral therapy, dose adjustment based on renal function, and pre-authorization for use of formulary-restricted antimicrobials. During the 6 year study period (3 years before and 3 years after implementation), over 2400 charts were reviewed (over 2100 from patient with pneumonia). The mean age of the patients was 62 years.

A similar intervention was evaluated in a second ITS analysis.[63] The focus of the study was on changes in resistance patterns of common Gram-negative organisms after a computerized decision support system for antimicrobial prescribing was implemented. The computer program was developed specifically for the ICU setting and provided prescribing recommendations based on local antimicrobial susceptibility profiles of bacteria and patient-specific information (clinical information and allergies). The overall goal of the intervention was to reduce use of broad-spectrum antimicrobials. No patient demographic data were reported.

The outcomes reported in studies of computerized decision support are presented in Table 12. Results are reported in Appendix D, Tables 31 to 38.

Table 12. Computerized Decision Support Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Nowak 2012[24]	X	X		X	
Yong 2010[63]	X	X	X		
McGregor 2006[22]	X			X	
Barenfanger 2001[23]	X			X	

Patient Outcomes

The RCT comparing computerized alerts to standard care review of antimicrobial treatment reported no significant difference in in-hospital mortality (3.3% intervention arm vs. 3.0% control arm, p=0.55) or length of stay (3.8 days intervention arm vs. 4.0 days control arm, p=0.38). Findings were similar when the analysis included only patients who received system alerts. There was no significant difference in the percentage of patients experiencing diarrhea as a side effect (*C. difficile* testing; 5.7% intervention arm vs. 6.6% control arm, p=0.21).[22]

In the CCT, in the analysis of the total study sample, mortality did not differ significantly (11% in the study group vs. 10% in the control group, p=0.74) but length of stay was significantly shorter in the study group (11 days vs. 14 days, p=0.035).[23]

An ITS study reported non-significant differences in mortality, length of stay, and 30-day readmission for both patient groups (intra-abdominal sepsis, pneumonia) pre- to post-intervention.[24] These findings were based on an analysis of mean data (i.e., time series methods were not used). Incidence of CDI was analyzed with time series methods and significant differences in quarterly changes in rate of CDI were observed from pre- to post-intervention.

The other ITS study reported length of stay over the 7 year study period.[63] Average length of ICU stay was 4.2 days with yearly values decreasing from 4.4 days during the first year of the study to 4.0 days during the final year of the study. No statistical analysis was performed on length of stay.

Strength of evidence for these outcomes is presented in Table 13.

Table 13. Strength of Evidence for Computerized Decision Support Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
McGregor 2006[22]	RCT	Appropriateness	High	Mortality	NS, RR 1.11 [0.80, 1.53]	Low for Mortality
Barenfanger 2001[23]	CCT	Lower mortality, cost, and duration	High	Mortality	NS, RR 1.12 [0.62, 2.01]	
Nowak 2012[24]	ITS	Appropriateness, cost	High	Mortality	NS Sepsis: RR 0.50 [0.18, 1.38] Pneumonia: RR 0.96 [0.63, 1.47]	
McGregor 2006[22]	RCT	Appropriateness	High	Length of stay	NS, 3.8 days intervention, 4.0 days control (medians)	Low for Length of Stay
Barenfanger 2001[23]	CCT	Lower mortality, cost, and duration	High	Length of stay	Reduced, p=0.035	
Nowak 2012[24]	ITS	Appropriateness, cost	High	Length of stay	NS Sepsis: 7.2 (pre), 7.4 (post) Pneumonia: 5.9 (pre), 5.5 (post)	
Nowak 2012[24]	ITS	Appropriateness, cost	High	Readmission	NS Sepsis: RR 0.83 [0.46, 1.49] Pneumonia: RR 1.02 [0.83, 1.25]	Low for Readmission
Nowak 2012[24]	ITS	Appropriateness, cost	High	Incidence of CDI	Decreased, p=0.018	Low for Incidence of CDI
McGregor 2006[22]	RCT	Appropriateness	High	Incidence of CDI	NS, p=0.49	

RCT = randomized controlled trial; CCT = controlled clinical trial; ITS = interrupted time series; NS = not statistically significant; RR = rate ratio [95% confidence interval]

Prescribing Outcomes

Two ITS analyses reported antimicrobial consumption.[24,63] In one study, decreased use of quinolones, vancomycin, carbapenems, and piperacillin-tazobactam followed the intervention with little change in use of first line antimicrobials.[24] In the second study, use of 3rd and 4th generation cephalosporins, carbapenems, extended-spectrum penicillins, aminoglycosides, and fluoroquinolones (measured as DDD/1000 bed days) did not differ over the study period.[63]

Microbial Outcomes

Changes in antimicrobial resistance patterns of common Gram-negative organisms were evaluated in one ITS study.[63] Analyses were based on clinical microbiology isolates from all ICU patients admitted during the study period. An intervention to reduce broad-spectrum antimicrobial use was associated with reductions in the rates of resistance to key antimicrobials in several Gram-negative bacteria, notably *Pseudomonas* and inducible Enterobacteriaceae groups. For *Pseudomonas aeruginosa*, gentamicin susceptibility decreased prior to the intervention but then increased post-intervention with a significant difference between the pre- and post- intervention phases (change from pre-intervention trend reported as mean percent change per year: 11.6 [1.8, 21.5], p=0.02). A similar pattern was observed for imipenem with a significant difference between pre- and post-intervention (mean percent change per year: 18.3 [4.9, 31.6], p=0.009). Non-significant differences were observed for ceftazidime and ciprofloxacin susceptibility. Enterobacteriaceae with potentially inducible beta-lactamases were grouped. Significant increases in gentamicin (mean percent change 6.5 [2.7, 10.2], p=0.002) and ciprofloxacin (mean percent change 3.5 [1.3, 5.7], p=0.003) susceptibility were observed with no change in imipenem susceptibility. For *E. coli, Klebsiella*, and *Acinetobacter* no changes in susceptibility from pre- to post-intervention were noted. There was no adjustment for the large number of comparisons.

Costs

In the RCT by McGregor, total antimicrobial costs during the 3 month study period were $285,812 for patients in the intervention arm versus $370,006 for patients in the control arm (23% savings). Average saving per patient was $37.64.[22]

The CCT reported average total cost, average variable cost (i.e., costs associated directly with patient care), and pharmacy costs.[23] In the analysis that included the total study sample, average total costs and average variable costs were significantly lower in the study group (both p=0.008). Pharmacy costs did not differ significantly (p=0.104).

An ITS study reported that the slope of antimicrobial dollars per patient day (ADPD) differed significantly from pre- to post-intervention (p=0.009). The authors estimated that if costs would continue to increase at the pre-intervention pace, more than $1.7 million dollars was saved over the 4 years of the intervention.[24]

Protocols (k=4)

Key Findings

- ***Patient Outcomes:*** In clinically stable adults with CAP, protocols for switching from IV to oral antimicrobials did not have an effect on mortality; hospital length of stay was significantly shorter in the early switch groups. Systematic reassessment at 72 hours was associated with reduced mortality and no change in length of stay.

- ***Prescribing Outcomes:*** Protocols for switching patients with CAP from IV to oral therapy reduced the duration of IV therapy. Systematic reassessment was not associated with improved appropriateness of prescribing.
- ***Microbial Outcomes:*** Susceptibility of *P. aeruginosa* to imipenem increased following introduction of ertapenem.
- ***Cost Outcomes***: No studies reported cost outcomes.

Characteristics of Studies

Four studies described the implementation of protocols.[25-27,64] All were intended to alter antimicrobial timing, drug selection, tailoring, and route of delivery. Risk of bias was medium for all four studies. Three studies were conducted in Europe[25-27] and one in the United States.[64] Two studies reported the inclusion of additional stewardship components with order form and weekly audit and feedback in one study[27] and guidelines in the other.[26]

Two RCTs were designed to compare protocols for early switch from IV to oral antimicrobials to usual care.[25,26] Neither study provided details about how the criteria for switching therapies were developed or who was responsible for administering the protocol. In one study, the protocol also included early mobilization and use of predefined criteria for hospital discharge.[25] Usual care was defined as treatment according to the practices of individual attending physicians. In the other study, usual care was seven days of IV treatment.[26] Both studies enrolled patients with CAP but one study was limited to patients with severe CAP.[26] In that study, more than 80% of patients were in pneumonia severity class IV or V. In the other study, more than 60% were in class IV or V. Both studies were conducted at more than one hospital. Patient characteristics were similar (mean ages 69 and 71 years, 65% and 66% male).

Another study, an ITS analysis,[27] looked at the effect of systematic reassessment of the antimicrobial prescription after approximately 3 days of treatment on the quality (i.e., appropriateness) of antimicrobial prescriptions. The study was conducted in the medical ICU of an urban university teaching hospital. Sixty two patients were studied during a 3 month period before the intervention and 52 were studied during a 4 month period after the intervention. The mean age was 62 years and 62% were male. The majority of infections were in the lungs (64%). Baseline characteristics were similar for the two study periods.[27]

The fourth study, also an ITS study, involved a policy for autosubstitution of ertapenem for ampicillin-sulbactam.[64] The study was conducted in a community teaching hospital; no details were provided regarding the administration of the policy. No patient characteristics were reported. The focus was on the susceptibility of antimicrobial agents against *Pseudomonas aeruginosa.*

Outcomes reported are presented in Table 14 with detailed results reported in Appendix D, Tables 39 to 45.

Table 14. Protocol Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Carratala 2012[25]	X	X			
Pulcini 2011[27]	X	X			
Goldstein 2009[64]		X	X		
Oosterheert 2006[26]	X	X			

Patient Outcomes

In the two RCTs of switching from IV to oral therapy, mortality did not differ significantly between intervention and control groups though hospital length of stay was significantly reduced.[25,26] In one study, mortality from day 4 through a 28 day follow-up was 4% (5/132) in the intervention group and 6% (8/133) in the control group (RR=0.63 [0.21, 1.88]).[26] In the other study, 30-day mortality was 2% (4/200) in the intervention group and 1% (2/201) in the control group (RR=2.01 [0.37, 10.85]).[25] Mean lengths of hospital stay were 9.6 days (intervention) and 11.5 days (control) ($p<0.05$) in one study;[26] median lengths of stay were 3.9 days (intervention) and 6.0 days (control) ($p<0.001$) in the other.[25] One study reported 30-day readmission with no significant difference between groups (9.1% intervention, 7.5% control; RR=1.21 [0.63, 2.33]).[25] Clinical deterioration, reported in one study, did not differ between groups (6% intervention, 5% control, $p>0.05$).[26] Another study reported a significant difference in drug reactions (4.5% intervention vs. 15.9% control, $p<0.001$) but no difference in medical complications (20.0% intervention vs. 24.4% control, $p=0.34$).[25]

The systematic reassessment study also reported mortality and length of stay. There was a significant reduction in mortality post-intervention (8% post-intervention vs. 23% pre-intervention; $p=0.03$) although it is unclear whether this was ICU mortality or hospital mortality.[27] Length of stay did not differ (13.8 days both pre- and post-intervention).

None of the protocol studies reported incidence of CDI. Strength of evidence for patient outcomes is presented in Table 13.

Prescribing Outcomes

Both studies of protocols for switching from IV to oral therapy reported decreased length of IV treatment. In one study, the mean duration of IV therapy was significantly shorter in the intervention group versus the control group (3.6 days vs. 7.0 days, $p<0.05$).[26] In the second study, the median duration was significantly shorter in the intervention group (2.0 days vs. 4.0 days, $p<0.001$).[25] One of the studies reported mean length of overall antimicrobial treatment with no significant difference between the intervention and control groups (10.1 and 9.3 days, respectively; mean difference 0.8 days, [-0.6, 2.0]).[26] The other study reported median time to antimicrobial therapy with no significant difference between groups (3.3 days intervention vs. 4.0 days control, $p=0.45$).[25]

In the systematic reassessment time series study, a trend analysis revealed no change in level (-0.14 [-0.30, 0.02], $p=0.72$) or trend (-0.0004 [-0.04, 0.03], $p=0.59$) of appropriateness of antimicrobial therapy after the intervention. The prevalence of inappropriate therapies also did not decrease (a change from 43% to 38%, $p=0.86$).[27]

The ITS study of autosubstitution looked at use of ertapenem during three time periods: prior to the introduction of ertapenem, after ertapenem was added to the formulary, and after the autosubstitution policy was implemented.[64] Median DDDs for ertapenem were 0, 8, and 44 during the three time periods. No statistical analysis was reported. The change in slope for imipenem use from the first time period to the second was significant (change=-4.46, $p<0.001$). Use of other antimicrobials (levofloxacin, cefepime, cefoxitin, and piperacillin-tazobactam) was unchanged during the study period.

Microbial Outcomes

In the study of an autosubstitution protocol, susceptibility of *P. aeruginosa* to imipenem increased following introduction of ertapenem to the formulary (slope for trend=1.74, $p<0.001$) and the trend was unchanged following the addition of the autosubstitution policy (slope=0.02; $p=0.85$). The decreased use of imipenem that accompanied the increased use of ertapenem was significantly related to the improved susceptibility of *P. aeruginosa* to imipenem.[64]

Costs

None of the studies reported costs.

Table 15. Strength of Evidence for Protocol Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Carratalà 2012[25]	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR 2.01 [0.37, 10.85]	Low for Mortality
Oosterheert 2006[26]	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR 0.63 [0.21, 1.88]	
Pulcini 2011[27]	ITS	Appropriateness	Medium	Mortality	Reduced, p=0.03	
Carratalà 2012[25]	RCT	Evaluate effectiveness of early switch	Medium	Length of stay	Reduced, WMD 2.1 [1.7, 2.7]	Low for Length of Stay
Oosterheert 2006[26]	RCT	Evaluate effectiveness of early switch	Medium	Length of stay	Reduced, WMD 1.9 [0.6, 3.2]	
Pulcini 2011[27]	ITS	Appropriateness	Medium	Length of stay	NS, p=0.99	
Carratalà 2012[25]	RCT	Evaluate effectiveness of early switch	Medium	Readmission	NS, RR 1.21 [0.63, 2.33]	Low for Readmission

ITS = interrupted time series; RCT = randomized controlled trial; NS = not statistically significant; RR = rate ratio [95% confidence interval]; WMD = weighted mean difference

Laboratory Tests (Findings from Systematic Reviews and Recent Trials)

Key Findings

- ***Patient Outcomes:*** Procalcitonin to guide initiation or duration of antimicrobial therapy for adults with acute respiratory infection or in the ICU with any infection had no effect on mortality. One study reported an increase in ICU length of stay and increased need for mechanical ventilation in the procalcitonin group.
- ***Prescribing Outcomes:*** Systematic reviews reported reductions in antimicrobial use with procalcitonin testing while recent RCTs reported no differences.
- ***Microbial Outcomes:*** Microbial outcomes were not reported.
- ***Cost Outcomes***: Cost outcomes were not reported.

Procalcitonin, the prohormone of calcitonin, has been identified as a marker for the diagnosis of bacterial infections. Procalcitonin levels increase in response to bacterial infection but not viral infection. Levels decrease when the infection is resolved.

A recent high quality Cochrane systematic review and meta-analysis of individual patient data looked at studies of procalcitonin monitoring in patients with acute respiratory infections (ARIs).[65] The review included studies from both inpatient and outpatient settings. A second recent review by Agarwal and Schwartz, of moderate to high quality, included the studies conducted in the ICU that were cited in the Cochrane review but reported data from patients with any type of infection.[66]

Characteristics of Studies Included in Systematic Reviews

Both reviews included prospective RCTs in which procalcitonin cut-off ranges were used to guide initiation and discontinuation of antimicrobial therapy in one study group. The Cochrane review provided more details about the studies.[65] Studies were eligible for inclusion if the control group received antimicrobials without use of procalcitonin levels. Therapy for patients in the control group may have been directed by guidelines but studies in which providers had access to other biomarkers were excluded. The Cochrane review included studies of adults with an acute respiratory infection; the primary diagnoses were upper respiratory tract infection (13% of patients enrolled) or lower respiratory tract infection (87% of patients enrolled including 48% with community-acquired pneumonia). Of 14 studies eligible for the review, 2 were done in primary care settings, 2 enrolled outpatients treated in the emergency room, 5 enrolled patients admitted via the emergency department, and 5 enrolled ICU patients. Approximately 24% of the total patient enrollment was from primary care, 62% from emergency department, and 14% from ICU settings.[65] The second review included the five studies that enrolled ICU patients and a study reported only in abstract form.[66]

Seven of the studies in the Cochrane review were conducted in Switzerland (one of these studies included a hospital in the United States), three in Germany, two in China, and one each in France and Denmark.[65] The five ICU studies were from Switzerland (k=2), Germany (k=2), and France (k=1). The additional study included in the Agarwal review was from Belgium.[66] Primary outcomes of interest in the Cochrane review were all-cause mortality (up to 30 day follow-up) and setting-specific treatment failure.[65] The primary outcome in the Agarwal review was duration or intensity of antimicrobial therapy.[66] Both reviews reported length of stay.

Studies Published After the Systematic Reviews

We identified 2 RCTs published after the systematic reviews.[67,68] The study by Jensen was conducted in nine medical/surgical ICUs in Denmark.[67] Unlike many studies, this was a drug escalation intervention. Daily procalcitonin measurements were taken and elevated levels prompted additional cultures, acute diagnostic imaging, and expanded spectrum of antimicrobial therapy. The trial included 1200 patients; median age was 67 years and 55% were male. Nearly 70% of the patients were experiencing respiratory failure and 43% had circulatory failure.

The second study enrolled patients from eight ICUs in France.[68] Procalcitonin levels were evaluated at 6 hours and on days 3 and 5. Results were used to guide initiation and discontinuation of antimicrobials. The trial was terminated early due to low enrollment. Baseline data were reported for 58 of 62 patients randomized (4 patients withdrew consent) with median age of 57 years and 74% male gender.

Patient Outcomes

In the Cochrane review, overall mortality was 5.7% (118/2085) in the procalcitonin group and 6.3% (134/2126) in the control group.[65] The adjusted odds ratio was 0.94 (95% CI 0.71, 1.23). Among patients treated in the emergency department, there were no differences in the outcomes of mortality (4.7% procalcitonin vs. 4.5% control; p=0.90), a combination of mortality or ICU admission (9.8% procalcitonin vs. 11.2% control, p=0.16), or length of hospital stay (median of 8 days for both groups, p=0.28). For patients treated in the ICU, there were no significant differences between treatment groups for mortality (19.9% procalcitonin vs. 23.8% control, p=0.44), length of ICU stay (median of 12 days in both groups, p=0.39), or length of hospital stay (21 days for procalcitonin group vs. 24 days for control group, p=0.39).

The Cochrane review also reported outcomes by diagnosis.[65] Mortality did not differ between treatment groups for any of the diagnoses. Among patients with community-acquired pneumonia, mortality was 9.2% in the procalcitonin group and 10.8% in the control group (p=0.47). Among patients with ventilator-associated pneumonia, the corresponding rates were 6.3% and 10.3% (p=0.49).

In the Agarwal review, studies were not pooled.[66] Five of the six studies of ICU patients with any infection reported mortality with no significant differences observed between the procalcitonin and control groups. Six studies reported ICU length of stay with significantly shorter lengths of stay in the procalcitonin groups in two of the six studies. Three studies reported hospital length of stay with no differences between groups in any of the studies.

Of the recent studies, Jensen reported 28 day mortality was 31.5% (190/604) in the procalcitonin group and 32.0% (191/596) in the control group (Hazard Ratio=0.98 [0.83, 1.16]).[67] ICU length of stay was longer (6 days vs. 5 days, p=0.004) and ICU days with mechanical ventilation were greater (3,569 days vs. 2,861 days, p<0.001) in the procalcitonin group. There was also evidence of increased organ failure in the procalcitonin group in an analysis based on "all admitted days in hospitals" rather than ICU days.

The second study reported mortality data for the 62 patients randomized.[68] No significant differences were reported between groups at day 5 (10% in each group), at ICU discharge (23% in the procalcitonin group, 33% in the control group, p=0.40), or at hospital discharge (same

as ICU discharge). ICU length of stay (22 days for the procalcitonin group vs. 23 days for the control group, p=0.58) and hospital length of stay (27 days and 33 days, respectively, p=0.22) did not differ significantly.

Prescribing Outcomes

In the Cochrane review, initiation of antimicrobials was significantly lower in the procalcitonin group (64% vs. 84%, p<0.001).[65] Duration of antimicrobial use in those receiving antimicrobials (median of 7 days vs. 10 days, p<0.001) and total exposure of antimicrobials (considering all randomized patients) (median of 4 days vs. 8 days, p<0.001) were also significantly lower in the procalcitonin group. These differences were maintained among patients treated in the emergency department and the intensive care unit with the exception that 100% of patients in both groups received antimicrobials in the intensive care unit.

By disease category (upper acute respiratory infection, community-acquired pneumonia, and ventilator-associated pneumonia), the initiation of antimicrobials, duration of antimicrobials, and total exposure of antimicrobials were significantly less among patients in the procalcitonin group with the exception of those with ventilator-associated pneumonia (all of whom were treated with antimicrobials).[65]

Agarwal reported duration of antimicrobial therapy.[66] Each of the included studies reported duration outcomes although definitions varied among the studies. Five of the six studies reported decreased duration of antimicrobial therapy.

Among the recent studies, no difference in time to appropriate prescribing for patients with infections other than bloodstream infections was reported in one trial (0.2 days for the procalcitonin group vs. 0.4 days for the control group, p=0.61).[67] For blood stream infection, there was a significantly shorter time to appropriate therapy in the procalcitonin group (-0.1 days vs. 0.8 days, p=0.02). In the second study, the median time on antimicrobial therapy was the same for the two study groups (5 days).[68] At 5 days after randomization, among 27 survivors in the procalcitonin group 18 (67%) were taking antimicrobials compared with 21 of 26 survivors (81%) in the control group (RR=0.83 [0.60, 1.14]).

KEY QUESTION #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Key Findings

- Six studies provided information on intervention components associated with effective antimicrobial stewardship. Consistent and persistent effort from qualified personnel employing effective communication skills and often supported by electronic medical records or computerized decision support systems were central themes through these studies.

Six studies included in our review provided additional information on intervention components associated with effective antimicrobial stewardship. We summarize those studies below.

Goldwater provided insights into successful implementation of programs to influence prescribing.[19] The study compared a therapeutic interchange protocol with standard educational tools for modify fluoroquinolone prescribing. The therapeutic interchange protocol was presented and approved at medical staff department and medical executive committee meetings. It was noted that "consistent and persistent effort" was needed to maintain changes in prescribing patterns and "qualified personnel" are needed to track compliance with prescribing guidelines. Effective communication was also mentioned including newsletters, direct mailings, notes or stickers in medical records, and direct conversations.

The need to tailor antimicrobial stewardship to individual wards or ICUs was also noted by Meyer et al.[20] The authors cited potential differences in prescribing practices and resistance patterns across facilities or units within a single facility. The study focused on changes in antimicrobial use following implementation of a guideline to reduce duration of antimicrobial therapy for patients in a neurosurgical ICU. The leadership of an "experienced intensive care physician who was responsible for educating the rotating neurosurgeons" was also noted as a factor in the success of the intervention.

