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 Study design	Timing Intervention	 Control	Use Intervention	 Control	Selection Intervention	 Control	Dose Intervention	 Control	Duration 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 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
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 Study design	Timing Intervention	 Control	Use Intervention	 Control	Selection Intervention	 Control	Dose Intervention	 Control	Duration 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	Timing		Use		Selection		Dose		Duration	
Study design	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	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		Use		Selection		Dose		Duration	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	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