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Number 9

Closing the Quality Gap:
A Critical Analysis of Quality Improvement Strategies
Volume 4—Antibiotic Prescribing Behavior

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850 or by email to **epc@ahrq.gov**.

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Structured Abstract

Objective: Unnecessary prescribing of antibiotics is a major problem in the US and worldwide, contributing to the problem of antimicrobial resistance (AMR). This review examines the effects of quality improvement strategies on reducing inappropriate prescribing of antibiotics, targeting both prescribing of antibiotics for non-bacterial illnesses ("the antibiotic treatment decision") and prescribing of broad-spectrum antibiotics when narrow-spectrum agents are indicated ("the antibiotic selection decision").

Search Strategy and Inclusion Criteria: We evaluated studies examining the effectiveness of quality improvement (QI) strategies targeting outpatient antibiotic prescribing for acute illnesses. Studies were identified by searching the Cochrane Collaboration's Effective Practice and Organisation of Care registry and MEDLINE®. We included randomized and quasi-randomized controlled trials, controlled before-after studies, and interrupted time series that reported measures of antimicrobial use. QI strategies were classified as clinician education, patient education, provision of delayed prescriptions, audit and feedback, clinician reminders, and financial or regulatory incentives. Our primary outcomes were the percentage of patients prescribed an antibiotic (for antibiotic treatment studies); or the percentage of patients prescribed a recommended antibiotic or guideline-concordant antibiotic therapy (for antibiotic selection studies). Secondary outcomes included effects on antimicrobial resistance, intervention safety (disease outcomes and adverse events), prescribing costs, and patient satisfaction.

Data Collection and Analysis: Two reviewers abstracted data on the components of the QI intervention, study population, targets, and outcomes. We compared the effects of QI strategies in terms of the median effect achieved for the primary outcomes, using nonparametric tests; studies not eligible for median effects analysis were summarized qualitatively.

Main Results: Fifty-four studies reporting a total of 74 trials met the inclusion criteria; 34 studies (reporting 41 trials) addressed the treatment decision, and 26 studies (reporting 33 trials) addressed the selection decision. Six studies evaluated both decisions. Study methodologic quality was generally fair. Nearly all studies took place in outpatient primary care clinics.

Studies addressing the antibiotic treatment decision: Most studies addressed prescribing for acute respiratory infections (ARIs). Interventions were effective at reducing prescribing, with a median absolute effect of -8.9% [interquartile range (IQR) -12.4% to -6.7%]. No individual QI strategy (or combination of strategies) was more effective at reducing prescribing. Within clinician education, active educational strategies appeared more effective than passive strategies. When extrapolated to a population level, strategies targeting general antibiotic prescribing appeared to reduce antibiotic prescribing more than strategies targeting prescribing for a single condition. Few studies addressed secondary endpoints; patient satisfaction was not worsened by QI interventions, but effects on AMR or costs could not be assessed.

Studies addressing the antibiotic selection decision: Interventions targeted prescribing for ARIs or urinary tract infections (UTIs). Interventions were effective, with a median absolute improvement in prescribing of recommended antibiotics of 10.6% (IQR 3.4% to 18.2%). Clinician education alone appeared more effective than education in combination with audit and

feedback, but this finding likely represents confounding. Very few studies addressed secondary outcomes.

Conclusion: Quality improvement efforts appear generally effective at reducing both inappropriate treatment with antibiotics and inappropriate selection of antibiotics. While no single QI strategy was more effective than others, active clinician education may be more effective than passive education, particularly for addressing the antibiotic treatment decision. Greater reductions in overall prescribing may be achieved through efforts targeting prescribing for all acute respiratory infections, rather than targeting single conditions. The available evidence is of only fair quality, and further research on the cost-effectiveness and potential harms of these interventions is needed.

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Appendixes and Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

Executive Summary

The introduction of antibiotic therapy into medical practice has yielded substantial benefits for patients over the past 6 decades. However, the benefits of antibiotic use to individual patients come at a societal cost: the emergence of antimicrobial resistance (AMR) among bacterial pathogens. Once confined to the inpatient setting, resistant bacteria are now common community-acquired infections as well. Antibiotic use encourages the development and spread of antibiotic-resistant bacteria by at least two mechanisms: (1) by applying selective pressure, encouraging development of new strains of antibiotic-resistant bacteria, and (2) by eliminating normal bacterial flora in human hosts, which promotes colonization and spread of existing antibiotic-resistant strains. The increasing prevalence of antibiotic resistance has led to the use of more expensive and broad-spectrum antibiotics for empiric treatment of common outpatient infections, and increased morbidity and mortality among patients hospitalized with serious community-acquired infections.

Reducing inappropriate use of antibiotics is a critical step in slowing the progression of current levels of resistance, and in preventing the emergence of new strains of antibiotic-resistant bacteria. Accomplishing this requires a two-part approach. First, the use of antibiotics in conditions for which these drugs provide little or no benefit must be reduced. Second, antibiotics prescribed for patients who do require antimicrobial therapy must be appropriately targeted, and inappropriately lengthy treatment courses should be shortened.

In this fourth volume of the *Closing the Quality Gap* series, we critically analyze quality improvement strategies to reduce inappropriate antibiotic prescribing. We focus on interventions targeting antibiotic prescribing for acute illnesses in the outpatient setting, primarily acute respiratory infections (ARIs). Prescribing for acute conditions accounts for the majority of antibiotics dispensed in the US, and is thus likely to have the greatest influence on AMR patterns. We examined the effect of quality improvement strategies on antibiotic treatment (the decision to prescribe antibiotics for illnesses for conditions generally not requiring antibiotic therapy) and antibiotic selection (the choice of one antibiotic over another for illnesses requiring antibiotic treatment). Our review includes studies on the effect of prescribing-focused QI strategies on AMR, clinical outcomes, costs of prescribing, and patient satisfaction.

We structured the review to address the following key threshold questions:

1. *Are quality improvement strategies to improve outpatient antibiotic use effective?*
2. *What are the critical components of effective intervention strategies?*
3. *Which patients and conditions should be targeted in order to exert the maximal impact on antibiotic prescribing?*
4. *What are the limitations of current research in this field, and which areas require further study?*

As in previous reviews in this series, we performed a rigorous search of the published literature using the Cochrane Collaboration Effective Practice and Organisation of Care (EPOC) database, supplemented by targeted MEDLINE® searches. We classified QI interventions according to a modification of a taxonomy used in previous volumes of this series. The QI strategies were classified as follows:

1. Clinician education
2. Patient education

3. Provision of delayed prescriptions
4. Audit and feedback
5. Clinician reminder systems
6. Financial or regulatory incentives for patients
7. Financial or regulatory incentives for clinicians

Educational strategies were subdivided into active or passive strategies, based on whether or not the learner was actively engaged in the learning process.[1] We analyzed the QI strategies for their effects on antimicrobial prescribing, defined as the change in the percentage of patient visits at which an antibiotic was prescribed (for treatment decision studies) or the change in the percentage of visits at which a recommended antibiotic was prescribed (for selection decision studies). We quantitatively synthesized the studies by determining the median effect of studies using a particular QI strategy (or combination of strategies), and rigorously evaluated for the presence of potential confounders or effect modifiers. Formal meta-analysis was not possible due to heterogeneity among the included studies. For details on the statistical methodology used, please refer to *Closing the Quality Gap, Volume 1—Series Overview and Methodology* (AHRQ publication No. 04-0051-1).

From a sample of 521 potentially relevant articles, we reviewed the full text of 147 articles. Of these, a total of 54 articles, reporting a total of 74 comparisons, met our inclusion criteria and were reviewed. The treatment decision was addressed in 34 articles (41 separate comparisons), and the selection decision was addressed in 26 articles (totaling 33 comparisons); six articles evaluated both the treatment and selection decision. Among these studies, 24 comparisons for the treatment decision presented data amenable to median effects analysis, and 22 comparisons for the selection decision were similarly amenable to quantitative analysis.

Based on our findings, we reached the following conclusions:

1. Quality improvement strategies are moderately effective at reducing the inappropriate prescribing of antibiotics and improving the appropriate selection of antibiotics.

Overall, interventions targeting the antibiotic treatment decision were effective at reducing prescribing, with a median effect of -8.9% (interquartile range (IQR) -12.4% to -6.7%); indicating an absolute reduction in antibiotic prescribing rates of 8.9% in intervention groups compared with comparison groups. Similar effects were also apparent in studies not meeting criteria for quantitative analysis. We did not find evidence for confounding or effect modification by study design or other moderating factors.

Antimicrobial resistance was measured in only two studies, neither of which demonstrated a reduction in resistance despite a reduction in prescribing rates; however, the limited duration of followup (6 months) was likely insufficient to detect potential effects on resistance rates. Strategies to reduce antibiotic prescribing were not associated with increased use of health services, increased duration of illness symptoms, or decreased patient satisfaction. Costs were reduced in the two studies measuring this outcome.

[1] Active clinician education strategies included academic detailing (educational outreach), consensus-building sessions, and educational workshops. Active patient education strategies included one-on-one or group educational meetings. Passive educational strategies (for both clinicians and patients) included distribution of educational materials (e.g., waiting room pamphlets for patients) and lectures (e.g., traditional CME for clinicians).

Interventions targeting the antibiotic selection decision were also effective, with a median absolute improvement of 10.6% (IQR 3.4% to 18.2%) in prescribing of recommended antibiotics in the intervention groups compared with the comparison groups. Most studies used either clinician education alone or clinician education combined with audit and feedback. Interventions targeted both ARIs and urinary tract infections (UTIs), with some interventions targeting general prescribing; no significant differences were found for QI strategies targeting different disease processes or patient populations. In four studies, duration of antibiotic therapy for urinary tract infections was assessed, with effects ranging from no benefit to a reduction in mean antibiotic duration of approximately 2 days.

No studies assessed the effect of interventions targeting antibiotic selection on resistance, health services utilization, or disease outcomes. Three studies measuring prescribing costs showed 20-30% relative reductions attributable to the intervention.

We conclude that QI strategies are moderately effective at improving prescribing behavior, with regard to both antibiotic treatment and antibiotic selection decisions. Organizations should compare studies performed in similar settings, and with similar patient and provider populations, in order to identify specific QI strategies that are most likely to be effective in their own setting. Several particularly salient studies (representative of the types of interventions and settings encountered in our review) are summarized in Appendix A[*], to provide a starting point for considering important implementation factors. Appendix B contains summaries of all included studies organized by setting and patient population in order to facilitate identification of relevant studies.

2. Although no single quality improvement strategy is clearly superior, active clinician education may be more effective in certain settings.

Studies predominantly used clinician education strategies or clinician education in combination with patient education; smaller numbers of studies used audit and feedback, or other combinations of strategies. We did not find definitive evidence for superiority of one strategy (or combination of strategies) over another, within either the antibiotic treatment studies or antibiotic selection studies. Delayed prescribing interventions achieved large absolute reductions in ultimate antibiotic consumption, but these studies operated under the assumption that the "default" practice was to uniformly administer antibiotics (even when they might not be indicated, as in acute cough illness). In the treatment studies, the trend suggested that active educational strategies were more effective (p=0.11), an effect also seen in studies not eligible for median effects analysis. Among antibiotic selection studies, the addition of audit and feedback conferred significantly less benefit than clinician education alone (3.4% vs. 13.9%, P=0.03). This finding may in part be explained by confounding: clinician education-alone studies were more likely to have a small sample size, and smaller studies were associated with larger median effects. This effect may be mediated through publication bias, a higher level of engagement between the study directors and target physicians and/or greater intensity of the intervention. In contrast to interventions aimed at the treatment decision, interventions using active educational strategies to improve antibiotic selection were not significantly associated with larger median effects. However, in each of the five studies where active and passive educational strategies were compared head-to-head, the active strategies were superior.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

3. Interventions targeting prescribing for all acute respiratory tract infections may exert a greater effect on overall prescribing than interventions targeting specific types of acute respiratory infections.

Most treatment studies targeted prescribing for ARIs; there were no significant differences in effectiveness for interventions targeting specific ARIs vs. general ARIs, or for interventions targeting children vs. adults. Among antibiotic selection studies, there was no difference in median effects among interventions targeting general ARIs, specific ARIs, or UTIs. In an effort to maximize the relevance of interventions targeting the antibiotic treatment decision at the health system level, we conducted a separate analysis extrapolating study effect sizes to the population level, determining the number of antibiotics per 1000 person-years that could be saved as a result of the intervention. Interventions targeting prescribing for all ARIs have more impressive effects when their impact is extrapolated to the population level (35-85 antibiotic prescriptions saved per 1000 person-years), even though the individual study effect sizes are more modest. In contrast, condition-specific interventions (e.g., those targeting prescribing for pharyngitis in children), reporting large effects within the study population, have smaller effects on prescribing at the population level (e.g., 5-15 antibiotics saved per 1000 person-years). The greater population effects of strategies targeting prescribing for all ARIs (as opposed to focusing on a single condition or patient age range) could result in relatively higher cost savings as well, depending on the nature and intensity of the intervention.

4. Study design and quality should be improved. Studies that formally evaluate the cost effectiveness of interventions to improve antibiotic treatment and selection are needed, and studies should evaluate the potential harms of such interventions.

As noted in previous reviews of diabetes and hypertension QI strategies in this series,[1, 2] the methodological quality of included trials was only fair. In both treatment and selection studies, approximately half the trials were non-randomized; most failed to document the rationale for selection of the comparison group. Other basic quality problems such as inadequate concealment of allocation and unit-of-analysis errors appeared frequently. Moreover, studies consistently failed to describe the theoretical basis for their intervention or the rationale for choice of the QI strategies used, and did not document the reach of the intervention (i.e., the extent to which the target population actually received the intervention). These differences may affect the internal and external validity of the studies. In addition, it is also likely that our results were confounded by substantial inter-study variations in patient population, disease target, and clinical settings, as well as many unmeasured confounding variables such as local factors, the culture of medical practice, and the health care system structure.

Future studies should aim for higher methodological standards, and should maximize the applicability of their interventions by clearly defining the characteristics of the intervention, the setting, and the participants. Few studies evaluated potential harms to patients that could result from reducing antibiotic use, such as adverse clinical consequences or increased use of health services. In addition, our conclusions are limited to fairly short term intervention effects. Most importantly, very few studies reported any information on the implementation costs, and no studies performed a formal cost effectiveness analysis. Documentation that QI strategies recover their implementation costs through savings in antibiotic costs would greatly enhance the appeal of such programs to health systems.

Technical Review

Chapter 1. Introduction

Rationale for Reducing Excess Antibiotic Use in Ambulatory Practice

The introduction of antibiotic therapy into medical practice has yielded substantial benefits for patients over the past 6 decades. Recently, however, there has been a growing awareness that the benefits of antibiotic use to individual patients come at a societal cost: the emergence of antimicrobial resistance (AMR) among bacterial pathogens.[3, 4] Though initially restricted to hospital settings, antibiotic resistance is now growing among important community-acquired bacterial pathogens, particularly *Streptococcus pneumoniae* (SP),[5-7] *Staphylococcus aureus,*[8, 9] and *Escherichia coli*.[10-12]

Although the problem of antibiotic resistance can be viewed from many perspectives, a pragmatic viewpoint approaches it as a problem of antibiotic prescribing practices. Antibiotic use promotes the development and spread of antibiotic-resistant bacteria by at least two mechanisms: (1) selective pressure that enhances the proliferation and sustainability of bacterial strains that contain mutations conferring resistance to a specific antibiotic (or class of antibiotics), and (2) elimination of an individual's normal flora, thus conferring a survival advantage to antibiotic-resistant bacteria should exposure to antibiotics occur (i.e., creating a susceptible host). While development of antibiotic resistance primarily occurs via the first mechanism, the rapid rise in prevalence of antibiotic-resistant bacteria is primarily a function of the second mechanism. Carriage, transmission, and infection with antibiotic-resistant bacteria are strongly associated with prior antibiotic use.[13-16]

Community-acquired antibiotic-resistant infections affect morbidity, mortality, and health care costs. Treatment failures have been reported in patients with pneumococcal meningitis after treatment with penicillin, chloramphenicol, clarithromycin, ceftriaxone, and cefotaxime.[17-22] The management of children with recurrent or persistent otitis media or sinusitis has become significantly more difficult as a result of the emergence of high rates of drug-resistant *Streptococcus pneumoniae* (DRSP) in this subgroup.[23-25] One US study reported an association between high-level DRSP and excess mortality among patients surviving more than 4 days in the hospital, after controlling for age and comorbidity,[26] and another demonstrated an increased risk of suppurative complications for patients with bacteremic pneumonia due to DRSP.[27]

The emergence of drug-resistant bacteria has implications not only for patients with documented resistance, but for all patients who *might* have such infections. Currently, the specter of DRSP and other resistant bacteria has led to recommended empiric treatment regimens for a variety of infections (such as community-acquired pneumonia[28, 29]) that include antibiotics previously reserved for life-threatening infections; antibiotic resistance to these powerful agents--often our last lines of defense--will certainly accelerate as a result. Only 6 years after the introduction of extended-spectrum macrolides, macrolide resistance among *S. pneumoniae* increased from 10% to 20%.[30] In Canada, where ambulatory use of levofloxacin (the agent of choice for treatment of DRSP infections) has been very high, investigators have already detected the emergence of levofloxacin resistance.[7] Previous optimistic predictions about "the end of the era of infectious diseases" have increasingly been replaced by dire predictions of a new "post-antibiotic era."[3, 31, 32]

Reducing inappropriate use of antibiotics is a critical step in preventing or slowing the progression of resistance. Progress will require a two-part approach. First, it is critical to reduce the use of antibiotics in conditions for which these drugs provide little or no benefit. Second, it is important to modify the choice of drug given to patients who *do* require antimicrobial therapy, and in some cases to shorten inappropriately lengthy treatment courses. Based on the best evidence and mathematical modeling to date, reductions in antibiotic consumption may not lead to major reductions in existing levels of antibiotic resistance among community-acquired bacterial infections,[33-35] although studies have demonstrated reduced levels of resistance to specific antibiotics.[36] However, ecological studies do support the notion that the amount of antibiotic consumption in a community directly influences how rapidly new resistance emerges or rises.[7, 37]

Current Antibiotic Prescribing Practice Patterns in US Ambulatory Practices

In the US, the majority of outpatient antibiotic prescriptions are for acute respiratory tract infections (ARIs)[2]; in 1998, an estimated 76 million ambulatory office visits for ARIs resulted in 41 million antibiotic prescriptions.[38] Based on a comparison of bacterial prevalence estimates to prescribing rates, it appears that 55% of total antibiotics prescribed for ARIs in 1998 (n=22.6 million prescriptions) were unlikely to be treating a bacterial infection, resulting in a total cost for excess antibiotic prescriptions of approximately $726 million.

In response to efforts to publicize overuse of antibiotics,[39, 40] initial progress to reduce inappropriate antibiotic prescribing was made. Between 1990 and 2000, antibiotic prescription rates for adults and children with ARIs declined significantly. Unfortunately, prescribing rates stabilized in 1999-2000.[40]

In addition to the general inappropriate use of antibiotics in conditions not requiring antimicrobial therapy, increasing attention has been paid to the choice of antibiotic for patients receiving such therapy. The use of broad-spectrum antibiotics (quinolones, second- and third-generation cephalosporins, newer-generation macrolides, and amoxicillin-clavulanate) in community-based settings rose from 24% of total adult antibiotic prescriptions in 1991-1992 to 48% 7 years later.[41] A similar rise (23% to 40%) was observed in children.

A variety of national and international organizations have recommended action to improve antibiotic treatment and selection.[3] In 1996, a task force convened by the Centers for Disease Control and Prevention (CDC) outlined strategies for addressing this epidemic, highlighting the importance of promoting judicious antibiotic use in ambulatory practice.[42] The issue was further underscored by a subsequent Institute of Medicine (IOM) report on antimicrobial resistance,[43] as well as in the recommendations from a US federal multi-agency task force that created the "Public Health Action Plan to Combat Antimicrobial Resistance."[44] In collaboration with the CDC, the National Committee for Quality Assurance and the Council for Affordable Quality Healthcare are creating quality measures for appropriate antibiotic use for inclusion in the Health

[2] The terms acute respiratory infection (ARI) and upper respiratory infection (URI) are frequently used interchangeably in the literature. For this report, we use ARI to refer to these conditions.

[3] Key initiatives include the CDC's "Get Smart" campaign (http://www.cdc.gov/drugresistance/community/), the WHO's Global Strategy for Containment of Antimicrobial Resistance (http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_DRS_2001_2_EN/en/), and the Association for Prudent Use of Antimicrobials (http://www.tufts.edu/med/apua/).

Plan Employer Data and Information Set (HEDIS)[45]. Other countries have also developed their own campaigns, some with striking success.[36] Almost 30 countries in Europe have combined their efforts to monitor trends in antibiotic use.[46] Finally, in the seminal IOM report "Priority Areas for National Action: Transforming Health Care Quality,"[47] antibiotic overuse (as a major part of medication management) was identified as one of 20 priority areas for improving health care quality -- a designation reflecting not only the severity of the problem, but also the substantial potential to narrow the gap between actual and best practices.

The Purpose of This Evidence-based Practice Center Report

In this report, we systematically review published research articles evaluating interventions to improve antibiotic prescribing practices. Our intent is to identify the most effective strategies for improving the use and selection of antibiotics. We focus our review on acute infectious illnesses in the outpatient setting, and separately review (1) the antibiotic ***treatment*** decision (i.e., the use of antibiotics for conditions generally not requiring antibacterial therapy), and (2) the antibiotic ***selection*** decision (i.e., the choice of one antibiotic over another, for conditions requiring antibacterial therapy). In particular, our research questions are:

1. Which QI strategies are most effective in reducing unnecessary antibiotic treatment of acute illnesses?
    - A. Are particular QI strategies more effective for certain target conditions?
    - B. Are particular QI strategies more effective in specific patient populations?
    - C. Do QI strategies to reduce unnecessary antibiotic treatment affect clinical outcomes?
        1. Do they reduce adverse drug events?
        2. Do they improve clinical outcomes?
        3. Do they increase return visits or illness-related hospitalizations?
    - D. Do QI strategies to reduce unnecessary antibiotic treatment have downstream patient- and system-level consequences?
        1. Do they reduce antimicrobial resistance?
        2. Do they reduce antibiotic/pharmacy costs?
        3. Do they decrease patient satisfaction?

2. Which QI strategies are most effective in improving antibiotic selection for the treatment of acute illnesses?
    - A. Are particular QI strategies more effective when the goal is (i) to reduce use of broad-spectrum agents, or (ii) to increase use of broad-spectrum agents (i.e., due to local resistance patterns)?
    - B. Are particular QI strategies more effective at improving optimal dosing and duration of a selected antibiotic therapy?
    - C. Are particular QI strategies more effective for certain target conditions?
    - D. Are specific QI strategies more effective in specific patient populations?
    - E. Do QI strategies to improve antibiotic selection affect clinical outcomes?
        1. Do they reduce adverse drug events?