Barenfanger reported on an intervention that used a commercially available software program that linked laboratory susceptibility testing results to the pharmacy and notified pharmacists of potential problems with the patient's treatment regimen.[23] The intervention also included pharmacist education focused on microbiologic topics. Shorter lengths of stay and cost savings were noted for the intervention group; mortality was unchanged. The authors reported that physicians in the intervention group accepted the intervention because the electronic antimicrobial susceptibility report offered information that was not previously available to physicians. Pharmacists were able to provide physicians with recommendations for antimicrobials that would be more appropriate for a particular patient based on the susceptibility report. Physicians in the control group (usual hospital practice) were less likely to welcome the pharmacists' suggestions. In that group, pharmacists obtained paper copies of the susceptibility reports for patients tested the previous day. The reports were correlated with the patients' current therapy and, unless the changes needed were urgent and needed to be communicated by telephone, notes were placed in the patients' charts. Pharmacists received information that was already available to physicians and therefore there were more likely to be disagreements about therapy.

McGregor commented on the time savings associated with use of a computerized clinical decision support system.[22] The commercially available system was designed to generate alerts for the antimicrobial management team when treatment was inappropriate or inadequate. The management team then communicated with the physician. The comparator was manual chart review and recommendations for changes to patient therapy. It was reported the antimicrobial management team spent 4.1 person-hours per day making interventions on the control arm and 3.2 person-hours per day on the intervention arm. The primary advantage of the computer system was in identifying patients that needed interventions.

In a trial to reduce the use of broad-spectrum antimicrobials among ICU patients, the timing of the intervention was considered important.[6] Patients who received 3 days of therapy with the targeted antimicrobials were enrolled. Cases were reviewed at day 3 and at day 10. The authors

commented that by day 3, microbiologic data and the early "clinical trajectory" of the patient could be incorporated into the recommendation.

A study conducted in three departments of a general hospital in Singapore discussed features of their program.[8] It was noted that audit with non-immediate feedback and formulary restriction policies were already in place with limited effectiveness (i.e., approximately 40% of prescriptions were considered sub-optimal). The program was modified to enable a "whole-system" approach. Components included one-page antimicrobial guidelines for infections of major organs, an algorithm for IV to oral conversion, and a 2-stage audit of prescriptions with immediate concurrent feedback. The goal was to maintain physician autonomy while nurturing optimal prescribing. A computerized system was used to identify patients prescribed the audited antimicrobials. Clinical pharmacist compiled and reviewed the patient information. Complicated cases were subsequently reviewed and evaluated by an infectious disease physician, microbiologist, and pharmacist. If the prescription was determined to be inappropriate, verbal and/or written information was conveyed to the prescribing physician. All prescribing information was compiled for quarterly updates to departments including the appropriateness of prescriptions, the acceptance rate of interventions, and recommended areas for improvement.

KEY QUESTION #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

Key Findings

- ***Hospital Setting:*** None of the studies identified in our search for recent evidence were conducted at VA medical centers. Nearly all were conducted in university-affiliated teaching hospitals with only six studies conducted in community hospitals. Nine studies were conducted in ICUs. Because intervention components, study design, patient populations, and targeted infection or antimicrobial use differed across studies with no study directly attempting to replicate previous findings we caution against inferring that any outcome variation was due to hospital setting or unit.
- ***Suspected Patient Condition:*** Lung infections were the most frequently reported specific patient condition (seven studies). Results appeared qualitatively similar in these studies compared with the overall findings. Due to limited information and variability in study design, intervention and patient characteristics we urge caution in trying to assess whether effectiveness varies by suspected patient condition.

Hospital Type

None of the studies included in our review was conducted at a VA medical center. Most studies were conducted in university-affiliated or teaching hospitals. The exceptions were four studies conducted in general or community hospitals,[6,8,14,58] three conducted in multiple hospitals,[19,25,26] two of which included community hospitals,[19,25] and two that did not specify hospital setting.[15,16] One study used healthcare administrative databases from Ontario, Canada.[13]

With few studies conducted in community hospitals it is difficult to reach any conclusions about differences in effectiveness. Three ITS studies of audit and feedback interventions were carried out in community hospitals. In one study, the aim was to reduce use of broad-spectrum

antimicrobials. Data from over 4,600 patients treated in three ICUs of a single community hospital were included.[6] An antimicrobial stewardship pharmacist reviewed records of patients who had received 3 days of therapy with one of the targeted antimicrobials and, if it appeared that therapy could be optimized, consulted with a senior infectious disease pharmacist and an infectious diseases physician. Suggested changes were entered in a database, a note was placed in the patient chart, and the pharmacist verbally communicated with members of the care team. A similar review was completed on the tenth day of therapy. No changes in mortality, length of stay, or CDI were observed following introduction of the stewardship program. A significant decrease in use of broad-spectrum antimicrobials was reported.

A second study piloted a stewardship intervention in three departments of a community hospital.[8] An antimicrobial stewardship team developed guidelines for treatment of infections and an audit and feedback program was implemented. Clinical pharmacists reviewed patient records and made recommendations for changes to therapy. Complex cases were discussed with an infectious disease physician. The focus was on broad-spectrum and high cost antimicrobials. Over 1,500 prescriptions were reviewed. Mortality was unchanged following the intervention. There was a decreased level of targeted antimicrobials post-intervention but the change in trend was not significant. There was no change in the level of overall antimicrobial use but a significant increasing trend.

The third study was designed to discourage the use of quinolones and third-generation cephalosporins.[58] The study site was a 480-bed hospital serving a population of approximately 230,000. The focus was on microbial outcomes and antimicrobial usage in the ICU and hospital-wide. The guidelines used in the study were approved by the Antimicrobial Stewardship Committee (details of the Committee membership were not reported). A senior microbiologist attended ward rounds and provided prescribing advice. Post-intervention there were significant reductions in the use of third-generation cephalosporins both hospital-wide and in the ICU while use of ciprofloxacin was reduced only in the ICU. There was a significant change in the level of MRSA hospital-wide.

One study used a restrictive intervention.[14] The ITS study took place in a 233-bed community hospital. Antimicrobials were classified as high-, medium-, or low-risk with restrictions on the use of the high-risk group. Weekly audit and feedback were used to encourage adherence to the policy. Mortality, length of stay, and readmission were not reported. There was a significant change in trend for CDI post-intervention; change in level was not significant. There were significant decreases in level of use for both high-risk and overall antimicrobials but no changes in trend.

A CCT of implementation of a guideline to change prescribing habits (replacement of ciprofloxacin with levofloxacin) was conducted in four hospitals.[19] At a 151-bed community hospital and a 656-bed tertiary facility, a therapeutic interchange program was put in place with pharmacists intervening when a non-preferred fluoroquinolone was prescribed. At a 232-bed community and rehabilitation hospital and a 339-bed community hospital, standard educational tools were used to encourage prescribing of the preferred antimicrobial. Pharmacists at the standard educational tools hospitals were more involved in patient rounds. No information was provided about availability of infectious diseases specialists or clinical microbiologists. It

was noted that therapeutic interchange had been effectively used at one of the study hospitals for approximately three years prior to the study. The authors found a significantly higher rate of prescription of the preferred agent at the therapeutic interchange hospitals (96% of patients compared with 48% of patients at the standard educational tools hospitals, $p<0.001$). There were differences in the sites of infection between the two intervention groups with more abdominal infections treated with fluoroquinolones at the standard educational tools sites and more blood infections and prophylactic use of fluoroquinolones at the therapeutic interchange sites.

An RCT of a protocol to reduce the duration of IV therapy and length of stay for patients with CAP enrolled patients at a 900-bed university hospital and a 300-bed private hospital.[25] Randomization of patients was stratified by hospital. The intervention consisted of a printed checklist placed in the charts of intervention group patients to remind their providers about the protocol. Length of stay was reported by hospital site. At the university hospital, mean length of stay was 4.0 days in the intervention group and 6.0 days in the usual care group (difference = -2.0 [-2.7, -1.3]; $p<0.001$). At the community hospital, mean length of stay was 3.7 days in the intervention group and 6.3 days in the usual care group (difference = -2.6 days [-3.2, -1.7]; $p<0.001$). The authors did not comment on differences between the hospital sites.

In their narrative review, MacDougall and Polk commented on differences between teaching and non-teaching hospitals.[48] They noted that surveys of hospitals or physician members of infectious diseases societies have typically found that larger hospitals and teaching hospitals were more likely to have antimicrobial restriction programs than smaller hospitals or non-teaching hospitals. The authors suggested that the increased likelihood of finding of antimicrobial control programs at teaching hospitals might be due to greater perceived need for control of antimicrobial prescribing, greater availability of resources and staff to oversee the program, or lesser need to allow for physician autonomy.

Hospital Unit

We also looked at effectiveness by unit within the hospital. Our review of recent evidence identified eight studies conducted in an ICU, seven in medical wards, fifteen in mixed medical/surgical/ICU, two in acute care, and eight that didn't report the hospital unit. Mortality, length of stay, and antimicrobial outcomes from the eight ICU studies and one multi-site study that reported ICU findings are presented in Table 16. Additional data on ICU studies may be found in the section on Laboratory Tests.

Overall, the findings from ICU studies were similar to findings from all eligible studies.

Five studies reported mortality. A CCT of audit and feedback enrolling patients with any infection found decreased mortality in the intervention group.[4] An ITS study enrolling patients with CAP found significantly higher mortality following guideline implementation.[20] The other three studies found no significant difference in mortality before and after an intervention.[5,9,27]

Four studies reported length of stay finding no differences before and after an intervention.[6,9,20,27] The goal of one study was to reduce duration of treatment in patients with respiratory infections.[20]

Antimicrobial prescribing outcomes were reported in eight studies. Significant decreases in consumption were reported in four studies[6,12,20,57] with no difference in a third study.[63]

Compliance with guideline recommended therapy was reported in one study with significant improvement following the intervention.[62] However, in two studies, quality of therapy was not different post-intervention.[9,27]

Table 16. Studies Conducted in Intensive Care Units

Author, year	Study design	Intervention type	Goal	Infection site	Mortality	Length of Stay	Antimicrobial Prescribing
Cairns 2013[57]	ITS	Audit and Feedback	Reduction in broad-spectrum antimicrobials	Any	NR	NR	*Broad-spectrum use* decreased level and increased rate of change (both p<0.001)
Elligsen 2012[6]	ITS	Audit and Feedback	Reduction in broad-spectrum antimicrobials	Any	Before: 13.1% After: 14.4% p=0.20	Before: 6.9 days After: 6.9 days p=0.92	*Broad-spectrum use (monthly)* Before: 644 days of therapy per 1000 pd After: 503 days of therapy per 1000 pds (p<0.0001)
Weiss 2011[4]	CCT	Audit and Feedback	Reduce mortality (exploratory analysis)	Any	With prompting: OR=0.48, 95% CI 0.26-0.88 p=0.014	NR	NR
Bornard 2011[9]	ITS	Audit and Feedback	Improve quality of prescriptions	Any	Before: 3.0% After: 3.0% p=1.0	Before: 8 days After: 19 days p=0.72	*Appropriate therapies* Change in level p=0.67 Change in trend p=0.055
Peto 2008[12]	ITS	Formulary Restriction or Pre-authorization	Avoid unnecessary antimicrobial usage	Blood	NR	NR	*Mean antimicrobial consumption* Before: 162.9 DDD/100 pd After: 101.3 DDD/100 pd "significant"
Mangino 2011[62]	ITS	Guideline without Feedback	Improve adherence to clinical pathway	CAP HAP HCAP	NR	NR	*Compliant empiric therapy* Pre-intervention: 79/257 (30.7%) Post: 66/151 (43.7%) p=0.01
Meyer 2007[20]	ITS	Guideline without Feedback	Reduce duration of antimicrobial treatment	CAP	ICU Before: 80/1964 (4.1%) After: 162/2354 (6.9%) p<0.001	Before: 3.1 days After: 3.1 days p=ns	*Antimicrobial use density* Before: 949.8 DDD/1000 pd After: 626.7 DDD/1000 pd "significant"

Author, year	Study design	Intervention type	Goal	Infection site	Mortality	Length of Stay	Antimicrobial Prescribing
Yong 2010[63]	ITS	Computer Decision Support	Reduction in broad-spectrum antimicrobials to improve local resistance patterns	Any	NR	NR	Trend analysis: use of antimicrobials to cover Gram-negative bacteria was stable during study period Observed improved susceptibility of Gram-negative isolates
Pulcini 2011[27]	ITS	Protocol	Improve quality of prescriptions	Any	*Day 7* Pre-intervention: 3/62 (5%) Post: 2/52 (4%) p=0.18	Pre-intervention: 13.8 days Post: 13.8 days	*Quality of therapy (day 3)* Pre-intervention: Appropriate 27/62 (43) Inappropriate 21/62 (34) Unnecessary 14/62 (23) Post- Appropriate 20/52 (38) Inappropriate 19/52 (37) Unnecessary 13/52 (25) p=ns

DDD = defined daily dose; pd = patient days; NR = not reported; ns = not significant; RCT = randomized controlled trial; CCT = controlled clinical trial; ITS = interrupted time series; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Suspected Patient Condition

Our review included six studies of inpatients with CAP and other respiratory tract infections,[15,16,21,25,26,62] one of patients with either lung or abdominal infections,[24] and one of patients with bloodstream infections.[12] The remaining studies either included patients with any type of infection or did not report the infection site.

The ITS study of patients with bloodstream infections found mean antimicrobial consumption was significantly reduced following a stewardship intervention.[12] The intervention restricted authorization allowing only ICU consultants to prescribe antimicrobials. ICU consultants or infectious diseases specialists were available for bedside consultation five days per week and provided 24 hour telephone support seven days per week. No other outcomes of interest were reported in this study.

A summary of the seven studies enrolling patients with respiratory infections is presented in Table 17. The findings for patients with respiratory infections did not differ from the overall findings of this review.

Mortality was reported in six studies with five finding no difference in mortality either between intervention and control groups or before and after implementation of the intervention.[15,16,24-26] The exception was a CBA study that reported increased mortality in the intervention cohort compared with the control post-intervention cohort.[21]

For length of stay, an RCT of a protocol for reducing duration of IV therapy and length of stay[25] and a CBA study of guidelines for improving appropriate timing and duration of treatment[21] reported significant reductions in the intervention groups.

Six of the studies reported antimicrobial prescribing outcomes. Five reported on appropriate antimicrobial prescribing. Three studies found improved appropriate initial prescribing in the intervention group or following the intervention[15,16,62] while one found no difference.[21] Two studies reported on treatment within four or eight hours of presentation with both finding improvements in this outcome associated with the intervention.[16,21] Two RCTs reported on treatment duration with one reporting shorter duration of IV therapy in the intervention group[25] and one finding no difference between intervention and control.[26]

Table 17. Studies Enrolling Patients with Respiratory Infections (CAP, VAP, HAP, HCAP)

Author, year	Study design	Intervention type	Goal	Mortality	Length of Stay	Antimicrobial Prescribing
Schouten 2007[16]	CCT	Guideline with Feedback	Increase quality of antimicrobial use	*Intervention* CAP patients 20/318 (7.2) p=0.58 COPD/CB patients 10/269 (4.3) p=0.35 *Control* CAP patients 15/207(8.7) COPD/CB patients 5/237 (2.6)	*Intervention* CAP patients 8.0 days (median) p=0.47 COPD/CB patients 11.5 days (median) p=0.89 *Control* CAP patients 10.0 days (median) COPD/CB patients 11.4 days (median)	*Empirical regimen - correct indication, compliant with guidelines* OR=2.63 (95% CI 1.57 to 4.42) *Initiation of antimicrobial within 4 hrs of presentation, CAP patients* OR=3.59 (95% CI 1.02 to 12.6)
Schnoor 2010[15]	RCT	Guideline with Feedback	Improve quality of care	*30 day overall mortality* Intervention: 3.6% Control: 3.8% p=ns	Intervention: 10.0 days Control: 10.9 days p=ns	Adj odds of inpatients receiving appropriate treatment – intervention relative to control (OR=1.8, 95% CI 1.1 to 2.8)
Mangino 2011[62]	ITS	Guideline without Feedback	Improve adherence to clinical pathway	NR	NR	*Compliant empiric therapy* Pre-intervention: 79/257 (30.7%) Post: 66/151 (43.7%) p=0.01
Capelast-egui 2004[21]	CBA	Guideline without Feedback	Improve process of care and final outcome	*30 day* Adj OR=1.8 (1.1 to 2.9) versus control (cohort 2) group	Significant reductions in adjusted mean duration - intervention vs. all other groups p<0.001	*Appropriate use* Adj OR=1.1 (0.7 to 1.7) versus control (cohort 2) group *Antimicrobials within 8 hrs of presentation* Adj OR 2.3 (1.7 to 3.0) versus control (cohort 2) group

Author, year	Study design	Intervention type	Goal	Mortality	Length of Stay	Antimicrobial Prescribing
Nowak 2012[24]	ITS	Computerized Decision Support	Effectiveness of data mining program	*Pre* 45/1163 (4.0%) *Post* 38/1023 (3.7%) p>0.05	*Pre* 5.9 (4.9) days *Post* 5.5 (7.8) days p>0.05	NR
Carratalà 2012[25]	RCT	Protocol	Reduce duration of IV therapy and length of stay	*Intervention* 4/200 (2.0%) *Control* 2/201 (1.0%) Difference 1.0 (95% CI -1.4 to 3.4%)	*Intervention* 3.9 days (median) *Control* 6.0 days (median) Difference -2.1 (95% CI −2.7 to -1.7)	*Duration of IV treatment* Intervention 2.0 days (median) Control 4.0 days (median) Difference -2.0 (95% CI −2.0 to -1.0)
Oosterheert 2006[26]	RCT	Protocol	Effectiveness of early switch from IV to oral therapy	*Intervention* 5/132 (4%) *Control* 8/133 (6%) Difference 2% (95% CI −3% to 8%)	*Intervention* 9.6 (5.0) days *Control* 11.5 (4.9) days Difference 1.9 (95% CI 0.6 to 3.2)	*Overall antimicrobial treatment* Intervention 10.1 days Control 9.3 days p=ns

DDD = defined daily dose; pd = patient days; NR = not reported; ns = not significant; IV = intravenous; RCT = randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after; ITS = interrupted time series; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

KEY QUESTION #4. What are the harms of inpatient antimicrobial stewardship programs?

Key Findings

- Only two studies reported *possible* harms associated with antimicrobial stewardship programs. Other "harms" could include significant increases in adverse patient, microbial, or prescribing outcomes due to the ASP intervention although this was rarely reported.

Of the studies included in our review, harms were rarely reported. Only two studies reported *possible* harms associated with antimicrobial stewardship programs. Both were studies with audit and feedback as the primary intervention. One study that aimed to alter prescribing *anecdotally* suggested that two patients may have been inappropriately switched to a narrower-spectrum antimicrobial. A chart review at one week after acceptance of the ASP recommendation revealed that the patients' condition had deteriorated. When subsequently switched back to broad-spectrum antimicrobials, the patients improved.[60] However, no evidence was presented that the intervention led to inappropriate discontinuation of antimicrobials. A study that aimed to reduce unnecessary treatment reported that the intervention was terminated.[7] One reason provided was that prescribing physicians were not happy with restrictions although a formal survey was not reported. Other "harms" could include statistically significant adverse increases in patient, microbial, or prescribing outcomes due to the ASP intervention as reported for Key Questions #1. Low quality evidence across ASP programs showed that this rarely occurred.

KEY QUESTION #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

Key Findings

- ***Barriers to Implementation:*** Four studies described implementation barriers; two included provider surveys. Suggestions for improving adherence to ASPs included involvement of stakeholders and opinion leaders in guideline and program development, addition of quality improvement cycles, understanding the prescribing culture, and collaboration between physicians and pharmacists. Eight studies provided data on resources required to implement an ASP program. Included were composition of a antimicrobial stewardship team, physician and pharmacist workloads, and equipment costs.
- ***Sustainability:*** Most reviewed studies were one year or less and did not comment on sustainability.
- ***Scalability:*** None of the studies included in our review reported on scalability.

Barriers to Implementation

Provider Adherence or Acceptance

Our review included a study of implementation of guidelines to increase the quality of antimicrobial use for patients with lower respiratory tract infection.[16] The authors described a qualitative study of barriers to appropriate antimicrobial use conducted prior to the intervention study.[70] In the qualitative study, interviews were conducted with 11 residents, 6 consultants, 2 microbiologists, 2 emergency department nurses, 2 pulmonary ward nurses, and 1 clinical pharmacist. The interview questions were open-ended and focused on a clinical case (a patient with CAP) with questions about barriers to appropriate use of antimicrobials as outlined in six key recommendations for care: 1) prescription of a guideline-adherent empirical antimicrobial regimen, 2) timely initiation of therapy, 3) adjustment of regimen to accommodate decreased renal function, 4) switching from IV to oral therapy based on existing criteria, 5) streamlining empirical therapy into pathogen-directed therapy based on culture results, and 6) culturing blood samples, and culturing and Gram-staining sputum samples. Responses identified barriers to adherence related to *knowledge* (lack of familiarity or experience, lack of awareness or insight), *attitude* (lack of agreement with the guideline including applicability to patient, lack of confidence in guideline developer, and disagreement about interpretation of the evidence; lack of outcome expectancy; inertia of existing practice), and *external barriers* (guideline unclear; presence of conflicting guidelines; social pressure; lack of communication between professionals; organizational constraints such as lack of time or resources, antimicrobials not present, or lack of provider continuity on wards). The authors recommended development of evidence-based guidelines with involvement from representatives of all relevant clinical specialties, journal-club sessions for discussion of controversies in the literature, and feedback/tutorial sessions.[16] In the intervention study, they included a key lecture by an opinion leader, feedback at the hospital level, and consensus critical-care pathways. A second phase allowed for adjustment of intervention components based on individual hospital baseline results.[16]

Schnoor reported low provider attendance at educational sessions.[15] The study involved multiple hospitals and multiple sentinel practices (the total number of providers was not reported) but only 12 practitioners attended the first educational session and only 4 attended the second session. The authors suggested that adding audits or a continuous quality improvement cycle to the intervention might increase physician compliance but noted high cost as a barrier. A questionnaire sent to study physicians following the implementation phase found that physicians viewed guidelines as "helpful to improve the quality of care" (n=13), as "good educational tools" (n=10), and as a "helpful guide in decision making" (n=16) with fewer describing guidelines as "cookbook" (n=4) or "oversimplified" (n=5). The most commonly reported reason for non-adherence to guidelines was "related to the patient." It was also reported that "inadequate care at home" led to low-risk patients being hospitalized. Additional reasons for non-adherence were failure of the symptom assessment index included in the guideline to include underlying diseases, dissenting opinions of patients, and difficulty changing one's behavior. When the 17 "sentinel practices" involved in the study were asked which version of the guideline they used "frequently" for supporting treatment decisions, 3 reported using an interactive electronic (compact disk) version of the guideline, 7 reported using the guideline posters, and 15 reported using the short printed version of the guideline. The response rate for the questionnaire was not reported.

The authors of an audit and feedback study suggested several factors that may have contributed to the successful implementation of their stewardship program.[8] Understanding the local prescribing culture, providing a working environment conducive to prudent prescribing, obtaining support from management and buy-in from providers, and offering a non-restrictive policy that allowed for prescriber autonomy were considered key elements of the program.