2. Do they improve clinical outcomes?
3. Do they increase return visits or illness-related hospitalizations?

F. Do QI strategies to improve antibiotic selection have downstream patient- and system-level consequences?
1. Do they reduce antimicrobial resistance?
2. Do they reduce antibiotic/pharmacy costs?
3. Do they decrease patient satisfaction?

In order to maximize the relevance of our findings for organizations that are considering implementing these interventions, we summarize the existing evidence by attempting to answer the following questions:

1. Are quality improvement strategies to improve outpatient antibiotic use effective?
2. What are the critical components of effective intervention strategies?
3. Which patients and conditions should be targeted in order to exert the maximal impact on antibiotic prescribing?
4. What are the limitations of current research in this field, and what areas require further study?

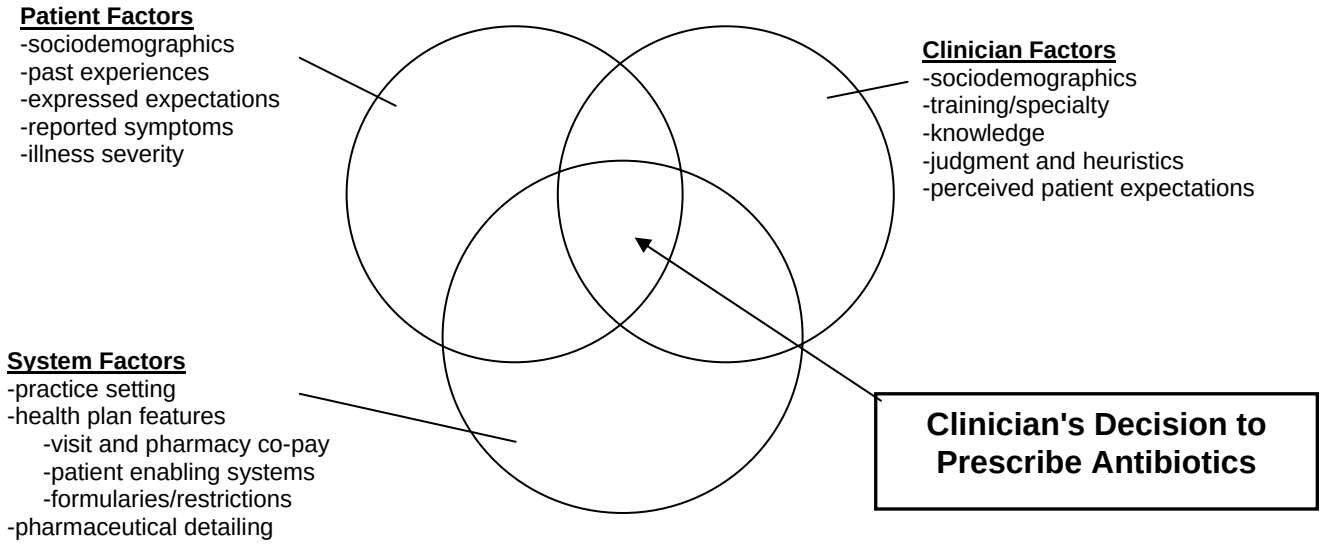
An Explanatory Model of Antibiotic Prescribing Behavior

The decision to prescribe antibiotics is the result of complex interactions among patient, physician, and system factors, and effective strategies to improve antibiotic prescribing behavior may need to address each of these domains. Previous research on the influence of these factors on office-based antibiotic prescribing is summarized below. Most of this research has focused on the antibiotic treatment decision, although several studies have explored factors that influence antibiotic selection.

Past research has identified the characteristics of successful QI programs across a variety of disease states and clinical settings.[48-51] While this work provides an important framework for examining QI strategies, factors that drive antibiotic prescribing decisions draw on a differently prioritized set of inputs from those that impact physician behavior in other clinical settings.

Specifically, the management of common outpatient infections and the decision to prescribe antibiotics, particularly when they are not indicated, can be viewed within a sociocultural and social ecological context in addition to the traditional biomedical perspective. The various inputs to this decision are presented in the adaptation of Kleinman and colleagues' model[52] for clinician decisionmaking in Figure 1.

Figure 1. Factors affecting the decision to prescribe antibiotics.



Clinician Factors

Patient and parent expectations are consistently identified as the primary factor influencing unnecessary prescribing of antibiotics.[53-58] Nonetheless, internal clinician factors such as knowledge, experience, and training also play a role, suggesting that intervention strategies include efforts to improve clinician education.

Despite strong evidence that antibiotics are ineffective for acute bronchitis, 50 – 80% of adults with bronchitis are prescribed them.[38, 59, 60] Practice-based studies repeatedly show that there are few or no predictors of antibiotic treatment for acute bronchitis, suggesting that the diagnosis of acute bronchitis is often viewed as an indication for antibiotic treatment. Antibiotic prescribing for uncomplicated ARIs is strongly associated with the presence of purulent manifestations (purulent nasal discharge, purulent phlegm production, and tonsillar exudate).[61] These findings suggest that clinicians appear to use a heuristic (or "rule of thumb") for deciding which patients with ARIs to treat with antibiotics, one that pays particular heed to the presence of purulence. However, purulence does not predict bacterial infection or antibiotic responsiveness among patients with ARIs.[62-66]

Other studies have found that clinician specialty and level of training are also associated with antibiotic use for these conditions. High prescribers of antibiotics for colds, ARIs, and bronchitis are more likely to be older,[67] and to practice in rural locations.[38] In a national study of antibiotic treatment of ARIs in emergency departments, antibiotics were prescribed less often by house staff than by staff or other physicians, and more often to adults than children, regardless of specific ARI diagnosis.[68] In several national studies evaluating antibiotic selection, physician specialty was one of the strongest independent predictors of antibiotic selection, suggesting possible differences in knowledge or the "culture of prescribing."[69-71]

Public/Patient Factors

Multiple studies demonstrate that patients who seek care for ARIs expect to receive antibiotics,[69-73] and that patients or parents who expect antibiotics receive them more frequently.[54, 55, 57, 58] These expectations are strongly associated with the patient's previous experiences of receiving antibiotic treatment for these illnesses,[74] and appear to arise from misperceptions about antibiotic efficacy for viral illnesses.[75] Illness labeling may play an important role in conveying antibiotic treatment necessity. For example, referring to an acute cough illness as a "chest cold" was associated with much lower beliefs that antibiotics are necessary treatment than when the same illness was called "bronchitis."[76]

Although patients and parents frequently expect antibiotics for ARIs, most studies find that satisfaction appears more closely related to how much time the doctor spent explaining the illness rather than whether the patient received an antibiotic.[55, 57, 77, 78] In a setting where antibiotic prescribing for acute bronchitis had been reduced by 50%, patient satisfaction with care and number of return office visits did not change.[77]

Patient sociodemographic factors are also associated with excess antibiotic use for ARIs, and may in part be related to varying knowledge, attitudes, and expectations in different population groups as well as clinician attitudes about these groups. Antibiotic prescription rates for ARIs appear to be lower among blacks than whites,[38, 79] which may account for the lower relative risk of carriage or infection with antibiotic-resistant bacteria among black populations.[14, 38, 79-81] Similarly, black patients receiving an antibiotic for ARI were less likely to be given a broad-spectrum agent than white counterparts.[69] Age also plays an important role. The frequency of antibiotic treatment for colds, ARIs, and bronchitis is greatest among the very young (age < 5 years) and lowest among the elderly (age > 64 years).[38, 60] The mechanisms by which these sociodemographic factors influence clinician decisionmaking are not known, but are probably related to varying patient expectations for antibiotics and/or clinician judgments about the ability to adequately discuss treatment choices with patients whose backgrounds differ from theirs, or who have low health literacy.[82]

Health Care Delivery System Factors

Health plan and physician practice characteristics may act as barriers to, or facilitators of antibiotic prescribing for ARIs. Health plans can influence their members' propensity to seek care and expectations for care by instituting visit and pharmacy co-payments,[83] requiring prior authorization for urgent care or same-day clinician visits, and making telephone advice service available.[84] Lack of insurance also exerts an effect.[69] Health plans can influence clinician behavior by restricting formularies. Such restrictions influence both prescription antibiotic selection and patients' access to alternatives to antibiotic treatment, including non-prescription agents.[69] Practice characteristics such as location, clinician panel size, protocols for mid-level clinicians, exposure to pharmaceutical sales representatives, and availability of pharmaceutical samples also affect access and treatment decisions. For example, clinicians with greater patient workloads prescribe antibiotics for ARIs more frequently.[38, 85, 86] Lack of patient continuity and inadequate followup care mechanisms may provide additional challenges to antibiotic improvement programs based in acute care settings such as urgent care clinics and emergency departments.

Chapter 2. Methods

Scope

This report focuses on QI strategies to reduce unnecessary or inappropriate antibiotic treatment in the outpatient setting. Changes in outpatient antibiotic use are likely to have the greatest impact on efforts to arrest the development and spread of antibiotic-resistant bacteria that cause community-acquired infections. We restricted our focus to antibiotic treatment of acute illnesses, excluding studies of prophylactic antibiotic use and antibiotic therapy for chronic illnesses, both to minimize the conceptual heterogeneity of our approach and because chronic and prophylactic antibiotic use account for a small fraction of total outpatient antibiotic use.

As noted earlier, we reviewed strategies to affect antibiotic use in two realms: the antibiotic treatment decision, and the antibiotic selection decision. Studies in the "treatment decision" group addressed the dichotomous decision of whether or not to treat with antibiotics at all. These studies evaluated QI strategies to reduce the prescribing of unwarranted antibiotics, either overall or for a specific condition or patient population. Studies in the "antibiotic selection" group evaluated QI strategies to increase adherence to recommended choices of antibiotics in situations where antibiotic treatment is warranted.

Definitions of Quality Improvement Terms Used in This Report

For the purposes of this report, we used quality improvement terminology in accordance with the Institute of Medicine report described in previous volumes of the *Closing the Quality Gap* series[1] as follows:

- **Quality gap:** the difference between health care processes or outcomes observed in practice, and those potentially achievable on the basis of current professional knowledge. The difference must be attributable in whole or in part to a deficiency that could be addressed by the health care system.

- **Quality improvement strategy:** any intervention strategy aimed at reducing the quality gap for a group of patients representative of those seen in routine practice.

- **Quality improvement target:** the outcome, process or structure that the QI strategy targets, with the goal of reducing the quality gap. For this report, the main QI target was clinician prescribing behavior, either in terms of the decision to prescribe an antibiotic or the selection of an antibiotic.

Classification of Interventions

A single study may include different study arms (groups of subjects), and each arm may receive a different QI intervention. For the purposes of this report, each intervention type was abstracted separately and evaluated as a separate comparison. For example, a single study could

contain three arms: a control or comparison group (depending on whether the study was an RCT or not), a group receiving clinician and patient education, and a group receiving clinician education only. We would consider such a *study* to contain two *trials* (two separate comparisons against the comparison group).

The intervention(s) used in a study sometimes included more than one QI strategy. Each type of QI strategy was abstracted separately, although considered part of the same intervention. Interventions containing two or more different QI strategies (as defined by the categorization listed below) were considered multifaceted interventions. For example, an intervention using (a) audit and feedback and (b) clinician education was defined as a multifaceted intervention, using two QI strategies. Finally, a study could contribute to both "treatment" and "selection" groups if the intervention clearly attempted to influence both the decision to prescribe and the selection of antibiotic, and reported these outcomes appropriately.

Classification of Quality Improvement Strategies

We classified QI strategies targeted at improving antibiotic prescribing in the following manner:

QUALITY IMPROVEMENT STRATEGIES[4]
Clinician education Interventions designed to increase understanding of clinical care principles, or awareness of specific practice recommendations. Specific subtypes of clinician education included passive strategies, where clinicians are not actively engaged in the learning process (e.g., distribution of educational materials, lectures, and meetings such as traditional CME); and active strategies, where clinicians interact and actively participate in their education in one-on-one or small group settings (e.g., workshops, consensus-building sessions, and educational outreach visits). In active strategies, the teacher can actively assess comprehension, and tailor information appropriately; whereas, in passive strategies there is little or no real-time monitoring of whether the information was received and understood by the learner.
Patient education Interventions designed to promote increased understanding of target conditions or to teach specific prevention or treatment strategies. As with clinician education, patient education can also be subdivided into passive strategies (distribution of educational materials) and active strategies (one-on-one or group educational workshops). Mass media efforts (e.g., television announcements or billboards) are a type of passive education usually targeted at patients, but potentially exerting influence on clinicians as well.

[4] Other commonly used QI strategies include patient reminders (efforts to improve adherence to self-care or keeping appointments), facilitated relay of clinical data to providers (provision of data outside of normal chart-based means), promotion of patient self-management (distribution of materials or access to a resource that enhances self-care), and organizational change (changes in the structure or delivery of care to improve efficiency or breadth of care). These strategies are commonly applied in chronic disease management, but are less applicable to an acute illness model, and were only featured in one included study.[87]

Provision of delayed prescriptions

In this strategy, patients are given an antibiotic prescription, but instructed to fill the prescription only if their condition does not improve with supportive measures after a specified period of time. We considered delayed prescriptions to be a unique category. This strategy does not reduce antibiotic prescribing by the clinician *per se*, and it assumes that the "default" practice is to uniformly administer antibiotics (even when they might not be indicated, as in acute cough illness). Delayed prescriptions incorporate elements of patient self-management and patient incentives (e.g., guarantee of a "back-up" medication—antibiotics) to attempt to reduce actual antibiotic use.

Audit and feedback

Summary of clinical performance of health care delivery over a specified period of time, provided to the target clinicians by an individual or organization (e.g., the proportion of a clinician's patients with acute bronchitis for whom the clinician prescribed an antibiotic). Profiling, in which the performance of an individual, clinic or health system is compared with peers, and benchmarking, when the reference point is some established quality standard, would also be considered audit and feedback.

Clinician reminders and decision support systems

A paper-based or electronic system, intended to help a clinician incorporate specific information into a clinical decision. Decision support systems combine reminders with a prompt to follow a recommended pathway of clinical care.

Financial and regulatory incentives or disincentives

Inducements or disincentives that influence individuals to take a desired course of action. We considered incentives for patients and clinicians separately. Common types of financial incentives to patients to reduce unnecessary health care services include office-visit and prescription drug co-payments; capitated insurance plans are an example of financial incentives to clinicians to promote efficient care. A common regulatory disincentive targeted at clinicians is the requirement to submit extra documentation to receive approval to prescribe a restricted drug.

Inclusion and Exclusion Criteria

The inclusion criteria were adapted from previous volumes of the *Closing the Quality Gap* series.[1, 2] Included studies were required to:

- Evaluate an intervention incorporating one of the QI strategies defined above to improve the quality of outpatient antibiotic prescribing for acute illnesses in the outpatient setting (clinic, urgent care, or emergency department).

- Use either (1) an experimental design with a comparison group assigned by the investigators, including patient- or cluster-randomized controlled trials (RCT), quasi-

RCT[5] design, and controlled before-after (CBA)[6] studies; or (2) when a comparison group was not employed, use of an interrupted time series (ITS) with a clearly defined intervention time period, and at least three measurements before and after the intervention.

- Report at least one measure of antimicrobial agent use.

Trials that reported outcomes related to antimicrobial use, such as antimicrobial resistance rates, prescribing costs, health services utilization, or satisfaction with care, were included only if they also measured antimicrobial prescribing. For example, a study of antimicrobial costs to a health care system would be excluded if costs were the only outcome measured; however, if the study also measured antimicrobial prescribing (and met the other methodologic criteria above) the study would be included. We also included studies that assessed the effect of QI strategies on the dose or duration of antimicrobial therapy, where these outcomes were targets of the intervention.

We anticipated that some interventions would give rise to multiple publications. In these situations, we regarded the first publication as the primary study, but included additional information on the intervention or results from the other publications as warranted. In cases where results of an intervention were described at multiple time points in multiple studies, we abstracted data from the short-term followup article, judging that longer-term followup might address the sustainability of an intervention rather than its effectiveness, and in an attempt to maintain consistency of intervention time periods to maximize our ability to pool results across studies.

Literature Search and Review Process

To identify studies for potential inclusion, we searched the electronic database of the Cochrane Registry Effective Practice and Organisation of Care (EPOC) group (Appendix C[*]). The EPOC database catalogs studies that attempt to "improve professional practice and the delivery of effective health care services." The database includes the results of extensive periodic searches of MEDLINE® (from 1966-present), EMBASE (1980-present), and CINAHL® (1982-present), as well as hand searches of specific journals and article bibliographies.[88] The strategy for identification of appropriate studies has a sensitivity of 92.4%.[88] The main EPOC registry primarily includes studies of clinician and system-targeted interventions, identified from a larger database of quality-improvement related studies compiled by Cochrane search experts. To maximize our search yield, we searched the main registry as well as the larger database of QI articles identified for possible inclusion but not meeting criteria for entry in the main registry. We searched for studies relating to antimicrobial prescribing, using terms specific to antimicrobials and prescribing practices as well as specific target conditions (e.g., pharyngitis, urinary tract infection) (Appendix C). We searched the EPOC registry through October 2004. To

[5] "Quasi-RCT" refers to studies described as randomized where randomization was altered by investigators, or where a method of patient assignment was used that is not truly random (e.g. assignment by even/odd medical record number or date of clinic visit.)

[6] Controlled before-after studies are non-randomized trials with a contemporaneous comparison group.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

identify more recent studies, we performed a targeted search of MEDLINE® from June 2004 to November 2004 using similar search terms (Appendix C). In addition, we hand-searched the reference lists of each article that met all inclusion criteria. We included only English-language studies.

A trained research assistant and a physician-investigator (SRR) screened titles and abstracts of the retrieved citations for relevance. If reviewers could not make a decision based on the title and abstract alone, the article automatically moved to full-text review. All full-text reviews were performed by a trained research assistant and at least one core investigator (SRR, MAS, RG). In that stage, reviewers abstracted detailed information on study characteristics, study design, measures of study quality, and outcomes, which were recorded on standardized abstraction forms (Appendix D[*]). Disagreements on the abstracted fields were resolved by consensus, occasionally involving discussion with another core investigator.

Outcome Measures

For studies evaluating the antibiotic treatment decision, the principal outcome measure was the proportion of office visits in which a clinician prescribed an antibiotic. For studies evaluating the antibiotic selection decision, the primary outcome measures were proportion or volume of total antibiotic prescriptions written for a recommended antibiotic, or written in compliance with a specific guideline. Other forms of antibiotic utilization outcomes (e.g., antimicrobial prescriptions per person-year, antimicrobial prescriptions per clinician-year) were abstracted as well, including studies that did not report data in the form of our primary outcome measures.

Secondary outcome measures (in articles that also reported a measurement of antimicrobial prescribing) included clinical and health system effects of antibiotic prescribing, including intervention effects on adverse drug events, clinical outcomes, return visits or illness-related hospitalizations, antimicrobial resistance, costs of prescribing, patient satisfaction, and duration of office visits.

Assessment of Study Quality

In order to assess the overall quality of the literature, we assessed studies based on key elements that increase internal validity and translatability. However, once studies met our inclusion criteria, we did not exclude any on the basis of study quality, nor did we weight statistical analyses by study quality, as this process may unduly influence the results of meta-analysis.[89] Study factors that influence internal validity were chosen based on the methodology of the Cochrane Collaboration, and factors influencing translatability were chosen based on prior literature in the field. They were:

- Factors affecting study internal validity
    - Method of treatment assignment
        - Were study subjects randomized, and if so, was the randomization process described?

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

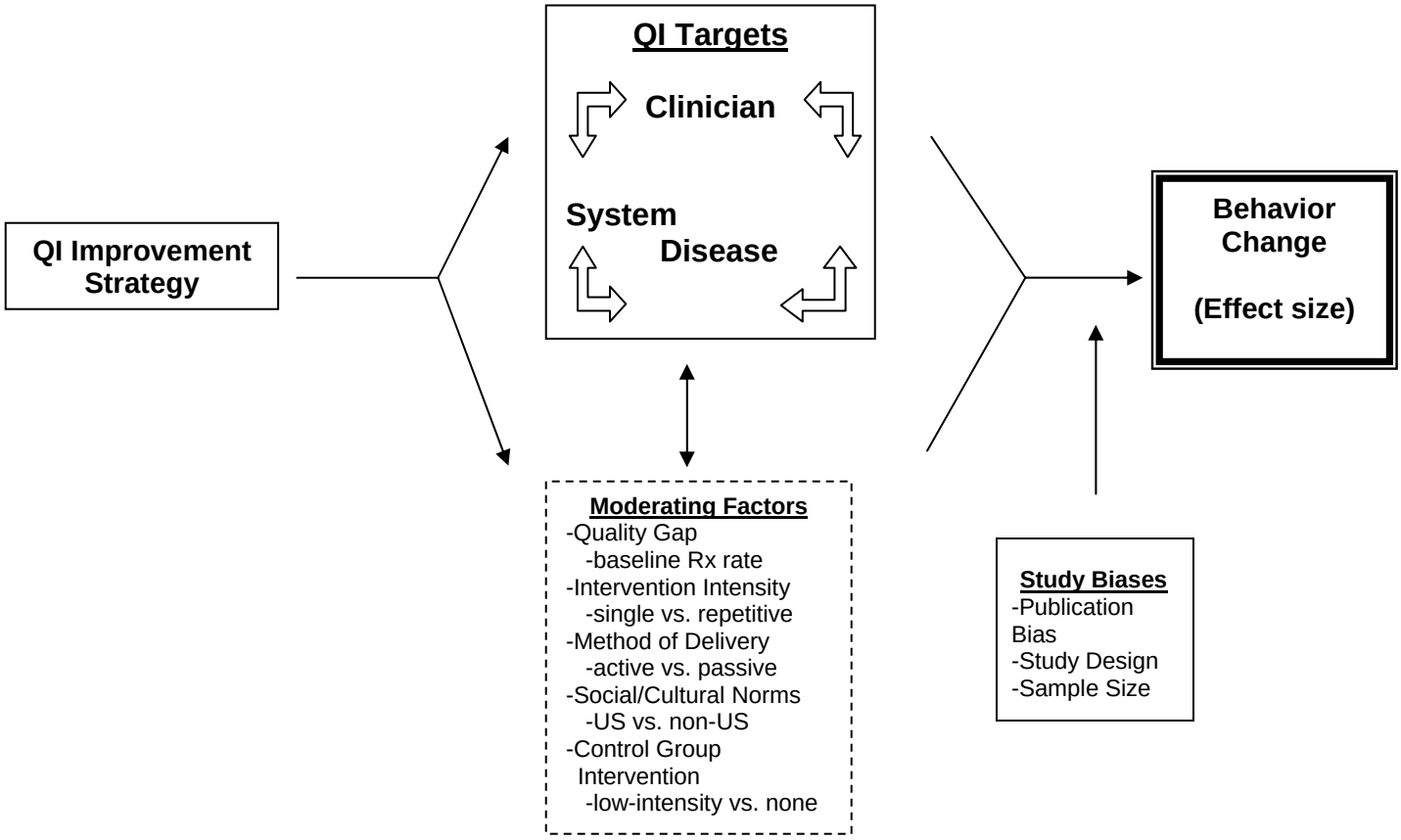
        - For non-randomized studies, was the rationale for selection of the comparison group explained, and a baseline observation period included (to assess selection bias)?
    - Blinding
        - Were the outcome assessors blinded to treatment group assignment?
    - Statistical analyses
        - Was a unit-of-analysis error present? If so, were appropriate statistical methods used for correction?