A study of a data-mining program to identify cases and make recommendations concluded that the success of the stewardship program was due to collaboration between the pharmacist and the infectious disease physician.[24] Earlier attempts (using only passive interventions such as formulary restriction or guidelines) were not successful in reducing costs or improving rates of infection.

Several studies, primarily of audit and feedback interventions, reported acceptance of the intervention recommendations.[1,3,6,8,24,57] Teo reported an overall acceptance rate of 70%.[8] Recommendations were made by the antimicrobial stewardship team (infectious disease physician, microbiologist, clinical pharmacists). The most frequent recommendations were for discontinuation of therapy or narrowing or broadening therapy. Another study reported an acceptance rate of 74%.[57] Recommendations came from the stewardship team (stewardship pharmacist and infectious disease registrar and/or physician). Modifications to prescriptions for restricted broad-spectrum antimicrobials were most common followed by recommendations to discontinue therapy. In the study by Elligsen, an antimicrobial stewardship pharmacist, in consultation with a senior infectious disease pharmacist, reviewed the records of all ICU patients prescribed one of the targeted broad-spectrum antimicrobials. If it appeared that a modification of therapy was appropriate, an infectious disease physician reviewed the case. The acceptance rate was 82%.[6] The most frequent recommendations regarded discontinuation of therapy and change to an alternate antimicrobial. Lesprit reported that over 90% of recommendations made by a single infectious disease physician were adopted by the treating physicians.[1] The most

frequent modifications recommended were switching from IV to oral therapy, de-escalation of therapy, shortening duration of therapy, and stopping therapy. In another study, all prescriptions for levofloxacin, vancomycin, and carbapenems were reviewed by an infectious disease physician. Approximately 50% of attending physicians complied with recommendations to discontinue or modify the initial prescription. Compliance varied somewhat for the three targeted antimicrobials: levofloxacin 40%, carbapenems 70%, and vancomycin 88%.[3]

One study of computerized decision support also reported acceptance. Following implementation of a stewardship program that involved computer-generated reports and recommendations which were subsequently reviewed by pharmacists and infectious disease physicians, it was reported that 80% of recommendations were accepted by prescribers within 48 hours.[24] Recommendations most frequently related to appropriateness of empiric therapy, de-escalation of therapy once laboratory results were available, discontinuation of therapy if infection was not clearly documented, and changes to duration of therapy.

Resources

Several studies reported on resources required. For an audit and feedback program in which an antimicrobial monitoring team provided real-time review of orders for restricted antimicrobials with intervention as needed, the team included an infectious diseases physician at 50% effort, a clinical pharmacist with infectious diseases training at 80% effort, and a data analyst at 5% effort. Direction of the stewardship program was considered part of the infection control program and no additional resources were required. The program was implemented at a single large (admissions per year ranging from over 28,000 the first year of the program to over 38,000 in the final year), tertiary care teaching medical center.[7]

An audit and feedback program in the medical and surgical wards (650 beds) of a hospital involved post-prescription review by one infectious disease physician followed by verbal or written communication with the prescribing physician, if needed.[1] For prescriptions not requiring further intervention, the median time for review was 6 minutes. For prescription requiring screening, data review, and interaction with the prescribing physician, the median time for review was 15 minutes (with a range of 10 to 60 minutes). The mean daily time required was 2.5 hours. Over a 24-week period, the study enrolled 376 patients in the intervention group. The estimated cost of the intervention (including ward visits by the infectious disease physician) was €2,147.

In another audit and feedback program, it was estimated that the weekly workload for the infectious disease physician was approximately three hours.[9] The infectious disease physician visited the 10-bed ICU three times per week to provide feedback to prescribers and conducted approximately 2 training sessions per month. A bacteriologist spent approximately one hour per week on stewardship, meeting five days per week with the intensivists to discuss laboratory results.

An audit and feedback program at a single 430-bed hospital and involving week-day antimicrobial stewardship rounds (a stewardship pharmacist and an infectious disease specialist) was reported to require a full-time pharmacist and 8 to 10 hours per week of infectious disease physician time.[57] The program was implemented in both the ICU and the general wards.

Staffing for an antimicrobial stewardship program was reported in a study of guidelines implemented with feedback.[18] The study was conducted at one hospital. The Antimicrobial

Management Team included one full- and one part-time microbiology consultant, three infection control nurses, and one antimicrobial pharmacist who was on-site and did ward rounds three days per week. After the introduction of a narrow-spectrum antimicrobial policy, the antimicrobial pharmacist was on-site and performing ward rounds five days per week (week days only). The change was made to promote adherence to the revised guideline.

Another study described the time required for different phases of their intervention.[62] The authors noted the importance of leaders to champion the project, active involvement of stakeholders, and benchmarking. Designated as a performance improvement project, the intervention included development of a consensus pathway (based on existing national-level guidelines), identification of quality performance indicators for assessing guideline compliance, and creation of a form for data collection and a repository for data storage. This phase required three months. Each of the four participating academic care centers then customized the pathway based on local epidemiology and hospital formulary and developed educational tools to facilitate implementation. This phase required approximately six months. Educational efforts included slide sets for presentations at grand rounds and other lectures and printed materials. With monthly rotations by house staff, educational programs were needed throughout the implementation.

The cost of purchasing commercially available computer software that could link susceptibility test results to pharmacy data and identify patients receiving potentially inappropriate therapy was reviewed by Barenfanger.[23] It was estimated that implementation of the intervention would save $2,932,000 at the study hospital (a 450-bed community teaching hospital). The list price of the software was $44,500 so even after the software purchase, the savings were substantial.

Nowak reported that the data-mining software used for the antimicrobial stewardship intervention was already being used for other clinical needs.[24] Implementation costs, therefore, were limited to the time required to modify the software to generate the reports for stewardship. It was also noted that existing pharmacists were able to perform the stewardship components that were already in place before the software was introduced (i.e., conversion from IV to oral therapy and dosage adjustments) and infectious disease physicians were able to review cases and write recommendations. A new antimicrobial stewardship pharmacist was added to review the computer generated reports and augment them with additional information from the medical record. It was estimated that the antimicrobial stewardship pharmacist spent 3 to 4 hours per day compiling the reports and the infectious disease physician spent 30 to 60 minutes per day reviewing them.

Sustainability

One study reported on sustainability. An audit and feedback antimicrobial stewardship program was put in place in 2001 and continued to 2008.[7] Other components of the program were preauthorization for use of certain antimicrobial agents and guidelines for ordering. Defined daily dose data were reported for the final five years of the program and for two years following program termination. The DDD/1000 patient-days increased by 5.2% (p=0.014) during the 2 years after the program. No change was noted for length of stay, mortality, or readmissions. The drug-related group case mix index was also unchanged. It was noted that the program was discontinued so that the funding could be used to provide additional infectious diseases

physicians for consultation. There was also some dissatisfaction with the requirement for preauthorization. Given that costs increased after the program while patient outcomes (i.e., mortality, length of stay, readmission) were unchanged, the stewardship program was modified and restarted.

Scalability

None of the studies included in our review reported on scalability. Most were conducted in a single hospital or included additional hospitals as comparator sites. Within a single hospital, many studies were conducted in either the ICU or general medical wards. No study that implemented a stewardship program in multiple sites (i.e., medical and surgical wards) provided information about factors associated with implementing the program in different wards.

SUMMARY AND DISCUSSION

SUMMARY OF FINDINGS BY KEY QUESTION

Key Question #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

a. **Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)**
b. **Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?**

Our systematic review of studies evaluating antimicrobial stewardship, found multiple studies that provide low level evidence that ASP programs may be associated with an improvement in antimicrobial prescribing practices and costs without negative effects on patient outcomes such as mortality, length of hospital stay, CDI, and readmissions. We caution readers in over-interpretation of findings. Despite identifying numerous studies and additional systematic reviews, the quality of the available evidence is low, prescribing improvements often not sustained, and generalizability to settings, patients or health conditions beyond those specifically studied, difficult. Few studies were randomized controlled trials. The ability to control for secular trends or other confounding variables was limited. Thus most of our findings indicate "associations" of outcomes with interventions rather than cause and effect.

Among the recent studies, the greatest body of evidence of effectiveness is for decreasing inappropriate antimicrobial use or increasing appropriate antimicrobial use, especially for prospective audit and feedback interventions. There is also some evidence of the effectiveness of audit and feedback interventions on decreasing duration of antimicrobial use. There is limited evidence of effectiveness based on antimicrobial selection or timing.

New findings included in our report are generally in agreement to conclusions from a recently updated Cochrane review that characterized interventions in a slightly different fashion.[53] Although this review included 89 studies, reported findings are based on few studies with only one prescribing outcome captured per study. As noted previously, we have concerns about selective outcome reporting bias and selective analysis reporting bias in the review.

Key Question #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Six studies provided information on intervention components associated with effective antimicrobial stewardship. Key components identified included: consistent and persistent effort from qualified personnel, effective communication skills, support from electronic medical records or computerized decision support systems.

Key Question #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

None of the 35 studies identified in our search for recent evidence were conducted at VA medical centers. Nearly all were conducted in university-affiliated teaching hospitals. However, the recent Cochrane review included nine studies from VA hospitals noting improvement in CDI (k=2) and microbial outcomes (k=3) with mixed results for prescribing outcomes (k=3) and no change in mortality (k=1). Nine studies were conducted in ICUs and findings were similar to the overall findings.

Lung infections were the most frequently reported specific patient condition (seven studies). Results appeared qualitatively similar in these studies compared with the overall findings.

Key Question #4. What are the harms of inpatient antimicrobial stewardship programs?

Only two studies included in this review reported *possible* harms associated with antimicrobial stewardship programs and both provided only anecdotal evidence. Other "harms" could include significant increases in adverse patient, microbial, or prescribing outcomes due to the ASP intervention although few studies reported these outcomes.

Key Question #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

Four of the thirty-five studies identified for our review described barriers to implementation. Suggestions for improving adherence to ASPs included involvement of stakeholders and opinion leaders in guideline and program development, addition of quality improvement cycles, understanding the prescribing culture, and collaboration between physicians and pharmacists. We identified one study that addressed sustainability finding that antimicrobial costs continued to decrease over the seven years the program was in place while costs increased during the two years after program termination. A similar trend was observed for defined daily doses per 1000 patient-days. None of the studies included in our review reported on scalability.

LIMITATIONS

We noted wide variation in populations enrolled, specific interventions utilized (even in our broad program categorization), country, hospital and unit setting and conditions and objectives assessed. There was no replication of findings from one study to another and individual studies were typically relatively small in size and short in follow-up duration. Furthermore, the studies were done in many different nations with disparate health systems, hospital organizations, staffing patterns, methods of paying for antimicrobials and for healthcare in general, formularies, systems of care, etc. Because of differences across studies and no study directly attempting to replicate previous findings we caution against inferring that any outcome variation was due to hospital setting or unit or whether effectiveness varies by suspected patient condition.

Few eligible studies were high methodological quality (randomized, controlled, double blinded trial). It would be difficult to blind investigators or participants in a trial of antimicrobial stewardship. Nearly all the studies were done in single centers and there were substantial controlled and uncontrolled influences on outcomes. The typical study was done by infectious disease pharmacists or infectious disease physicians who tried to influence antimicrobial therapy and performed formative evaluation to assess the impact of their intervention(s). Studies were often done within an existing system with available resources and measured conveniently available variables. Studies like this are more practical than large, well powered, externally funded randomized trials, but the results are also less reliable. Indeed, we are unaware of funding opportunities that are likely to support high quality, large, randomized trials of antimicrobial stewardship.

Since few studies of antimicrobial stewardship are randomized controlled trials, studies are unlikely to be entered in a registry before they are done. There is a substantial risk of reporting and publication bias—that outcomes showing a benefit of some kind are more likely to be described and studies with positive outcomes more likely to be published than studies showing no benefit or harms.

Furthermore, studies of antimicrobial stewardship with the incidence of CDI as an outcome are often initiated in response to an increase in or relatively high incidence of CDI. Many report a decrease in CDI incidence after an intervention is introduced. Unless the study is a randomized controlled trial, it is difficult to know if the decreased incidence reflects an effect of the intervention, termination of an outbreak, or regression to the mean.

Effective interventions may have been effective because of uncharacterized or unreported characteristics of the setting. These interventions may not be effective in different settings.

A number of studies present aggregate data on antimicrobial use from the entire study population rather than data on individual cases for which the intervention was applied. There are advantages associated with use of aggregate data in terms of the total hospital antimicrobial costs, but use of aggregate data does not adequately account for changes in use for cases with interventions or other defined patient groups.

DISCUSSION

Most studies demonstrated an effect on at least one of the studied outcomes, and in nearly all these cases the effect favored the stewardship intervention. Most of the significant findings involved secondary prescribing, microbial, or cost outcomes rather than a significant change in the patient-centered outcomes we considered. Studies were not designed to adequately assess impact on mortality or other clinical outcomes. It is reassuring however, that reported improvements in prescribing and costs were not accompanied by deleterious effects on patient outcomes of mortality, length of stay, hospital readmission, and CDI. Furthermore, because a growing body of literature supports the assertion that antimicrobial use contributes to antimicrobial resistance, costs, adverse events, and other important clinical outcomes, the finding that multiple stewardship strategies can decrease antimicrobial use is encouraging. Thus evidence provided in this review suggests that there are several strategies available to clinicians that can decrease antimicrobial prescribing and limit costs, without any apparent harms.

One of the goals of stewardship is to reduce the amount of inappropriate antimicrobial use, which estimates place at 30-60% of all antimicrobial use. Only a handful of the included studies specified that the reductions in antimicrobial use came through reducing inappropriate use; possibly, some of the reductions in use involved appropriately prescribed antimicrobials. However, since most studies involved providing guidance, feedback, or opportunities to re-evaluate antimicrobial use, versus outright cessation of such use, it seems unlikely that necessary antimicrobials were discontinued at an increased rate when compared with usual clinical care. It is also possible that as use of targeted antimicrobials decreased, physicians may have used other drugs instead, a phenomenon referred to as "squeezing the balloon."[71] Future studies of antimicrobial stewardship should attempt to systematically assess changes in use of all antimicrobials, since cessation of potentially life-saving antimicrobials is one of the main hypothetical harms of antimicrobial stewardship.

Unfortunately there are few data on sustainability, scalability or specific components of interventions most likely to be effective. Suggestions for improving adherence to ASPs included involvement of stakeholders and opinion leaders in guideline and program development, addition of quality improvement cycles, understanding the prescribing culture, and collaboration between physicians and pharmacists. Studies that described ASPs noted that the composition of antimicrobial stewardship teams varied but often included a physician, pharmacist, and microbiologist. Most reviewed studies were one year or less and did not comment on sustainability. The Cochrane review found that effects were often not sustained beyond six months but with limited data on long-term effects the authors recommended future studies assess effects at one year or longer.[53] None of the studies included in our review reported on scalability.

No study directly compared one intervention with another. This is unsatisfying in one sense, in that policy-makers looking for the most effective strategy for antimicrobial stewardship are left without an answer. However, the converse of this is that multiple strategies have been associated with reductions in antimicrobial use and costs, without any signal of associated harm. Accordingly, if antimicrobial stewardship is something that an organization decides to undertake, the decision as to which strategy to adopt can be tailored to fit the available resources. Given our previous concerns about the quality and applicability of data we urge that implementation be prospectively reevaluated based on ongoing evaluation of effectiveness, harms, costs and sustainability.

Although the recent Cochrane review[53] included nine studies conducted in VA hospitals, we found no recent studies meeting eligibility criteria that were conducted in VA healthcare settings. One recently completed VA study that did not meet our inclusion criteria was a survey of 152 VA Medical Centers.[72] Responses were received from 140 centers (response rate of 92%) and 130 of those had inpatient services. Forty-nine facilities with inpatient services (38%) reported that they had an antimicrobial stewardship team. Of those with teams, 45 of 49 (92%) had involvement of infectious disease physicians, 39 of 49 (80%) had involvement of pharmacists, and 37 of 49 (76%) had involvement of a clinical microbiology laboratory director. Fifty-five percent interfaced with the infection control committee, 31% interfaced with information technology support staff, and 29% interfaced with hospital administration. In addition, results should soon be available from a recently completed controlled before and after trial at two VA hospitals involving an audit and feedback intervention for increasing guideline concordant care for patients with catheter-associated urinary tract infection.[73]

Most of the published studies come from urban academic medical centers. This may reflect where the preponderance of stewardship efforts take place or, more likely, it may reflect where people involved in stewardship efforts have the resources and time to evaluate their interventions and write and submit manuscripts. As a result, it is difficult to draw conclusions about whether effectiveness varies by hospital setting.

We found substantial variability of the hospital settings of the published stewardship interventions, from entire hospitals, to specific wards, to ICUs. No article compared efforts in two or more settings. There were nine articles on interventions in ICUs and six were effective in some way. ICUs are typically smaller units with a relatively small group of prescribers, and ICUs often operate with protocols for common, high stakes conditions. Antimicrobial use is common, and often empirical. Antimicrobial resistance is common in patients in ICUs. Without precise comparative data, we are left with the impression that an intervention targeting antimicrobial use in a hospital's ICUs might be a logical place to start and might be more likely to yield valuable results than interventions in other settings or hospital wide.

No study was designed specifically to identify harms of stewardship interventions, and few studies reported on harms. Studies not meeting eligibility criteria have reported on harms of stewardship interventions. Nicks et al. reported on a survey of emergency room physician level of understanding of the Center for Medicare and Medicaid Services (CMS) guidelines for community-acquired pneumonia.[74] Many hospitals track adherence to the core measures related to the CMS guidelines. More than half of the respondents (55%; 95% CI = 47% to 70%) reported prescribing antimicrobials to patients they did not believe had pneumonia in an effort to comply with the CMS guidelines, and 42% (95% CI = 34% to 50%) of these stated that they did so more than three times per month. Only 40% (95% CI = 32% to 48%) of respondents indicated a belief that the guidelines improve patient care.

Some stewardship interventions have been perceived by providers as barriers to efficient workflow, however, we did not find high quality clinical trials documenting barriers to implementation of stewardship programs. A number of articles discussed anecdotal experience with barriers. The major types of barriers were cost of the intervention, provider resistance, and lack of adequate information systems to support stewardship efforts or evaluation of the efforts. One study that did not meet eligibility criteria reported evidence that providers alter their prescribing behavior to circumvent restrictions.[75] The intervention was a requirement for prior approval of certain antimicrobial agents that was in place between 8am and 10pm. The authors observed a disproportionate number of orders for restricted drugs between 10pm and 11pm which suggested that providers wanting to order these drugs and not obtain prior approval simply waited until after the restriction was in place to order them.

RECOMMENDATIONS FOR FUTURE RESEARCH

A typical antimicrobial course is complex, involving several decisions over hours to days or even weeks. There are many clinical, imaging, and laboratory inputs to monitor, and courses are often given to complex, heterogeneous patients. These characteristics make it difficult to conduct well-designed trials to accurately assess most outcomes.

Direct comparisons of different stewardship strategies have inherent appeal, but since there are multiple such strategies, larger comparative-effectiveness studies may need to wait until further research winnows the field down to a more manageable number of strategies for such studies. It is not easy to judge whether interventions in which authorship, review, and dissemination of guidelines occurred on a local level and/or interventions which accommodated local epidemiology were associated with better outcomes than other studies but these factors are worth consideration for future studies.

Hospitals and healthcare systems in the United States and many other countries have recognized the need for antimicrobial stewardship. The Veterans Health Administration, the Joint Committee on Accreditation, and many other organizations now expect that hospitals will take steps to increase the quality of, and diminish unnecessary, antimicrobial use. Several strategies for antimicrobial use have been proposed,[49] but there is little high quality evidence on comparative effectiveness. Future research is sorely needed to clarify the benefits, potential harms, barriers, sustainability, and costs of antimicrobial stewardship programs. Generous funding for comparative effectiveness trials would be ideal. Large healthcare organizations should recognize that units within them will likely be conducting one or more stewardship activities. These organizations should strongly consider organizing these activities in a way that provides useful information on comparative effectiveness. Healthcare payers should recognize that large amounts of money will be spent on antimicrobial stewardship and that these expenditures can be more efficiently utilized if comparative research is done to identify the most effective approaches and strategies. Given that it may be hard to avoid cross-over or contamination in studies randomized at the subject level, cluster RCTs may be the most feasible way to provide high-quality evidence. Large healthcare organizations could play a role since they could provide the multiple sites—but shared data—that would make such a study feasible.

CLINICAL CONSIDERATIONS

Until high quality comparative effectiveness research becomes available, hospitals and healthcare systems will feel pressure to do something. There is currently no definitive blueprint for how to improve antimicrobial use most effectively. However, the literature on stewardship and implementation science provides a tentative roadmap that will allow hospitals to move forward. The following reflects our synthesis of this literature.

The first step should be to use existing information or gather new information to determine where antimicrobial use might be less than ideal or is in need of improvement. Data on antimicrobial use by clinical unit, type of patients, provider groups, and by individual providers should be gathered and analyzed locally wherever possible. Usage should be compared with available national guidelines or benchmarks.[76] For example, a hospital might want to analyze antimicrobial therapy for a common, important disease like community acquired pneumonia to determine how often antimicrobial therapy is consistent with guidelines,[77] how often therapy is timely, how often cases with syndromes that are not likely to represent community acquired pneumonia are in fact treated as if they were, how often therapy is adjusted appropriately as clinical circumstances evolve, and how often the route and duration of therapy fit with guidelines. If there is substantial room for improvement, an intervention designed to effect that improvement would then be designed.

Hospitals and healthcare systems typically have many of the components necessary for many stewardship activities. Among these are infection prevention programs, microbiology laboratories, pharmacy services, infectious disease physicians, electronic medical record systems, continuous improvement programs, and staff or trainee education and certification programs. All of these can contribute to stewardship activities, and all should be part of planning and implementation efforts to identify areas of improvement and design strategies to improve use. It is important to inform hospital and healthcare system leaders of the need for stewardship based on local conditions and anticipated benefits and seek their support in the form of policies, procedures, and financial support.

Formative evaluation should be integral to any stewardship activity. The formative evaluation component can be built upon the information that is gathered to identify the need for the intervention in the first place. Formative evaluation will inform the participants and hospital administrators whether the program is effective. If not, the program can be strengthened, or another approach can be taken. If an intervention is effective, formative evaluation can help determine if the intervention should be continued. If a problem with antimicrobial use has been solved, it may be possible to redirect efforts and resources to solve another problem. Antimicrobial therapy is a continuously evolving area of medicine. New drugs are developed and marketed, antimicrobial susceptibilities change over time, and disease patterns change. Change and local variation are constants in antimicrobial therapy, and formative evaluation can help an organization ensure that it is ahead of the curve rather than behind it.