- Factors affecting study translatability
    - Study design
        - Did the study document a quality gap in antibiotic prescribing in the study population?
        - Did the study address prescribing for a specific condition (as opposed to prescribing in general)?
        - Did the comparison group receive usual care (no intervention) or a low-intensity intervention?
        - Did the study measure prescribing by chart review, or through use of administrative claims data? (Chart review is a more accurate reflection of the clinician's prescribing patterns, since administrative claims data captures only when a patient fills a prescription. Prior studies suggest that about 10 – 15% of antibiotic prescriptions identified on chart review are missed on searches of administrative claims.[90])

An Explanatory Model for Evaluating the Different QI Strategies To Improve Antibiotic Prescribing Behavior

A comparison of effects for QI strategies with different targets must also take into account the possibility that contextual factors, such as intervention delivery, setting, and population factors, could confound (or be responsible for) the observed associations between QI strategies and behavior change. We have constructed the following model for guiding evaluation of QI strategies in light of these possible confounding and moderating factors (Figure 2). Some of these factors may bias the results of an individual study—for example, sample size or the type of intervention delivered to the comparison group. They may also act as effect modifiers or confounders of the observed association between a QI strategy and median effect size. We also examined certain intervention and population factors, which are not typically considered "confounders" at the individual study level (e.g., study design), but which could influence the overall association between QI strategy and median effect size at the summary level.

Figure 2. Evaluation of QI strategies for confounders and moderators.



Statistical Analysis

We expected that the identified studies would exhibit significant heterogeneity, due to variations in study populations (e.g., by age or condition), methodologic features, and characteristics of the interventions (e.g., intensity) or the context in which they were delivered (e.g., magnitude of quality problem, alignment with attitudes of patients and clinicians). Our conventional random-effects meta-analysis confirms the existence of marked heterogeneity, which persisted even after stratifying studies by various design and intervention features (Appendix E*).

Therefore, as our primary approach to the analysis, we chose a framework based on the median effect size, comparing groups of studies that shared specific features of interest. This approach was first developed in a large review of strategies to foster the implementation of clinical practice guidelines[91] and subsequently applied to the reviews of QI strategies for diabetes and hypertension care in previous volumes in this series.[1, 2]

To calculate the median effect size, we calculated the net effect size for each study reporting dichotomous outcomes by subtracting the difference between post-intervention and pre-

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

intervention rates in the comparison group from the difference between post-intervention and pre-intervention rates in the intervention group. Thus, in the treatment group, negative effect sizes indicate a reduction in antibiotic prescribing (lower rate of prescribing in the intervention group, post-intervention); in the selection group, positive effect sizes indicate an increase in prescribing of a recommended antibiotic in the intervention arm compared with the comparison arm.

The median effect for a group of studies is simply the median of the individual effect sizes of individual studies. Using the median effect approach allows preservation of the natural study units, and allows comparisons across different methodologic features or effect modifiers (e.g., baseline adherence).

In order to minimize multiple comparisons and spurious associations, we followed a structured approach to the evaluation of each research question based on our model above. In the first step, we assessed whether the crude median effect size varied between different QI strategies using non-parametric rank-sum tests (Wilcoxon or Kruskal-Wallis, as appropriate). We next sought to determine if other study characteristics could potentially act as effect modifiers or confounders of the observed relationship between QI strategy and median effect size. To do this, we established two criteria that had to be met for a variable to be considered a confounder or effect modifier: (1) the distribution of QI studies differed across strata of the study characteristic, and (2) the median effect size of studies varied across the study characteristic. For the first step, we analyzed contingency tables comparing the distribution of the number of studies for each QI strategy across dichotomized levels of each study factor (study factors were dichotomized due to the limited number of studies in our sample). The variables analyzed in this fashion included those we used to assess study translatability, along with other intervention characteristics and study population factors. For this purpose, each group of studies (treatment and selection), was examined for the following factors: country of study (US vs. other), effective sample size (above vs. below median sample size), baseline prescription or compliance rate (above vs. below median prescribing rate), intervention characteristics (repeated vs. one-time intervention, multifaceted vs. single QI strategy, use of passive vs. active QI strategies), type of comparison group (no intervention vs. low-intensity intervention), and target populations (specific disease target vs. no disease target; children targeted vs. children not targeted). To preserve power, we only included QI strategies represented by more than three interventions. A p-value of < 0.20 (by Fisher's exact test) was used as the threshold to consider the variable a potential effect modifier or confounder. We chose this liberal threshold to reduce the chance of missing potential confounders simply due to relatively small numbers of studies. When a factor was identified as a potential effect modifier or confounder through its association with the QI strategy, for the second step we then tested whether the factor was associated with the outcome (median effect size) using the non-parametric rank-sum tests noted above.

In addition to this analysis, we also performed stratified analyses to assess for differences in median effect sizes based on presence or absence of our prespecified quality criteria for internal validity, as these factors could bias individual study results. All statistical analyses were performed using STATA version 8.2 statistical software (Stata Corp., College Station, TX).

Calculation of Effective Sample Sizes

Cluster randomized trials, in which treatment allocation occurs at the level of clinicians or groups (e.g., randomization by clinic), are an increasingly encountered form of evaluation in QI research.[92] Allocating treatment in this manner is sometimes done out of convenience, but sometimes reflects the investigator's desire to avoid contamination. If treatment were assigned randomly at the patient level, clinicians would have some patients in each group and might therefore change their behavior for control and intervention patients.[93, 94] In cluster-randomized trials, some of the care that patients within each group receive is similar, and thus the two groups cannot be considered truly independent. Correction for this non-independence results in a smaller effective patient sample size for each study.[95-99] The effective sample size N is equal to: $N_{Effective} = (k*m) / (1 + (m-1)*ICC)$ where 'k' represents the number of clusters, 'm' denotes the number of observations per cluster, and 'ICC' equals the intra-cluster correlation coefficient. We used ICCs calculated from an existing database of prescriptions and clinician characteristics collected as part of the Minimizing Antibiotic Resistance in Colorado Project (AHRQ R01 HS13001). This database consists of all office visits and antibiotic prescription claims related to ARIs in Denver and Colorado Springs Metropolitan Statistical Areas from four large managed care organizations. This analysis showed an ICC of 0.055 for clustering at the clinician level, and 0.033 for clustering at the clinic level. The effective sample sizes calculated in this fashion were used for stratified analyses, as described above. These numbers fall within the range of values for ICCs found in quality improvement trials in primary care settings.[98]

Calculation of the Population Effect Size

Because certain patient populations and conditions are much more common than others, the median effects approach does not identify which interventions would have the greatest effect on total antibiotic use at the population level. Thus, we took a payor and public health perspective in standardizing changes in antibiotic prescriptions to the community level. An additional advantage of this approach is that it also allows inclusion of studies that were not eligible for the median effects analysis due to differences in how outcomes were measured. In order to standardize the observed median effects at the community level, we used data from the 2002 National Ambulatory Medical Care Survey (NAMCS)[100] (Figure 3) to extrapolate the relative reductions in antibiotic prescribing for specific conditions and age groups to absolute reductions in antibiotic prescribing in the general population, expressing results across studies as antibiotic prescriptions saved per 1000 person-years. This model assumes that the observed effect in each study lasted for 1 year. Using US Census estimates and NAMCS for 2002, we estimated that the US population of 283.1 million persons yielded 83.17 million ARI office visits in 2002. When interventions did not target a specific condition or age group, we multiplied total number of ARI office visits by the absolute net change in proportion of visits at which antibiotics were prescribed as a result of the intervention, then divided by the US population to estimate antibiotics saved per person-year. When studies focused on specific conditions and age groups, we used data from NAMCS to estimate the number of condition-specific office visits for the relevant age group(s), and divided by 283.1 million to standardize this effect to the general population. For studies that expressed results as antibiotic prescriptions per person-year, we

multiplied the absolute change in prescriptions per person-year by the number of (condition-specific) office visits to arrive at the population effect.

To estimate the cost of antibiotic prescriptions, we used the average wholesale price for a 7-day supply (except for azithromycin, which was 5 days) published by Red Book in January 2002. Because we did not have data on specific antibiotic prescriptions, we calculated the weighted average cost for a single prescription within each antibiotic class based on the distribution of specific antibiotic prescriptions within each class derived from the National Ambulatory Medical Care Survey in 2002. Based on this methodology, the weighted average costs for a single prescription within each antibiotic class in 2002 was the following: tetracyclines ($5.24), cephalosporins ($46.94), macrolides ($41.91), penicillins ($28.36), quinolones ($52.97), other ($37.18). These costs do not include the cost of dispensing the prescription.

Figure 3. Ambulatory antibiotic prescriptions for various ARIs, by age group.

	Ambulatory Antibiotic Prescriptions (in millions)				
	0-4 years	**5-14 years**	**15-44 years**	**45-64 years**	**≥ 65 years**
bronchitis	2.10	1.10	3.76	3.10	2.69
otitis media	7.88	3.45	1.55	0.88	0.33
pharyngitis	2.90	7.32	4.70	1.26	0.29
pneumonia	0.62	0.70	0.47	0.79	0.64
sinusitis	1.41	2.19	6.55	5.17	1.08
URI not otherwise specified	6.84	4.27	4.98	2.57	1.59
Total ARIs	**21.74**	**19.03**	**22.01**	**13.76**	**6.63**

Figure 3 Legend

Calculated number of ambulatory antibiotic prescriptions, stratified by type of acute respiratory infection (ARI) and agegroup. Data compiled from 2002 National Ambulatory Care Medical Survey.[100]

Particularly Salient Studies

Although the median effects analysis and systematic review outlined above provides the most comprehensive summary of the body of evidence, we recognize the limitations of such analyses in providing concrete examples for stakeholders. We have thus identified three particularly salient studies that illustrate the following three virtues: first, studies that met a high number of our prespecified quality criteria; second, studies that would be easily translatable to other settings; third, studies incorporating representative types of quality improvement strategies. The final studies chosen for highlighting were identified by discussion among the core investigators. These studies are summarized in Appendix A[*].

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

Chapter 3. Results

Our search strategy (Figure 4) yielded a total of 521 citations (509 from the EPOC database and 12 additional studies identified from MEDLINE®). Of these, we excluded 374 after title and abstract review, the majority of which (N=222) were outside our scope due to a focus on inpatient antimicrobial use, antimicrobial use in chronic diseases, or prescribing of medications other than antimicrobials. We reviewed the full text of the remaining 147 articles. Many of these (N=35) were excluded due to ineligible study design (e.g., single-group or before-after studies). Other reasons for exclusion included lack of eligible study outcomes (N=9), inappropriate focus (N=13), and unavailable full-text article (N=5[7]). Our final sample included 54 articles, six of which reported the effects of an intervention on both the antibiotic treatment decision and the antibiotic selection decision (Tables 1A and 1B).

Studies To Improve the Antibiotic Treatment Decision

Studies Meeting Inclusion Criteria

Our final sample included 34 studies reporting a total of 41 trials (i.e., 41 separate comparisons against comparison groups). Of these, 24 trials (from 17 studies[87, 101-116]) reported data as the percentage of visits where an antimicrobial was prescribed before and after the intervention, and thus were suitable for median effect size analysis. Three other studies[117-119] reported this outcome but did not report complete pre- and post-intervention data; these were excluded from median effects analyses and instead were summarized qualitatively.

The other trials included nine studies[120-128] that reported a variety of continuous outcomes, such as antibiotic prescriptions per person-year[120, 122, 123] or antibiotic prescriptions per provider[121, 123-125]; these studies were analyzed separately in a qualitative fashion. Five studies of delayed prescribing[129-133] were also analyzed separately, as pre-intervention prescribing data were not provided.

Settings, Goals, and Target Population of Studies

Appendix B[*] contains summaries of each included study. These tables organize studies by the setting and patient population in which the outcome was measured. We chose to group studies by the measured population, rather than the targeted population, in order to help stakeholders identify the studies whose results are most applicable to their settings. These tables also contain the QI strategies used, and specific details of the interventions themselves, as well as the individual study results.

Nearly all of the studies took place in outpatient primary care clinics (N=32), with two conducted in an urgent care or walk-in clinic.[102, 108] Most studies took place outside the US

[7] These included three studies published only as abstracts on the International Network for Rational Use of Drugs Web site (www.inrud.org) and two studies for which the journal could not be located.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

Figure 4. Search strategy and article triage.

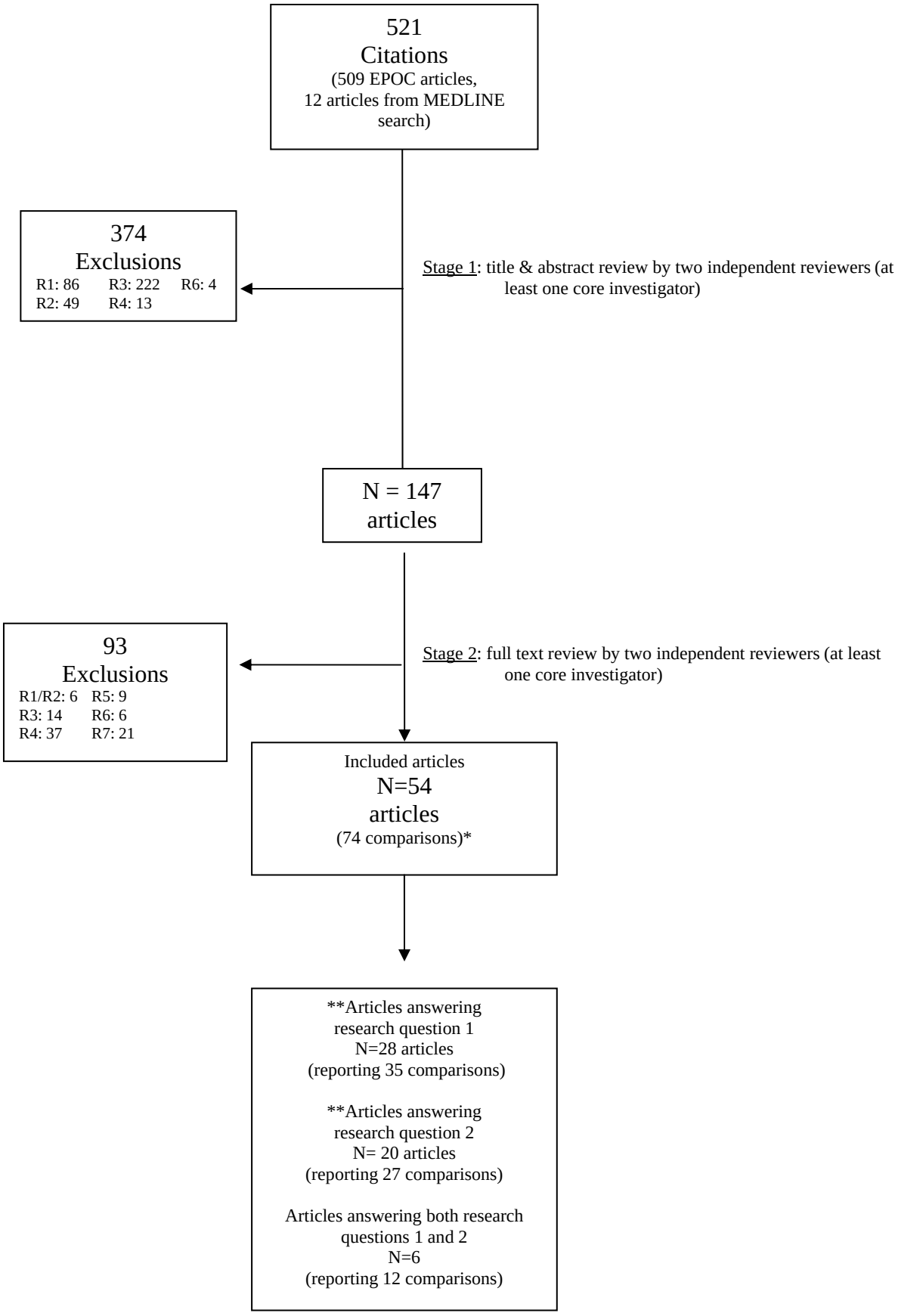


Figure 4 Legend

Reasons for Exclusion
R1 = Not an evaluation of an intervention

R2 = Not a QI strategy

R3 = Ineligible topic (focused on inpatient care, antimicrobial use in chronic disease, not related to antimicrobial use)

R4 = Ineligible study design

R5 = No eligible outcomes

R6 = Foreign language article

R7 = Other (outcomes data not available for entire population studied, e.g., only presented in subgroups, article not available, duplicate article)

****** Research question 1: Which quality improvement strategies reduce prescribing of antibiotics for nonbacterial illnesses?
****** Research question 2: Which quality improvement strategies improve selection of the appropriate antibiotic for treatment of bacterial illnesses?

The core investigators (who were responsible for full-text article abstraction and data analysis) were SRR, MAS, and RG

(N=24), including 11 from Europe,[87, 101, 102, 104, 106, 112, 114, 127, 129, 130, 133] three from Australia,[114, 125, 128] two from Canada,[118, 119] two from Africa,[105, 116] and the remainder from other countries. Of the 28 trials which reported the period during which the study was conducted, 22 took place in the last decade.[87, 101, 102, 105-109, 111-113, 118, 119, 121, 122, 125-128, 131-133]

Most included studies sought to reduce the prescribing of antibiotics for targeted conditions in which antibiotics are generally not recommended (Table 1C). Six studies did not identify a specific target condition, instead focusing on reducing overall antibiotic prescribing in a broader population.[115, 116, 120-122, 125] Among the 28 studies with a specific disease focus, nearly all (N=26) addressed antibiotic prescribing for acute respiratory infections; two other studies[103, 117] addressed prescribing for acute diarrhea. Antibiotic prescribing for children was targeted in 13 studies[102, 110, 113, 115, 117, 119, 122, 123, 126-129, 132]; however, no studies specifically addressed prescribing for elderly patients or patients of lower socioeconomic status. Five studies[107, 111, 117, 122, 126] selected patients with a specific type of insurance (e.g., managed care or Medicaid enrollees). The median baseline prescribing rate was 31.0% in interventions targeting general ARIs (N=9 studies supplying data, IQR 21.4% to 37.0%), but, among interventions targeting a specific ARI (N=5 studies supplying data), prescribing rate ranged as high as 78% in a study examining acute bronchitis[111] and 95% in a study examining pediatric otitis media.[102]

Intervention Characteristics

Interventions utilized a variety of combinations of QI strategies targeted at both clinicians and patients. Educational strategies were most commonly used, with 27 trials (from 22 studies[87, 102-106, 108-117, 121, 122, 124-126, 128]) using some form of clinician education and 18 (from 15 studies[87, 101, 102, 107-111, 113, 122, 126-128, 132, 133]) using patient education; 12 trials (from 10 studies[87, 102, 108-111, 113, 122, 126, 128]) provided education to both clinicians and patients. Audit and feedback to individual clinicians or groups of clinicians was used in 12 trials (from 11 studies[101, 106-108, 111, 114, 117, 121, 124-126]), frequently in combination with clinician education (N=10 trials[106, 108, 101, 111, 114, 117, 121, 124-126]). Delayed prescribing was used in five studies,[129-133] clinician reminders in two,[118, 119] with patient self-management and financial and regulatory incentives used in one study each[87, 128]

(both in combination with other strategies). One[87] trial used organizational change. No trials used patient reminders or facilitated relay of clinical data. The median number of QI strategies used per trial was two (range one to six), with the majority of trials (N=22) using more than one strategy (Table 2).

Within the broad categories of patient and clinician education, interventions incorporated a mix of passive and active educational elements. Active educational strategies for clinicians included educational outreach ("academic detailing"), workshops, and consensus-building sessions; active strategies for patients consisted of one-on-one or group interactive educational sessions. More than half of trials (N=17, from 16 studies[103-106, 108-110, 112-114, 117, 121, 122, 124, 126, 128]) using clinician education used at least one active strategy, including educational outreach visits (academic detailing) in 10 trials, workshops in eight trials, and consensus-building sessions in four trials (some trials used more than one of these strategies.) Most clinician education efforts used more than one sub-strategy, such as combining educational outreach visits with distribution of written material. In contrast, patient education approaches were nearly exclusively passive (N=15 trials[87, 101, 102, 107-111, 113, 122, 126-128, 132, 133]), using only distribution of written materials. Educational efforts most commonly took place in the clinician's office or another clinical setting, but two studies[109, 122] used mass media efforts to attempt to educate the entire population of a geographic area.

The proportion of visits at which an antibiotic was prescribed was the primary outcome in 32 trials (from 25 studies),[87, 101-119, 129-133] with the remaining studies reporting the total number of antibiotic prescriptions (expressed as either prescriptions per patient or prescriptions per clinician). Scant information was provided on secondary outcomes. The safety of the intervention was addressed in only six trials (from five studies[87, 108, 111, 131, 133]) which reported the effects of the intervention on the rate of return visits; four trials addressed patient satisfaction,[101, 129-131] and four assessed the clinical outcome of the disease being studied. [112, 129-131] No study reported the rate of adverse drug events. Only two studies[109, 113] reported the effect of an intervention on antimicrobial resistance, and two other studies[112, 121] reported information on the costs of prescribing.

Quality of Included Studies

The methodologic quality of included studies was generally fair. Most trials were randomized controlled trials (N=24, from 20 studies) [87, 103, 105, 107, 112, 114, 115, 118-120, 123-126, 128-133]; five trials (from three studies)[101, 110, 116] used a quasi-randomized design, with allocation altered by the investigators to assure equivalent demographic characteristics between control and intervention groups (e.g., using alternating patients, or even/odd identifying numbers). For analytic purposes, these trials were grouped with the remaining 12 trials, which used a nonrandomized CBA design. Among these 12 trials, only 5 (from four studies[108, 111, 117, 122]) explicitly explained the criteria used for selecting the comparison group. The comparison groups received a low-intensity intervention in seven trials[118, 119, 121, 125, 130, 132, 133] and no intervention in 34 trials.

Outcome assessors were clearly defined as being blinded to treatment group assignment in two trials. The unit of analysis and unit of allocation differed in 22 trials; 14 of these trials (in 11 studies[103, 104, 106-110, 117, 122, 124, 127]) failed to statistically correct for this difference. Prescribing behavior was measured directly by chart review in 18 trials, with the remainder using pharmacy or other administrative databases.

As has been documented in previous reviews of QI studies, included trials frequently failed to describe the theoretical basis for their intervention, and failed to document key intervention and study characteristics.[51, 134] Most of the trials (N=28) did not document the extent of the antibiotic prescribing quality gap in their patient population. Few trials explained the rationale for selecting the QI strategies in their intervention, and almost all trials failed to document the reach of the intervention (e.g., the percentage of clinicians who actually attended the educational session). The median length of followup was 6 months (in the 39 trials reporting this information); eight trials had followup of 1 year or greater.

Effectiveness of Specific QI Strategies and Combinations of Strategies

Table 3 summarizes the median effect size of net changes in antibiotic prescribing rates for the 24 trials that provided sufficient information to calculate effect size, with individual study effect sizes shown in Figure 5. (The five delayed prescribing trials are summarized separately in Table 6.) Overall, the calculated median effect size across all QI interventions was -8.9% (IQR -12.4% to -6.7%). The smallest median effect size was seen in the two studies that used patient education only (-4.9%, IQR -9.9% to -0.2%), with slightly greater effects seen in studies using clinician education alone (-8.1%, IQR -13.7% to -7.0%). No single strategy appeared to be more effective than the others (p=0.848 by Kruskal-Wallis test). The two most common intervention types were clinician education only (N=9) or clinician education combined with patient education (N=6). There was no difference in median effects between these two strategies (p=0.478). Twelve studies used multiple QI strategies (six with clinician and patient education, two with clinician education and audit and feedback, one with patient education and audit and feedback, and three with patient education, clinician education, and audit and feedback). Studies using multiple QI strategies were not more effective than those using single strategies (p=0.82 by Wilcoxon rank-sum test).

Independent of QI strategy, we examined whether any of the selected study characteristics was associated with effect size. To maximize power, we restricted these analyses to the two dominant QI strategies (clinician education vs. clinician education combined with patient education). None of these factors appeared to have a strong influence on the overall effect size (Table 4). With regard to intervention characteristics, trials using active educational strategies appear to have slightly larger median effects (-13.7% compared with -7.0%,) but this relationship was not statistically significant (p=0.11 by Wilcoxon rank-sum test for studies with the two dominant QI strategies (Table 5); p=0.33 for all studies). Repeated interventions also did not exert stronger effects on prescribing behavior. Similarly, non-US studies had greater median effects than studies conducted in the US (median effect -8.9% compared with -3.0%), but this relationship was also not statistically significant (p=0.15 for studies with the two dominant QI strategies). Interventions targeting a specific disease were also not significantly more likely to reduce prescribing than interventions targeting general prescribing (p=0.66). We could not evaluate for the effect of the type of comparison group, as all 15 trials had a no-intervention comparison group.

Figure 5. Net reduction in antibiotic prescribing rate for individual studies (antibiotic treatment studies).

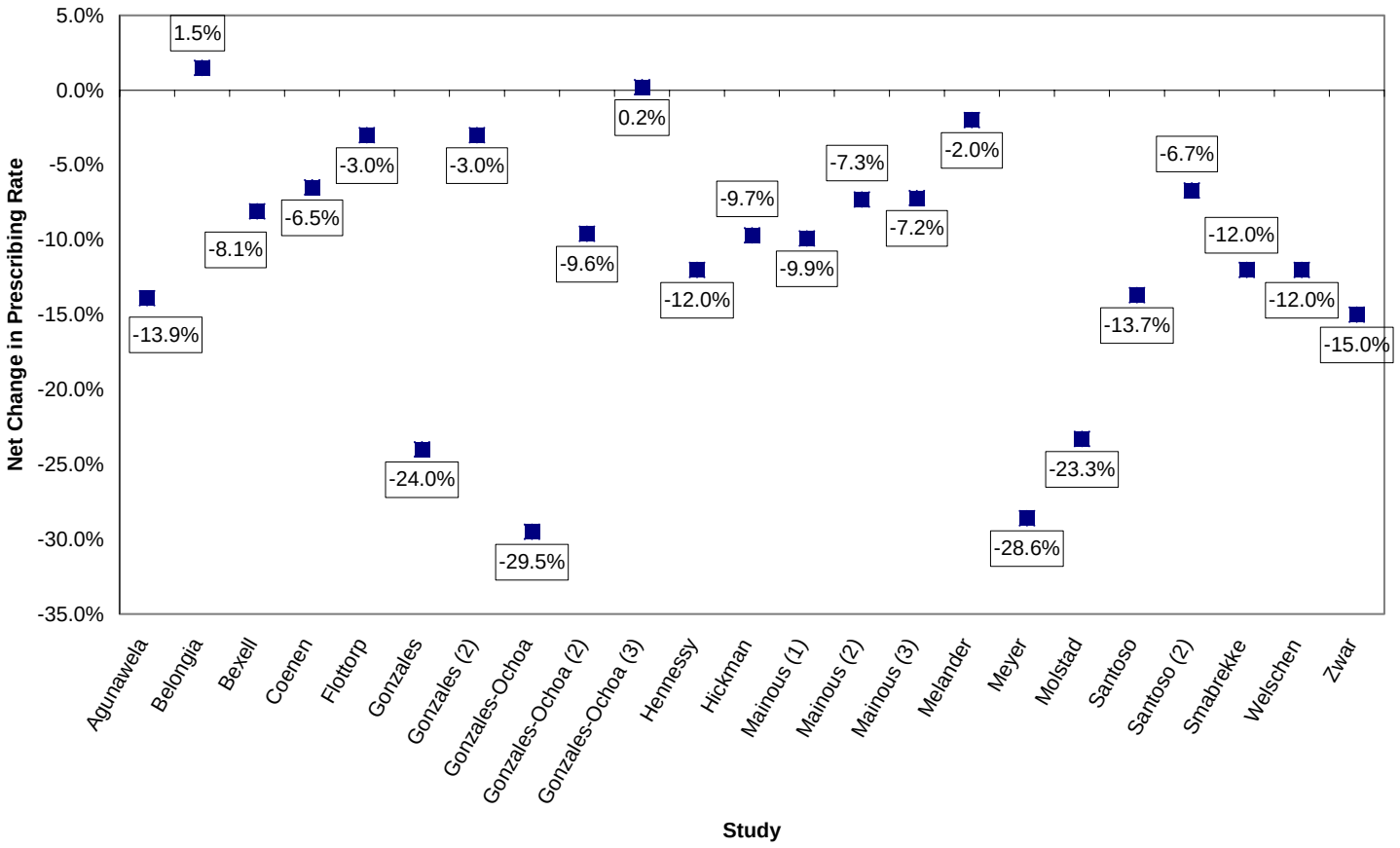


Figure 5 Legend

Effect size for each study (N=24) that supplied sufficient information for analysis. Percentages show the net change in the percentage of visits at which an antibiotic was prescribed, calculated as: Net Δ in prescribing = (Post-intervention prescribing rate – Pre-intervention prescribing rate)$_{\text{intervention group}}$ - (Post-intervention prescribing rate – Pre-intervention prescribing rate)$_{\text{control group}}$.

We further stratified the studies by study design and sample size to assess if these factors correlated with median effect size. No statistically significant relationship was found for either variable (p=0.77 and 0.75 respectively). We also hypothesized that trials with higher baseline rates of prescribing antibiotics might be more likely to demonstrate significant effects (the "low-hanging fruit" effect); this also was not borne out (p=0.82).

As we did not observe a difference in median effects among QI strategies, our assessment of potential confounding by moderating factors and study biases amounts to evaluating for potential negative confounding, which would result in a spurious finding of no difference among groups (Table 5). We identified study design (RCT vs. CBA) and study location (US vs. other) as meeting the threshold of association (P<0.20) with the dominant QI strategies (clinician education vs. clinician and patient education). However, neither of these factors was significantly associated with overall median effects (P=0.52 and 0.15, respectively), eliminating them as confounders. We did not find evidence that the presence or absence of our prespecified quality criteria affected study results, as there was no significant difference in median effects for studies with or without any of the internal validity or translatability elements. For example, studies where prescribing was measured by chart review showed no difference in median effects

than studies in which prescribing was measured by other means (median effect -9.6% and -7.3%, respectively; p=0.47.); and as noted above, no difference was found in median effects between randomized and nonrandomized studies.

Delayed Prescription Studies

Five studies used delayed prescriptions, where patients were asked to fill their prescription after a specified period of time if their symptoms did not improve, as the primary strategy to reduce antibiotic use, with two of these studies[132, 133] also incorporating a patient educational intervention (Table 6). All trials evaluated ARIs, with two studies enrolling children with otitis media,[129, 132] and one each evaluating adults with the "common cold,"[130] acute cough,[131] and acute bronchitis.[133] These trials enrolled and randomized patients judged to not need antibiotics by the treating physician. Notably, these trials were methodologically sound: all trials were RCTs (randomized by patient) and had prescribing measured by chart review. Antibiotic use was measured by patient report in three studies[130, 132, 133]; in two, patients in the intervention group were required to return to the office to collect their prescription.[129, 131] All had sample sizes below the median for all treatment studies.

For these studies, we calculated the post-intervention difference between antibiotic use in the intervention group and the control group. The median difference was -46.7% (IQR -55.0% to -26.7%), indicating a marked reduction in antibiotic use in the intervention groups; however, the post-intervention median rate of antibiotic use in the control groups was still 87.0% (IQR 63.0% to 98.5%). This raises the possibility that delayed prescribing strategies may appear more effective only because of artificially high rates of antibiotic use in the comparison group (since the protocols called for near-universal antibiotic treatment in the control group), which under non-study conditions might have had a lower antibiotic prescription rate.

Studies Not Eligible for Median Effect Size Analysis

Twelve studies[117-128] met all of our inclusion criteria, but did not report outcomes in a fashion compatible with those included in the median effects analysis. Six of these studies[120-122, 125, 126, 128] targeted overall antibiotic prescribing, while five targeted upper respiratory infections,[118, 119, 123, 124, 127] and one[117] acute diarrhea. Four studies[122, 123, 126, 127] exclusively addressed prescribing of antibiotics to children. The overall methodologic quality of these trials was variable. Eight[118-120, 123-126, 128] of the 12 studies were RCTs, and all four nonrandomized trials clearly explained the rationale for selection of the comparison group. However, only one study[120] documented blinding of outcome assessors. The baseline quality gap was documented in only three studies[122, 124, 126], and only two studies[118, 119] measured prescribing rates by chart review, with the others all using administrative claims data.

Five of the trials addressing general prescribing used multi-faceted strategies involving combinations of patient education, clinician education, and audit and feedback to address antibiotic use in large patient and clinician populations. Two of these[121, 125] delivered a combined clinician education and audit and feedback intervention to all clinicians in a geographic area, either via passive mailings[125] or through interactive workshops[121]; neither documented a significant reduction in overall antibiotic use. Combinations of patient and clinician education were used in two studies. A reduction of 1.13 prescriptions per 100 visits was achieved in an Australian study[128] that used consensus-building sessions and a clinical

guideline as well as patient education. Perz et al[122] delivered an educational intervention to patients and clinicians, with use of educational outreach and mass media efforts, and achieved an 11% intervention-attributable reduction in antibiotic prescription rates (a decrease of about 0.16 antibiotic courses per Medicaid managed care child [0-15 years of age] per year). Finkelstein et al[126] combined active clinician education, audit and feedback, and patient education to achieve reductions of about 0.06 antibiotic courses per commercial managed care enrolled child (0-5 years of age) per year.

Clinician reminders were used in three studies.[118, 119, 123] Christakis et al[123] used a computer-delivered reminder for prescribing in pediatric otitis media; there was no significant reduction in overall antibiotic use, but the intervention did lead to a significant improvement in prescribing for the appropriate duration of therapy. McIsaac et al[118, 119] conducted two separate studies using a chart-based reminder to use a validated scoring system for antibiotic prescribing in sore throat cases, but both failed to significantly reduce prescribing.

Active clinician education and audit and feedback interventions were used for two condition-specific studies. One[124] achieved a reduction of 6.4 prescriptions per clinician per 6 months for ARIs. Another,[117] targeting prescribing behavior in acute diarrhea, demonstrated absolute reductions of 15.2% for antibiotic prescribing and 20.2% for antiparasitics in the intervention group, but comparable comparison group values were not provided. Pediatric otitis media was addressed in another study using delayed prescribing[127], which achieved a significant reduction of 17 prescriptions per clinic per month. Finally, one study[120] (the Rand Health Experiment) allocated patients to either a free or cost-sharing insurance plan. Antibiotic use decreased by 0.43 antibiotic courses per insured person (non-elderly families) per year in the cost-sharing group.

Population Effect Size

In this analysis, we found that interventions targeting all ARIs in adults (Figure 6) translate into the largest effects at the general population level, with savings of 35-85 antibiotics per 1000 person-years. In the median effects analysis, these studies appear to have only modest effect sizes, but the larger population to which they apply outweighs the modest effect. Conversely, highly effective condition-specific interventions (or interventions targeting children) may not project to large reductions in prescribing at the population level. Two studies not included in the median effects analysis can also be compared in this manner. At the population level, Perz et al[122] extrapolate to 23 antibiotic courses saved per 1000 per person-year, and Finkelstein et al[126] to five antibiotic courses saved per 1000 per person-year (Figure 6).

Figure 6. Population-level effect of studies targeting the antibiotic treatment decision.

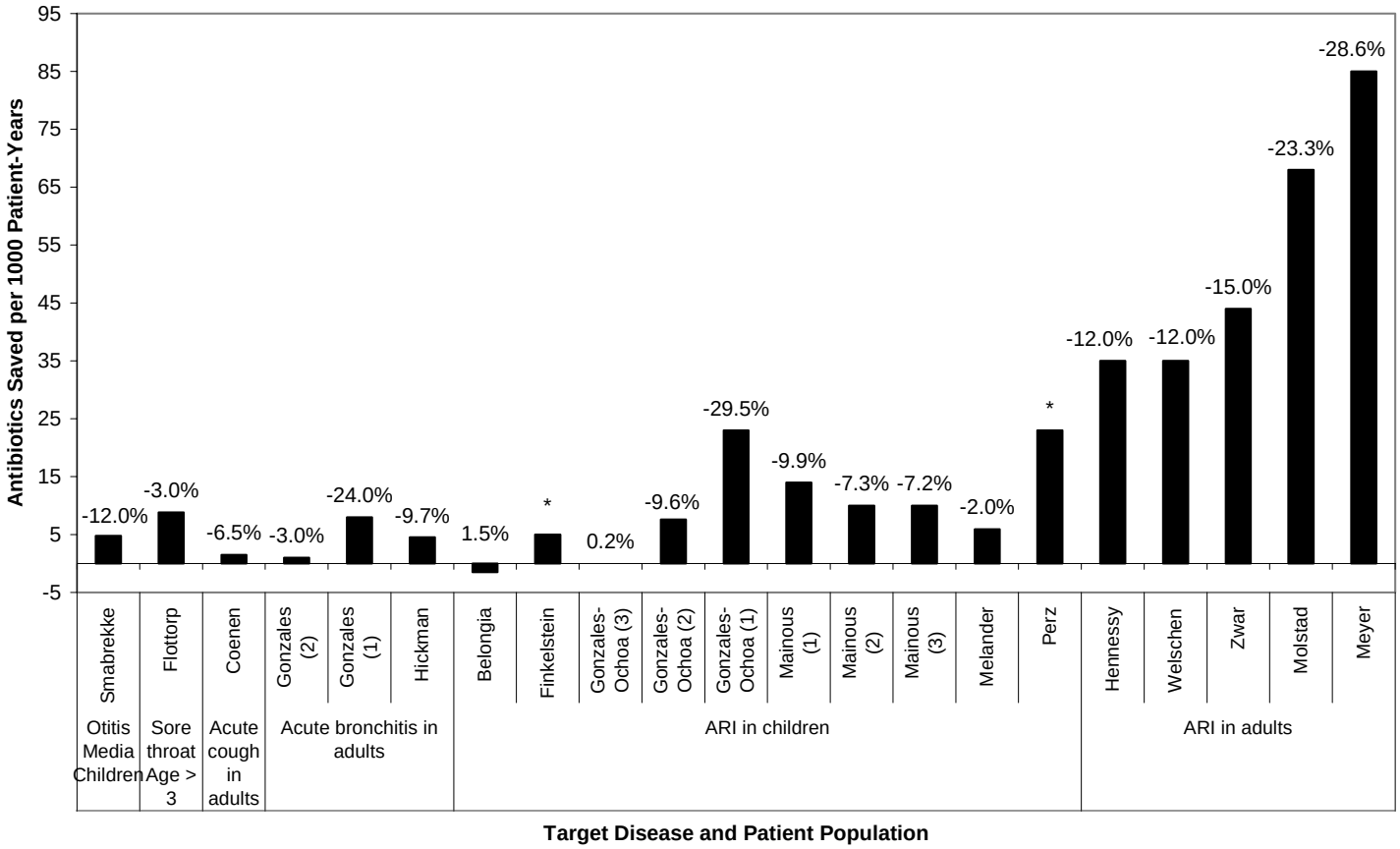


Figure 6 Legend

Bars show the potential antibiotic prescriptions saved per 1000 person-years of observation for each individual study. Studies are grouped by target condition and target population. These results were extrapolated from individual study effect sizes based on visit rates from the 2002 NAMCS survey and census data. Percentages show the individual study effect size, expressed as net change in the percentage of visits at which an antibiotic was prescribed.

*Studies by Perz et al and Finkelstein et al reported continuous data (antibiotics prescribed per person-year) so effect sizes are not provided.

For a 100,000-member health maintenance organization (HMO), these studies suggest that a QI strategy targeting all ARIs for patients of all age groups would result in a savings of approximately 3000 to 8000 antibiotic prescriptions per year. Figure 7 shows the range of antibiotic cost savings that could be obtained from reducing antibiotic prescribing across a range of population-level reductions in prescribing and antibiotic cost estimates. These cost estimates do not take into account the implementation cost of the intervention itself. Assuming average costs of $30 - $50 per antibiotic prescription, the organization would save between $90,000 and $400,000 in antibiotic costs (Figure 7).

Figure 7. Projected cost savings from antibiotic treatment interventions.

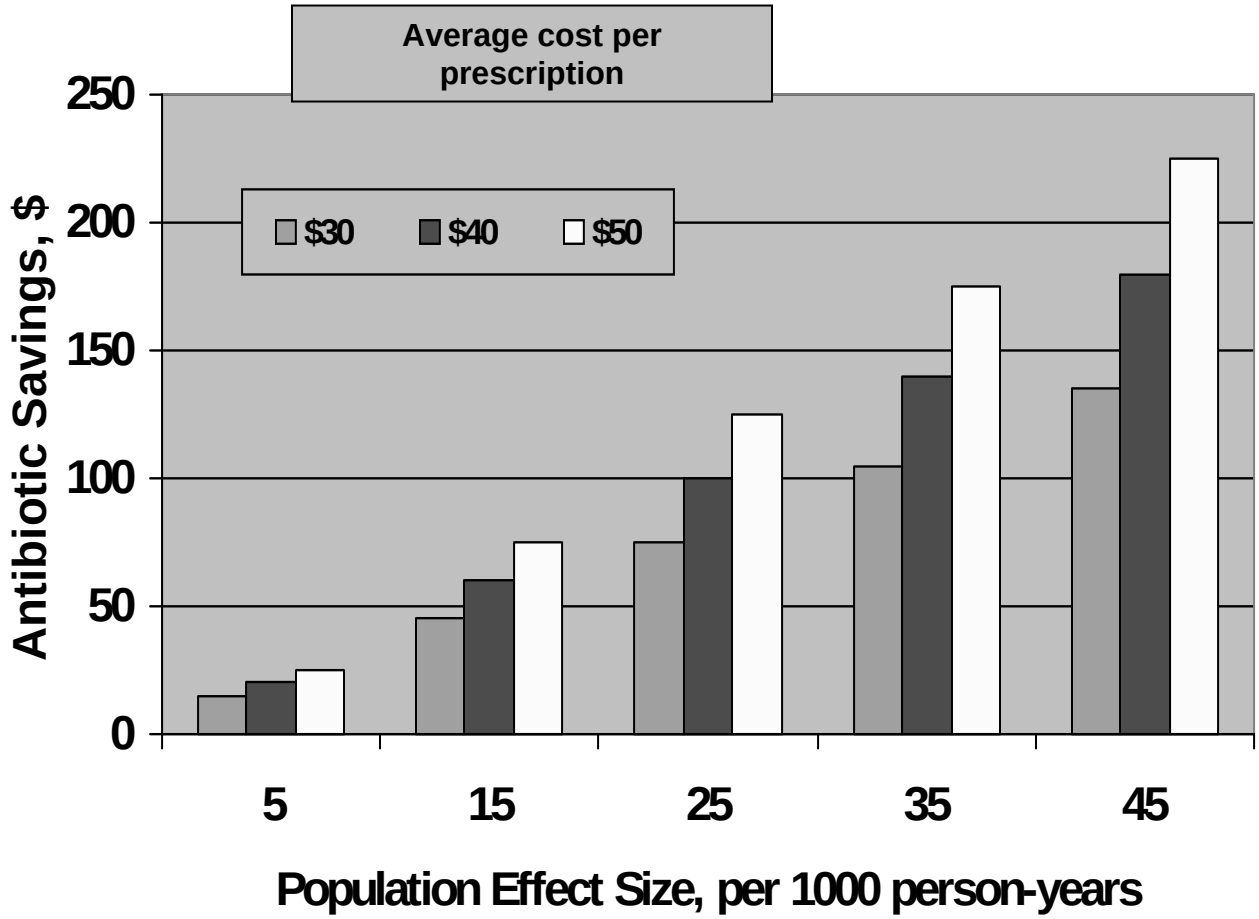


Figure 7 Legend

This figure represents the potential savings in antibiotic costs that could be obtained through reductions in antibiotic prescribing, for a 100,000 member Health Maintenance Organization (HMO). The reduction in antibiotic prescribing is expressed as number of antibiotic prescriptions saved per 1000 person-years of observation. Costs are expressed as thousands of dollars saved.

Within-Study Comparisons

In five studies, investigators examined more than one type of intervention. These five studies[103, 107, 110, 111, 115] evaluated a total of nine comparisons of intervention and comparison groups. In two studies[103, 115] the interventions consisted of either passive or active clinician education; in both cases, the active education intervention resulted in a significantly larger effect size. Another study[107] evaluated three strategies: passive patient education alone, audit and feedback alone, or both strategies. The absolute rate of antibiotic prescribing increased in all intervention groups, although the rate of increase was significantly less in the groups receiving patient education. Another study evaluated three comparisons[110]: intervention groups received either active clinician education, passive patient education, or a combination of both strategies.

The largest absolute reduction in prescribing was found in the combined strategy group, with no overall reduction found in the patient education only group. Finally, a study examining acute bronchitis in adults[111] carried out a "limited intervention" consisting of passively distributed educational materials targeted at patients and clinicians, and a "full intervention" with active clinician education, audit and feedback, and patient education. The full intervention resulted in a significant reduction in prescribing, while the limited intervention had no overall effect.