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APPENDIX A. SEARCH STRATEGY

Database: Ovid MEDLINE(R

1 antibiot$.mp. or exp antibiotics/
2 antimicrob$.mp.
3 exp Anti-Bacterial Agents/
4 exp Anti-Infective Agents, Urinary/
5 exp Cross Infection/
6 exp Community-Acquired Infections/
7 exp Respiratory Tract Infections/
8 exp Wound Infection/
9 exp Catheter-Related Infections/
10 exp Vancomycin Resistance/ or exp Vancomycin/ or vancomycin.mp.
11 aminoglycosides.mp. or exp Aminoglycosides/
12 fluoroquinolones.mp. or exp Fluoroquinolones/
13 broad spectrum antibiotics.mp.
14 carbapenems.mp. or exp Carbapenems/
15 exp Cephalosporins/ or broad spectrum cephalosporins.mp.
16 or/1-15
17 exp Education/ or education.mp.
18 information campaign.mp.
19 audit.mp.
20 feedback.mp. or exp Feedback/
21 dissemination.mp. or exp Information Dissemination/
22 provider reminders.mp.
23 computerized medical records.mp. or exp Medical Records Systems, Computerized/
24 exp Physician Incentive Plans/ or financial incentives.mp.
25 discharge planning.mp.
26 guideline implementation.mp.
27 guideline adherence.mp. or exp Guideline Adherence/
28 exp Quality Assurance, Health Care/ or quality assurance.mp.
29 program evaluation.mp. or exp Program Evaluation/
30 exp Practice Guideline/
31 exp Physician's Practice Patterns/
32 exp Drug Prescriptions/
33 exp Drug Utilization/
34 or/17-33
35 randomized controlled trial.mp. or exp Randomized Controlled Trial/
36 controlled clinical trial.mp. or exp Controlled Clinical Trial/
37 intervention study.mp. or exp Intervention Studies/
38 Comparative Study/
39 experiment.mp.
40 time series.mp.
41 pre-post test.mp.

42 (randomized controlled trial or controlled clinical trial).pt.
43 (randomized controlled trials or random allocation or clinical trial or double blind method or single blind method).sh.
44 exp clinical trial/
45 (clin$ adj25 trial$).ti,ab.
46 ((singl$ or doubl$ or trebl$ or trip$) adj25 (blind$ or mask$)).ti,ab.
47 (research design or placebos).sh.
48 (placebo$ or random$).ti,ab.
49 exp Double-Blind Method/
50 exp cohort studies/ or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or comparative study/ or follow-up studies/ or prospective studies/ or cohort.mp. or compared.mp. or multivariate.mp. (4148897)
51 ("time series" or pre-post or "Before and after" or intervention).tw.
52 or/35-51
53 16 and 34 and 52
54 limit 53 to english language
55 limit 54 to humans
56 limit 55 to yr="2000 -Current"
57 (influenza$ or antimalar$ or malaria$ or prophylax$).mp.
58 56 not 57

APPENDIX B. RISK OF BIAS CRITERIA*

I. RISK OF BIAS FOR STUDIES WITH A SEPARATE CONTROL GROUP

Randomised controlled trials (RCTs)
Non-randomised contolled trials (NRCTs)
Controlled before-after (CBA) studies

Was the allocation sequence adequately generated?
Score "Low risk" if a random component in the sequence generation process is described (eg Referring to a random number table). Score "High risk" when a nonrandom method is used (eg performed by date of admission). NRCTs and CBA studies should be scored "High risk". Score "Unclear risk" if not specified in the paper.

Was the allocation adequately concealed?
Score "Low risk" if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes were used. CBA studies should be scored "High risk". Score "Unclear risk" if not specified in the paper.

Were baseline outcome measurements similar?[1,2]
Score "Low risk" if performance or patient outcomes were measured prior to the intervention, and no important differences were present across study groups. In RCTs, score "Low risk" if imbalanced but appropriate adjusted analysis was performed (e.g. Analysis of covariance). Score "High risk" if important differences were present and not adjusted for in analysis. If RCTs have no baseline measure of outcome, score "Unclear risk".

Were baseline characteristics similar?
Score "Low risk" if baseline characteristics of the study and control providers are reported and similar. Score "Unclear risk" if it is not clear in the paper (e.g. characteristics are mentioned in text but no data were presented). Score "High risk" if there is no report of characteristics in text or tables or if there are differences between control and intervention providers. Note that in some cases imbalance in patient characteristics may be due to recruitment bias whereby the provider was responsible for recruiting patients into the trial.

Were incomplete outcome data adequately addressed?[1]
Score "Low risk" if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score "High risk" if missing outcome data was likely to bias the results. Score "Unclear risk" if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

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* Source:
http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/Suggested%20risk%20of%20bias%20criteria%20for%20EPOC%20reviews.pdf. Accessed 5 June 2013.

[1] If some primary outcomes were imbalanced at baseline, assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.

[2] If "Unclear risk" or "High risk", but there is sufficient data in the paper to do an adjusted analysis (e.g. Baseline adjustment analysis or Intention to treat analysis) the criteria should be re scored as "Low risk".

Was knowledge of the allocated interventions adequately prevented during the study? [1]
Score "Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.

Was the study adequately protected against contamination?
Score "Low risk" if allocation was by community, institution or practice and it is unlikely that the control group received the intervention. Score "High risk" if it is likely that the control group received the intervention (e.g. if patients rather than professionals were randomised). Score "Unclear risk" if professionals were allocated within a clinic or practice and it is possible that communication between intervention and control professionals could have occurred (e.g. physicians within practices were allocated to intervention or control)

Was the study free from selective outcome reporting?
Score "Low risk" if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score "High risk" if some important outcomes are subsequently omitted from the results. Score "Unclear risk" if not specified in the paper.

Was the study free from other risks of bias?
Score "Low risk" if there is no evidence of other risk of biases

II. RISK OF BIAS FOR INTERRUPTED TIME SERIES (ITS) STUDIES
Note: If the ITS study has ignored secular (trend) changes and performed a simple t-test of the pre versus post intervention periods without further justification, the study should not be included in the review unless reanalysis is possible.

Was the intervention independent of other changes?
Score "Low risk" if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/ historic events during study period. If events/variables identified, note what they are. Score "High risk" if reported that intervention was not independent of other changes in time.

Was the shape of the intervention effect pre-specified?
Score "Low risk" if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention; Score "High risk" if it is clear that the condition above is not met.

Was the intervention unlikely to affect data collection?
Score "Low risk" if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention); Score "High risk" if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).

Was knowledge of the allocated interventions adequately prevented during the study?[3]
Score "Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.

Were incomplete outcome data adequately addressed?[3]
Score "Low risk" if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score "High risk" if missing outcome data was likely to bias the results. Score "Unclear risk" if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

Was the study free from selective outcome reporting?
Score "Low risk" if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score "High risk" if some important outcomes are subsequently omitted from the results. Score "Unclear risk" if not specified in the paper.

Was the study free from other risks of bias?
Score "Low risk" if there is no evidence of other risk of biases. e.g. should consider if seasonality is an issue (i.e. if January to June comprises the pre-intervention period and July to December the post, could the "seasons' have caused a spurious effect).

[3] If some primary outcomes were assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes	Thank you
Yes. I think the questions asked are very clear and are the correct ones to be asking for this issue	Thank you
No. Objectives: I assume that the objectives refer to the five "Key Questions" that were posed as there are no "Objectives" The Key Questions posed are clear.	Thank you
The Scope of the synthesis and the definition of which studies constitute "Antibiotic Stewardship" interventions are problematic. The authors cite the standard definition for Antimicrobial Stewardship Programs (ASP) and the context for the synthesis is developed from that perspective, rather than the broader perspective of " Antibiotic Stewardship provider targeted intervention to improve antibiotic prescribing in hospitals". This is important because many clinician directed interventions to improve antibiotic prescribing have not been conducted in the formal context of ASP or " Prospective Audit and Feedback" or "Formulary Restriction". Many of the endpoints of these additional published studies have included many of the same endpoints of interest posed in the Key Questions for this synthesis.	We recognize that there are many observational studies and reports of implementation of stewardship programs at individual hospitals or within a health care system. The gold standard for evidence of effectiveness, however, is a controlled trial, preferably randomized. We did broaden our search to include controlled before and after studies and interrupted time series. Given that we did find numerous trials of these designs, we did not find it necessary to expand our search further to include observational studies.
The authors cite a recent Cochrane Systematic review that reviews the evidence in support of Antibiotic Stewardship from the perspective or "persuasive" versus "restrictive" interventions (analogous to Prospective audit w feedback and formulary restriction). The Cochrane review is well done and extensive, yet the authors of the ESP synthesis fail to sufficiently integrate evidence from the Cochrane analysis; limiting the current analysis to a relatively narrow focus. The types of studies (RCT, ITS, etc.) included for review in the current synthesis are appropriate.	We have expanded our reporting of findings from the Cochrane review and have attempted to integrate their findings with our findings.
Methods: The search strategy (Appendix A) is acceptable and the authors clearly state that there intent is to focus on literature published since 2000 because of the Cochrane analysis; however the study selection process for inclusion is not transparent and needs further description. The criteria utilized to select studies (pg 17) were reasonable, but it is not clear which "persuasive" interventions (#2) were excluded (pg 19, n=127 articles excluded) and why. A key component of Audit and Feedback approach to ASP involves education.	Methods: We excluded studies of interventions that were *exclusively* education. If education was part of the audit and feedback or guideline intervention, the study was included. Audit and feedback, guidelines with feedback, and guideline without feedback most closely fit with the Cochrane category of "persuasive" interventions.
Pg 19. Literature flow. Not very clear how criteria were used to exclude articles at the abstract level. Please explain.	We have added information on abstract and full text review to the Study Selection section.
Were reviewers blinded to author when reviewing studies/abstracts? Was there an algorithm for excluding full text articles (based on exclusion criteria) that might be included as an appendices?	Reviewers were not blinded to author. We had a list of exclusion criteria (see Study Selection section) and an abstract or article was excluded if it met any of the criteria.
It is unclear to me why the Cochrane review utilizing very similar definitions and quality assessments includes 89 studies including 52 studies conducted in the U.S.(8 within the VA) yet this systematic review includes 29 studies, virtually none of which were in the 2013 Cochrane. Some of the VA studies in the Cochrane analysis are frequently cited in the literature regarding ASP. Please explain and justify the discrepancy.	We have deleted from our report any references cited in the 2013 Cochrane Review. The Cochrane review includes studies published from 1980 to 2006 (EMBASE) or 2009 (EPOC Register). It includes studies in pediatric settings and studies of prophylactic antimicrobials – two areas we chose to exclude. None of the studies from our search were done in VA hospitals. We have added a summary of the VA studies cited in the Cochrane review.

REVIEWER COMMENT	RESPONSE
It would be illuminating to include an appendix with excluded full text articles that were reviewed, (+/-) the major reason for exclusion. Quality assessment: No issues. Didn't see quality assessments of Structured reviews. Did I miss them? Data Synthesis: Perhaps if a larger number of studies were included for each Key Question there would be less heterogeneity and it might be possible to perform meta-analyses on select outcomes? Pg 19 Indicates that 29 studies and 3 systematic reviews were included in the "synthesis", yet the description of the Cochrane results is limited to a ½ page with the findings limited to 3 sentences. In this reviewers opinion, this in unacceptable given findings in the Cochrane meta-regression, meta-analyses indicating a larger effect size for restrictive interventions on secondary outcomes antibiotic use/ inappropriate prescribing and Clostridium difficile rates, as well as reductions in pneumonia mortality with improved prescribing. (see comments in item 4) Rating body of evidence: No Issues	We are aware that some reviews include a list of excluded studies but we have chosen not to do so Quality assessment: We rated the quality of the reviews using the AMSTAR criteria but had failed to note that for the Davey 2013 review. All three reviews now have a quality rating assigned. As noted above, we have expanded our reporting of findings from the Cochrane review. Interestingly, the meta-analyses for clinical outcomes in the Cochrane review are based on small subsets of the 89 included studies (i.e., 3, 4, 5, 6, and 11 studies).
Yes	
Yes. The main objective for this review that needs to be more clearly stated is how exactly it serves as a complement to the recently published Cochrane review on interventions to improve antibiotic prescribing practices for hospital inpatients. Is the objective of this review to serve as a systematic review that only focuses on studies published since 2000 (i.e. a "more modern, 21st century" version of what was done in the Cochrane review) or was it to review studies that were left out of the Cochrane review (which only reviewed studies to 2006)? There are actually two studies included in this review (Fine 2003, Micek 2004) that were also included in the Cochrane review; I would recommend leaving these out of this review if the purpose is to only update what was done in the Cochrane review. However, I think it is fine for the purpose of this review to be a "more modern 21st century" version of what was done in the Cochrane review, but I would take care to include otherwise eligible studies that might have been disqualified solely because they appear in the Cochrane review (I cannot tell if this has been done)	Our original intention was to update the 2009 Cochrane review which was based on studies published to 2003. However, we also wanted to base our report on the categorization of interventions as described by Dellit (2007). Subsequently, the 2013 Cochrane review was published. We chose to keep our original search dates and include studies that met our eligibility criteria. We have now modified our review to remove any study included in the Cochrane review and we have attempted to better integrate their findings with our findings. However, as per currently accepted AHRQ-EPC methods we have not formally pooled results from the Cochrane review into our report. Instead we devote a separate section to the Cochrane review and provide some additional summary of all results in the discussion.
Yes. The statement of the questions and scope seem reasonable. The methods are fairly clear overall, but the application of the methods could perhaps be clearer. There are some problems, I think, with how well this uniquely supports the conclusions it makes. The 2013 Davey study covers much of the same ground—though only through to 2013. It might be useful to highlight those studies that are incorporated here that are not in the Davey study. Also, although I agree in general with the conclusions of this manuscript, I think that for the purposes of VA, it might be useful to consider a broader range of studies.	The Cochrane review (Davey 2013) literature search dates are 1980 to 2006 (in EMBASE). The EPOC Register was searched in 2007 and 2009. We identified 30 studies published after 2006. We are unclear as to what "broader range of studies" should be included. We focused our report on adult inpatient settings that met minimal criteria for reducing risk of bias outcomes.
The objectives and scope are clear. However, the methodology (e.g., exclusion criteria for studies included in the evidence based synthesis, data points included in summary tables) could be expanded for more clear comprehension.	We have made some changes to the Study Selection and Data Abstraction sections to make this information clearer.
2. Is there any indication of bias in our synthesis of the evidence?	
No	
No	

REVIEWER COMMENT	RESPONSE
Yes. No bias indicated regarding quality assessments of included studies or ratings for the body of evidence. However, these are dependent upon the studies that are included in the synthesis. Inclusion of additional studies or further elaboration on the Cochrane findings may impact rating the body of evidence, particularly the effects on antibiotic use, antibiotic resistance, and CDI. While likely not intentional this reviewer perceived a slight bias relative to pharmacy related interventions based on a comment that physician recommendations were accepted at a higher rate than pharmacists (which was a finding of the paper reviewed), however the Cochrane review included a number of pharmacy directed /authored manuscripts, and other studies have shown that inclusion of pharmacists in ASP result in improved appropriate prescribing and reduced CDI rates. PMID 11438891, PMID 23719885. The document should be reviewed from that context for bias, and future ESP of Antibiotic Stewardship topics should include at least consultation with an ID pharmacist in addition to physicians.	As noted above, consistent with prior AHRQ-EPC methods we have rated the quality and strength of evidence separately for studies we identified and reviewed and specifically noted this as an extension of the Cochrane review. We have revised considerably the section describing the updated Cochrane review and excluded any studies reported there to minimize overlap and confusion to readers. The statement about physician vs. pharmacist recommendations was inaccurate in the draft report. We have corrected that statement. We have reviewed the suggested references: PMID 11438891 Gross 2001: not eligible for inclusion (a case-control study which was also excluded from the Cochrane review) PMID 23719885 Cappelletty 2013: not eligible for inclusion (before and after study) Several of our Stakeholders and Technical Expert Panel members were ID pharmacists.
No	
No	
No	
No	
3. Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?	
Yes. I am puzzled by the exclusion of several studies: These studies seem to meet the criteria for study selection in that per my perusal they did not meet the exclusion criteria listed on page 8 and were not included in the previous Cochrane Review. All studies were published prior to December 2012 and thus I believe would have been captured by the literature review. 1. Cosgrove SE et al. Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. Infect Control Hosp Epidemiol. 2012 Apr;33(4):374-80. doi: 10.1086/664771. 2. Lesprit P, Landelle C, Girou E, Brun-Buisson C. Reassessment of intravenous antibiotic therapy using a reminder or direct counselling. J Antimicrob Chemother. 2010 Apr;65(4):789-95. doi: 10.1093/jac/dkq018. 3. Elligsen M, Walker SA, Pinto R, Simor A, Mubareka S, Rachlis A, Allen V, Daneman N. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. Infect Control Hosp Epidemiol. 2012 Apr;33(4):354-61. doi: 10.1086/664757. 4. Bornard L, et al. Impact of an assisted reassessment of antibiotic therapies on the quality of prescriptions in an intensive care unit. Med Mal Infect. 2011 Sep;41(9):480-5. doi: 10.1016/j.medmal.2010.12.022. 5. Jenkins TC et al. Decreased Antibiotic Utilization After Implementation of a Guideline for Inpatient Cellulitis and Cutaneous Abscess. Arch Intern Med. 2011;171(12):1072-1079. 6. Arnold FW et al. Improving antimicrobial use in the hospital setting by providing usage feedback to prescribing physicians. Infec Control Hosp Epidemiol. 2006; 27:378-382.	Thank you for the suggested references. We have reviewed them for possible inclusion. 1. Cosgrove 2012: Not eligible for inclusion (before and after study) 2. Lesprit 2010: Not eligible for inclusion (before and after study) 3. Elligsen 2012: Added to review (audit and feedback) 4. Bornard 2011: Added to review (audit and feedback) 5. Jenkins 2011: Not eligible for inclusion (before and after study) 6. Arnold 2006: Not eligible for inclusion (before and after study)

REVIEWER COMMENT	RESPONSE
The following articles are relevant but while epublished in 2012 the print versions are from 2013 and thus may be out of scope 1. Lesprit P, Landelle C, Brun-Buisson C. Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomized controlled trial. Clin Microbiol Infect. 2013 Feb;19(2):E91-7. doi: 10.1111/1469-0691.12062. Epub 2012 Nov 15. 2. Lesprit P, Landelle C, Brun-Buisson C. Unsolicited post-prescription antibiotic review in surgical and medical wards: factors associated with counselling and physicians' compliance. Eur J Clin Microbiol Infect Dis. 2013 Feb;32(2):227-35. doi: 10.1007/s10096-012-1734-3. Epub 2012 Aug 24. It would be useful to have a table of 217 articles excluded because of study design exclusions	We updated our literature search date to June 2013. The first Lesprit study cited has been added to our review (audit and feedback). The second study was not eligible because it is not one of our included study designs. When we review studies, we do not keep track of all of the reasons a study may be ineligible. Therefore studies excluded for other reasons may also have been ineligible because of study design.
Nguyen et al. J Antimicrob Chemother 2008;61;714 Lewis et al. Infect Control Hosp Epidemiol 2012;33:368 Cappelletty et al. Evaluating the impact of a pharmacist's absence from an AST. Am J Health-sys pharm. 2013;70:1065 (may not meet inclusion criteria but useful information on what happens when ASP is taken away) Pellerin et al. Infect control Hosp Epidemiol 2012;33:432 Leander et al. Infect control Hosp Epidemiol 2012;33:434 Apisarnthanarak A. et al. Clin Infect Dis. 2006;42(6):768-75. Valiquette L, Cossette B, Garant MP, Diab H, Pepin J. Clin Infect Dis 2007;45(20):S112-S121. Rattanaumpawan. J Antimicrob Chemother 2011; 66: 2655–2658 Kaki et al. J Antimicrob Chemother 2011; 66: 2655–2658 (systematic review of ASP in ICU) Liew et al. Eur J Clin Microbiol Infect Dis (2011) 30:853–855 Stano et al. In vivo 2012;26(3)469. Diazgranados et al. American Journal of Infection Control. 40(6):526-9, 2012 Aug Cairns et al. Medical Journal of Australia. 198(5):262-6, 2013 Mar 18. Wong et al. Annals of Pharmacotherapy. 46(11):1484-90, 2012 Nov Aldeyab et al. Journal of Antimicrobial Chemotherapy. 67(12):2988-96, 2012 Dec Niwa et al. International Journal of Clinical Practice. 66(10):999-1008, 2012 Oct. Nowak et al. American Journal of Health-System Pharmacy. 69(17):1500-8, 2012 Sep 1 Yam et al. American Journal of Health-System Pharmacy. 69(13):1142-8, 2012 Jul 1 Liew et al. Int J Antimicrobial Agents 2012;40:55 Advic et al. Clin Infect Dis 2012;54:1581 Teo et al. Eur J clin Micro Infect Dis 2012;31:947 Beardsley et al. Infect control Hosp Epidemiol 2012;33:398 Cosgrove et al. Infect Control Hosp Epidemiol 2012;33:374 Talpaert et al. J Antimic Chemother 2011;66:2168 Enoch et al. QJM 2011:104:411 Lima et al. Brazilian J Infect Dis 2011;15:1 Cheng et al. Eur J Clin Micro Infect Dis 2009;28:1447 Goldstein et al. Antimic Agents Chemother 2009;53:5122 Wong-Beringer et al. Pharmacotherapy 2009;29:736	Thank you for the suggestions. We have reviewed each of the suggested studies for possible inclusion We have *included* the following studies: Lewis 2012 (formulary restriction and preauthorization) Cairns 2013 (audit and feedback) Aldeyab 2012 (formulary restriction and preauthorization) Nowak 2012 (computerized decision support) Teo 2012 (audit and feedback) Talpaert 2011 (guidelines with feedback) Goldstein 2009 (protocol studies) The following studies were *not eligible:* Nguyen 2008 (case control study) Cappelletty 2013 (before and after study) Pellerin 2012 (letter) Leander 2012 (before and after study) Apisarnthanarak 2006 (before and after study) Valiquette 2007 (response to an outbreak rather than stewardship) Rattanaumpawan 2011 (case control study) Kaki 2011 (systematic review – we had already looked at this review for possible references missed in our search) Liew 2011 (case series) Stano 2012 (not effect of an intervention) Diazgranados 2012 (before and after study) Wong 2012 (before and after study) Niwa 2012 (before and after study) Yam 2012 (before and after study) Liew 2012 (looks at accepted versus rejected recommendations rather than effect of intervention) Advic 2012 (before and after study) Beardsley 2012 (before and after study) Cosgrove 2012 (before and after study) Enoch 2011 (observational study) Lima 2011 (before and after study) Cheng 2009 (before and after study) Wong-Beringer 2009 (before and after study)

REVIEWER COMMENT	RESPONSE
Yes. See item 4 regarding Cochrane	See response in item #4.
No	
Yes. I found a few studies that were not included that may meet criteria for inclusion: Audit and feedback studies: 1. Elligsen M, Walker SA, Pinto R, Simor A, Mubareka S, Rachlis A, Allen V, Daneman N. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. Infect Control Hosp Epidemiol 2012;33(4):354-61. 2. Solomon DH, Van Houten L, Glynn RJ, Baden L, Curtis K, Schrager H, Avorn J. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Arch Int Med 2001;161:1897-1902. Formulary restriction and pre-authorization 1. Lewis GJ, Fang X, Gooch M, Cook PP. Decreased resistance of Pseudomonas aeruginosa with restriction of ciprofloxacin in a large teaching hospital's intensive care and intermediate care units. Infect Control Hosp Epidemiol 2012;33(4):368-73 Protocol: 1. Carratala J, Garcia-Vidal C, Ortega L, Fernandez-Sabe N, Clemente M, Albero G, Lopez M, Castellsague X, Dorca J, Verdaguer R, Martinez-Montauti J, Manresa F, Gudiol F. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia. Arch Int Med 2012;172(12):922-8. 2. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. Am J Respir Crit Care Med 2000;162:505-11.	Thank you for the suggested references. We have reviewed each of the studies for possible inclusion. Audit and feedback 1. Elligsen 2012: added 2. Solomon 2001: included in Cochrane review Formulary restriction 1. Lewis 2012: added Protocol 1. Carratala 2012: added 2. Singh 2000: included in Cochrane review
As I related above, I think that there are other studies. The following PMID relates a time-series study 16465632. Other studies may be worthy of mention that were supported by the CDC epicenters. Although the quality of these other studies leave much to be desired, I wonder whether they might be important.	Thank you for the suggested reference. This study (Madaras-Kelly 2006) is included in the Cochrane review.
Refer to my colleagues' comments regarding concern of Cochrane review and others studies that should be considered for inclusion.	See responses above.
4. Please write any additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.	
I fully accept that the intent of this report is to not duplicate the previous Cochrane review on this topic. However, I believe that it is quite important to put the findings of this review into the proper context, the Cochrane review providing that context. As it now stands, the only meaningful assessment of the findings of the Cochrane review appear on page 20; this discussion provides the types of outcomes assessed in the Cochrane review but provides only a terse summary regarding what the impact of various stewardship interventions was on some of the outcomes evaluated in the Cochrane analysis; note that no mention is made of the microbial outcomes (colonization or infection with C. difficile or antimicrobial-resistant bacteria) considered in the Cochrane analysis. In contrast there is a good discussion of what the Cochrane review on laboratory (pro-Calcitonin) testing on pages 66-67. This model should be used for a presentation of the Cochrane findings on the impact of inpatients antimicrobial stewardship programs.	We have added more information from the Cochrane and how our findings are similar or dissimilar.

REVIEWER COMMENT	RESPONSE
I recommend that the discussion clearly indicate that the intermediary mechanism by which antimicrobial stewardship leads to changes in clinical, microbiological and economic outcomes is through changes in antimicrobial utilization. There needs to be more emphasis on the degree to which the various interventions achieved this intermediary endpoint. Inherently interventions that do not change usage are unlikely to change outcomes. For interventions that do change utilization, there are many uncertainties as to what types of changes most affect the outcomes (e.g,, length of therapy, breadth of therapy, or change in use of certain drug classes [e.g. fluoroquinolones vs. broad-spectrum beta-lactams). It is probably worth stating that few or no studies are sufficiently well powered to or even attempt to answer such granular questions.	We agree and provided additional emphasis on that throughout the document. In particular we have noted that positive changes in prescribing, microbial and cost outcomes may be sufficient to affect clinical practice policy if there is sufficient evidence that they do not result in untoward effects on clinical outcomes. Because most studies were not specifically designed to assess clinical outcomes addressing this issue is somewhat more difficult-though we believe we have addressed as robustly as the data allow. We have also added information to the discussion.
MAJOR POINTS	
- The Cochrane review categorized studies as being Persuasive interventions, restrictive interventions and structural interventions. To facilitate comparison of the results of ESP and Cochrane reviews it would be useful to clearly state how the various categories investigated in the ESP review (Audit and Feedback, etc.) correlate with these Cochrane categories	As noted above, we have attempted to integrate the findings from the Cochrane review with our findings (including how our intervention categories mesh with the Cochrane categories)
- It is important to emphasize the lack of harms of stewardship programs.	We have added that results suggest that clinical outcomes were not adversely affected. There are little specific data on harms so that the data do not allow us to “emphasize the lack of harms.”
- Tables 2-11, 13: The titles of these tables should be changed to Strength of Evidence for Guidelines without Feedback Studies, by CLINICAL Outcome as no data are provided regarding microbiological, prescribing or economic outcomes. The exclusion of tabular presentation of these other outcomes increases the difficulty in quickly assessing the study-to-study findings in these important realms.	We have made this change. We pre-specified that patient outcomes were our primary outcome and therefore chose to evaluate strength of evidence for the clinical outcomes. We have created separate overview tables for clinical and prescribing outcomes.
- page 47, table 9, Capelastegui2004: The outcome, mortality is presented as “Reduced, OR 1.8 [1.1, 2.9]”. This is very confusing. I expect that the study presented the OR for death before the intervention vs. after the intervention; if so the OR should be inverted so that the data presentation is more logical.	Pg 47 Capelastegiu: This is a controlled before/after study. The reported OR was for the control hospital cohort post-intervention with the intervention hospital as the reference so that an OR>1.0 indicates lower mortality at the intervention hospital. We have added a footnote to the table.
- page 47, table 9, Meyer2007: The outcome, mortality is presented as “Reduced, p<0.05”. In contrast the text on page 46 states: “The ITS aimed at reducing duration of treatment reported an increased number of deaths in the ICU after the intervention (6.9% vs. 4.1%, p<0.001).(Meyer 2007) “. Similar the text on page 65, 3rd full paragraph: text states “An ITS study enrolling patients with CAP found significantly higher mortality following guideline implementation.(Meyer 2007)”. The inconsistency between the text and the table should be resolved. Note that Table 14 also shows the mortality as having increased after the intervention in the Meyer2007 study.	Pg 47 Meyer: Thank you. We have corrected this. Mortality increased after the intervention in this study.
- page 62, last paragraph: the text indicates says that the Barenfanger 2001 demonstrated that “Lower mortality, shorter lengths of stay, and cost savings were noted for the intervention group”. In contras the text on page 11 states that “mortality did not differ significantly (10% in the control group, 11% in the study group, p=0.074) and table 11 reports the RR for mortality in the Barenfanger study as being 1.12 (0.62, 2.01).	Pg 62 Baranganger – Thank you. We have corrected this. This study included several analyses and our reporting is now consistent.

REVIEWER COMMENT	RESPONSE
- page 70, harms of therapy: It seems inconsistent with the data driven presentation throughout the rest of the document to report that authors "speculated that two patients may have had antimicrobials stopped unnecessarily. When the antimicrobials were subsequently restarted, the patients improved.(Yeo 2012) "Without any quantitative analysis this borders on the anecdotal and would seem to have no place in the presentation. If retained, there would need to be a tabular presentation of the totality of findings across all studies.	Pg 70 We have emphasized that these are anecdotal findings. While we agree that presenting data would be ideal they are not provided. We believe that including this information is preferable to excluding.
MINOR POINTS Page 1. Please change my title Page 2, line 3. Indicate the date of the literature used in the prior Cochrane review. Page 3. RESULTS section: reverse the order of these two sentences "We also summarize three systematic reviews that were relevant to this topic. Eight were RCTs, four were CCTs, four were CBA studies, and thirteen ITS studies." Page 4: Formulary Restrictions and… Add "AMS" (last sentence) to list of abbreviations Page 13: 4th paragraph, line 6. Insert "of" between the phrase "increased risk death…" Page 33: 3rd text paragraph, 1st line; insert "in" into the phrase "..conducted a University hospital…". Page 40, table 7, last row: The outcome is incidence of CDI while the strength of evidence, by outcome is "Low for readmission". This should be corrected. Page 72:3rd full paragraph: Change "infectious control program" to "infection control program" Page 75, last paragraph: Pulcini2011 is cited but the reference does not appear in the reference list	MINOR POINTS Thank you for your careful read of our draft report. Pg 1. We have made this change. Pg 2. We have added literature search dates. Pg. 3. We have made this change. Pg 4. We have replaced AMS with ASP throughout. Pg 13. We have made this change Pg 33. This paragraph has been modified and the correction has been made. Pg 40. We have made this correction. Pg 72. We have made this change. Pg 75. Pulcini 2011 has been added to the reference list.
First let me say that it is obvious how much work this report was and we appreciate it immensely. Although the Cochrane Group just released an updated review on this same topic, it only included studies up until 2006 and as I could tell from this review, there have been many studies published since.	Thank you.
Some of my suggestions are small details and others relate to the overall report 1. Probably my biggest concern regarding this report is that it only includes information published AFTER the Cochrane analysis. While I understand the reason for this and there should not be a need to redo that analysis, it makes it appear that this is all the relevant literature there is, which is misleading unless someone had thoroughly read the Cochrane analysis. Although there is a very small paragraph in the introduction about that analysis, it doesn't do justice to the volume of literature published prior to this report. In fact, the Cochrane analysis found that in those 89 studies found that antimicrobial prescribing was reduced 35-42%, that ASP's decreased Clostridium difficile infections (CDI) by 68%, decreased resistance in gram-negative bacteria by 25%, gram-positive resistance by 10% and improved mortality by interventions aimed to improve prescribing in CAP. I think it would be important to include that data either as a summary table in the introduction or divided through the report under the areas that are being reviewed in the current report. (a nice example is listed on page 60 where the Cochrane PCT review is discussed)	1. As noted above, we have added more information (including summary tables) from the Cochrane review and we have attempted to integrate the Cochrane findings and our findings. It is worth noting that although the review included 89 studies, many of the outcomes are based on far fewer studies. The observed reduction in prescribing was based on 76 studies and the median changes ranged from 3.5% to 42.3%. However, the reported decrease in CDI was based on 5 studies, gram-negative bacteria on 9 studies, gram-positive bacteria on 7 studies, and mortality in CAP patients on 4 studies

REVIEWER COMMENT	RESPONSE
2. I found the current version extremely difficult to read. The text was dense and covered in details, and the tables, while very useful, were really busy. Would it be possible to have the evidence summaries made much more visible and useful, so that busy people could avoid the majority of the text and just read the summaries? I'd also love to see Forest plots as these are very useful to get information quickly and visually from a prolonged document. Again – adding the prior studies to a forest plot from the Cochrane analysis would be a way to combine / incorporate the data and be VERY useful. The audit and feedback section, in particular, was almost impossible to read and retain any useful information.	2. We have put the prescribing outcomes on a separate table from the clinical outcomes. We have also placed summaries by outcome at the start of the sections about each of the interventions. We have created forest plots for mortality and appropriate prescribing. Due to the use of effect sizes in the Cochrane review, we did not feel it was appropriate to add to their plots.
3. I appreciate the attempt to break the sections by type of intervention, but as many studies (and existing ASP programs) look at multiple ways to improve antimicrobial use, I wonder if it wouldn't be more effective to divide by OUTCOME first (i.e. clinical, microbial, use, cost), and then break out by type of intervention. I think that would be easier to read and more clinically useful, and there might be less overall repetition of studies in the text.	3. We appreciate the suggestion but have decided to leave sections organized by intervention. We recognize that many interventions are multifaceted and we have attempted to clarify studies that used multifaceted interventions throughout the report.
4. In tables, in addition to RR and CI, I always find raw numbers useful, as that gives a more realistic understanding of the actual effect. This might fit in Executive summary table 2 or in the Appendix tables (include the results from each along with study characteristics). Sometimes it's very useful to be able to quickly review that for a specific study.	4. The Appendix tables provide raw numbers where reported. Many studies merely commented that findings were not significantly different. We thought adding to the summary tables would make the table more "busy."
5. In the introduction, nothing is mentioned about the dwindling antibiotic pipeline and why this is a crisis now. The Cochrane analysis has a really nice statement about that in their introduction – maybe something similar could be mentioned.	5. We have added this to the introduction.
6. Executive summary table 1 – I feel the wording "no improvement in mortality" is misleading. In general, these types of interventions are not expected to reduce mortality, and as stated in the text are more balancing outcomes. More useful to say "no difference was seen" I love executive summary table 2 – lots of good information in a small space.	6. We agree and have modified the statements on Exec Summary Table 1 to focus on differences as you suggested.
7. Mention is made several times that there were "no VA studies". There are many wonderful examples of studies from the VA in the Cochrane analysis. It just sounds bad to say the VA hasn't participated in this.	7. As noted above, we have added a summary of the VA studies cited in the Cochrane review and mention a VA study from which results are expected soon.
8. Figure 1 – I'd like more information about the 217 studies that were excluded as "not included study design". Why were they excluded and do any of those provide useful details that cannot be obtained from the referenced studies?	8. As noted above, when we review studies, we do not keep track of all of the reasons a study may be ineligible. Therefore studies excluded for other reasons may also have been ineligible because of study design. A listing, therefore, would not be accurate. We pre-specified our inclusion criteria for study designs with approval from our Technical Expert Panel.
9. Page 24 – under audit and feedback, CDI should be listed under microbial outcomes, not clinical outcomes. The headings and bullet points are very useful. Maybe outlining this section will make it more pop more so people are drawn to the summaries. For the other key findings sections, these headings weren't used. Is there a reason they aren't consistent?	9. Because "screening asymptomatic individuals for *C. difficile* colonization is rare almost all individuals diagnosed with CDI have clinical signs and symptoms. Therefore, we believe that this is most appropriately classified as a clinical outcome. We have added headings and bullet points to each intervention category.
10. Tables 2,4,6,8,10,12 are really useful	10. Thank you.
11. I still find table 1 really busy. This is the meat of the entire report and should be the most helpful piece. I still think it would be more effective to have the outcomes on the left column (use, cost, prescribing, microbial) and have the types of interventions on subsequent columns.	11. We have split the table into two tables – one for clinical outcomes and one for prescribing outcomes – to make the table more reader-friendly.
12. The strength of evidence tables are useful and well done	12. Thank you.
13. Again, the lack of inclusion of prior studies make some activities look like there isn't much data. Formulary restriction and preauthorization, for example, was one of the first ASP initiatives done and was well studied in the 1970's – late 1990s. As a result, very few people feel the need to replicate this very large body of data. Some type of summary of the existing data would give perspective.	13. We recognize this limitation and have attempted to incorporate findings from the Cochrane report (with literature search dates from 1980 to 2006) in our review.

REVIEWER COMMENT	RESPONSE
14. For key questions #2, 3, 4 and 5 – there is no summary of the final results. 15. I found tables 14 and 15 very helpful, especially if someone is trying to look at ICU specifically or respiratory tract infections 16. The summary and discussion at the end was extremely well written and brings in many of the additional points support ASP even considering the weakness of the current evidence. Again, I think when you look at the total body of work for ASP it is much more impressive than the current review suggests, although admittedly most of the studies are weak in design. 17. References – Fine 2003 and Pulchini 2011 aren't listed in the references. Schouten 2007 – there are two references listed and the tables don't address which one is being referred to. 18. The evidence tables in Appendix D are excellent. I think they would be further enhanced by including results, including the actual outcomes (% mortality, incidence of CDI and MDRO, and actual costs avoided or usage changes)	14. Summaries have been added. 15. Thank you. 16. Thank you. As noted, we have attempted to include more information from the Cochrane review in our review. 17. Fine 2003 has been deleted (already in Cochrane review), Pulcini has been added, and we have noted the correct Schouten reference in the text. 18. Thank you. We reported information as provided by authors which often didn't include actual outcome data.
There are two approaches that can be taken to improve the synthesis. The first approach would be to dedicate a section for each Key Question and incorporate the findings of the prior systematic reviews, perhaps adding sections to relevant tables. The second approach would be to expand the definition of studies to include more studies that were identified in the Cochrane analysis, and include the relevant studies directly in this synthesis. The quality of the studies included in the Cochrane analysis has already been determined using similar assessments of quality. In either approach full synthesis should include both studies reviewed as well as findings from other "syntheses". Because the data are not formally analyzed, the heterogeneous nature of the studies, and description of individual study findings seem to meld together. While the authors do a reasonable job of summarizing the findings at the end of the paper, the text could be improved substantially by integration of the findings at the end of each outcomes section and Key Question. Currently, this is inconsistent from section to section.	We have attempted to integrate the findings from the Cochrane review into our review so that our review provides an update We have standardized the reporting format for each intervention section (Key Question #1) and added summary points for each key question.
I was on the TEP of this report and was therefore able to provide feedback and recommendations throughout the process. I appreciated how responsive the authors were to feedback. They have produced a very nice and thorough overview of this complicated topic. The main drawback of this report is that the studies done on this topic are not of very high quality. This is not something that the authors can change. However, they do an excellent job of highlighting this limitation. I do wonder if they should also comment on how a disruptive innovation is necessary to tackle this problem – perhaps, the focus should be away from ASP and toward appropriate diagnosis. But, overall, an outstanding job.	Thank you. Given the length of the report and likely speculation regarding this point we have elected not to further comment.
Page 3, 3rd paragraph and page 14, last paragraph: Add "VA Greater Los Angeles Healthcare System" after "Chief, Infectious Diseases" and delete "Program" from "Antimicrobial Stewardship Task Force." Page 4: Audit and Feedback section: Would recommend inserting a brief definition of what the authors considered to represent "audit and feedback" and how it is distinguished from "preauthorization." For example, the Rattanaumpawan 2010 study fell under "preauthorization" even though the "drug use evaluation" done in the study was done up to 3 days following the prescription being written.	Pg 3. Thank you. We have made these changes. Pg 4. We have clarified that we considered studies to be "audit and feedback" if feedback on an individual patient basis was provided within 24 hours of the review and was provided directly to the prescriber (either written or verbally). The Rattanaumpawan study includes elements of audit and feedback and we have clarified throughout the report which studies were multifaceted.

REVIEWER COMMENT	RESPONSE
Page 6: Executive Summary Table 1 (and page 22, Table 1): Would report microbial outcomes in a similar format to how prescribing outcomes are reported (i.e. "+" for positive relationship, "≈" for no clear relationship, "-" for negative relationship). For example, under "Prospective Audit and Feedback" Microbial Outcomes, would say "mixed outcome ≈ 1 study; decrease in MRSA ≈ 2 studies."	Pg. 6.
Page 13, 9th line up from bottom: Insert "of" between "risk" and "death."	Pg 13. Thank you. We have made this change.
Page 20, "Existing Systematic Review" section: I would include a more in-depth discussion of the existing Cochrane review and define exactly how this current review is different. I'd delineate how the Cochrane review approaches the topic primarily by distinguishing restrictive versus persuasive interventions, while this review focus more on format of intervention (i.e. audit-feedback vs. formulary restriction vs. guidelines vs. CDS vs. protocol). It might be worth mentioning that the Cochrane review did find significant reduction in mortality for interventions intended to increase effective prescribing for pneumonia; I might break down the studies examined in that section according to our intervention formats.	Pg 20. We have added information about the Cochrane review (included studies, characterization of studies, outcomes) and clarified how the current review is different.
Page 33, 3rd line of the 1st paragraph under "Characteristics of Studies": Add "two were" between "and" and "ITS."	Pg 33. Thank you. With the addition of 2 studies, this paragraph has been modified.
Page 33, 2nd paragraph under "Characteristics of Studies": Explain why Rattanaumpawan study was included under formulary restriction and not audit and feedback (see above).	Pg 33. As noted above, we have added more information about multifaceted studies.
Page 55: last paragraph, 1st line: add "6" to "Oosterheert 200"	Pg 55. Thank you. References have been converted to superscript format.
Page 55, last paragraph, 6th line: Would recommend breaking up sentence by putting period before "however."	Pg 55. Thank you. To make the document more readable, many of the study details have been eliminated from the text and appear only on the Appendix tables.
Page 75: first paragraph, 1st line: Delete "that" prior to "low"	Pg 75. Thank you. We have made this change.
Page 84: References: Please add the Pulcini 2011 study (included in the Protocol section) to the references	Pg 84. Thank you, the reference has been added.
If my comments are off target then please ignore, but I am concerned that the conclusions of the synthesis are difficult and non-specific. There is more information in the literature that might be more helpful, albeit the studies are of low quality. The structure and policies that represent our best guesses for stewardship should be discussed.	We have attempted to clarify and refine the conclusions. We have reviewed other potentially eligible studies and included them if they met criteria. We have discussed the structures and policies whereby evidence may guide in stewardship implementation and have suggested areas for future research and evaluation of implemented programs; the latter is a particularly critical need given the low quality of existing data and the limited applicability to other settings.
Table 1 (page 23): It is challenging to quickly understand framework for data included in outcome columns. The reader may be misled with + and ≈ symbols.	We have created separate tables for clinical and prescribing outcomes to clarify the reporting.
5. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	
A fuller synthesis of the results of this analysis (supplemented by apparently missing articles as identified previously) with the results of prior Cochrane reviews would be quite useful.	We have added more information from the Cochrane review and have attempted to integrate their findings with our findings.
Please try to decrease the text and increase the use of Forest plots or graphs as described above	We have attempted to decrease the text. We have added forest plots for mortality and appropriate prescribing – the two outcomes where authors reported, or we were able to calculate, risk ratios.
A modification of the framework for a more user friendly version is much needed for stewardship implementers to read and comprehend these data. The repetition of studies in the text and tables should be streamlined.	We have attempted to create more reader-friendly tables and we have attempted to streamline the text and avoid duplication.