Special Populations and Secondary Endpoints

The median effect size of interventions targeted at children was not significantly different from interventions as a whole (median effect size -8.5% for 10 trials targeting children, -8.9% in the 14 trials not targeting children). The QI strategies used in these 10 trials were similar to the overall distribution, with two trials[107, 110] using patient education alone (targeted at parents of children), three using patient education combined with clinician education,[102, 110, 113] three using clinician education alone,[103, 110] and one trial each (from the same study[107]) using audit and feedback alone and patient education combined with audit and feedback. Eight[117, 122, 123, 126-129, 132] studies not used in our median effects analyses targeted children, including three studies[127, 129, 132] using delayed prescribing strategies for childhood otitis media; as discussed earlier, all showed much lower relative rates of antibiotic use. The other five studies included three community-based studies using multifaceted strategies discussed above[122, 126, 128], all of which significantly reduced antibiotic prescribing; one condition-specific study using reminders that failed to reduce prescribing[123], and one condition-specific study using a multifaceted information which reported only intervention group data.[117]

Two studies[109, 113] reported rates of antimicrobial resistance. Both trials used combined patient and clinician educational strategies to target antibiotic use at the community level. Although both exerted positive effects on overall antimicrobial use, the percentage of drug-resistant organisms (penicillin-resistant *S. pneumoniae*) did not significantly change in either case. The length of followup was 6 months in both studies, which may have been too short to detect significant changes.

Two studies assessed costs of antibiotic prescribing. One study,[121] which failed to document an overall reduction in antibiotic prescribing at the community level did show a reduction in total prescribing costs of 18.1% in the intervention group relative to control. An increase in the use of narrow-spectrum antibiotics may have been responsible for this savings. A Belgian study[102] using an active clinician educational intervention reduced antibiotic prescribing for acute cough and achieved a reduction in prescribing costs of 6.97 euros (approximately $9) per patient. The calculated antibiotic cost reductions in both these studies did not take into account the costs of the interventions themselves.

The safety of the intervention was addressed in seven trials (from six studies)[87, 108, 111, 112, 131, 133] that measured post-intervention use of health services. Five of these (from four studies)[111, 112, 131, 133] measured the rate of return office visits, and none found more return visits in the intervention group. One study[87] found no difference in the need for telephone consultation between groups. The only study that found a possible increase in health services utilization[108] documented a slight increase in the prescribing of antibiotics at a return visit if the patient did not receive antibiotics originally. The rate of return visits was not different, however. Four studies,[112, 129-131] three of which used delayed prescribing, measured the time to symptom resolution through patient interviews or diaries; none found a greater overall duration of patient

symptoms if patients did not receive antibiotics, although one study[129] of delayed prescribing in children with otitis media found a greater duration of distress in the delayed group. Four studies measured patient satisfaction[101, 129-131]; fewer patients were "very satisfied" with treatment in one study[131] of delayed prescribing, but no difference was present in the other studies. Adverse drug events were measured in only one study,[129] which found significantly less diarrhea in patients not receiving antibiotics, but no difference in the incidence of rash.

Studies To Improve the Antibiotic Selection Decision

Studies Meeting Inclusion Criteria

Twenty-six studies[102, 104, 106, 112, 114, 121, 135-154] on antibiotic selection, reporting data on 33 trials, met inclusion criteria for this review (Table 1B). Of these 33 trials, 22 (from 20 studies)[102, 104, 106, 112, 114, 121, 137, 138, 140-145, 147, 149-151, 153, 154] reported outcome data that allowed inclusion in the median effects analyses, including 19 that reported data on patient sample size. The remaining three trials[114, 140, 143] listed information on cluster sizes, from which an approximate sample size could be estimated; each of these three sample sizes were above the median sample size calculated from the other 19 trials. The 11 trials not suitable for median effects analysis were from six studies.[135, 136, 139, 146, 148, 152] Four of these studies[136, 139, 146, 148] did not report complete pre-intervention and post-intervention data, reporting only the percentage change. Of the other two, one study reported count data[152] and the other continuous data (antibiotic prescriptions per provider),[135] neither of which could be combined with dichotomous data.

Setting, Goals, and Target Population of Studies

Appendix B[*] contains summaries of each included study, grouped by measured population. The study intervention and results are summarized in these tables as well.

Most studies (21) were conducted outside of the United States, including 12 from Europe,[102, 104, 106, 112, 121, 136, 141, 146, 147, 151, 153, 154] four from Australia,[114, 138, 144, 149] three from Canada,[139, 143, 148] and two from other countries.[142, 150] Nearly all (22) were conducted in primary care settings. Other intervention sites included emergency rooms (one study), urgent care or walk-in clinics (one study), and other settings (two studies)[141, 148]; no interventions targeted specialists' offices. All but four studies reported the study dates; midpoints ranged from 1975 to late 2000, with 13 studies occurring over the past decade.

All studies focused on reducing the use of broad-spectrum or costly antibiotics or improving the selection of certain recommended antibiotics over others; no interventions attempted to increase the use of broad-spectrum or expensive agents in the face of increased antibiotic resistance. Four studies attempted to shorten the duration of prescriptions for acute illnesses, including one for which this was the exclusive antibiotic utilization outcome measured. No studies attempted to increase the duration of prescriptions. No studies focused on improving antibiotic dosing.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

The 26 eligible studies examined a variety of populations and conditions (Table 1D). Several studies focused on special patient populations, including elderly patients (two),[143, 148] children (three)[102, 137, 144] (including one[137] specifically on children in an HMO), and a Medicaid population (one).[135] Respiratory tract infections were the most commonly targeted condition (13 studies),[102, 104, 106, 112, 114, 137-141, 144, 150, 153] followed by urinary tract infections (eight),[136, 144-147, 149, 151, 154] and sexually transmitted diseases (one)[142]; one study examined both ARI and UTI prescribing.[144] Six studies did not examine a specific condition.[121, 135, 141, 143, 148, 152] Among 22 trials included in the median effects analysis, baseline rates of prescribing of recommended antibiotics in the comparison group ranged from 20% to 90% with a median of 57%.

QI Strategy Characteristics

Nearly all trials (30, from 23 studies) were targeted exclusively at clinicians, including 18 trials (from 13 studies[104, 106, 112, 135, 137-140, 144, 145, 149, 150, 152]) that provided clinician education only, nine trials[114, 121, 136, 141, 143, 146, 147, 153, 154] that combined clinician education with audit and feedback, and two trials (from one study[136]) that provided both of the above as well as a regulatory intervention directed at providers. In addition, one trial provided audit and feedback alone.[151] The remaining three trials provided both patient and clinician interventions, including a combination of clinician and patient education (two trials)[102, 142] and a combination of financial and regulatory interventions directed at clinician and patients (one trial).[148] No trials targeted patients exclusively, and none targeted the community.

The median number of QI strategies per trial was one (Table 7); 12 trials used two QI strategies and two trials employed three distinct QI strategies.

Among the 31 trials involving clinician education, 25 involved distribution of educational materials to clinicians, and six used meetings in which physicians were passive participants. In addition, at least one "active" educational strategy was employed in 20 trials (from 13 studies[112, 114, 136-140, 142, 144, 146, 147, 149, 152]) involving clinician education, including educational outreach (13 trials from 11 studies[112, 114, 136, 138-140, 142, 144, 149, 150, 152]), educational workshops (seven trials[121, 140, 142, 146, 147, 153, 154]), and consensus-building sessions (three trials[104, 137, 146]). Among trials providing education, approximately two-thirds (20) provided the education at the clinician's office or workplace; three provided off-site education, and the remainder did not clearly specify the site.

Several different antibiotic utilization outcomes were reported, often in the same study. These include the percentage of patients receiving a recommended antibiotic (14 trials) or being in compliance with a clinical guideline for prescribing (10 trials), antibiotic dose or prescription duration (four trials), and other outcomes (six trials). Outcomes other than antibiotic utilization were reported infrequently, including antibiotic cost data in four studies[121, 140, 143, 144] and clinician satisfaction in one trial.[140] No studies provided data on clinical outcomes, health services utilization, or antimicrobial resistance.

Quality of Included Studies

Many of the studies did not meet most of the prespecified quality criteria. Randomized controlled designs were used in 13 trials (from 12 studies),[112, 114, 135, 138, 139, 142-144, 146, 147, 153, 154] 19 used CBA designs(from 13 studies),[102, 104, 106, 121, 136, 137, 140, 141, 145, 149-152] and one employed an ITS design.[148] Among 19 trials using a non-randomized comparison group, nine described the rationale for selection of the comparison population.

Treatment assignment was frequently allocated at levels (i.e., clinician, clinic, community) that differed from the unit of analysis (i.e., patient; N=16 studies). In nine of these studies[104, 137, 140-143, 145, 151, 152] investigators failed to statistically correct for differences between the unit of analysis and unit of allocation. Antibiotic prescribing outcomes were assessed using chart review data in nine trials; another 21 used administrative data, and three used other methods.

Nine trials reported empiric evidence for a quality gap in the population under study. Usual care was provided to the control group in 24 trials, whereas in nine the comparison group received some form of low-intensity intervention.

The duration of study followup (either following or concurrent with the study) was less than 1 year in 21 trials. The remaining eight trials that provided this data reported followup periods ranging from 1 – 1.5 years.

Effect of Interventions on Antibiotic Selection

Table 8 summarizes the median effect of each type of intervention on selection of recommended antibiotics in the 22 interventions that reported results in a manner suitable for this approach. (Individual study effect sizes are shown in Figure 8.) The median absolute effect was a 10.6% net improvement (IQR 3.4% - 18.2%) in the rate of recommended antibiotic prescribing in intervention groups compared with comparison groups. Clinician education combined with audit and feedback had the smallest median effect (3.4%), while the combination of clinician and patient education had the largest effect (22.8%). These differences in median effect sizes were not statistically significant (P=0.18). However, the efficiency of this statistical test is impaired by the presence of two groups (clinician education combined with patient education, and audit and feedback alone) with low sample sizes (two and one, respectively) in each group. To limit the effect of intervention types with small sample sizes on the tests of significance, we compared the two QI strategies for which more than three trials contributed data (the "dominant" QI strategies); in this subset of studies, clinician education alone was more effective than clinician education combined with audit and feedback (13.9% vs. 3.4%, P=0.03).

Figure 8. Effect sizes for each included study (antibiotic selection studies)

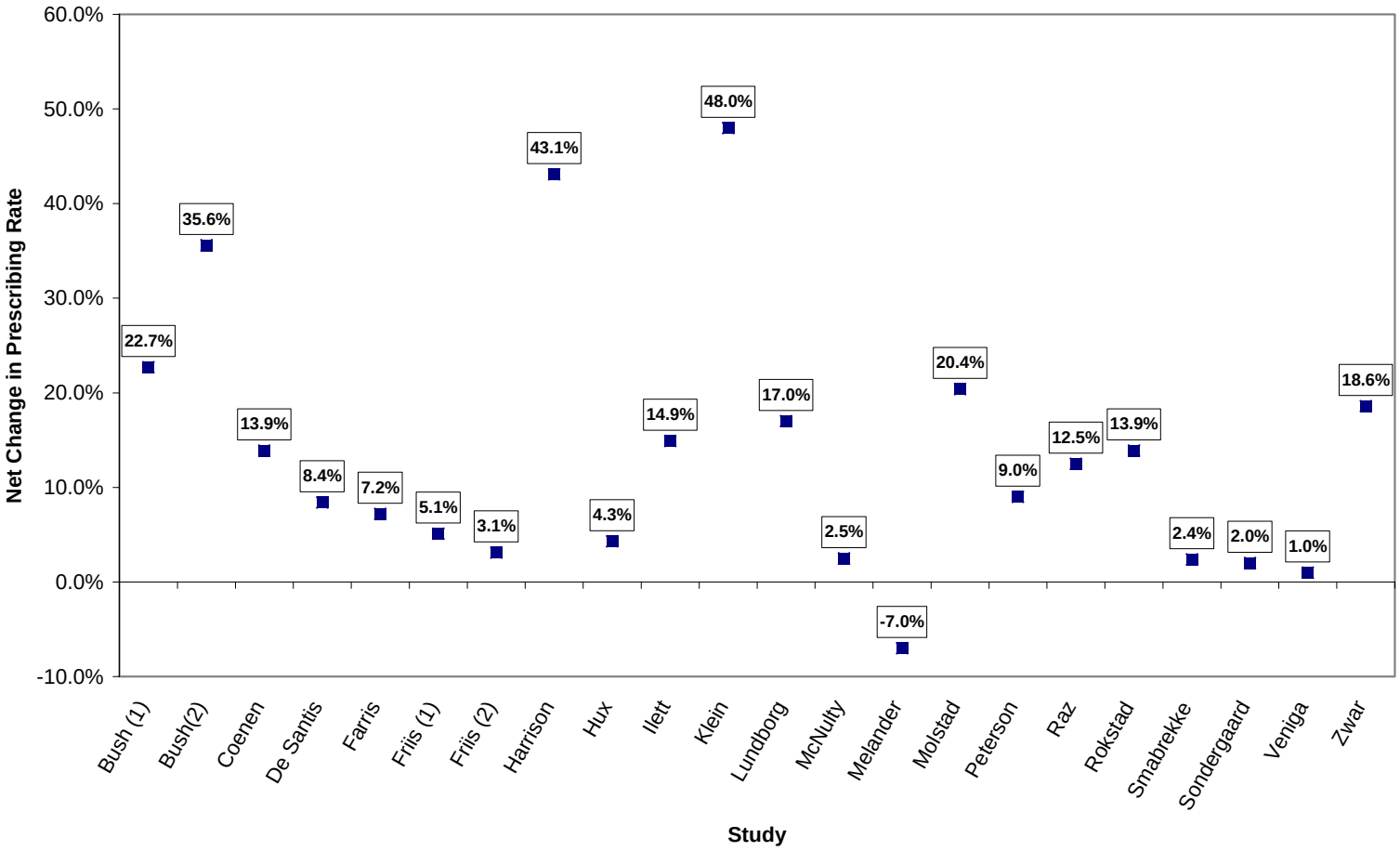


Figure 8 Legend

Effect size of each study (N=22) that supplied sufficient information for analysis. Percentages show the net change in percentage of patients prescribed a recommended antibiotic, calculated as: Net Δ in prescribing = (Post-intervention prescribing rate – Pre-intervention prescribing rate)$_{\text{intervention group}}$ - (Post-intervention prescribing rate – Pre-intervention prescribing rate)$_{\text{control group}}$.

Table 9 shows the distribution of potential confounders of the association between QI strategy and effect on prescribing for the two dominant intervention types. Among these 19 trials, the absolute difference in effect between each confounder stratum ranged from 2.3% for RCTs vs. CBA trials, to 20.8% for trials conducted inside vs. outside the US. In our assessment of potential confounders, three study characteristics were not evenly distributed across our "dominant" QI strategies: study design (RCT vs. CBA, p=0.18 by Fisher's exact test), sample size (above vs. below the median, p=0.15), and target disease (specific disease targeted vs. general prescribing targeted, p=0.16).

Table 5 shows the effect of these potential confounders on the median effect size. Although randomized and non-randomized interventions were unevenly distributed across the two dominant QI strategies, this uneven distribution did not appear to impact the median effect size of these QI strategies (p=0.62 for difference in median effect size). The median effects of interventions targeting prescribing in general was also not significantly different from interventions targeting a specific disease (p=0.19). However, interventions with below-median sample size showed a greater median effect size than those with above-median sample size (P=0.06 for difference). As almost all clinician education combined with audit and feedback interventions were above the median sample size (compared with about half of the clinician education-alone interventions), the presence of positive confounding must be considered (i.e., the larger median effect size for clinician-education alone interventions compared with clinician education and audit and feedback can be partially explained by the greater number of above-median sample size studies in the latter group).

Study country and type of comparison group were also significantly associated with median effect size, with trials conducted inside the US and trials employing a "usual care" comparison group showing greater median effect sizes than their counterparts (P<0.05 for comparison with non-US interventions and interventions using a "limited intervention" control group, respectively; Table 5). However, because these study characteristics were evenly distributed among interventions employing the dominant QI strategies, they did not meet our criteria as a confounder of the relationship between QI strategy and outcome effect. Other potential confounders that did not have a significant impact on median effect size included baseline prescribing rate, use of active vs. passive educational strategies, and single vs. repeated interventions (P>0.2 for all). Only one study[137] targeted children, and the two trials comprising this study reported larger effects than studies not targeting children. With regard to our prespecified quality criteria, no factors potentially affecting internal validity had a significant effect on median effects, nor did factors potentially affecting translatability.

No studies attempted to increase the use of broad-spectrum antibiotics (e.g., in the face of resistant organisms), so we were unable to compare the efficacy of such interventions with those that aimed to decrease broad-spectrum antibiotic use.

Studies of Duration of Antibiotic Therapy

Four studies evaluated the effect of interventions on reducing the duration[146, 147, 151, 154] of antibiotic prescriptions, all for women with UTIs. Three of these interventions used active forms of clinician education (workshops, supplemented in one study by consensus-building sessions) combined with audit and feedback. The results were mixed. One intervention[146] was associated with a 13% increase in the percentage of antibiotic prescriptions for short-course regimens in the intervention group compared with the comparison group; the second study[147] found that the

intervention had little effect on antibiotic duration (relative increase of antibiotic duration 0.06 days), while the third[154] documented a relative decrease in defined daily doses equivalent to a reduction of 1.89 days in antibiotic duration in the intervention compared with comparison group. Using a similar calculation of defined daily doses per prescription, an intervention using only audit and feedback found a relative decrease in antibiotic duration of 0.55 days in the intervention group compared with the comparison group.[151]

Studies Not Eligible for Median Effect Size Analysis

Eleven trials in six studies[135, 136, 139, 146, 148, 152] met inclusion criteria for this review but did not present data amenable for inclusion in the median effects analyses. The majority of these (seven trials from three studies)[135, 148, 152] targeted antibiotic selection in general, while three trials (from two studies)[136, 146] focused on UTIs and one on ARIs.[139] The methodologic quality of these interventions was generally similar to those that were included in the median effects analysis: among 11 trials, four (from three studies)[135, 139, 146] used randomized controlled designs, but all non-randomized trials used a comparable comparison group and adequately described the rationale for its selection. However, none of the trials measured prescribing by chart review.

The majority of these interventions evaluated the effect of clinician educational outreach alone or in combination with other QI strategies. One study[152] evaluated the effects of outreach performed by a physician or pharmacist on prescribing of contraindicated antibiotics (antibiotics deemed unsafe for routine office use) and of oral cephalosporins. Both types of interventions were compared to a comparison group that received either no intervention or a passive mailed intervention (which had no effect relative to the no intervention group). Outreach performed by a physician achieved relative reductions of 85% and 50% in the number of prescriptions per patient over a 1-year period for oral cephalosporins and contraindicated antibiotics, respectively, compared with 67% and 35% reductions by the pharmacist-educator and 41% and 33% reductions in the comparison group. (Data on absolute reductions were not presented.)

Another study comprising two interventions found that educational outreach reduced non-recommended antibiotic prescribing 31% relative to the comparison group, compared with a relative reduction of 10% in physicians receiving only printed materials. Both of these relative reductions were in part attributable to a 12% increase in non-recommended antibiotic use in the comparison group over the study period.[135]

Other interventions employed variations on the classic approach to educational outreach. One study using pharmaceutical sales representatives to promote amoxicillin use for children with otitis media documented a non-significant 1.4% increase in adjusted market share for this drug in regions receiving outreach compared with control regions.[139] Finally, another study evaluated two multifaceted interventions that included feedback delivered via distribution of a workbook or educational outreach. These investigators found a 0% and 12% improvement in the workbook and educational outreach groups (respectively) compared with the comparison group, based on an outcome of mean percent change in recommended antibiotic prescribing per 1000 patients over a 3-month period.[136]

One study used an interrupted time series design to evaluate financial and regulatory incentives designed to reduce fluoroquinolone prescribing to elderly patients in a Canadian province. After implementation, use of this drug class fell from 20.2% to 4.2% of all antibiotic drug claims registered with the province's prescription drug insurance plan.[148]

Comparisons Within Studies

Five studies evaluated two or more separate interventions; three of these studies[135, 136, 152] are described in the section above, and the remainder are described below. One study documented a 5.1% improvement in recommended antibiotic prescribing by physicians invited to lectures sponsored by a local department of clinical microbiology, compared with a 1.1% improvement in physicians invited to similar lectures sponsored by a pharmaceutical company; the control group and both intervention groups all received written materials.[141] The other study compared antibiotic prescribing for pediatric otitis media among three small sites of a health maintenance organization, where one site developed and implemented a consensus guideline for treatment of this condition, the second site implemented this guideline through meetings and written materials, and the third site served as control.[137] Guideline-concordant prescribing improved 13.0% at the development site and 0.1% at the implementation site, and fell 22.6% at the control site. Of note, baseline concordance was substantially lower at the development site (64.3%) than at the other two sites (87.8% and 89.6%).

As noted above, nine trials (from five studies)[121, 138, 141, 152, 153] provided some form of lower-intensity activity in a comparison group that was considered in the study to be a control arm; five of these (from four studies)[121, 138, 141, 153] presented data suitable for median effects analysis. These five trials were a heterogeneous group, including one intervention comparing educational outreach to a comparison group receiving low-intensity feedback (with 8.4% relative improvement in the intervention arm relative to control),[138] one comparing antibiotic workshops to a comparison group receiving microbiology tutorials (2.5% relative improvement in the intervention arm),[121] one comparing mailed audit and feedback to distribution of written materials (2% relative superiority in the intervention arm),[153] and two interventions from one study comparing meetings to distribution of written materials (5.1% and 1.1% relative improvement in the intervention arms).[141, 153] Overall, the median effect size of interventions whose efficacy was compared with that of a low-intensity control was lower than those whose comparison group received no form of activity (median effect 3.1% vs 14.4%, P=0.04; Table 5).

Among these studies, there were nine comparisons of active vs. passive provider education (either as distinct intervention arms, or as an intervention arm and low-intensity intervention control arm). In all nine, the active form of education resulted in greater improvement than the passive one.[121, 135-138, 152]

Special Populations and Secondary Endpoints

The median effect of trials focusing on ARIs and UTIs was identical (12%), with similar median effects across different types of interventions. Three studies enrolled children[102, 137, 139] (one of which[137] focused specifically on children enrolled in an HMO); the median effect of interventions in these studies was similar to the overall effect of non-age-targeted studies. Two studies enrolled the elderly[143, 148]; the first achieved a 4.3% improvement over control using a combination of passive clinician education with audit and feedback (similar to the median effect for all studies in this category),[143] while the second (an interrupted time series) documented a 16% absolute reduction in fluoroquinolone use after implementation of financial and regulatory incentives.[148]

No studies looked at clinical outcomes, including adverse drug reactions, clinical status, or health services utilization. Similarly, no studies evaluated the effect of interventions on

antimicrobial resistance, or visit duration. A single study[140] that evaluated clinician attitudes documented a mean response of 4.0 (on a 5-point Likert scale, 5="strongly agree" and 1="strongly disagree") regarding clinicians' opinions of the intervention as an appropriate mechanism to optimize medication use.