APPENDIX D. EVIDENCE TABLES

Table 1. Audit and Feedback Interventions: Study Characteristics

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (n)	Study design
Cairns 2013[57] Pacific (Australia)	Evaluate effect of program on broad-spectrum antimicrobial use	Antimicrobial stewardship ward rounds with review and feedback	Web-based antimicrobial approval system for restricted antimicrobials	Stewardship pharmacist, ID registrar and/or physician	Computerized approval system	Usual care (pre-intervention)	ITS
Lesprit 2013[1] Europe (France)	Evaluate clinical impact of program	Post-prescription review followed by direct interaction with prescribing physician	Guidelines, education, presence of ID physician, systematic evaluation of positive blood cultures by ID physician	ID physician	Computer-generated listing of antimicrobials prescribed	Usual care by ward physician (ID physician available as needed)	RCT
Elligsen 2012[6] North America (Canada)	Evaluate impact of program	Antimicrobial stewardship pharmacist reviewed records for all patients receiving 3 days of therapy with broad-spectrum antimicrobials; consulted with senior ID pharmacist and then ID physician if opportunity for optimization of therapy; approved suggestions were placed in patient chart and verbally conveyed to members of critical care team; similar review on 10th day of therapy	NR	Antimicrobial stewardship pharmacist, senior ID pharmacist, ID physician, critical care team	NR	Usual care (pre-intervention)	ITS
Magedanz 2012[59] South America (Brazil)	Improve appropriate-ness	Stage 1: physician reviewed antimicrobials, provided written feedback (in record within 24 hours) Stage 2: pharmacist added to team to follow patients prospectively Stage 3: fluoroquinoloness, 3rd generation cephalosporins, carbapenems, and vancomycin all restricted, penicillins encouraged	Pharmacist suggested de-escalation based on cultures, and IV to PO switch after 3 days	ID physician (2 hours daily) and (later phase) ID trained pharmacist (4hours/day)	See staff	Usual care (pre-intervention)	ITS

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (n)	Study design
Standiford 2012[7] North America (US)	Decrease ineffective or excessive antimicrobials, identify IV to PO conversion, suggest ID consults when appropriate Prioritize restricted drugs, areas of medical center not served by specialized ID MDs	Prospective audit and feedback, and pre-authorization requiring page to ID fellow 24 hours/day. Preauthorization was present before and after the prospective audit and feedback	Guidelines and policies where applicable	ID doc (50% effort); ID pharmacist (80% effort), data analyst (5% effort)	Used "Pharm-Watch" as a decision support system "designed to assist in antimicrobial utilization"; implemented 1/2 way through program	Usual care (pre-intervention)	ITS
Teo 2012[8] Pacific (Singapore)	Evaluate impact of whole-system stewardship program	2-stage audit of selected antimicrobials with feedback if inappropriate	Guidelines for antimicrobial use, protocol for IV to oral conversion	Team - ID physician, clinical micro-biologist, clinical pharmacists	IT system to identify patients prescribed the audited anti-microbials, stewardship team	Usual care (pre-intervention)	ITS (Note: only antimicrobial consumption data analyzed as ITS)
Weiss 2011[4] North America (US)	Improve mortality	Prompting during daily rounds. A non-care providing resident physician (the prompter) initiated discussion with attending physician if any parameters overlooked: 1) empiric antimicrobial utilization, 2) mechanical ventilation weaning, 3) central venous catheters (CVCs), 4) Foley urinary catheters, and 5) DVT and 6) stress ulcer prophylaxis. (n=140)	Checklist for these parameters	Resident physician	NR	Usual care (with checklist but no prompting) (n=125)	CCT
Yeo 2012[60] Pacific (Singapore)	Decrease inappropriate prescribing of selected number of antimicrobials	Prospective audit and feedback for carbapenems, 3rd and 4th generation cephalosporins, piperacillin-tazobactam, and vancomycin	None	Full time pharmacist, supported by micro-biologist and an ID physician (both 10% effort)	NR	ITS-but used prescribed antimicrobials for other patients in same hospital over same period as a control	ITS
Bornard 2011[9] Europe (France)	Improve quality of prescriptions	ID specialist visit 3x/week with real time feedback to prescribers	Education, daily meetings of intensivists and bacteriologist	ID physician, bacteriologist	NR	Usual care (pre-intervention)	ITS

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (n)	Study design
Dunn 2011[10] Europe (Ireland)	Increase switch rate from IV to oral and thus decrease duration of IV and costs	Application of stickers for switch to oral antimicrobial therapy to the drug chart; contacted by pharmacists if necessary (n=72 in phase 2)	None	Clinical pharmacists	NR	Usual care (n=44 in phase 2) (included pharmacist review of chart and contacting provider)	CBA (wards designated as intervention or control)
Manuel 2010[5] Europe (Switzerland)	Improve appropriateness	Standardized review of intravenous antimicrobial therapy three days after prescription	None	ID physician	NR	Usual care	CCT (prospective, cross-over study over 2 6-month periods in 2 similar wards
Camins 2009[2] North America (US)	Improve appropriateness	Antimicrobial utilization team. 390 prescriptions of target drugs piperacillin-tazobactam, vancomycin, or levofloxacin	Pocket cards with institutional AM GL for all physicians	ID physician (faculty member) and an ID clinical pharmacist	Microbiology lab, institutional antimicrobial guidelines	Usual care (pocket cards reflecting institutional guidelines) (n=394 prescriptions of target drugs)	RCT (internal medicine teams)
Liebowitz 2008[58] Europe (UK)	Reduce cephalosporin and ciprofloxacin prescribing (intermediate) in order to reduce rate of MRSA bacteremia	Clinical microbiologist rounded with some teams (n=NR): B: Guidelines published + education + advice available	None	Clinical microbiologists (European model)	NR	Usual care (pre-intervention)	ITS
Masia 2008[3] Europe (Spain)	Reduction in consumption of targeted antimicrobials	Prospective audit and feedback vs. control for all levofloxacin, vancomycin, and carbapenem prescriptions. N=146 (8 of original 154 excluded) for intervention group, n=132 (10 of original 142 excluded)	None	Pharmacist and an ID physician; no time commitment given	NR	Daily review by pharmacist who recorded data but made no intervention	RCT, unit of randomization =prescription for one of the drugs; patients could be enrolled >1 time (during admission or re-admission)

ID = infectious disease; IV = intravenous; NR = not reported; RCT = randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after; ITS = interrupted time series

Table 2. Audit and Feedback Interventions: Site, Patient, and Infection Characteristics

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Cairns 2013[2]	Tertiary teaching	Medical and surgical wards, ICU	N=2254 identified as requiring review by stewardship team post-intervention (i.e., receiving ≥ 1 restricted antimicrobial for non-standard indication, approval expired, or pharmacist alert been created); recommendations for n=779 (median age 66 years, 65% male)	Already had formal ID consult; admitted under lung transplant/cystic fibrosis, hematology and bone marrow transplant, or burns services (ID physicians performed regular rounds for these services)	All	NR
Lesprit 2013[1]	University	Medical and surgical wards	N=854; treated with one of 15 targeted antimicrobials for at least 3 days	ID physician advice requested within first 3 days of initiating therapy for the infectious episode, acute leukemia, expected survival <30 days After randomized, excluded if antimicrobial therapy was discontinued, hospital discharge, transfer to ICU, or death	All (most frequent: urinary tract-24%, lower respiratory-21%, skin and soft tissue-16%, digestive tract-13%)	In subset of 352 with microbiological documentation, most frequent were enterobacteriacae-22%, Gram-positive cocci-10%
Elligsen 2012[6]	Tertiary care	Three level III ICUs (general critical care, cardiovascular, burn)	N=717 stewardship team evaluations; suggestion for change in 247 orders (34%)	NR	Multiple	NR
Magedanz 2012[59]	Unclear	Medical unit (cardiology patients)	NR	NR	NR	Multiple
Standiford 2012[7]	University	Mixture	NR	None	All	Multiple
Teo 2012[8]	"General"	Surgery, renal medicine and endocrinology departments (only 3 that volunteered)	Evaluated 1,535 prescriptions in 1,099 patients (included 168 prophylactic prescriptions); no age/gender data	NR	Multiple	NR
Weiss 2011[4]	University, urban	MICU	Adults	Patients physically located in different ICU >first 72 hours of ICU stay; patients transferred from different ICU service; patients transferred to different ICU service within 12 hours of MICU admission	All	All
Yeo 2012[60]	University	Medical (oncology unit)	556 patients, with 580 stewardship recs; 1,276 cases of audited antimicrobials; no age/gender data	NR	All	Multiple

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Bornard 2011[9]	Teaching	Medical ICU	All patients receiving antimicrobial therapy; included 37 antimicrobial courses before and 44 after the intervention (patients could be included more than once)	Prophylactic antimicrobial therapy, transfer of patient, death, discharge before day 4 of antimicrobial therapy	All	NR
Dunn 2011[10]	Teach, University, Urban	Medical (admitted from ED)	Adult patients admitted via ED for ≥72 h under care of single medical consultant (ward, not ICU) and who received AM within 4 days. n=120 in phase 1, 116 in phase 2; median age 62 in phase 2	Died within 72 h of admission; transferred to critical care ward; prolonged course of IV antimicrobial required; or if no suitable oral antimicrobial drug for continuation	Multi (respiratory infection=57%, skin/ soft tissue=15%, urinary tract=12%)	NR
Manuel 2010[5]	Urban university hospital	Two GIM wards	GIM patients	Prescriptions to continue therapy as opposed to prescriptions to initiate course	All	All
Camins 2009[2]	Teach, University, Urban	General Hospital (GIM and step-down)	N unclear, possibly 784; mean age 54; 83% black	NR	Multi (17% pneumonia, 14% complicated UTI; 7% blood stream, 5% bacteriuria; 4% uncomplicated UTI)	Multiple (unselected)
Liebowitz 2008[58]	Community Rural	ICU and general	NR	NR	Multiple	Staph (MRSA)
Masia 2008[3]	University	Medical and surgical units, no ICUs	All patients older than 14 years with a new prescription started during study period. Intervention group: median age 68; IQR 51-78.3. Control: Median 71; IQR 56-80	ID consultant advice requested, pre-surgical prophylaxis	Multiple	Multiple

NR = not reported; GIM = general internal medicine; ICU = intensive care unit; MICU = medical intensive care unit; ED = emergency department; UTI = urinary tract infection; IQR = interquartile range

Table 3. Audit and Feedback Interventions: Clinical/Patient Outcomes

Author year	30-day readmission n/N (%)		Mortality n/N (%)		Incidence of *C. difficile* n/N (%)		Length of stay mean days (SD)		Adverse Events n/N (%)	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Lesprit 2013[1] RCT	*60 day, for relapsing infection* 13/376 (3.4) p=0.01	30/377 (7.9)	*60 day in-hospital* 37/376 (9.8) p=0.91	38/377 (10.1)	NR	NR	Median (IQR) 15 (9-25) p=0.95	15 (9-27)	NR	NR
Elligsen 2012[6] ITS	NR	NR	14.4% (post) p=0.20**	13.1% (pre)	11 cases (post)**	16 cases (pre)	6.9 (23) (post) p=0.92**	6.9 (23) (pre)	NR	NR
Standiford 2012[7] ITS	Not significantly different after implementation**		Not significantly different after implementation**		NR	NR	Not significantly different after implementation		NR	NR
Teo 2012[8] ITS	NR	NR	*Overall mortality* Pre: 0.441 deaths/100 inpatient-days Post: 0.438 (p=0.854)** No difference between accepted (42/342, 12%) vs. rejected (13/94, 14%) intervention groups (p=0.70)**		NR	NR	NR	NR	NR	NR
Weiss 2011[4] CCT	NR	NR	14/140 (10.0%) p=0.041	26/125 (20.8%)	NR	NR	*ICU* 3.5 (4.3) p=0.07	4.9 (7.0)	NR	NR
Yeo 2012[60] ITS	NR	NR	NR	NR	NR	NR	NR	NR	32 (5.5%) of cases deteriorated clinically; 2 subsequently placed back on broad-spectrum antimicrobials and improved to point of discharge; most deterioration (24/32) attributed to progression of malignancy	
Bornard 2011[9] ITS	NR	NR	Death at day 7: pre 1/37 (3%); post 1/44 (3%) (p=1.0) Death in ICU stay: pre 6/37 (16%); post 7/44 (16%) (p=0.97)*		NR	NR	Pre: 18 (20) days Post: 19 (23) days (p=0.72)*		NR	NR
Dunn 2011[10] CBA	NR	NR	No significantly differences between groups in either phase		NR	NR	No significantly differences between groups in either phase		Phase 2: reinstatement of IV 1/72 (1.4) (7% in Phase 1); Hospital-acquired infection 3/72 (4.2) (2.7% in Phase 1)	Reinstatement: 1/44 (2.3) (0% in Phase 1); Hospital-acquired infection 0% (4.3% in Phase 1)
Manuel 2010[5] CCT	NR	NR	Not significantly different		NR	NR	Not significantly different		NR	NR

Author year	30-day readmission n/N (%)		Mortality n/N (%)		Incidence of *C. difficile* n/N (%)		Length of stay mean days (SD)		Adverse Events n/N (%)	
Study design	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Camins 2009[2] RCT	NR	NR	11/390 (3)	18/394 (5)	NR	NR	Median/IQR7 (1-50)	8 (2-86)	NR	NR
Masia 2008[3] RCT	31/146 (21.2%)	20/132 (15.2%)	In hospital 40/140 (28.6%)	In hospital 33/129 (25.6)	NR	NR	Median/IQR: 14 (8-25)	13.5 (8-21)	NR	NR

ITS = interrupted time series; NR = not reported; RCT = randomized controlled trial; IQR = interquartile range
*Numbers are courses of antimicrobial therapy (not patients); analysis of means
**Analysis of means

Table 4. Audit and Feedback Interventions: Prescribing Outcomes

Author year	Timing		Use		Selection		Dose		Duration	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cairns 2013[57] ITS	NR	NR	ICU: total broad-spectrum use decreased immediately by 16.6% (95% CI -19.9%, -13.2%; p<0.001); rate of change increased 1.0% (0.7%, 1.4%) per month (p<0.001) General wards: total broad-spectrum use decreased immediately by 9.9 (-15.7%, -3.7%) (p<0.001); rate of change increased 0.2% (-0.4%, 0.8%) per month (p=0.49)		NR	NR	NR	NR	NR	NR
Lesprit 2013[1] RCT	NR	NR	NR	NR	NR	NR	NR	NR	Median (IQR) Total Course: 6 (4-9) days p<0.001 Broad-spectrum: 2 (0-5) p<0.001 IV: 3 (0-6) p=0.004 Oral: 4 (0-7) p=0.84	Total: 7 (5-9) days Broad-spectrum: 4 (0-7) IV: 4 (0-8) Oral: 4 (0-7)
Elligsen 2012[6] ITS	NR	NR	Mean monthly broad-spectrum use: 503 days of therapy/1000 pd (post) p<0.0001 Decreased level (119 days/1000 pd) (post) (p=0.005) Change in trend (-8.0 days/1000 pd) (post) (p=0.128)	644 days of therapy/1000 pd (pre)	NR	NR	NR	NR	NR	NR

Author year Study design	Timing Intervention	 Control	Use Intervention	 Control	Selection Intervention	 Control	Dose Intervention	 Control	Duration Intervention	 Control
Magedanz 2012[59] ITS	NR	NR	*Overall from Phase 1 to 3*† Reduction in total DDD: 48.9 DDD/100 pd to 36.9 DDD/100 pd; p=0.001		*Targeted antimicrobials:* Carbapenems: decreased level and trend from Phase 1 to Phase 2† then no change Fluoroquinolones: increased level from Phase 1 to Phase 2; trend decreased throughout 3rd Generation Cephalosporins: no change Vancomycin: decreased level from Phase 1 to Phase 2 then no change		NR	NR	NR	NR
Standiford 2012[7] ITS	NR	NR	Total antimicrobial use (DDD/1000 pd) decreased from 2004-8 from 1,512 to 1,073 (29% reduction; p=0.014); similar reduction for antibacterials (1,174 to 851, 27.5% reduction; p=0.03), antifungals (150 to 120, 20% reduction [24% reported], p=0.001), and antivirals (142 to 63, 55% reduction [57% reported], p= 0.001)		NR	NR	NR	NR	NR	NR
Teo 2012[8] ITS	NR	NR	Decreased level of consumption of audited antimicrobials (-1.3 DDD/100 pd, 9.9%; p=0.032); change in trend not significant (+0.301, p=0.07) No change in level of total antimicrobials (-1.7 DDD/100 pd, p=0.248); significant increasing trend (+0.992, p=0.004)		NR	NR	NR	NR	NR	NR
Yeo 2012[60] ITS	NR	NR	Significant reversal of prescription trends for audited antimicrobials (specifically cephalosporins and vancomycin) and evaluated antimicrobials	No similar reversal seen in the other hospital wards over same period	NR	NR	NR	NR	NR	NR
Bornard 2011[9] ITS	NR	NR	Appropriate therapies: Change in level: 0.07 (95% CI -0.12, 0.25), p=0.67 Change in trend: 0.09 (95% CI -0.004, 0.22), p=0.055		NR	NR	NR	NR	NR	NR

Author year	Timing		Use		Selection		Dose		Duration	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Dunn 2011[12] CBA	NR	NR	Phase 2: IV courses switched on appropriate day 72%; p=0.02 (no difference in phase 1)	56%	NR	NR	NR	NR	Phase 2: duration of IV treatment: 72 hrs (median); p=0.02 (no difference in phase 1)	96 hrs (median)
Manuel 2010[5] CCT	NR	NR	NR	NR	NR	NR	NR	NR	Time to antimicrobial therapy modification: 3.9 (5.2)* days; p=0.007	5.0 (6.0)* days
Camins 2009[2] RCT	NR	NR	Appropriate initial use 305/390 (78%); p<0.001 Appropriate definitive use: 92/112 (82%); p<0.001	229/394 (58%) 60/138 (73%)	NR	NR	Volume of inappropriate use: 2.0 DDD (median) (range=0.5-16.0); p<0.001	4.0 (range 0.3-16.5)	Inappropriate use: 2 days (median) (range 1-16); p<0.001	5 days (range 1-20)
Liebowitz 2008[58] ITS	NR	NR	NR	NR	Hospital-wide: Reduction in use of ciprofloxacin (12.3 to 2.4, p=0.09) & 3rd generation cephalosporin (36.5 to 9.0, p<0.001 ICU: Reductions in IV ciprofloxacin (56.9 to 8.2, p=0.014) & 3rd generation cephalosporins (29.2 to 1.3, p<0.001) (Unit=DDDs/1000 occupied bed-days)		NR	NR	NR	NR

Author year	Timing		Use		Selection		Dose		Duration	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Masia 2008[3] RCT	NR	NR	Total DDD per patient of targeted antimicrobials, median (IQR) 8 (4-12); p=0.04	10 (6-16)	NR	NR	NR	NR	Days receiving targeted antimicrobials, median (IQR) 4 (3-7); p=0.002: Days of carbapenem use median (IQR) 4 (3-7); p<0.0001: *(significant results only)*	median (IQR) 6 (4-10): median (IQR) 8 (7-12)

DDD = defined daily dose; ITS = interrupted time series; pd = patient-days; NR = not reported; RCT = randomized controlled trial; CBA = controlled before and after; IV = intravenous; IQR = interquartile range
*Mean (standard deviation)
†Phase 1 = baseline; Phase 2 = addition of infectious diseases physician; Phase 3 = addition of antimicrobial stewardship pharmacist

Table 5. Audit and Feedback Interventions: Microbial Outcomes

Author year	Institutional resistance		Resistance in study population	
	Intervention	Control	Intervention	Control
Lesprit 2013[1]	NR	NR	*Secondary infection and/or colonization in 6 months following randomization* MRSA: 11/376 (2.9%); p=0.82 ESBLE: 12/376 (3.2%); p=0.34	MRSA: 10/377 (2.6%) ESBLE: 17/377 (4.5%)
Elligsen 2012[6]	Increase in gram-negative susceptibility to meropenem in post-intervention period (83.4% vs. 78.2%, p=0.03); no change for ceftriaxone, piperacillin-tazobactam, ciprofloxacin, or ceftazidime**		NR	NR
Magedanz 2012[59]	Ceftazidime-resistant *Klebsiella* increased from 12% to 16% (stages 1 and 2) to 42% (stage 3). Carbapenem-resistant *Pseudomonas* decreased from 6% and 7% (stages 1 and 2) to 1% (stage 3)**		NR	NR
Yeo 2012[60]	NR	NR	No significant differences	
Liebowitz 2008[58]	Hospital-wide: Change in level of MRSA (p=0.04) but not MSSA (p=0.55); MRSA colonization unchanged; MRSA bacteremia rate reduced by 63% ICU: MRSA bacteremia unchanged (p=0.40); decreased bloodstream infections (4.2 to 0.27 per 1000 occupied bed-days)		Non-significant decrease in colonization	

NR = not reported; MRSA = Meticillin-resistant *Staphylococcus aureus*; ESBLE = extended spectrum B-lactamase-producing enterobacteriacae
**Analysis of means

Table 6. Audit and Feedback Interventions: Cost and Harms Outcomes

Author year	Healthcare cost		Program cost		Opportunity cost		Drug cost		Harms	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Lesprit 2013[1]	NR	NR	€2147 (including antimicrobial review and ward visits by ID physician)	NR	NR	NR	€17,440	€22,130	NR	NR
Elligsen 2012[6]	NR	NR	NR	NR	NR	NR	Antimicrobial costs decreased by $95,000/year ($3.20/pd) post-intervention compared with pre-intervention (23.7%)		NR	NR
Magedanz 2012[59]	NR	NR	NR	NR	NR	NR	Mean monthly costs per stage (1, 2, and 3) were $30,727.56, $18,034.89, and $9,623.73 (p<0.0001)		NR	NR
Standiford 2012[7]	Cost of ID physician (50% of time) and pharmacist (80% of time) to the program		NR	NR	NR	NR	*Total antimicrobial cost*s Before program: $44,181/1000 pd First year of program: $35,974/1000 pd Sixth year of program: $23,933/1000 pd		Stewardship program discontinued because of some dissatisfaction over preauthorization requirements and so funding could be used to provide personnel for additional infectious diseases consultation throughout medical center	
Teo 2012[8]	NR	NR	NR	NR	NR	NR	Savings of $198,575 due to decreased consumption of audited antimicrobials over 12 months; patients saved $91,194 due to intervention		NR	NR
Yeo 2012[60]	Cost-savings for patients averaged $3,758.35 each month		NR	NR	NR	NR	NR	NR	Two patients deteriorated when antimicrobials were stopped but improved when restarted	
Dunn 2011[10]	NR	NR	NR	NR	NR	NR	Decreased by €6.41 per patient in Phase 2 vs. Phase 1	Decreased by €1.69 per patient	NR	NR

Author year	Healthcare cost		Program cost		Opportunity cost		Drug cost		Harms	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Manuel 2010[5]	NR	NR	NR	NR	NR	NR	Cost of all drugs in intervention and control groups €18,385 vs. €21,042 (IRR 0.87; 95% CI 0.87, 0.88); broad spectrum €8,327 vs. €9,471 (IRR 0.88; 95% CI 0.87, 0.89); IV drugs €17,770 vs. €20,220 (IRR 0.88; 95% CI 0.87, 0.89) Cost of all drugs on wards not different for all antimicrobials or intravenous antimicrobials but higher in intervention wards €6,276 vs. €5,570 (IRR 1.13; 95% CI 1.12, 1.14)		NR	NR
Masia 2008[3]	NR	NR	NR	NR	NR	NR	Median (IQR): €118.5 (37.2-299.3) €100.0 (39.4-224.5) p=0.45		NR	NR

IQR = interquartile range; IRR = incidence rate ratio; NR = not reported; IV = intravenous; pd = patient-days; € = euro; £ = pound sterling

Table 7. Audit and Feedback Interventions: Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcomes reporting	Other
Lesprit 2013[1] RCT **Medium**	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk	
Weiss 2011[4] CCT **High**	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk	High risk	Unclear	
Dunn 2011[10] CBA **High**	High risk	High risk	Low risk	Unclear: some differences not tested statistically	Low risk	Low risk	High risk	Unclear	Did not reach numbers from power calculation; unit of analysis was patients; unit of allocation was ward
Manuel 2010[5] CCT **High**	High risk	High risk	Unclear	Low risk	Unclear	Low risk	High risk	Unclear	
Camins 2009[2] RCT **High**	Low risk	Low risk	Unclear	Low risk: some differences (gender, race, bloodstream infection, and bacteremia)	Unclear	Low Risk: reported blinding; adequacy question-able	High Risk	Unclear	
Masia 2008[3] RCT **Medium**	Low risk	Low risk	Unclear	Low risk	Low risk: missing data on a small proportion in each arm	Low risk	High risk: "a certain influence on the pre-scribing patterns of the control group was unavoidable"	Low risk	

RCT = randomized controlled trial; CBA = controlled before and after; CCT = controlled clinical trial

Table 8. Audit and Feedback Interventions: Risk of Bias Assessment for ITS Studies

Author year Risk of bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Cairns 2013[57] **High**	Yes	High risk: existing review of ICU cases; change in ICU guidelines	Unclear	Low risk	Unclear	Unclear	Low risk
Elligsen 2012[6] **Medium**	Yes	Low risk: had control conditions	Unclear	Low risk	Low risk	Low risk	Low risk
Magedanz 2012[59] **High**	Yes	High risk: levofloxacin introduced during study period	Low risk	Unclear	Low risk	Unclear	High risk: no report on rate of switch to oral drugs
Standiford 2012[7] **High**	Yes	High risk: computer decision support added halfway through study period	Unclear	Unclear	Low risk	Unclear	High risk: IV to oral only reported for 1 year, making it a de-facto pre-post
Teo 2012[8] **High**	Yes	High risk: consumption was decreasing prior to implementation	Unclear	Low risk	Unclear	Unclear	High risk: no appropriateness data prior to intervention
Yeo 2012[60] **Low**	Yes	High risk: noted increase in vancomycin use in association with a *Bacillus cereus* outbreak	Low risk	Low risk	Low risk	Low risk	Low risk
Bornard 2011[9] **High**	Yes	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear
Liebowitz 2008[58] **Medium**	Yes	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk

ITS = interrupted time series; IV = intravenous

Table 9. Formulary Restriction and Preauthorization Interventions: Study Characteristics

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship Resources	Comparator or second intervention (n)	Study design
Aldeyab 2012[14] United Kingdom	Impact of restricted use of high-risk antimicrobials	Restriction	Guidelines, weekly audit and feedback	Antimicrobial management team (not specified)	Audit tool	Usual care (pre-intervention)	ITS
Lewis 2012[61] North America (US)	Effect of restriction on resistance	Restriction of ciprofloxacin (pre-approval required)	Audit and feedback	Clinical pharmacist, ID physician	Electronic extraction of inpatient antimicrobial dispensing data	Usual care (pre-intervention)	ITS
Rattanaumpawan 2010[11] Pacific (Thailand)	Pre-authorization	Pre-authorization (antimicrobial authorization group) and audit and feedback (n=462 patients)	Guidelines	Pharmacy personnel and ID physicians	NR	No-authorization group (n=486 patients)	RCT
Peto 2008[12] Europe (Hungary)	Pre-authorization	Pre-authorization (1,757 Post patients)	Audit and feedback	ID physicians and ICU consultants	NR	Usual care (pre-intervention)	ITS
Mamdani 2007[13] North America (Canada)	Formulary restriction	Restrictive	NR	NR. Ontario's Drug Quality and Therapeutics Committee	NR	Usual care (pre-intervention)	ITS

ID = infectious disease; ITS = interrupted time series; NR = not reported; RCT = randomized controlled trial; CDI = *Clostridium difficile* infection

Table 10. Formulary Restriction and Preauthorization Interventions: Site, Patient, and Infection Characteristics

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Aldeyab 2012[14]	Acute	Medical, cardiology, surgical, gynecology, ICU	Adult inpatients	NR	Multiple	NR
Lewis 2012[61]	Teaching	Intermediate care and ICU (11 units)	NR	NR	Multiple	Focus on *Pseudomonas aeruginosa, Enterobactor aerogenes, Enterobacter cloacae, Acinetobacter baumannii, Stenotrophomonal*
Rattanaumpawan 2010[11]	University	Mostly medicine and surgery	N=948; men 53%; mean age 63	NR	Multiple	NR, *Pseudomonas aeruginosa* infection (confirmed or suspected) was one of the indications of targeted antimicrobials
Peto 2008[12]	University	ICU	N=3,403; critically ill or in need of expert care; middle-aged; mean age 57 years	NR	Blood (bacteremia)	Several, *Staphyloccocus aureus* most common
Mamdani 2007[13]	NR	NR	Database of 1.4 million: elderly, age at least 65 years	NR	Multiple	Not specified

ICU = intensive care unit; NR = not reported

Table 11. Formulary Restriction and Preauthorization Interventions: Clinical/Patient Outcomes

Author year	30-day readmission n/N (%)		Mortality n/N (%)		Incidence of *C. difficile* n/N (%)		Length of stay mean days (SD)		Adverse Events n/N (%)	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Aldeyab 2012[14] ITS	NR	NR	NR	NR	*Trend* significant post-intervention (CDI incidence rate reduced by 0.0047/100 bed-days per month, p=0.008) *Level* change not significant		NR	NR	NR	NR
Rattanaumpawan 2010[11] RCT	NR	NR	All deaths 205/462 (44.4), p=0.58; Death due to infection 136/462 (29.4); p=0.05	All deaths 207/486 (42.5); Death due to infection 172/486 (35.4)	NR	NR	30.4 (SD 28.7); p=0.80	30.7 (SD 29.7)	Antimicrobial allergy 2/462 (0.04), p=0.10; Antimicrobial-associated diarrhea 25/512* (4.9); p=0.21	Antimicrobial allergy 7/486 (1.4); Anti-microbial-associated diarrhea 18/536* (3.6)
Peto 2008[12] ITS	NR	NR	Post: 64.3 deaths/1000 pts; p=0.44**	Pre: 66.2 deaths/ 1000 pts	NR	NR	Post: 2.4 (3.8) days; p=0.214**	Pre: 2.6 (4.7) days	NR	NR
Mamdani 2007[13] ITS	NR	NR	No significant difference in mortality (p=0.62)**		NR	NR	NR	NR	NR	NR

ITS = interrupted time series; RCT = randomized controlled trial; NR = not reported; pts = patients
*Prescriptions
**Analysis of means

Table 12. Formulary Restriction and Preauthorization Interventions: Prescribing Outcomes

Author year	Timing		Use		Selection		Dose		Duration	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Aldeyab 2012[14] ITS	NR	NR	*Level of use* of high-risk antimicrobials decreased following intervention (coeff -17.3; p<0.001) as did total antimicrobial use (coeff -14.2; p=0.007) *Trend* changes were not significant		NR	NR	NR	NR	NR	NR
Lewis 2012[61] ITS	NR	NR	Significant decreasing *trend* (p=0.003) in use of ciprofloxacin (87.09 DDD/1000 pd in 2004, 8.04 DDD/1000 pd in 2010) Increase in group -2 carbapenems (11.96 to 28.19 DDD/1000 pd, p=0.013)		NR	NR	NR	NR	NR	NR

Author year Study design	Timing Intervention	 Control	Use Intervention	 Control	Selection Intervention	 Control	Dose Intervention	 Control	Duration Intervention	 Control
Rattanaumpawan 2010[11] RCT	NR	NR	NR	NR	NR	NR	DDD (all antimicrobials) 10,737.9 DDD (all antimicrobials/ episode) 21.0 DDD (targeted antimicrobials) 2972.6 DDD (targeted antimicrobials/ episode) 5.8	DDD (all antimicrobials) 13,528.3 DDD (all antimicrobials/ episode) 26.2; DDD (targeted antimicrobials) 3696.4 DDD (targeted antimicrobials/ episode) 7.2	All antimicrobials 12.7 (SD 9.8) days (p<0.01) Targeted antimicrobials, 7.5 (SD 6.9) days (p<0.01)	All antimicrobials 16.4 (SD 14.8) days Targeted antimicrobials 9.3 (SD 7.7) days
Peto 2008[12] ITS	NR	NR	*Mean antimicrobial consumption* Before Implementation: 162.9 DDD/100 pd (95% CI 158.3, 167.6) After Implementation: 101.3 DDD/100 pd (95% CI 100.7, 102.0)		NR	NR	NR	NR	NR	NR
Mamdani 2007[13] ITS	NR	NR	*Fluoroquinolone prescription rates* After Implementation: 17.1 prescriptions/1000 elderly persons vs. predicted use = 43.6 prescriptions/1000 elderly persons (per quarter); p<0.01 Approximately 30% higher than expected use of sulfonamide (p=0.01) and urinary anti-infectives (primarily nitrofurantoin and trimethoprim; p<0.01) observed within 1 year after implementation		NR	NR	NR	NR	NR	NR

DDD = defined daily dose; pd = patient-days; ITS = interrupted time series; NR = not reported; RCT = randomized controlled trial
*Prescriptions

Table 13. Formulary Restriction and Preauthorization Interventions: Microbial Outcomes

	Institutional resistance		Resistance in study population	
Author year	**Intervention**	**Control**	**Intervention**	**Control**
Lewis 2012[61]	13.2% decrease in carbapenem-resistant *P. aeruginosa* isolates following intervention (decrease of 3.8% per year, p=0.035); percentage stable prior to intervention 13.7% decrease in ciprofloxacin-resistant isolates over study period (3.9% per year, p=0.002); decrease in slope consistent before and after intervention Non-significant downward trend for cefepime-resistant isolates Non-significant increased trend for piperacillin-tazobactam-resistant isolates Decreasing trend in rates of carbapenem- (2.1 cases/10,000 pd per year), ciprofloxacin-, and cefeprime- (1.8 cases/10,000 pd per year) resistant *P. aeruginosa* infections (all p<0.001) Increasing trend in rate of piperacillin-tazobactam-resistant isolates No significant effect on susceptibilities of other isolates		NR	NR

Table 14. Formulary Restriction and Preauthorization Interventions: Cost and Harms Outcomes

	Healthcare cost		Program cost		Opportunity cost		Drug cost		Harms	
Author year	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Rattanaumpawan 2010[11]	NR	NR	NR	NR	NR	NR	Difference in expenditures between groups: $147,793 Total cost of target antimicrobials: $275,480 Cost of target antimicrobials/ episode: $538.10	Total cost of target antimicrobials: $374,241 Cost of target antimicrobials/ episode: $661.30	NR	NR

NR = not reported

Table 15. Formulary Restriction and Preauthorization Interventions: Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcomes reporting
Rattanaumpawan 2010[11] RCT **High**	High risk	High risk	Low risk	High risk: significantly higher morbidity in intervention arm	Low risk	Low risk: independent outcomes assessment	Unclear	Low risk

CBA = controlled before and after; CCT = controlled clinical trial; RCT = randomized controlled trial

Table 16. Formulary Restriction and Preauthorization Interventions: Risk of Bias Assessment for ITS Studies

Author year Risk of bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Aldeyab 2012[14] **High**	Yes	Unclear: isolation and infection control policies	Unclear	Low risk	Low risk	Unclear	Low risk
Lewis 2012[61] **High**	Yes	High risk: other infection control policies	Unclear	High risk: system change	Low risk	Unclear	Unclear
Peto 2008[12] **Medium**	Yes	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Mamdani 2007[13] **Low**	Yes	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

ITS = interrupted time series

Table 17. Guidelines with Feedback Studies: Study Characteristics

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (n)	Study design
Talpaert 2011[18] United Kingdom	Reduce broad-spectrum antimicrobial use	Guideline	Feedback (ward rounds 5 times/week), education, face-to-face discussions	Antimicrobial management team (microbiologist and antimicrobial pharmacist) consulted; program administered by clinicians and ward pharmacists	NR	Usual care (pre-intervention)	ITS
Schnoor 2010[15] Europe (Germany)	Improve adherence to pneumonia guidelines and outcomes	Guideline	Education, posters, guideline distribution, reminders with before/after data every 2nd month	Personalized tutor	NR	Personalized tutors at control sites told about study but guide-line not actively implemented	RCT; randomized at the level of the "local clinical centre"
Schouten 2007[16] Europe (Netherlands)	Appropriate use (route, switching, guideline adhere)	Guideline	Education, feedback reports	Pharmacist, physician, microbiologist, pulmonologist, quality improvement officer	External quality improvement facilitator for analysis of barriers, areas for improvement	Usual care	CRCT (n=6)
Fowler 2007[17] United Kingdom	Reinforce narrow-spectrum antimicrobial policy	Guideline	Feedback every 8-12 weeks (individual antimicrobial usage and CDI rates)	NR	NR	Usual care (pre-intervention)	ITS

ID = infectious disease; NR = not reported; ITS = interrupted time series; CRCT = cluster randomized control trial; RCT = randomized controlled trial; CBA = controlled before and after trial; ITS = interrupted time series; CDI = *C. difficile* infection

Table 18. Guidelines with Feedback Studies: Site, Patient, and Infection Characteristics

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Talpaert 2011[18]	Acute general	Medical and surgical wards including ICU	Adults (no information provided)	NR	Multiple	NR
Schnoor 2010[15]	NR, 11 hospitals and 34 sentinel practices	Mix of inpatients (not further characterized) and outpatients	Intervention group: baseline (n=238) mean age 58 yrs; follow-up (n=275) mean age 56 yrs Control: baseline (n=302) mean age 61 yrs; follow-up (n=348) mean age 61 yrs	Immunodeficiency, florid tuberculosis, possible nosocomial infection	Lungs	Multiple
Schouten 2007[16]	Multiple	GIM and respiratory	CAP patients, post intervention (n=525) mean age 70 yrs, male 53% COPD/CB post intervention (n=506) mean age 69 yrs, male 46%	Nursing home resident, underlying immune-deficiency, treated with antimicrobials for another culture-proven infection during admission, LRTI and discharged is past 30 days, transferred to another hospital or ICU or died within 24 h of admission, very poor prognosis and admitted for palliative care	Lungs (LRTI; pneumonia, exacerbation COPD)	Not specified
Fowler 2007[17]	Teaching	Acute care wards (3)	Age greater than 80 years (n=6,129)	NR	Multiple	Not specified

CAP = community acquired pneumonia; COPD/CB = chronic obstructive pulmonary disease/chronic bronchitis; ICU = intensive care unit; GIM = general internal medicine; LRTI = lower respiratory tract infection; NR = not reported

Table 19. Guidelines with Feedback Studies: Clinical/Patient Outcomes

Author year Study design	30-day readmission n/N (%) Intervention	 Control	Mortality n/N (%) Intervention	 Control	Incidence of *C. difficile* n/N (%) Intervention	 Control	Length of stay mean days (SD) Intervention	 Control	Adverse Events n/N (%) Intervention	 Control
Talpaert 2011[18] ITS	NR	NR	NR	NR	IRR=0.34 (95% CI 0.20, 0.58), p<0.001 (decreased incidence of CDI with intervention) IRR=0.93 (95% CI 0.88, 0.99), p=0.015 (decreased trend in CDI following intervention)*		NR	NR	NR	NR
Schnoor 2010[15] RCT	NR	NR	30 day overall mortality: Baseline 5.2%, Follow-up 3.6%; p=ns between groups	Baseline 2.9%, Follow-up 3.8%	NR	NR	Baseline: 10.7 (7.6). Follow-up: 10.0; p=ns between groups	Baseline: 11.4 (9.5). Follow-up: 10.9	NR	NR
Schouten 2007[16] CRCT	NR	NR	CAP patients 20/318 (7.2); p=0.58 COPD/CB patients 10/269 (4.3); p=0.35	CAP patients 15/207 (8.7) COPD/CB patients 5/237 (2.6)	NR	NR	CAP patients 8.0 (median); p=0.47 COPD/CB patients 11.5 (median); p=0.89	CAP patients 10.0 (median) COPD/CB patients 11.4 (median)	NR	NR
Fowler 2007[17] ITS	NR	NR	Reported that crude mortality was unaltered by intervention (fluctuated randomly between 4.7% and 21.0%)		Decrease in CDI associated with intervention IRR=0.35 (95% CI 0.17, 0.73), p=0.009		Reported that length of stay fluctuated randomly between 11.9 and 13.5 days		NR	NR

CAP = community acquired pneumonia; CDI = *Clostridium* difficile infection; COPD/CB = chronic obstructive pulmonary disease/chronic bronchitis; ITS = interrupted time series; RCT = randomized controlled trial; CRCT = cluster randomized control trial; CBA = controlled before and after study; NR = not reported; ns = not statistically significant; IRR = incidence rate ratio

*CDI data based on all patients age greater than 2 years old

Table 20. Guidelines with Feedback Studies: Prescribing Outcomes

Author year Study design	Timing		Use		Selection		Dose		Duration	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Talpaert 2011[18] ITS	NR	NR	NR	NR	*Antimicrobials Targeted for Decreased Use*: Fluoroquinolone – reduced by 105.33 DDD/1000 OBD (95% CI -176.48, -34.18) (58.5%, p=0.006) Cephalosporin - reduced by 45.93 DDD/1000 OBD (95% CI -67.74, -24.11) (45.8%, p<0.001) Total antimicrobial, clindamycin, co-amoxiclav, and amoxicillin use did not change significantly Significant trend for decreased use of co-amoxiclav post-intervention (p=0.005) and decreased total antimicrobial use (p=0.047) *Antimicrobials Targeted for Increased Use:* Increased level of use (p<0.05) for penicillin, macrolides, gentamicin, nitrofurantoin, trimethoprim No change in level for doxycycline or vancomycin No changes in trend		NR	NR	NR	NR
Schnoor 2010[15] RCT	NR	NR	Adjusted odds of receiving appropriate antimicrobial treatment – intervention group relative to control (OR=1.8, 95% CI 1.1, 2.8)		NR	NR	NR	NR	*Patients at guideline-concordant duration*: Increased from 46.9% to 51.9%; +5.0% (p=ns)	Decreased from 56.7% to 53.8%; -2.9%
Schouten 2007[16] CRCT	Initiation of antimicrobial within 4 hrs (CAP patients) Increase from 55.2% to 62.9%; OR=3.59 (95% CI 1.02, 12.6)	Decrease from 68% to 51.6	Guideline concordant empirical antimicrobial regimen - Increase from 50.3% to 64.3%; OR=2.63 (95% CI 1.57, 4.42)	Decrease from 53.7% to 45.6%	NR	NR	Antimicrobials adapted based on renal function Increase from 79.5% to 95.1%; OR=12.9 (95% CI 3.64, 45.8)	Decrease from 95.8% to 92.4%	Optimal duration (5 to 7 days), (COPD/CB patients) Increase from 25.8% to 37%; OR=2.22 (95% CI 0.96, 5.12)	Decrease from 51.8% to 42.9%

Author year Study design	Timing		Use		Selection		Dose		Duration	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Fowler 2007[17] ITS	NR	NR	*Targeted for decreased use:* Level and trend (all p≤0.035) for cephalosporins and amoxicillin/clavulanate *Targeted for increased use:* Level of amoxicillin (p=0.001); trend for benzyl penicillin (p=0.012)		NR	NR	NR	NR	NR	NR

CAP = community acquired pneumonia; COPD/CB = chronic obstructive pulmonary disease/chronic bronchitis; DDD = defined daily dose; OBD = occupied bed days; NR = not reported; ns = not statistically significant; OR = odds ratio; RCT = randomized controlled trial; CRCT = cluster randomized control trial; ITS = interrupted time series; CBA = controlled before and after

Table 21. Guidelines with Feedback Studies: Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcomes reporting
Schnoor 2010[15] RCT **High**	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear: all providers were informed about study	Low risk
Schouten 2007[16] CRCT **High**	Unclear: 6 hospitals randomized by coin flip	High risk	Unclear	Unclear: control and intervention sites were similar; there were differences in the patient populations	High risk: little detail on reasons for exclusion	Low risk	Low risk	Low risk

CBA = controlled before and after; CCT = controlled clinical trial; RCT = randomized controlled trial

Table 22. Guidelines with Feedback Studies: Risk of Bias Assessment for ITS Studies

Author year Risk of Bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Talpaert 2011[18] **Medium**	Yes	Low risk: new building but did not appear to be a factor	Unclear	Low risk	Low risk	Low risk	Low risk
Fowler 2007[17] **Medium**	Yes	Unclear: already had a restrictive policy, audit and feedback, isolation	Unclear	Low risk: data already being collected	Low risk	Low risk	Low risk

ITS = interrupted time series

Table 23. Guidelines without Feedback Studies: Study Characteristics

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (core activity) (n)	Study design
Mangino 2011[62] North America (US)	Assess and improve outcomes for adults with HAP in ICU	Guideline with multifaceted strategy	Education, de-escalation of therapy	Multidisciplinary teams	NR	Usual care (pre-intervention)	ITS
Meyer 2007[20] Europe (Germany)	Reduce duration	Guideline	NR	Multidisciplinary team (intensive care specialist, infection control physician, microbiologist, pharmacist)	NR	Usual care (pre-intervention)	ITS
Capelastegui 2004[21] Europe (Spain)	Appropriateness, timing, duration	Practice guideline for CAP	NR	Unclear	NR	Usual care	CBA
Goldwater 2001[19] North America (US)	Reduce costs without sacrificing patient care	Interchange/switch therapy (2 hospitals, n=1,323 patients)	Meetings, newsletter, signs, direct mailing	Pharmacy, prescriber	NR	Education plus meetings, newsletters, signs, direct mailing (2 hospitals; n=554 patients)	CCT (unit is hospitals)

CAP = community acquired pneumonia; CBA = controlled before and after; CRCT = cluster randomized control trial; HAP = hospital-acquired pneumonia; ID = infectious disease; ITS = interrupted time series; NR = not reported; RCT = randomized controlled trial; IV = intravenous

Table 24. Guidelines without Feedback Studies: Site, Patient, and Infection Characteristics

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Mangino 2011[62]	University	ICU	N=432 (17 excluded for missing data); mean age 58 yrs; male 65%	NR	Lung	NR
Meyer 2007[20]	University	Neuro-surgical ICU	1300 over 1 year	Copy strains, defined as an isolate of the same species showing the same susceptibility pattern throughout the period of one month in the same patient, no matter what the site of isolation	Multiple	MRSA, Coagulase-negative staphylococci, *Streptococcus pneumoniae*, *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Pseudomonas aeruginosa*
Capelastegui 2004[21]	University	NR	Intervention cohort (n=417), mean age 71 yrs, male 65% Preintervention cohort (n=377), mean age 67 yrs, male 62% Control cohort 1 (n=467), mean age 70 yrs, male 64% Control cohort 2 (n=645), mean age 69 yrs, male 60%	Tested positive for HIV, chronically immunosuppressed or had been hospitalized during the previous 14 days	Lungs (CAP)	Not specified

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Goldwater 2001[19]	Intervention hospitals were community & community/ rehab; comparators were community and tertiary	Unclear	n=1877 (2040 hosp); mean age 65 yrs, male 43%	Antimicrobial other than fluoroquinolones (may have received others before fluoroqinolone tx)	Respiratory 30.3%; genitourinary 23.4%; abdominal 11.6%; other 12.1%	Gram + 33.5%; Gram - 66.5%

ICU = intensive care unit; HIV = Human immunodeficiency virus; MRSA = methicillin-resistant S*taphylococcus aureus*; MSSA = methicillin-sensitive S*taphylococcus aureus*; NR = not reported

Table 25. Guidelines without Feedback Studies: Clinical/Patient Outcomes

Author year	30-day readmission n/N (%)		Mortality n/N (%)		Incidence of *C. difficile* n/N (%)		Length of stay mean days (SD)		Adverse Events n/N (%)	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Meyer 2007[20] ITS	NR	NR	*ICU mortality:* 162/2354 (6.9%) p<0.05**	80/1964 (4.1%)	NR	NR	3.1 p=ns**	3.1	CVC-associated bloodstream infections rate 0.4; Catheter-associated UTIs 8.1; both p=ns	CVC-associated bloodstream infections rate 0.8; Catheter-associated UTIs 7.5
Capelastegui 2004[21] CBA	Pre-intervention 7/377 (1.9) Intervention 10/417 (2.4)	Cohort 1 (pre) 15/467 (3.2) Cohort 2 (control) 12/654 (1.8) Adj OR=0.8 (0.3, 2.0)*	*30 day* Pre-intervention 39/377 (10.3) Intervention 37/417 (8.9)	Cohort 1 (pre) 44/467 (9.4) Cohort 2 (control) 71/654 (10.9) Adj OR=1.8 (1.1, 2.9)*	NR	NR	Pre-intervention 7.3 (5.9) Intervention 5.7 (4.3) Significant reduction in adjusted mean - intervention versus all other groups p<0.001	Cohort 1 (pre) 9.1 (5.9) Cohort 2 (control) 8.8 (6.3)	NR	NR
Goldwater 2001[19] CCT	NR	NR	Therapeutic interchange: 50/1473 (3.4%); p=ns	Standard education tools: 18/567 (3.2%)	NR	NR	Therapeutic interchange: 12.1 (SD 18.8); p<0.05	Standard education tools: 10.5 (SD 23.1)	Therapeutic interchange: Total 11/1473 (0.7%) (skin, GI, CNS, fever, nephro, thrombo-cytopenia); all p=ns	Standard education tools: Total 9/567 (1.6%)