Four studies looked at cost outcomes,[121, 140, 143, 144] of which three presented data in usable form. Each of these three interventions decreased cost by approximately 20-30%. One study using clinician education and audit and feedback documented a median $3.37 (31%) increase in the mean cost of an antibiotic prescription in the comparison group, compared with no change in costs in the intervention group.[143] Two studies evaluated the total cost of antimicrobials in a health care system, with one[144] finding an 18% relative decrease in total antimicrobial costs attributable to non-recommended antibiotics in the intervention group compared to the comparison group, and the other a 9% rise in total antibiotic costs in the comparison group, compared with a 10% decrease in the intervention arm.[121]

Chapter 4. Discussion

Summary

The published medical literature supports the benefits of QI interventions to reduce unnecessary antibiotic prescribing and improve antibiotic selection in primary care practices. Overall, efforts to reduce prescribing of antibiotics for non-bacterial acute illnesses reduced prescription rates by an absolute value of 8.9% (IQR -12.4% to -6.7%). Interventions to improve antibiotic selection resulted in a 10.6% absolute increase in the rate of recommended antibiotic prescribing (IQR 3.4% - 18.2%). Similar effects were observed in studies not eligible for median effects analysis. The quality of included studies was generally fair, with similar problems to those seen in the prior reports on hypertension and diabetes in the *Closing the Quality Gap* series.

We did not find definitive evidence for the superiority of individual QI strategies or combinations of strategies. Active educational strategies appeared to be more effective than passive education, though this comparison did not achieve statistical significance in either antibiotic treatment or antibiotic selection studies. However, we also found evidence for the increased effectiveness of active educational strategies in studies not eligible for median effects analysis and in within-study comparisons in both groups (treatment and selection). In the selection studies, the combination of clinician education and audit and feedback appeared less effective than clinician education alone; this finding is likely due to confounding by sample size.

Study results were consistent across patient populations and disease processes. Interventions reported from outside the US appeared less effective than those based in America particularly in the selection group, but very few US-based studies were eligible for quantitative analysis. Very few included studies presented data on antimicrobial resistance, clinical outcomes, or costs, and no firm conclusions can be reached regarding these outcomes. Limited data does indicate that patient satisfaction is not impaired by interventions to reduce antibiotic use.

Limitations

As noted in the Methods section, we were not able to perform meta-analysis or meta-regression due to the limited number of eligible studies and significant heterogeneity. Our alternative quantitative analysis approach consisted of calculating median effect sizes stratified by presence or absence of study design and intervention characteristics, then comparing these results using non-parametric tests. This approach does allow for quantitative comparisons among groups, but is limited in its ability to control for important confounders, and does not directly incorporate measures of study quality into the analysis of summary effects. As well, even the few statistically significant results we found have not been corrected for multiple comparisons.

In our analysis, we attempted to account for as many measurable potential confounders and effect modifiers as possible. However, we were limited by the description of the intervention and study setting provided in each article. Undoubtedly, many potential moderating factors go unmeasured simply due to lack of adequate description in the literature. These can include factors that can increase the likelihood of intervention success (e.g., a high degree of support

from top management) and factors that decrease the likelihood (e.g., lack of resources to ensure adequate intervention reach).[51] We attempted to be as specific as possible in measuring the intensity of the interventions. However, intervention intensity may largely reflect the characteristics of individuals providing the intervention, including their own investment in the process and their relationships with the target population, neither of which was directly measured.[155] We attempted to abstract information on all facets of the intervention; despite these efforts, unmeasured confounders may yet have influenced our results. The combination of limited statistical power and the likelihood of unmeasured confounders cautions against using strict interpretations of our quantitative findings.

Although we did find greater effects in studies with smaller sample size in the selection studies, we did not find the same relationship in interventions targeting the treatment decision. One explanation for significant differences in effect sizes when stratified by sample size or other methodologic features is publication bias, the preferential publication of positive studies. Publication bias occurs more frequently for small sample size studies, resulting from the propensity for smaller studies and trials with less rigorous designs to be published if they report large improvements.[156] In two previous reviews[1, 2] of the QI literature, we identified significant inverse relationships between study sample size and the magnitude of reported effects (i.e., smaller studies reported larger effect sizes). Sample size may also be correlated with other important methodologic features, such as blinding. Other biases may influence individual study results. Studies of prescribing behavior targeting clinicians may be spuriously influenced by the Hawthorne effect[157] (in which the knowledge that one's behavior is under observation changes behavior). Another potential concern is that clinicians may engage in "code shifting," listing a patient's diagnosis as one usually requiring antibiotics (e.g., pneumonia) instead of one not warranting antibiotics (e.g., bronchitis). However, this concern has not been borne out in the literature.[111, 158, 159]

Evidence indicates that a clinician's decision to prescribe an antibiotic depends on a variety of factors relating to the health care system and patient beliefs and expectations, and is not solely dependent on the clinician's subjective beliefs or knowledge of evidence-based practice. In this light, it is reasonable to hypothesize that effective strategies to reduce inappropriate antibiotic prescribing should target multiple domains (clinician, patient, and health system). However, while nearly all included strategies targeted clinicians and many targeted patients, very few studies examined the effect of health system factors such as formulary restrictions or drug co-payments. Also, few interventions targeting clinicians specifically addressed the physician-patient interaction; helping clinicians understand and manage patient expectations for antibiotics could theoretically be more efficacious. Despite these omissions, we did find that strategies targeting patients or clinicians can positively influence prescribing rates. Further research on the effectiveness of health system-level interventions, as well as assessment of the interaction between the health system and clinician and patient-level interventions, will add greatly to our ability to design effective QI programs.

Finally, our results are limited to the short observation periods, as most followup periods were less than 1 year. Intervention designs that lead to sustained changes in antibiotic prescribing over multiple years might be different, with repeated public education/awareness and health system modifications playing a more dominant role.

Thus, many of the findings in this review raise more questions than they answer, and should be construed as hypothesis-generating. The interactions between each of the components of an intervention and the population it targets (as outlined in the conceptual framework in the

introduction) are complex, and the limited number of studies available for analysis allow only a relatively rudimentary evaluation.

Conclusions

Despite the above caveats, the available studies do illustrate several distinct and effective approaches to improving prescribing behavior in a range of settings. While firm conclusions cannot be drawn, our data are consistent with several concepts, as described below. In the discussion, we will address the questions most relevant to stakeholders considering undertaking quality improvement efforts to reduce the inappropriate use of antibiotics. Organizations should examine their specific clinical settings as well as their clinician and patient populations, and compare studies performed in similar settings to identify specific QI strategies that are most likely to be effective in their own setting. To assist with this process, Appendix A* provides examples of key studies, and Appendix B provides details of each included study organized by setting and measured population.

1. Are quality improvement strategies to improve outpatient antibiotic use effective?

Our review found that the vast majority of published studies reported clinically significant improvements in antibiotic treatment and selection. The magnitude of these effects compares favorably to those achieved by quality improvement efforts in other settings. These findings were consistent across diverse patient populations and clinical settings. More than half the included studies were performed in the last decade; the concomitant decline in antibiotic prescribing in US ambulatory practices suggests that efforts to promote judicious antibiotic use are succeeding. However, inappropriate prescribing rates remain high, and inappropriate selection of antibiotics presents a continuing challenge.

In addition to benefiting patients and the community by reducing the adverse consequences of inappropriate antibiotic use, effective interventions may result in cost savings, although definitive evidence is lacking.

2. What are the critical components of effective intervention strategies to improve outpatient antibiotic use?

Antibiotic treatment studies. Within the antibiotic treatment studies, we were able to compare studies using clinician education alone with those using clinician and patient education. The addition of patient education to clinician education did not result in greater reductions in antibiotic prescribing, a finding that withstood evaluation for potential negative confounding. No distinct differences emerged among strategies, with the exception of a possible trend toward greater effectiveness in studies using active educational strategies. This finding was supported by systematic evaluation of studies that were not incorporated in the median effects analysis.[122, 126, 128]

Potential negative confounding by unmeasured variables and limited power may affect our finding of an apparent lack of additional benefit of patient education over clinician education

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/medigap/medigap.pdf

alone. Although studies included in median effects analyses did not show an additional benefit, two large population-based studies[122, 126] not incorporated in median effects analyses did demonstrate reductions in antimicrobial prescribing with a combined clinician and patient educational intervention. Of note, these studies were conducted in the U.S., but most included studies were from outside the U.S. It is conceivable that different practice styles, levels of baseline prescribing rates, and patient expectation of antibiotic treatment may make patient education more important in the U.S. than outside the country.

Antibiotic selection studies. Most selection trials eligible for median effects analysis employed one of two main QI strategies: clinician education alone, or clinician education in combination with audit and feedback. The absolute difference in median effect between these strategies was substantial; interventions adding audit and feedback to clinician education were less effective than interventions employing clinician education alone. The effectiveness of other types of QI strategies is difficult to systematically assess, since there were only three studies for all other categories of QI strategies.

The surprising finding that adding audit and feedback to clinician education results in smaller effects on prescribing may be explained in part by confounding. Interventions employing clinician education alone were substantially more likely to have below-median sample size; these smaller studies had overall larger effect sizes. While this may reflect publication bias, it is also possible that low sample size is acting as a proxy for studies that use local relationships and leadership to achieve greater clinician "buy-in" than studies spread over many sites. In addition to publication bias and sample size already noted, there may be other subtle confounders. For example, interventions that employed audit and feedback may have used less intensive methods to implement the clinician education component, spreading their energies among several intervention strategies rather than focusing on one. These possibilities are intriguing, but not directly testable in this analysis. A prudent conclusion may be that we are unable to definitively assess the relative efficacy of clinician education alone vs. clinician education combined with audit and feedback, but that we found no evidence to suggest that the combined approach is superior to clinician education alone.

Unlike the antibiotic treatment studies, there was no prominent association between the presence of active vs. passive types of educational interventions and antibiotic prescribing outcomes. It is difficult to assess whether this lack of association is true, or is merely negatively confounded by other observed or unobserved variables, compounded by limited power to detect differences due to low sample sizes. Other findings suggest that active educational interventions may in fact produce better outcomes. First, the differences in median effect size between active and passive techniques were in the expected direction, and of similar magnitude to differences observed in treatment studies, in which a trend (P=0.11) toward an association was observed, suggesting insufficient power. In addition, studies that compare two or more interventions to one another can be viewed as controlling for the many measured and unmeasured confounders that make inter-study comparisons so challenging.[160] In each of these cases, the active group outperformed the passive group.[135, 152]

Our overall results thus supply cautious support for including active clinician education in quality improvement efforts for improving antibiotic use. Combining other strategies with clinician education does not necessarily improve outcomes, but our ability to detect such differences was limited.

3. Which patients and conditions should be targeted in order to exert the maximal impact on antibiotic prescribing?

We did not find any evidence that targeting specific patient populations resulted in significant differences in study effects, in either antibiotic treatment or antibiotic selection studies.

When selecting an intervention target, stakeholders and policymakers may wish to consider the potential population-level intervention effect, rather than simply the target-specific effect. Interventions that have highly significant effects on antibiotic prescribing for single conditions or limited patient populations may not necessarily exert large effects on overall antibiotic prescribing rates. At the population level, targeting all ARIs appears to translate into larger reductions in antibiotic consumption than focusing on a single condition or patient age range, and this might be an important factor in the willingness of purchasers/payors of health care to invest in appropriate antibiotic use interventions.

Interventions targeting antibiotic selection appeared to be equally effective across different disease processes and patient populations. Thus, stakeholders should determine the quality gap in their unique patient population, and target interventions appropriately.

4. What are the limitations of current research in this field and what areas require further study?

Included studies rarely reported important measures of the potential harms of the intervention. These include the potential for increased use of health services (e.g., return visits due to persistent symptoms) and adverse clinical consequences (e.g., increasing rates of serious infections due to undertreatment). Patient satisfaction does not appear to be affected in the limited number of studies that did report this outcome.

More importantly, very few of the included studies (and none of the US-based treatment studies) documented the resources required for completion of the intervention and measurements. Only four[102, 121, 143, 144] studies reported the cost savings resulting from changing prescribing behavior. Thus, although an active clinician education intervention may be more effective than a passive intervention, we are unable to make any statement regarding the cost-effectiveness of such an intervention. Given the apparent benefit of other, potentially less resource-intensive interventions, further research should include formal reporting of both costs of and cost savings from QI interventions. Further studies should also clearly document intervention intensity and reach, the baseline quality gap, and any other local factors that could have affected the intervention or outcomes measurement.

Changes in antibiotic resistance rates should be monitored not only for declines in resistance rates, but also for changes in the rate of rise in existing or new resistance patterns. This will require longer-term followup than measured in most studies. Based on the best evidence and mathematical modeling to date, it is unlikely that reductions in antibiotic consumption will lead to major reductions in levels of antibiotic resistance among community-acquired bacterial infections.[33-35] However, ecological studies do support the notion that the amount of antibiotic consumption in a community directly influences how rapidly new resistance emerges or rises.[7, 37] As the benefits from preventing antimicrobial resistance will be seen largely by the community at large, health care organizations may be reluctant to invest heavily in programs to reduce antimicrobial use without a clear business case. A demonstration that these types of

interventions can recover their implementation costs through savings in antibiotic costs would be helpful. Our crude analysis in Figure 7 indicates that many of these interventions have the potential to be cost-neutral or cost-saving, depending on the cost of the intervention, the reduction in antibiotic prescriptions and the cost of antibiotics.

Study design and quality should be improved. Studies that formally evaluate the cost effectiveness of interventions to improve antibiotic treatment and selection are needed, and studies should evaluate the potential harms of such interventions.

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Listing of Excluded Studies

	Citation	Reason for exclusion
1	Using guidelines to change clinical practice: three case studies. HMO Practice 1996; 10(1): 30-36	Study design did not meet criteria for RCT, CBA, or ITS
2	Anokbonggo WW, Ogwal-Okeng J. W. Obua C. Aupont O. Ross-Degnan D. Impact of decentralization on health services in Uganda: a look at facility utilization, prescribing and availability of essential drugs. East African Medical Journal 2004:S2	Study design did not meet criteria for RCT, CBA, or ITS
3	Anonymous. North of England study of standards and performance in general practice. An overview of the study. Report no 50. Centre for Health Services Research, Ambulatory Care Programme 1991.	Overlaps with or duplicates another article that was included
4	Anonymous. Medical audit in general practice. II: Effects on health of patients with common childhood conditions. North of England Study of Standards and Performance in General Practice. BMJ 1992; 304:1484.	Other
5	Anonymous. Changing prescribing practices. Medicine Today 2001; 2:14.	Not an evaluation of a QI intervention
6	Barwitz HJ. Sore throat consultation--what is the value of a treatment guideline? German Original Beratungsanlass Halsschmerzen--was nutzt eine Handlungsleitlinie? MMW Fortschritte der Medizin 1999; 141:32.	Foreign language article article
7	Barwitz HJK. Common cold - Trial to rationalize management in general practice by recommendation. Zeitschrift fur Allgemeinmedizin 1999; 71(21-22):932	Foreign language article article
8	Batchelor B, Crook DW, Jones T, Bowler IC. Impact of guidelines for the diagnosis of urinary tract infection on trimethoprim susceptibility of Escherichia coli. Journal of Antimicrobial Chemotherapy 2002; 49:223.	Not an evaluation of a QI intervention
9	Beardon PH, Brown SV, Mowat DA, et al. Introducing a drug formulary to general practice--effects on practice prescribing costs. Journal of the Royal College of General Practitioners 1987; 37:305.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
10	Bowler IC, Atkins BL, Batchelor BI, et al. Impact of guidelines for the diagnosis of UTI letter; see comments. British Journal of General Practice 1998; 48:1790.	No eligible outcomes
11	Brook RH, Williams KN. Effect of medical care review on the use of injections: a study of the New Mexico Experimental Medical Care Review Organization. Annals of Internal Medicine 1976; 85:509.	Study design did not meet criteria for RCT, CBA, or ITS

12	Burr A. Impact of fundholding on general practice prescribing patterns. Pharmaceutical Journal 1992; 249 R8	No eligible outcomes
13	Chalker J. Improving antibiotic prescribing in Hai Phong Province, Viet Nam: the "antibiotic-dose" indicator. Bulletin of the World Health Organization 2001; 79:313.	Study design did not meet criteria for RCT, CBA, or ITS
14	Chiefari DM. Effect of a closed formulary on average prescription cost in a community health center. Drug Benefit Trends 2001; 13:45 - 52.	Study design did not meet criteria for RCT, CBA, or ITS
15	Chowdhury AKA, et al. Effect of standard treatment guidelines with or without audit on prescribing for acute respiratory infections in government health facilities in Bangladesh. International Network for Rational Use of Drugs 1996.	Article not available
16	Cohen R, Allaert FA, Callens A, et al. Medico-economic evaluation of an educational intervention to optimize children uncomplicated nasopharyngitis treatment in ambulatory care. Medecine et Maladies Infectieuses 2000; 30:691.	Foreign language article
17	de Silva MI, Mize GN, Rissing JP. Peer review of antibiotic use: positive impact on physician prescribing patterns. Qrb 1985; QualityReviewBulle:302.	Study design did not meet criteria for RCT, CBA, or ITS
18	Dickey FF, Mattar ME, Chudzik GM. Pharmacist counsling increases drug regimen compliance. Hospitals 1988; 49:85-86.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
19	Doyne EO, Alfaro MP, Siegel RM, et al. A randomized controlled trial to change antibiotic prescribing patterns in a community. Arch Pediatr Adolesc Med 2004; 158:577-83.	Other
20	Du B, Chen D, Liu D, Long Y, Shi Y, Wang H, Rui X, Cui N. Restriction of third-generation cephalosporin use decreases infection-related mortality. A controlled trial of a critical pathway for treating community-acquired pneumonia: the CAPITAL study. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. Critical Care Medicine 2003; 31:1088.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
21	Ekedahl A, Andersson SI, Hovelius B, Molstad S, Liedholm H, Melander A. Drug prescription attitudes and behaviour of general practitioners. Effects of a problem-oriented educational programme. European Journal of Clinical Pharmacology; 1995: 47(5): 381	Study design did not meet criteria for RCT, CBA, or ITS
22	Evans RS, Classen DC, Pestotnik SL, et al. Improving empiric antibiotic selection using computer decision support. Archives of Internal Medicine 1994; 154:878.	Study design did not meet criteria for RCT, CBA, or ITS

23	Finney JW, Friman PC, Rapoff MA, et al. Improving compliance with antibiotic regimens for otitis media. Randomized clinical trial in a pediatric clinic. American Journal of Diseases of Children 1985; 139:89-95.	No eligible outcomes
24	Font M, Madridejos R, Catalan A, et al. Improving drug prescription in primary care: a controlled and randomized study of an educational method . Spanish. Medicina Clinica 1991; 96:201.	Foreign language article
25	Friis H, Bro F, Mabeck CE, et al. An information campaign--an important measure in controlling the use of antibiotics. Journal of Antimicrobial Chemotherapy 1989; 24:993.	Study design did not meet criteria for RCT, CBA, or ITS
26	Friis H, Bro F, Eriksen NR, et al. The effect of reimbursement on the use of antibiotics. Scandinavian Journal of Primary Health Care 1993; 11:247.	Study design did not meet criteria for RCT, CBA, or ITS
27	Garcia Lirola MA, Cabeza Barrera J, Lirola Garcia E. Intervention to improve the quality of antibacterial drug prescribing practices in primary care. Farmacia Hospitalaria 1999; 23:42.	Foreign language article
28	Gonzales R, Steiner JF, Maselli J, et al. Impact of reducing antibiotic prescribing for acute bronchitis on patient satisfaction. see comments. Effective Clinical Practice 2001; 4:105.	No eligible outcomes
29	Gonzales R, Sauaia A, Corbett KK, et al. Antibiotic treatment of acute respiratory tract infections in the elderly: effect of a multidimensional educational intervention. Journal of the American Geriatrics Society 2004; 52:39.	Study design did not meet criteria for RCT, CBA, or ITS
30	Goode CJ, Tanaka DJ, Krugman M, et al. Outcomes from use of an evidence-based practice guideline. Nursing Economics. 2000; 18:202.	Study design did not meet criteria for RCT, CBA, or ITS
31	Gordis L. Evaluation of the effectiveness of comprehensive and continuous pediatric care. Pediatrics 1971; 48:766.	Not an evaluation of a QI intervention
32	Greenfield S, Friedland G, Scifers S, et al. Protocol management of dysuria, urinary frequency, and vaginal discharge. Annals of Internal Medicine 1974; 81:452.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
33	Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs: creating a customized practice model to improve the treatment of allergic rhinitis in a managed care population. American Journal of Managed Care 1999; 5:485.	Other

34	Guiscafre H, Martinez H, Reyes H, et al. From research to public health interventions. I. Impact of an educational strategy for physicians to improve treatment practices of common diseases. Archives of Medical Research 1995; 26:S31.	Study design did not meet criteria for RCT, CBA, or ITS
35	Gupta D, Mishra S, Chaturvedi P. ARI Control Programme: standard case management guidelines vs conventional treatment--an open study. Indian Pediatrics 1996; 33:41-43.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
36	Gurwitz JH, McLaughlin TJ, Fish LS. The effect of an Rx-to-OTC switch on medication prescribing patterns and utilization of physician services: the case of vaginal antifungal products. Health Services Research 1995; 30:672.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
37	Harris CM, Jarman B, Woodman E, et al. Prescribing--a suitable case for treatment. J R Coll Gen Pract 1984; 24:1-39.	Other
38	Harris CM, Fry J, Jarman B, et al. Prescribing--a case for prolonged treatment. J R Coll Gen Pract 1985; 35:284-7.	Other
39	Harris RH, MacKenzie TD, Leeman-Castillo B, et al. Optimizing antibiotic prescribing for acute respiratory tract infections in an urban urgent care clinic. J Gen Intern Med 2003; 18:326-34.	Study design did not meet criteria for RCT, CBA, or ITS
40	Hastings JE, Mott FD, Barclay A, et al. Prepaid group practice in Sault Ste. Marie, Ontario. I. Analysis of utilization records. Medical Care 1973; 11:91.	Not an evaluation of a QI intervention
41	Hemeryck L, McGettigan P, Feely J. Hospital antibiotic prescribing and feedback [letter; comment]. British Journal of Clinical Pharmacology 1997; 43:449-450.	Study design did not meet criteria for RCT, CBA, or ITS
42	Hueston WJ, Mainous AG, 3rd, Brauer N, et al. Evaluation and treatment of respiratory infections: does managed care make a difference? Journal of Family Practice 1997; 44:572.	Study design did not meet criteria for RCT, CBA, or ITS
43	Ives T, et al. Effect of an educational intervention on oral cephalosporin use in primary care. Arch Internal Med 1987; 147:44-47.	Study design did not meet criteria for RCT, CBA, or ITS
44	Jacobs B, Kambugu FS, Whitworth JA, Ochwo M, Pool R, Lwanga A, Tifft S, Lule J, Cutler JR. Social marketing of pre-packaged treatment for men with urethral discharge (Clear Seven) in Uganda. International Journal of STD & AIDS 2003; 14:216.	Study design did not meet criteria for RCT, CBA, or ITS
45	Juncosa S, Porta M. Effects of primary health care reform on the prescription of antibiotics: A longitudinal study in a Spanish county. European Journal of Public Health 1997; 7:54.	Other