ITS = interrupted time series; CBA = controlled before and after; CRCT = cluster randomized control trial; NR = not reported; ns = not statistically significant between groups; OR = odds ratio; RCT = randomized controlled trial; UTI = urinary tract infections; VAP = ventilator-associated pneumonia

*In this study, the post-intervention cohort was the reference group; ORs are for the control hospital cohort versus the intervention hospital cohort

**Analysis of means

Table 26. Guidelines without Feedback Studies: Prescribing Outcomes

Author year	Timing		Use		Selection		Dose		Duration	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Mangino 2011[62] ITS	NR	NR	*Empiric antimicrobials* 66/151 (43.7%) p=0.01	79/257 (30.7%)	NR	NR	NR	NR	NR	NR
Meyer 2007[20] ITS	NR	NR	Significant reduction in total AD (949.8 DDD/1000 pd before, 626.7 after; change = -323.1; 95% CI -444.6, -201.6); due to reduced 2nd generation cephalosporins (change = -100.6 DDD/1000 pd; 95% CI -150.1, 51.0), imidazoles (-100.3; 95% CI -127.9, -72.7), penicillins with b-lactamase inhibitor (-33.5; 95% CI -54.1, -12.9) and glycopeptides (-30.2; 95% CI -58.1, -2.4)		NR	NR	NR	NR	NR	NR
Capelastegui 2004[21] CBA	*Antimicrobials within 8 h* Pre: 202/377 (59.9) Intervention: 227/417 (60.1)	Cohort 1 (pre) 309/467 (73.9) Cohort 2 (control) 479/654 (76.6) Adjusted OR = 2.3 (1.7, 3.0)*	*Appropriate use* Pre: 269/377 (71.4) Intervention: 370/417 (89.2)	Cohort 1 (pre) 394/467 (86.2) Cohort 2 (control) 579/654 (89.6) Adjusted OR = 1.1 (0.7, 1.7)*	NR	NR	NR	NR	*Antimicrobial* Pre: 12.9 (6.3) days** Intervention: 11.4 (3.6) days *IV* Pre: 4.5 (5.5) days Intervention: 3.2 (2.9) days	*Antimicrobial* Cohort 1 (pre) 14.7 (5.6) days Cohort 2 (control) 14.5 (5.4) *IV* Cohort 1 (pre) 5.8 (4.8) Cohort 2 (control) 6.3 (5.2)
Goldwater 2001[19] CCT	NR	NR	Levofloxacin use 96.3%	47.8%; p<0.001	NR	NR	NR	NR	5.3 (4.7) days** p=ns	5.3 (4.2) days

DDD = defined daily dose; pd = patient-days; AD = antimicrobial usage density; ITS = interrupted time series; NR = not reported; RCT = randomized controlled trial; CBA = controlled before and after; CRCT = cluster randomized control trial; OR = odds ratio; IV = intravenous; ns = not significant

*In this study, the post-intervention cohort was the reference group; ORs are for the control hospital cohort versus the intervention hospital cohort

**Mean (standard deviation)

Table 27. Guidelines without Feedback Studies: Microbial Outcomes

Author year	Institutional resistance		Resistance in study population	
	Intervention	Control	Intervention	Control
Meyer 2007[20]	Two-year resistance proportions of selected pathogens showed a significant decrease in the MRSA proportion after the intervention: of 167 *S. aureus* isolates 8.4% were resistant in 2002–03, and of 208 *S. aureus* isolates only 2.9% were resistant in 2004–05		NR	

MRSA = methicillin-resistant S*taphylococcus aureus*

Table 28. Guidelines without Feedback Studies: Cost and Harms Outcomes

Author year	Healthcare cost		Program cost		Opportunity cost		Drug cost		Harms	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Meyer 2007[20]	NR	NR	NR	NR	NR	NR	Total antimicrobial costs/per 1000 pd (€) showed a significant decrease level from €13.16 before to €7.31 after the intervention, saving €5.86 (as reported)		NR	NR
Goldwater 2001[19]	NR	NR	NR	NR	NR	NR	$79.8 (87.5) per patient; p<0.001	$114.5 (132.6)	NR	NR

NR = not reported; pd = patient days; € = euro

Table 29. Guidelines without Feedback Studies: Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Capelastegui 2004[21] CBA **High**	High risk	High risk	High risk: difference in LOS	High risk: some differences in intervention site pre/post	Low risk: data from patient charts	Low risk	Low risk	Low risk
Goldwater 2001[19] CCT **High**	High risk	High risk	Unclear	Unclear: difference in site of infection	Unclear	Low risk	High risk: intervention already in place at one site; all providers notified of change	Low risk

CBA = controlled before and after; CCT = controlled clinical trial; RCT = randomized controlled trial; CRCT = cluster randomized control trial; LOS = length of stay

Table 30. Guidelines without Feedback Studies: Risk of Bias Assessment for ITS Studies

Author year Risk of Bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Mangino 2011[62] **Medium**	Yes	Low risk	Unclear	Low risk	Low risk	Unclear: missing data	Low risk
Meyer 2007[20] **Medium**	Yes	Low risk	Unclear	Low risk	Low risk	Low risk: database and laboratory data	Low risk

ITS = interrupted time series

Table 31. Computerized Decision Support Studies: Study Characteristics

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (n)	Study design
Nowak 2012[24] North America (US)	Evaluate clinical and cost outcomes of program	Data-mining software to develop reports on patients receiving antimicrobials	Already in place: -Education -Pathways -Protocol for IV to oral -Dose adjustment by renal function -Pre-authorization for restricted antimicrobials	Residency-trained pharmacist and ID physician	EMR and data-mining software	Education -Pathways -Protocol for IV to oral -Dose adjustment by renal function -Pre-authorization for restricted antimicrobials	ITS
Yong 2010[63] Pacific (Australia)	Reduce use broad-spectrum antimicrobials	Immediate feedback via electronic decision support system	Guidelines, laboratory testing	Unclear	The ADVISE (Antimicrobial Decision support for the Victorian Infectious Diseases SErvice) program	Usual care (pre-intervention)	ITS
McGregor 2006[22] North America (US)	Optimize therapy; minimize inappropriate and inadequate antimicrobial use	Computerized decision support	Existing stewardship program (manual review)	Infectious disease attending physician, clinical pharmacist	PharmWatch Web-based decision support system	Team manually reviewed patient charts	RCT
Barenfanger 2001[23] North America (US)	Lower mortality, cost, and duration	Computerized decision support	Education, guidelines, laboratory testing	Pharmacist	TheraTrac 2 computer software program	Manually reviewing hard copies of susceptibility testing data	CCT

ID = infectious disease; ITS = interrupted time series; RCT = randomized controlled trial; CCT = controlled clinical trial; ; EMR = electronic medical record; IV = intravenous

Table 32. Computerized Decision Support Studies: Site, Patient, and Infection Characteristics

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Nowak 2012[24]	Community Teaching	Medical and surgical wards	Adult inpatients Reviewed charts of: N=2186 treated for pneumonia, N=225 treated for intra-abdominal sepsis with 1596 recommendations to alter therapy	NR	Lungs or abdomen	NR
Yong 2010[63]	Teaching	ICU	No details, n=2838 Gram-negative organisms	Non Gram-negative organisms	Multiple	*Pseudomonas*, *Escherichia coli, Klebsiella* spp., *Acinatobacter*, Inducible Enterobacteriaceae, (B-lactamases e.g. *Serratia* sp., *Morganella* sp., *Citrobacter* sp., *Enterobacter* sp., *Proteus* sp.)
McGregor 2006[22]	University-affiliated	All wards except shock trauma, pediatrics, or cancer	Intervention (n=2,237); mean age 50.4 yrs, male 47% Control (n=2,270); mean age 49.6 yrs, male 46%	Patient on shock trauma, pediatric, or cancer wards	Multiple	NR
Barenfanger 2001[23]	University, community teaching	NR	Intervention (n=188); mean age 66.1 years Controls (n=190); mean age 65.6 years	NR	Multiple	Multiple

ICU = intensive care unit; NR = not reported

Table 33. Computerized Decision Support Studies: Clinical/Patient Outcomes

Author year Study design	30-day readmission n/N (%) Intervention	 Control	Mortality n/N (%) Intervention	 Control	Incidence of *C. difficile* n/N (%) Intervention	 Control	Length of stay mean days (SD) Intervention	 Control	Adverse Events n/N (%) Intervention	 Control
Nowak 2012[24] ITS	*Intraabdominal Sepsis* Pre: 22/111 (19.8) Post: 16/97 (16.7) *Pneumonia* Pre: 163/1118 (14.6) Post: 146/985 (14.8) Both p>0.05*		*Intraabdominal Sepsis* Pre: 12/123 (9.8) Post: 5/102 (4.9) *Pneumonia* Pre: 45/1163 (3.97) Post: 38/1023 (3.7) Both p>0.05*		Significant difference between pre- and post- ASP in quarterly changes in rate of CDI (p=0.018)		*Intraabdominal Sepsis* Pre: 7.2 (7.1) Post: 7.4 (8.3) *Pneumonia* Pre: 5.9 (4.9) Post: 5.5 (7.8) Both p>0.05*		NR	NR
Yong 2010[63] ITS	NR	NR	NR	NR	NR	NR	ICU Mean 4.2 days		NR	NR
McGregor 2006[22] RCT	NR	NR	73/2237 (3.3%) (p=0.55)	67/2270 (3.0%)	Patients tested: 127/2237 (5.7%) (p=0.21)	150/2270 (6.6%)	Median (IQR) 3.8 days (2.1 to 7.6) (p=0.38)	4.0 days (2.2 to 7.6)	NR	NR
Barenfanger 2001[23] CCT	NR	NR	21/188 (11.2) (p=0.74)	19/190 (10.0)	NR	NR	11.0 Difference (-2.7; 95% CI -5.1, -0.19)	13.7	NR	NR

NR = not reported; IQR = interquartile range; CI = confidence interval; RCT = randomized controlled trial; ITS = interrupted time series; CCT = controlled clinical trial; CDI = *Clostridium difficile* infection
*Analysis of means

Table 34. Computerized Decision Support Studies: Prescribing Outcomes

Author year Study design	Timing Intervention	 Control	Use Intervention	 Control	Selection Intervention	 Control	Dose Intervention	 Control	Duration Intervention	 Control
Nowak 2012[24] ITS	NR	NR	Decreased use of quinolones (total), vancomycin, carbapenems, & piperacillin-tazobactam* Unchanged or slight increased use of first line antimicrobials (exception was increase in use of linezolid)**		NR	NR	NR	NR	NR	NR
Yong 2010[63] ITS	NR	NR	*Trend* analysis - antimicrobials to cover Gram-negative bacteria including 3rd and 4th generation cephalosporins, carbapenems, extended-spectrum penicillins, amino-glycosides and fluoroquinolones remained stable during study period		NR	NR	NR	NR	NR	NR

DDD = defined daily dose; pd = patient-days; NR = not reported; ITS = interrupted time series; RCT = randomized controlled trial; CCT = controlled clinical trial
*Based on mean data from 4 years pre- and 4 years post-intervention (p values not reported)
**Institutional privileges to prescribe linezolid for empirical or definitive therapy of MRSA pneumonia were expanded during the 2nd year post-intervention

Table 35. Computerized Decision Support Studies: Microbial Outcomes

Author year	Institutional resistance		Resistance in study population	
	Intervention	Control	Intervention	Control
Yong 2010[63] ITS	*Pseudomonas aeruginosa*,1) gentamicin susceptibility decreased prior to the intervention but then increased post-intervention with a significant difference between the pre-and post- intervention phases (change from pre-intervention trend reported as mean percent change per year: 11.6 [1.8, 21.5], p=0.02); 2) imipenem with a significant difference between pre- and post-intervention (mean percent change per year:18.4 [4.9, 31.6], p=0.009). Non-significant differences were observed for ceftazidime (3.2 [-13.0, 6.6], p=0.51) and ciprofloxacin (-4.9 [-14.1, 4.2], p=0.28) susceptibility. *E. coli,* no imipenem-resistant isolates were observed and over 98% of all isolates were susceptible to 3rd generation cephalosporins, gentamicin, and ciprofloxacin with no changes over the study period (mean percent changes of -0.6 to 0.3, p values from 0.54 to 0.73). No significant changes over the study period were noted for *Klebsiella* species susceptibility (mean percent changes of 0.3 to 3.0%, p values 0.10 to 0.88). For *Acinetobacter* species, no significant changes in susceptibility to imipenem, gentamicin, or ciprofloxacin were observed over the study period (mean percent changes of 0.3 to 14.0, p values from 0.11 to 0.93). Enterobacteriaceae with potentially inducible beta-lactamases were grouped. Significant increases in gentamicin (mean percent change 6.5 [2.7, 10.2], p=0.002) and ciprofloxacin (mean percent change 3.5 [1.3, 5.7], p=0.003) susceptibility were observed with no change in imipenem susceptibility.			

NR = not reported

Table 36. Computerized Decision Support Studies: Cost and Harms Outcomes

Author year	Healthcare cost		Program cost		Opportunity cost		Drug cost		Harms	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Nowak 2012[24] ITS	NR	NR	NR	NR	NR	NR	Slope of ADPD (year-to-year change) differed significantly pre-post intervention (p=0.009)		NR	NR
McGregor 2006[22] RCT	NR	NR	NR	NR	NR	NR	$285,812 during 3 month study period	$370,006	NR	NR
Barenfanger 2001[23] CCT	Total standard cost $13,294 per patient; p=0.008	$18,601 per patient	NR	NR	NR	NR	Variable direct pharmacy cost of $1,227 per patient; p=0.104	$1,702 per patient	NR	NR

NR = not reported; CI = confidence interval; ITS = interrupted time series; RCT = randomized controlled trial; CCT = controlled clinical trial; ADPD = antimicrobial dollars per patient-day

Table 37. Computerized Decision Support Studies: Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
McGregor 2006[22] RCT **High**	High risk: medical record number	High risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Barenfanger 2001[23] CCT **High**	High risk: last name	High risk	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk

CCT = controlled clinical trial; RCT = randomized controlled trial

Table 38. Computerized Decision Support Studies: Risk of Bias Assessment for ITS Studies

Author year Risk of Bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Nowak 2012[24] **High**	Yes	High risk: other stewardship and prescribing changes	Unclear	Low risk	Low risk	Unclear	Low risk
Yong 2010[63] **Medium**	Yes	Unclear: antimicrobial approval system instituted in all other hospital units	Low risk	Low risk	Low risk: data from hospital pathology system	Low risk: data from hospital pathology system	Low risk

ITS = interrupted time series

Table 39. Protocol Studies: Study Characteristics

Author year Geographic area	Purpose of intervention	Intervention (core activity) (n)	Supplements to core activity	Intervention staff	Institutional stewardship resources	Comparator or second intervention (n)	Study design
Carratalà 2012[25] Europe (Spain)	Reduce duration of IV antimicrobial therapy and length of stay	3-Step Critical Pathway	Checklist added to medical chart of intervention patients	Physician	NR	Usual care	RCT
Pulcini 2011[27] Europe (France)	Improve quality (appropriateness) of prescriptions; improved documentation of process measures	Systematic reassessment	Order forms, process measures ("day 3 bundle")	Physician	NR	None (ITS)	ITS
Goldstein 2009[64] North America (US)	Evaluate effect of antimicrobial substitution	Autosubstitution of ertapenem for ampicillin-sulbactam	NR	NR	NR	None (ITS)	ITS
Oosterheert 2006[26] Europe (Netherlands)	Evaluate effectiveness of early switch	Switch from IV to oral antimicrobial therapy after 3 days	NR	Not reported (paper refers to a protocol)	NR	Usual care (7 days of IV antimicrobial therapy)	RCT

ID = infectious disease; ITS = interrupted time series; NR = not reported; RCT = randomized controlled trial; IV = intravenous

Table 40. Protocol Studies: Site, Patient, and Infection Characteristics

Author year	Hospital type	Site	Patients	Exclusion criteria	Suspected site of infection	Suspected organism
Carratalà 2012[25]	University public and private (2 sites)	NR	N=401 randomized; diagnosed with CAP in emergency department; mean age 71 years, 65% male; >60% were in pneumonia severity class IV or V	Neutropenia, HIV infection, transplantation using immunosuppressive drugs; also excluded if met 2 or more of following: ICU admission from ED, imminent death, shock, complicated pleural effusion, pregnancy, aspiration pneumonia, severe social problems	Lungs	*Streptococcus pneumonia, Legionella pneumophila, Haemophilus influenzae*
Pulcini 2011[27]	Teaching (1 site)	Medical ICU	N=114; all curative antimicrobial therapy patients	Prophylactic antimicrobials; transfer, death, or discharge before day 4; antimicrobial therapy began in another ward >4 days before admission	All	All
Goldstein 2009[64]	Community, teaching	NR	NR	NR	Multiple	Focused on susceptibility of *Pseudomonas aeruginosa*
Oosterheert 2006[26]	Teaching (5) and University (2)	General hospital wards	N=302 randomized; n=254 in "ITT"; n=229 in per protocol; severe pneumonia; mean age 69 years, 66% male; >80% were in pneumonia severity class IV or V	Needed mechanical ventilation, cystic fibrosis, history of colonization with Gram-negative bacteria, malfunction of digestive tract, life expectancy <1 month, infections other than pneumonia requiring treatment, severe immunosuppression	Lungs	*Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae, Streptococcus pneumnoiae, Staphylococcus aureus, Hemophilus influenzae, Mycoplasma catharralis,* other

CAP = community acquired pneumonia; ICU = intensive care unit; ED = emergency department; ITT = intention-to-treat analysis; NR = not reported

Table 41. Protocol Studies: Clinical/Patient Outcomes

Author year	30-day readmission n/N (%)		Mortality n/N (%)		Incidence of *C. difficile* n/N (%)		Length of stay mean days (SD)		Adverse Events n/N (%)	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Carratalà 2012[25] RCT	18/200 (9.1%) Difference 1.6% (95% CI -3.8%, 7.1%; p=0.59)	15/201 (7.5%)	30 day 4/200 (2.0%) Difference 1.0% (95% CI -1.4, 3.4; p=0.45)	2/201 (1.0%)	NR	NR	Median (IQR) 3.9 (2.8 to 5.8) Difference -2.1 (95% CI -2.7, -1.7; p<0.001)	Median (IQR) 6.0 (4.8 to 8.8)	Drug reactions 9/200 (4.5%) Difference -11.4% (95% CI -17.2, -5.6%; p<0.001)	32/201 (15.9%)
Pulcini 2011[27] ITS	NR	NR	Day 7: 2/52 (4%) ; p=0.18 At discharge 4/52 (8%); p=0.03*	Day 7: 3/62 (5%) Discharge 14/62 (23%)	NR	NR	13.8 (18.2); p=0.99	13.9 (14.9)	NR	NR
Oosterheert 2006[26] RCT	NR	NR	5/132 (4%) Difference 2% (95% CI −3%, 8%)	8/133 (6%)	NR	NR	9.6 (5.0), Difference 1.9 (95% CI 0.6, 3.2; p<0.05)	11.5 (4.9)	Clinical deterioration 8/132 (6%); p=ns	6/133 (5%)

ITS = interrupted time series; RCT = randomized controlled trial; NR = not reported; ns = not statistically significant; IQR = interquartile range
*Analysis of means

Table 42. Protocol Studies: Prescribing Outcomes

Author year Study design	Timing Intervention	 Control	Use Intervention	 Control	Selection Intervention	 Control	Dose Intervention	 Control	Duration Intervention	 Control
Carratalà 2012[25] RCT	Time to antimicrobial therapy Median (IQR) 3.3 (1-13) days p=0.45	4.0 (1-20) days	NR	NR	NR	NR	NR	NR	Duration of IV therapy Median 2.0 days Difference -2.0 days (95% CI -2.0, -1.0) p<0.001	Median 4.0 days
Pulcini 2011[27] ITS	NR	NR	*Quality of therapy-day 3* Appropriate 20/52 (38) Inappropriate 19/52 (37) Unnecessary 13/52 (25); p=0.86	 Appropriate 27/62 (43) Inappropriate 21/62 (34) Unnecessary 14/62 (23)	NR	NR	NR	NR	NR	NR
Goldstein 2009[64] ITS	NR	NR	*Ertapenem use (median DDD)*: Pre (0=9 months) 0 Formulary (10-19 months) 8 Substitution (20-48 months) 44 *Imipenem use (median DDD)* Pre 30 (slope over 9 months=3.18, p<0.001) Formulary 35 (slope=-4.46, p<0.001) Substitution 25 (little change in use) *Use of other antimicrobials* Levofloxacin, cefepime, cefoxitin, & piperacillin-tazobactam: constant		NR	NR	NR	NR	NR	NR
Oosterheert 2006[26] RCT	NR	NR	NR	NR	NR	NR	NR	NR	*Overall antimicrobial treatment* 10.1 days; p=ns *IV treatment* 3.6 (1.5) days; p<0.05	 9.3 days 7.0 (2.0) days

IQR = interquartile range; DDD = defined daily dose; ITS = interrupted time series; NR = not reported; ns = not statistically significant; RCT = randomized controlled trial; IV = intravenous

Table 43. Protocol Studies: Microbial Outcomes

	Institutional resistance		Resistance in study population	
Author year	**Intervention**	**Control**	**Intervention**	**Control**
Goldstein 2009[64]	*Susceptibility of P. aeruginosa to imipenem (median %)*: Pre (0=9 months) 69% Formulary (10-19 months) 75% (slope=1.74, p<0.001) Substitution (20-48 months) 88% (slope=0.02, p=0.85) For every unit decrease in monthly DDD of imipenem, there was an increase of 0.38% (p=0.008) in susceptibility of *P. aeruginosa* to imipenem in the same month. *Susceptibility of P. aeruginosa to other antimicrobials* Levofloxacin: increased (slope=0.53, p=0.021) Cefepime: increased (slope=0.54, p<0.001) Piperacillin-tazobactram: increased (slope=0.14, p=0.04)		NR	NR

DDD = defined daily dose

Table 44. Protocols Studies: Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Carratalà 2012[25] RCT **Medium**	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Oosterheert 2006[26] RCT **Medium**	Low risk	Low risk	Unclear	Low risk	Low risk (but not ITT)	Low risk	High risk: per protocol analysis with 229 of 302 randomized	Low risk

RCT = randomized controlled trial; ITT = intention to treat

Table 45. Protocol Studies: Risk of Bias Assessment for ITS Studies

Author year Risk of Bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Pulcini 2011[27] **Medium**	Yes	Low risk	Unclear	Low risk: data obtained from medical records	Low risk	Low risk	Low risk
Goldstein 2009[64] **Medium**	Yes	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk

ITS = interrupted time series