46	Kafle KK. Intervention test of training supervision on prescribing practices. 1995.	Article not available
47	Kinney WC. Rhinosinusitis treatment protocol: changing provider habits in primary care. Otolaryngology Head & Neck Surgery 2002; 126:614.	Study design did not meet criteria for RCT, CBA, or ITS
48	Leach RH, Wakeman A. An evaluation of the effectiveness of community pharmacists working with GPs to increase the cost-effectiveness of prescribing. Pharmaceutical Journal 1999; 263:206.	Study design did not meet criteria for RCT, CBA, or ITS
49	Lundborg CS, Tomson G, Wahlstrom R, et al. GPs' knowledge and attitudes regarding treatment of UTI and asthma in Sweden: A randomised controlled educational trial on guideline implementation. European Journal of Public Health 2000; 10:246.	No eligible outcomes
50	Margolis CZ, Warshawsky SS, Goldman L, et al. Computerized algorithms and pediatricians' management of common problems in a community clinic. Academic Medicine 1992; 67:282.	Study design did not meet criteria for RCT, CBA, or ITS
51	Mather JL, Bayliff CD, Reider MJ, et al. The impact of formulary reservations on drug utilization: a controlled trial. Canadian Journal of Hospital Pharmacy. 1994; 47:111-116.	Study design did not meet criteria for RCT, CBA, or ITS
52	Molstad S, Ekedahl. Antibiotics prescription in primary care: A 5-year follow-up of an educational programme. Family Practice 1994; 11:282-286.	Other
53	Mtango F, Neuvians D. Acute respiratory infections in children under five years. Control project in Bagamoyo District, Tanzania. Trans Roy Soc Trop Med Hyg 1986; 80:851.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
54	Munck AP, Gahrn-Hansen B, Sogaard P, et al. Long-lasting improvement in general practitioners' prescribing of antibiotics by means of medical audit. Scandinavian Journal of Primary Health Care 1999; 17:185-190.	Study design did not meet criteria for RCT, CBA, or ITS
55	Naivalulevu L. Training for rational drug use (prescriptions of antibiotics for coughs and colds in Fiji has been greatly reduced since health staff participated in training workshops). ARI News 1990; 19.	Study design did not meet criteria for RCT, CBA, or ITS
56	Needham A. Introduction and audit of a general practice antibiotic formulary. J Royal College of General Practitioners 1988; 38:166.	Study design did not meet criteria for RCT, CBA, or ITS
57	Newby D, A. Fryer J. L. Henry D. A. Effect of computerised prescribing on use of antibiotics. comment. Medical Journal of Australia 2003; 178:210.	Not an evaluation of a QI intervention

58	Obua C, Ogwal-Okeng JW, Waako P, Aupont O, Ross-Degnan D. Impact of an educational intervention to improve prescribing by private physicians in Uganda. East African Medical Journal 2004:S17.	Other
59	Ornstein SM, MacFarlane LL, Jenkins RG, et al. Medication cost information in a computer-based patient record system. Impact on prescribing in a family medicine clinical practice. Archives of Family Medicine 1999; 8:118-121.	Study design did not meet criteria for RCT, CBA, or ITS
60	Palmer NA, Dailey YM, Martin MV. Can audit improve antibiotic prescribing in general dental practice? British Dental Journal 2001; 191:253.	Study design did not meet criteria for RCT, CBA, or ITS
61	Paredes SP, et al. Intervention trial to decrease the inappropriate use of drugs during childhood diarrhoea. 2003.	Article not available
62	Perez Rodriguez MT, Catalan Ramos A, Parellada Esquius N. Criteria for the development of a formulary of drugs in a basic health area and impact on prescription (published erratum appears in Aten Primaria 1995 Mar 15;15(4):270). Spanish. Atencion Primaria 1994; 14:1128.	Foreign language article
63	Perez-Cuevas R, Guiscafre H, Munoz O, et al. Improving physician prescribing patterns to treat rhinopharyngitis. Intervention strategies in two health systems of Mexico. Social Science & Medicine 1996; 42:1185.	Other
64	Poses RM, Cebul RD, Wigton RS. You can lead a horse to water--improving physicians' knowledge of probabilities may not affect their decisions published erratum appears in Med Decis Making 1995 Apr-Jun;15(2):179. Medical Decision Making 1995; 15:65.	Study design did not meet criteria for RCT, CBA, or ITS
65	Putnam W, Curry L. Patient care appraisal in the ambulatory setting: effectiveness as a continuing medical education tool. Annual Conference on Research in Medical Education 1980; 19:207.	No eligible outcomes
66	Qazi SA, Rehman GN, Khan MA. Standard management of acute respiratory infections in a children's hospital in Pakistan: impact on antibiotic use and case fatality. Bulletin World Health Organization 1996; 74(5):501-7	Study design did not meet criteria for RCT, CBA, or ITS
67	Ray WA, Schaffner W, Federspiel CF. Persistence of improvement in antibiotic prescribing in office practice. JAMA 1985; 253:1774.	Overlaps with or duplicates another article that was included
68	Ray WA, Fink R, Schaffner W, et al. Improving antibiotic prescribing in outpatient practice. Nonassociation of outcome with prescriber characteristics and measures of receptivity. Medical Care 1985; 23:1307.	Other

69	Rosser W, Dunn L, Pilla J, et al. Using academic detailing to disseminate clinical practice guidelines [abstract]. Annual Meeting of International Society of Technology Assessment in Health Care 1997; 13:93.	Abstract; article not available
70	Saint S, Scholes D, Fihn SD, et al. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women. American Journal of Medicine 1999; 106:636-641.	Study design did not meet criteria for RCT, CBA, or ITS
71	Seppälä H, Klaukka T, Vuopio-Varkila J, et al. The Effect of Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group A Streptococci in Finland. N Engl J Med 1997; 337:441-446.	Study design did not meet criteria for RCT, CBA, or ITS
72	Sever CM, MacKinnon III GE. Evaluation of a criteria-based anti-infective formulary. P & T 1993; 18:770-776.	Study design did not meet criteria for RCT, CBA, or ITS
73	Shalansky SJ. Antibiotic interchange through educational interventions in a community hospital. American Journal of Hospital Pharmacy 1991; 48:2655-2657.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
74	Simon JL, Smith DB. Change in location of a student health service: a quasi-experimental evaluation of the effects of distance on utilization. Medical Care 1973; 11:59.	Not an evaluation of a QI intervention
75	Soumerai S. Economic and policy analysis of university-based drug "detailing". Medical Care 1986; 24:313.	Study design did not meet criteria for RCT, CBA, or ITS
76	Soumerai S. Predictors of physician prescribing change in an educational experiment to improve medication use. Medical Care 1987; 25:210.	Overlaps with or duplicates another article that was included
77	Soumerai SB, Avorn J, Taylor WC, et al. Improving choice of prescribed antibiotics through concurrent reminders in an educational order form. Medical Care 1993; 31:552.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
78	South M, Royle J, Starr M. A simple intervention to improve hospital antibiotic prescribing. comment. Medical Journal of Australia 2003; 178:207.	Study design did not meet criteria for RCT, CBA, or ITS
79	Stewart J, Pilla J, Dunn L. Pilot study for appropriate anti-infective community therapy. Effect of a guideline-based strategy to optimize use of antibiotics. Canadian Family Physician 2000; 46:851.	Other

80	Stuart ME, Macuiba J, Heidrich F, et al. Successful implementation of an evidence-based clinical practice guideline: acute dysuria/urgency in adult women. HMO Practice 1997; 11:150.	No eligible outcomes
81	Suchyta MR, Dean NC, Narus S, et al. Effects of a practice guideline for community-acquired pneumonia in an outpatient setting. American Journal of Medicine 2001; 110:306.	Study design did not meet criteria for RCT, CBA, or ITS
82	Temte JL, Shult PA, Kirk CJ, et al. Effects of viral respiratory disease education and surveillance on antibiotic prescribing. Family Medicine 1999; 31:101.	Study design did not meet criteria for RCT, CBA, or ITS
83	Thamer M, Ray NF, Henderson SC, et al. Influence of the NIH Consensus Conference on Helicobacter pylori on physician prescribing among a Medicaid population. Medical Care 1998; 36:646.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
84	Tierney W, Hui SL, McDonald CJ. Delayed feedback of physician performance versus immediate reminders to perform preventive care. Effects on physician compliance. Medical Care 1986; 24:659.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
85	Tseng R. An audit of antibiotic prescribing in general practice using sore throats as a tracer for quality control. Public Health 1985; 99:177.	Study design did not meet criteria for RCT, CBA, or ITS
86	Tumwikirize WA, Ekwaru PJ, Mohammed K, et al. Impact of a face-to-face educational intervention on improving the management of acute respiratory infections in private pharmacies and drug shops in Uganda. East Afr Med J 2004; Suppl:S25-32.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
87	Wahlstrom R, Kounnavong S. Sisounthone B. Phanyanouvong A. Southammavong T. Eriksson B. Tomson G. Effectiveness of feedback for improving case management of malaria, diarrhoea and pneumonia--a randomized controlled trial at provincial hospitals in Lao PDR. Tropical Medicine & International Health 2003; 8:901.	No eligible outcomes
88	Walley T, Murphy M, Codd M, et al. Effects of a monetary incentive on primary care prescribing in Ireland: changes in prescribing patterns in one health board 1990-1995. Pharmacoepidemiology & Drug Safety 2000; 9:591.	No eligible outcomes
89	Williams M. Evaluation of patient counselling on the use of antibiotics in community pharmacies.	Article not available
90	Wilson RG, Bojke C, O'Neill S, et al. Designing, specifying and evaluating a new repeat prescribing process for UK general practice. Studies in Health Technology & Informatics 2000; 77:219.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)

91	Wilson SD, Dahl BB, Wells RD. An evidence-based clinical pathway for bronchiolitis safely reduces antibiotic overuse. American Journal of Medical Quality 2002; 17:195.	Excluded topic (focused on inpatient care or antimicrobial use in chronic care)
92	Zwar NA, Gordon JJ, Sanson-Fisher RW. Evaluation of an educational program in rational prescribing for GP trainees. Australian Family Physician 1995; 24:833.	Other
93	Zwar N, Henderson J, Britt H, et al. Influencing antibiotic prescribing by prescriber feedback and management guidelines: a 5-year follow-up. Family Practice 2002; 19:12.	Other

Summary Tables

Table 1A. QI strategies and outcomes for antibiotic treatment studies

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Remind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Finkelstein J[1]	United States 12 practices affiliated with 2 managed care organizations	Children	ARI	RCT (--)	1997-1998 (12)	✓		✓		✓				Antibiotics prescribed per person-year
Angunawela I[2]	Sri Lanka General practitioners at rural primary care clinics	All patients	Not specified	RCT (1048)	1988 (2)			✓						% of pt visits resulting in ABX prescription
Angunawela I[3]	Sri Lanka General practitioners at rural primary care clinics	All patients	Not specified	RCT (1348)	1988 (2)			✓						% of pt visits resulting in ABX prescription

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Arroll, B[4]	New Zealand General practitioners	All patients	ARI (Common cold)	RCT (129)	-- (10 days)		✓							% of pt visits resulting in ABX prescription Clinical outcomes Pt/Clin Satisfaction
Belongia, E[5]	United States Multiple counties in Northern Wisconsin	Children	ARI (Common cold, Acute sinusitis, Pharyn-gitis, Bronchitis, Otitis media)	CBA (370)	1997 (4)	✓		✓						% of pt visits resulting in ABX prescription Antimicrobial resistance
Bexell, A[6]	Zambia General Practices	All patients	Not specified	QRCT (1113)	1991 (5)			✓						% of pt visits resulting in ABX prescription
Christakis, D[7]	United States Academic pediatric primary care clinic	Children	ARI (Otitis media)	RCT (--)	-- (8)				✓					Change in % of pt visits resulting in ABX prescription Duration of ABX therapy

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effective sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Delayed	Clin Ed	Clin Remind	Audit & Fdbck	Org Change	Pt Incentives	Clin Incentives	
Dowell, J[8]	UK General practitioners in Scotland	Adults	ARI (Cough)	RCT (194)	1997-1998 (--)		✓							% of pt visits resulting in ABX prescription Clinical outcome Health services utilization Pt/Clin Satisfaction
Flottorp, S[9]	Norway 142 General practices	All patients	ARI (Sore throat)	RCT (1739)	2000-2001 (9)	✓		✓	✓		✓	✓	✓	% of pt visits resulting in ABX prescription Health services utilization
Foxman, B[10]	United States 6 cities: Dayton, OH; Seattle, WA; Fitchburg, MA; Franklin County, MA; Charleston, SC; Georgetown County, SC	All patients	Not specified	RCT (--)	1975 (12)							✓		ABX prescriptions per person-year

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Gonzales, R[11]	United States 4 HMO primary care practices	Adults	ARI (Acute bronchitis)	CBA (1213)	1997-1998 (4)	✓		✓		✓				% of pt visits resulting in ABX prescription Health services utilization
Gonzales, R[12]	United States 4 HMO primary care practices	Adults	ARI (Acute bronchitis)	CBA (1197)	1997-1998 (4)	✓		✓						% of pt visits resulting in ABX prescription Health services utilization
Gonzales-Ochoa, E[13]	Cuba General practitioners in 4 areas of Havana	Children	ARI	QRCT (122)	1991 (12)	✓		✓						% of pt visits resulting in ABX prescription
Gonzales-Ochoa, E[14]	Cuba General practitioners in 4 areas of Havana	Children	ARI	QRCT (100)	1991 (12)			✓						% of pt visits resulting in ABX prescription
Gonzales-Ochoa, E[15]	Cuba General practitioners in 4 areas of Havana	Children	ARI	QRCT (100)	1991 (12)	✓								% of pt visits resulting in ABX prescription

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Gutierrez, G[16]	Mexico General practitioners at health care clinics of the Mexican Social Security Institute	All patients	Diarrhea	CBA (152)	-- (18)			✓		✓				% of pt visits resulting in ABX prescription
Hennessy, T[17]	United States 13 rural Alaskan villages	All patients	ARI	CBA (2163)	1998-1999 (6)	✓		✓						% of pt visits resulting in ABX prescription Antimicrobial resistance
Hickman, D[18]	United States Suburban community-based physician group	All patients	ARI (Acute bronchitis)	CBA (1943)	1998 (4)	✓		✓		✓				% of pt visits resulting in ABX prescription Health services utilization
Little, P[19]	UK General practices in southwest England	Children	ARI (Otitis media)	RCT (285)	-- (1 week)		✓							% of pt visits resulting in ABX prescription Clinical outcome Pt/Clin Satisfaction

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Macfarlane, J[20]	UK General practices	Adults	ARI (Acute bronchitis)	RCT (205)	1999-2000 (11)	✓	✓							% of pt visits resulting in ABX prescription Health service utilization
Mainous, A[21]	United States 8 Medicaid administrative regions in Kentucky	Children	ARI	RCT (2564)	1997 (1)	✓								% of pt visits resulting in ABX prescription
Mainous, A[22]	United States 8 Medicaid administrative regions in Kentucky	Children	ARI	RCT (2740)	1997 (1)					✓				% of pt visits resulting in ABX prescription
Mainous, A[23]	United States 8 Medicaid administrative regions in Kentucky	Children	ARI	RCT (2297)	1997 (1)	✓				✓				% of pt visits resulting in ABX prescription

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effective sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Delayed	Clin Ed	Clin Remind	Audit & Fdbck	Org Change	Pt Incentives	Clin Incentives	
McConnell, T[24]	United States New Mexico Medicaid program	All patients	ARI	RCT (--)	1997-1998 (?)			✓		✓				ABX prescriptions per provider Compliance to clinical guideline
McIsaac, W[25]	Canada Family physicians in Ontario	All patients	ARI (Sore throat)	RCT (396)	1996 (--)				✓					% of pt visits resulting in ABX prescription
McIsaac, W[26]	Canada Family physicians in Ontario	All patients	ARI (Sore throat)	RCT (99)	1998 (--)				✓					% of pt visits resulting in ABX prescription
Melander, E[27]	Sweden General practitioners	All patients	ARI	CBA (857)	1995 (--)			✓		✓				% of pt visits resulting in ABX prescription
Meyer, J[28]	South Africa Nurses in primary health clinics	All patients	ARI Diarrhea	RCT (383)	1997 (6)			✓						% of pt visits resulting in ABX prescription
O'Connell, D[29]	Australia General practitioners in rural area	All patients	Not specified	RCT (--)	1995 (7)			✓		✓				ABX prescriptions per 100 patient visits

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Perz, J[30]	United States 4 counties in Tennessee	Children	Not specified	CBA (--)	1997-1998 (12)	✓		✓						ABX prescriptions per person-year
Santoso, B[31]	Indonesia General practitioners in Yogyakarta and Java provinces	Children	Diarrhea	RCT (1638)	--			✓						% of pt visits resulting in ABX prescription
Santoso, B[32]	Indonesia General practitioners in Yogyakarta and Java provinces	Children	Diarrhea	RCT (1638)	--			✓						% of pt visits resulting in ABX prescription
Zwar, N[33]	Australia General practitioner trainees in New South Wales	All patients	ARI	RCT (--)	--			✓		✓				% of pt visits resulting in ABX prescription

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effective sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Delayed	Clin Ed	Clin Remind	Audit & Fdbck	Org Change	Pt Incentives	Clin Incentives	
McNulty, C[34]	UK General practices in Gloucestershire	All patients	Not specified	CBA (--)	1997 (7 weeks)			✓		✓				Total ABX prescriptions Cost
Welschen, I[35]	The Netherlands General practitioners in Utrecht	All patients	ARI	QRCT (1074)	2000-2001 (9)	✓		✓		✓				% of pt visits resulting in ABX prescription Pt/Clin Satisfaction
Molstad, S[36]	Sweden General practitioners at community health centers	All patients	ARI (Rhinitis, Pharyngitis, Acute bronchitis)	CBA (372)	1985 (2)			✓						% of pt visits resulting in ABX prescription
Cates, C[37]	UK General practitioners in outpatient clinics in Hertfordshire	Children	ARI (Otitis media)	CBA (--)	1997-1998 (12)	✓	✓							ABX prescriptions per clinic

Table 1A. QI strategies and outcomes for antibiotic treatment studies (continued)

Author	Setting and Target	Patient Population	Disease Target	Study Design (Effec-tive sample size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	Dela-yed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Pshetizky, Y[38]	Israel General practitioners	Children	ARI (Otitis media)	RCT (81)	1998-1999	✓	✓							% of pt visits resulting in ABX prescription
Smabrekke, L[39]	Norway Physicians and nurses at urgent care clinic	Children	ARI (Otitis media)	CBA (329)	1998-1999 (4)	✓		✓						% of pt visits resulting in ABX prescription
Wilson, E[40]	Australia General practitioners in Canberra	Children	ARI	RCT (--)	1998 (4)	✓	✓	✓						Prescriptions per 100 patient visits
Coenen, S[41]	Belgium General practitioners	Adults	ARI	RCT (238)	2001 (1)			✓					✓	% of pt visits resulting in ABX prescription Cost Health service utilization Clinical outcomes

Abbreviations: ARI = acute respiratory infection; UTI = urinary tract infection; ABX = antibiotics, CBA = controlled before-after study; RCT = randomized controlled trial; QRCT = quasi randomized controlled trial; Pt Ed = patient education; Delayed = provision of delayed prescriptions; Clin Remind = Clinician Reminder; Clin Ed = clinician education; Audit & Fdbck = clinician audit and feedback; Org Change = Organizational change; Pt Incentives = patient-directed financial or regulatory incentives; Clin Incentives = clinician-directed financial or regulatory incentives

Table 1B. QI strategies and outcomes for antibiotic selection studies

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Avorn, J[42]	United States Physicians in 4 state Medicaid programs (Arkansas, New Hampshire, Vermont, and the District of Columbia)	Medicaid patients	Not specified	RCT (--)	1980-1981 (6)			✓						% change in prescribing of contraindicated ABX
Avorn, J[43]	United States Physicians in 4 state Medicaid programs (Arkansas, New Hampshire, Vermont, and the District of Columbia)	Medicaid patients	Not specified	RCT (--)	1980-1981 (6)			✓						% change in prescribing of contraindicated ABX
Braybrook, S[44]	UK 66 family health practices in Wales	All patients	UTI	CBA (--)	1992-1993 (6)			✓		✓			✓	% change in prescribing of contraindicated ABX
Braybrook, S[45]	UK 66 family health practices in Wales	All patients	UTI	CBA (--)	1992-1993 (6)			✓		✓			✓	% change in prescribing of contraindicated ABX

Table 1B. QI strategies and outcomes for antibiotic selection studies (continued)

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Bush, P[46]	United States Pediatricians at 3 HMO sites in Washington, DC	Children enrolled in HMO	ARI (Otitis Media)	CBA (348)	1975-1976 (--)			✓						Compliance to clinical guideline
Bush, P[47]	United States Pediatricians at 3 HMO sites in Washington, DC	Children enrolled in HMO	ARI (Otitis Media)	CBA (247)	1975-1976 (--)			✓						Compliance to clinical guideline
De Santis, G[48]	Australia General practitioners in 8 rural and metropolitan Victorian Health Department regions	All patients	ARI (Tonsillitis)	RCT (788)	-- (3)			✓						Compliance to clinical guideline
Dolovich, L[49]	Canada Family physicians in Southern Ontario	Children	ARI (Otitis Media)	RCT (--)	--			✓						% change in market share of recommended ABX

Table 1B. QI strategies and outcomes for antibiotic selection studies (continued)

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Farris, KB[50]	United States Family physicians in HMO in southeastern Michigan	HMO patients	ARI (Otitis media, Sinusitis, Bronchitis, Community acquired pneumonia)	CBA (--)	1991-1992 (--)			✓		✓				% prescribed recommended drugs Cost Pt/Clin Satisfaction
Friis, H[51]	Denmark General practitioners in 5 counties	All patients	ARI	CBA (2600)	-- (3)			✓						% prescribed recommended drugs
Friis, H[52]	Denmark General practitioners in 5 counties)	All patients	ARI	CBA (2046)	-- (3)			✓						% prescribed recommended drugs
Hux, J[53]	Canada Family physicians in Ontario	Adults	ARI UTI	RCT (--)	1996-1997 (6)			✓		✓				Compliance to clinical guideline Cost
Ilett, K[54]	Australia General practitioners in the Perth metropolitan area	All patients	ARI UTI	RCT (2368)	1997 (2)			✓						% prescribed recommended drugs Cost

Table 1B. QI strategies and outcomes for antibiotic selection studies (continued)

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Klein, L[55]	United States Residents in academic emergency room and primary care center	Adults	UTI	CBA (44)	1978-1979 (--)			✓						Compliance to clinical guideline
Lagerlov, P[56]	Norway General practitioners	Adults	UTI	RCT (--)	1995 (--)			✓		✓				Duration of ABX therapy
Lundborg, C[57]	Sweden 36 General practitioner groups	Adult women	UTI	RCT (1734)	1995 (6)			✓		✓				Compliance to clinical guideline Duration of ABX therapy
MacCara, M[58]	Canada General practitioners	Adults	Not specified	ITS (--)	1997 (12)							✓	✓	Change in number of prescriptions for contraindicated ABX
McNulty, C[59]	UK 84 general practices in Gloucestershire	All patients	ARI UTI	CBA (121,85 7)	1997 (7)			✓		✓				% prescribed recommended drugs Cost
Peterson, G[60]	Australia General practitioners in Southern Tasmania	Adults	UTI	CBA (26,968)	1995 (5)			✓						% prescribed recommended drugs

Table 1B. QI strategies and outcomes for antibiotic selection studies (continued)

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Raz, R[61]	Israel Physicians and nurses at 3 community outpatient clinics	All patients	ARI (Pharyn-gitis)	CBA (3841)	1988 (1)			✓						% prescribed recommended drugs
Rokstad, K[62]	Norway General practitioners in 2 counties	Adults	UTI	CBA (210)	1989 (--)					✓				% prescribed recommended drugs Duration of ABX therapy
Schaffner, W[63]	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	Not specified	CBA (--)	1980-1981 (16)			✓						% change in prescriptions for contraindicated ABX
Schaffner, W[64]	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	Not specified	CBA (--)	1980-1981 (16)			✓						% change in prescriptions for contraindicated ABX
Schaffner, W[65]	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	Not specified	CBA (--)	1980-1981 (16)			✓						% change in prescriptions for contraindicated ABX

Table 1B. QI strategies and outcomes for antibiotic selection studies (continued)

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Schaffner, W[66]	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	Not specified	CBA (--)	1980-1981 (16)			✓						% change in prescriptions for contraindicated ABX
Sondergaard, J[67]	Denmark 181 general practices	All patients	ARI	RCT (6763)	1988-1989 (4)			✓		✓				% prescribed recommended drugs
Veninga, C[68]	Netherlands General practitioners	Adult women	UTI	RCT (3433)	1996 (5)			✓		✓				Duration of ABX therapy Compliance to clinical guideline
Melander, E[69]	Sweden General practices in 3 communities	All patients	ARI	CBA (68)	1995 (--)			✓		✓				% prescribed recommended drugs
Harrison, A[70]	South Africa Practitioners in 10 primary care clinics in rural KwaZulu - Natal)	Adults	STD	RCT (77)	1996-1997 (15)	✓		✓						Compliance to clinical guideline
Zwar, N[71]	Australia General practitioner trainees in New South Whales	All patients	ARI (tonsillitis, pharyngitis)	RCT (--)	--			✓		✓				Compliance to clinical guideline

Table 1B. QI strategies and outcomes for antibiotic selection studies (continued)

Author	Setting	Patient Population Target	Disease Target	Study Design (Sample Size)	Study Period (Duration/ months)	QI Strategies Employed								Outcomes Reported
						Pt Ed	De-layed	Clin Ed	Clin Re-mind	Audit & Fdbck	Org Change	Pt Ince-ntives	Clin Incen tives	
Molstad, S[72]	Sweden General practitioners at 3 community health centers	All patients	ARI (Rhinitis, pharyngitis, acute bronchitis)	CBA (209)	1985 (2)			✓						% prescribed recommended drugs
Smabrekke, L[73]	Norway Physicians at an acute care center	Children	ARI (Otitis media)	CBA (260)	1998-1999 (4)	✓		✓						% prescribed recommended drugs
Coenen, S[74]	Belgium General practitioners	All patients	ARI (Acute cough)	RCT (67)	2001 (1)			✓					✓	Compliance to clinical guideline

Abbreviations: ARI = acute respiratory infection; UTI = urinary tract infection; ABX = antibiotics, CBA = controlled before-after study; RCT = randomized controlled trial; ITS = interrupted time series; Pt Ed = patient education; Delayed = provision of delayed prescriptions; Clin Ed = clinician education; Clin Remind = clinician reminder; Audit & Fdbck = clinician audit and feedback; Org Change = organizational change; Pt Incentives = patient-directed financial or regulatory incentives; Clin Incentives = clinician-directed financial or regulatory incentive

Table 1C. Antibiotic treatment studies: target condition and population

	Studies targeting children		Studies targeting adults		Studies targeting entire population		Total
	Specific insurance	**No specific insurance**	**Specific insurance**	**No specific insurance**	**Specific insurance**	**No specific insurance**	
General ARI	2 [1,21]	5 [5,7,13,26,40]	0	1 [8]	0	7 [18,24,27,28, 33,35,36]	15
Specific ARI	0	4 [19,37-39]	1 [11]	2 [20,25]	1 [18]	3 [4,9,41]	11
Acute diarrhea	1 [16]	1 [31]	0	0	0	0	2
No specific disease target	1 [30]	0	0	0	0	5 [2,6,10,29,34]	6
Total	4	10	1	3	1	15	34

Antibiotic treatment studies classified according to target disease and population. "Specific insurance" refers to patients within a health maintenance organization (HMO), other managed care organization, Medicare, or Medicaid.

Table 1D. Antibiotic selection studies: target condition and population

	Studies targeting children		Studies targeting adults		Studies targeting entire population		Total
	Specific insurance	**No specific insurance**	**Specific insurance**	**No specific insurance**	**Specific insurance**	**No specific insurance**	
General ARI	0	0	0	0	1 [50]	5 [36,54,67,69, 71]	6
Specific ARI	1 [46]	2 [39,49]	0	0	0	3 [41,48,61]	6
Urinary tract infection	0	0	0	6 [55-57,60, 62,68]	0	2 [44,45]	8
Other disease	0	0	0	1 [70]	0	0	1
No disease target	0	0		2* [53,58]	2 [42,63]	2 [34,51]	6
Total	1	2	0	9	3	12	26

Antibiotic selection studies classified according to target disease and population. "Specific insurance" refers to patients within a health maintenance organization (HMO), other managed care organization, Medicare or Medicaid.
*--These studies both targeted elderly patients.

Table 2. Antibiotic treatment studies: number of QI strategies utilized

Number of QI strategies	Randomized Controlled Trial	Quasi-RCT	Controlled Before-After Study	Total
One	15 [2-4, 7, 8, 10, 19, 21, 22, 25, 26, 28, 31, 32, 41]	3 [6, 14, 15]	1 [36]	19
Two	6 [20, 23, 24, 29, 33, 38]	1 [13]	9 [5, 11, 16, 17, 27, 30, 34, 37, 39]	16
Three	2 [1, 40]	1 [35]	2 [11, 18]	5
Four	0	0	0	0
Five	0	0	0	0
Six	1 [9]	0	0	1
More than six	0	0	0	0
Total	24	5	12	

"Quasi-RCT" refers to studies described as randomized where randomization was altered by investigators, or where a method of patient assignment was used that is not truly random (e.g. assignment by even/odd medical record number or date of clinic visit.) "Controlled Before-After Study" refers to non-randomized controlled trials with a contemporaneous comparison group. Quasi-RCT's and Controlled Before-After studies were grouped together in statistical analyses.

Table 3. Median effect size of QI strategies on antibiotic treatment decision

	Median effect with QI strategy (Interquartile range)	
All comparisons (N=24)	-8.9% (-12.4% to -6.7%)	
Clinician Education alone (N=9)	-8.1% (-13.7% to -7.0)	P=0.848 for comparison across QI strategies P=0.478 for comparison of clinician education vs. clinician education and patient education
Clinician Education combined with Patient Education* (N=6)	-7.5% (-12.0% to -3.0%)	
Clinician Education combined with Audit and Feedback (N=2)	-8.5% (-15.0% to -2.0%)	
Clinician Education, Patient Education, and Audit and Feedback (N=3)	-12.0% (-18.0% to -10.9%)	
Patient Education alone (N=2)*	-4.9% (-9.9% to -0.2%)	
Audit and Feedback alone (N=1)	-7.3%	
Patient Education combined with Audit and Feedback (N=1)	-7.2%	

Percentages demonstrate the net reduction in prescribing of antibiotics. Values represent the median effect across studies with each QI strategy (or combination of strategies) with interquartile ranges. For categories with N=2, values in parenthesis represent the effects of the two studies in question.

The net change in antibiotic prescribing for each study was calculated as follows:
Net Δ in prescribing = (Post-intervention proportion prescribed antibiotics – Pre-intervention proportion prescribed antibiotics)$_{\text{intervention group}}$ - (Post-intervention proportion prescribed antibiotics – Pre-intervention proportion prescribed antibiotics)$_{\text{control group}}$.

The median value was then obtained from the values of the net Δ in prescribing for each subset of studies. Median effects for each QI strategy were compared using the nonparametric Kruskal-Wallis test, which tests the equality of each median effect.

*--Includes one study[10] with four additional QI strategies (Clinician Reminders, Organizational Change, Financial incentives for Patients, Regulatory Incentives for Clinicians.) No other study utilized any of these QI strategies.

Table 4. Antibiotic treatment studies: QI strategies and study modifiers

	Median effect overall (Interquartile range)	Provider education alone (N=9)	Provider education and Patient Education (N=6)
All comparisons (N=15)	-8.1% (-6.5% to -13.7%)	-8.1% (-13.7% to -7.0)	-7.5% (-12.0% to -3.0%)
Randomized Controlled Trials N=7	-7.0% (-13.7% to -6.7%)	-7.0% (-12.0% to -6.8%) N=6	-3.0% N=1
Controlled Before-After Trials N=8	-10.8% (-17.7% to -6.8%)	-9.6% (-16.5% to -8.9%) N=3	-12.0% (-12.0% to -3.0%) N=5
US-based Studies N=3	-3.0% (-12.0% to1.5%)	N=0	-3.0% (-7.5% to -0.3%) N=3
Non-US-based Studies N=12	-8.9% (-16.5% to -6.9%)	-8.1% (-13.7% to -7.0) N=9	-12.0% (-20.8% to -7.5%) N=3
Effective sample size below median N=12	-10.8% (-26.0% to -6.8%)	-9.6% (-23.3% to -7.0%) N=5	-12.0% (-20.8% to -5.3%) N=3
Effective sample size above median N=7	-7.0% (-12.0% to -3.0%)	-7.6% (-9.5% to -6.9%) N=4	-3.0% (-7.5% to -0.3%) N=3
Baseline prescription rate below median N=10	-7.0% (-9.6% to -7.0%)	-10.9% (-20.9% to -7.1%) N=6	-7.5% (-12.0% to -3.0%) N=4

Table 4. Antibiotic treatment studies: QI strategies and study modifiers (continued)

Baseline prescription rate above median N=5	-10.5% (-13.7% to -6.5%)	-7.0% (-8.3% to -7.0%) N=3	-14.0% (-29.5% to 1.5%) N=2
Repeated intervention N=5	-8.1% (-12.0% to -7.1%)	-7.0% (-7.6% to -7.0%) N=3	12.0% (-12.0%, -12.0%) N=2
One-time intervention N=10	8.2% (-23.3% to -3.0%)	-11.7% (-20.9% to -7.4%) N=6	-3.0% (-9.6% to -1.9%) N=4
Active educational strategy used N=7	-13.7% (-28.6% to -6.5%)	-18.6% (-24.5% to -11.9%) N=4	-12.0% (-20.8% to -5.3%) N=3
Only passive educational strategies used N=8	-7.0% (-8.9% to -4.9%)	-7.1% (-8.1% to -7.0%) N=5	-3.0% (-7.5% to -0.3%) N=3
Specific disease targeted (N=12)	-10.8% (-4.5% to -18.4%	-11.7% (-20.9% to -7.4%) N=6	-7.5% (-12.0% to -3.0% N=6
No specific disease targeted (N=3)	-7.0% (-8.1% to -7.0%)	-7.0% (-8.1% to -7.0%) N=3	N=0
Children targeted (N=6)	-10.8% (-13.7% to -6.7%)	-9.6% (-11.7% to -8.2%) N=3	-12.0% (-20.8% to -5.3%) N=3
Children not targeted (N=9)	-7.0% (-12.0% to -6.5%)	-7.6% (-19.5% to -6.9%) N=6	-3.0% (-7.5% to -3.0% (N=3)

Table 4 includes only the QI strategies used in >3 trials. Trials designated as quasi-Randomized Controlled Trials in Table 2 are grouped with Controlled Before-After studies in these analyses.

Table 5. Results of Wilcoxon rank-sum tests for differences between groups

	Treatment studies (N=15)			Selection studies (N=19)		
		Median effect (%) [Interquartile range]	P value for comparison		Median effect (%) [Interquartile range]	P value for comparison
Study design	**RCT (n = 7)**	-7.0% (-13.7% to -6.7%)	0.52	**RCT (n = 8)**	11.1% (3.2% to 16.0%)	0.62
	Non-RCT (n = 8)	-10.8% (-17.7% to -6.8%)		**Non-RCT (n = 11)**	8.8% (3.1% to 22.7%)	
Sample Size	**Below median (n = 8)**	-10.8% (-26.0% to -6.8%)	0.30	**Below median (n = 7)**	20.4% (8.4% to 35.6%)	0.063
	Above median (n = 7)	-7.0% (-12.0% to -3.0%)		**Above median (n = 12)**	6.2% (2.8% to 13.7%)	
Country	**US (n = 3)**	-3.0% (-12.0% to1.5%)	0.15	**US (n = 4)**	29.2% (14.9% to 41.8%)	0.028
	Non-US (n = 12)	-8.9% (-16.5% to -6.9%)		**Non-US (n = 15)**	8.4% (2.5% to 14.9%)	
Type of control group	**Usual care (n=15)**	Not performed	N/A	**Usual care (n=14)**	14.4% (7.2% to 20.4%)	0.041
	Limited interven-tion (n = 0)	Not performed		**Limited interven-tion (n = 5)**	3.1% (2.5% to 7.1%)	
Baseline prescribing rate	**Below median (n=5)**	-7.0% (-9.6% to -7.0%)	0.82	**Below median (n=9)**	13.9% (3.1% to 17.0%)	0.87
	Above median (n=10)	-10.5% (-13.7% to -6.5%)		**Above median (n=10)**	8.6% (4.3% to 20.4%)	
Use of active educational strategies	**Yes (n=7)**	-13.7% (-28.6% to -6.5%)	0.11	**Yes (n=12)**	11.1% (4.9% to 17.1%)	0.87
	No (n=8)	-7.0% (-8.9% to -4.9%)		**No (n=7)**	5.1% (3.1% to 22.7%)	
Repeated intervention	**Yes (n=5)**	-8.1% (-12.0% to -7.1%)	0.81	**Yes (n=8)**	6.8% (3.7% to 14.8%)	0.37
	No (n=16)	8.2% (-23.3% to -3.0%)		**No (n=11)**	13.9% (2.5% to 22.7%)	

Table 5. Results of Wilcoxon rank-sum tests for differences between groups (continued)

Specific disease targeted	**Yes (N=12)**	-10.8% (-4.5% to -18.4%	0.66	**Yes (N=17)**	12.5% (3.1% to 18.6%)	0.19
	No (N=3)	-7.0% (-8.1% to -7.0%)		**No (N=2)**	3.4% (2.5% to 4.3%)	
Children targeted	**Yes (N=6)**	-10.8% (-13.7% to -6.7%)	0.60	**Yes (N=2)**	29.2% (22.7% to 35.6%)	0.05
	No N=9)	-7.0% (-12.0% to -6.5%)		**No (N=17)**	8.4% (3.1% to 13.9%	

Results of nonparametric Wilcoxon rank-sum tests the hypothesis that the median effects in the two groups being compared are equal. This analysis is restricted to the subgroup of studies in the two dominant QI strategies: for treatment studies, clinician education and clinician education plus patient education; for selection studies, clinician education and clinician education plus audit and feedback. Trials designated as quasi-Randomized Controlled Trials in Table 2 are grouped with Controlled Before-After studies in these analyses.

Table 6. Delayed prescription studies

Study	Target condition	Rate of antibiotic use (comparison group)	Rate of antibiotic use (intervention group)	Reduction in antibiotic use ($Intervention_{post}$ – $Control_{post}$)
Arroll et al[4]	Common cold	87.0%	40.3%	46.7%
Dowell et al[8]	Uncomplicated ARI	100.0%	45.0%	55.0%
Little et al[19]	Pediatric otitis media	98.5%	24.0%	74.5%
MacFarlane et al[20]	Acute bronchitis	62.0%	47.0%	15.0%
Pshetizky et al[38]	Pediatric otitis media	63.0%	37.0%	26.0%

Studies using delayed prescriptions are those in which the antibiotic prescription is provided to the patient with instructions to use the prescription only if their condition did not improve with supportive measures within a set period of time. These studies did not report pre-intervention prescribing rates. In all studies, comparison group patients received antibiotic prescriptions with instructions to begin taking antibiotics immediately; the post-intervention control group percentages refer to the percent of patients who actually filled the prescription. In Dowell et al, the percentage of control group patients who used the antibiotic prescription was not stated. The studies by Macfarlane and Pshetizky also incorporated a brief educational intervention for patients.

Table 7. Antibiotic selection studies: number of QI strategies utilized

Number of QI strategies	Randomized Controlled Trial	Interrupted Time Series	Controlled Before-After Study	Total
One	6 [41-43, 48, 49, 54]	0	13 [36, 46, 47, 51, 52, 55, 60-66]	19 [36, 41-43, 46, 47, 48, 49, 51, 52, 54, 55, 60-66]
Two	7 [53, 56, 57, 67, 68, 70, 71]	1 [58]	4 [34, 50, 69, 73]	12 [34, 50, 53, 56-58, 67-71, 73]
Three	0	0	2 [44, 45]	2 [44, 45]
Four	0	0	0	0
Five	0	0	0	0
Six	0	0	0	0
More than six	0	0	0	0
Total	13 [41-43, 48, 49, 53, 54, 56, 57, 67, 68, 70, 71]	1 [58]	19 [34, 36, 44-47, 50-52, 55, 60-66, 69, 73]	

There were no quasi-RCT's among the antibiotic selection studies. Interrupted Time Series studies were required to report a clearly defined intervention time period, at least three data points before and after the intervention, and use appropriate statistical methodology. "Controlled Before-After Study" refers to non-randomized controlled trials with a contemporaneous comparison group.

Table 8. Median effect size of QI strategies on antibiotic selection decision

	Median effect with QI strategy (Interquartile range)	
All comparisons (N=22)	10.6% (3.4% to 18.2%)	
Clinician Education alone (N=11)	13.9% (8.6% to 21.6%)	p=0.182 for comparison across QI strategies p=0.028 for comparison of clinician education alone with clinician education and audit and feedback
Clinician Education combined with Audit and Feedback (N=8)	3.4% (1.8% to 9.7%)	
Clinician Education combined with Patient Education (N=2)*	22.8% (2.4% to 43.1%)	
Audit and Feedback alone (N=1)	13.9%	

Percentages demonstrate the net improvement in selection of the appropriate antibiotic. Values represent the median effect across studies with each QI strategy (or combination of strategies) with interquartile ranges. (For clinician education combined with audit and feedback, values in parenthesis represent the effects of the two studies in question.) Median effects were compared using the nonparametric Kruskal-Wallis test, which evaluates the null hypothesis that the observed effects are from the same study population. Individual study effect sizes calculated as:

Net Δ in prescribing recommended antibiotic = (Post-intervention recommended prescribing percentage – Pre-intervention recommended prescribing percentage)$_{\text{intervention group}}$ - (Post-intervention recommended prescribing percentage – Pre-intervention recommended prescribing percentage)$_{\text{control group}}$.

Table 9. Selection studies: QI strategies and study modifiers

	Median effect overall (Interquartile range)	Provider Education alone (N=11)	Provider Education and Audit and Feedback (N=8)
All comparisons (N=19)	8.8% (3.1% to 18.6%)	13.9% (8.4% to 22.7%)	3.4% (1.5% to 12.1%)
Randomized Controlled Trials N=8	11.1% (3.2% to 16.0%)	13.9% (11.2% to 14.4%) N=3	4.3% (2.0% to 17.0%) N=5
Controlled Before-After Trials N=11	8.8% (3.1% to 22.7%)	16.5% (7.8% to 25.9%) N=8	2.5% (2.5% to 4.7%) N=3
US-based studies N=4	29.2% (15.0% to 41.8%)	35.6% (29.2% to 41.8%) N=3	7.2% N=1
Non-US-based studies N=15	8.4% (2.5% to 14.9%)	10.6% (7.6% to 14.2%) N=8	4.9% (1.4% to 14.6%) N=7
Effective sample size below median N=7	20.4% (8.4% to 35.6%)	21.6% (15.5% to 32.4%) N=6	-7.8% N=1
Effective sample size above median N=12	6.2% (2.8% to 13.7%)	8.8% (5.1% to 12.5%) N=5	4.3% (2.1% to 12.1%) N=7
Baseline compliance below median N=9	13.9% (3.1% to 17.0%)	13.9% (5.1% to 14.9%) N=5	9.8% 2.4% to 17.4% N=4

Table 9. Selection studies: QI strategies and study modifiers (continued)

Baseline compliance above median N=10	8.6% (4.3% to 20.4%)	16.5% (9.1% to 22.5%) N=6	2.7% (-1.2% to 5.0%) N=4
Repeated intervention N=8	6.8% (3.7% to 14.8%)	6.8% (4.6% to 9.4%) N=4	10.7% (3.5% to 17.0%) N=4
One-time intervention N=11	13.9% (2.5% to 22.7%)	20.4% (14.4% to 29.2%) N=7	2.3% (-0.4% to 3.7%) N=4
Active provider educational strategy used N=12	11.4% (4.8% to 17.8%)	14.4% (10.0% to 19.0%) N=6	4.9% (1.4% to 14.6%) N=6
Only passive provider educational strategies used N=7	5.1% (3.1% to 22.7%)	12.5% (5.1% to 22.7%) N=5	3.2% (0.2% to 4.3%) N=2
Control group received no intervention N=14	14.4% (7.2% to 20.4%	17.7% (3.6% to 25.9%) N=8	5.8% (1.8% to 14.6%) N=6
Control group received low-intensity intervention N=5	3.1% (2.1% to 5.1%)	5.1% (4.1% to 6.8%) N=3	2.3% (2.0% to 2.5%) N=2
Studies targeting a specific disease N=17	12.5% (3.1% to 18.6%)	13.9% (8.6% to 21.6%) N=11	4.3% (1.3% to 14.6%) N=6
Studies not targeting a specific disease N=2	3.4% (2.5% to 4.3%)	N=0	3.4% (3.0% to 3.9%) N=2
Studies targeting children N=2	29.2% (22.7% to 35.6%)	29.2% (22.7% to 35.6%) N=2	N=0

Table 9. Selection studies: QI strategies and study modifiers (continued)

Studies not targeting children **N=17**	8.4% (3.1% to 13.9%	12.5% (8.4% to 14.9%) N=9	3.4% (1.8% to 9.7%) N=8

Table includes only the QI strategies used in >3 trials.

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APPENDIXES

to

"Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies Volume 4—Antibiotic Prescribing Behavior"

Prepared by the Stanford-UCSF Evidence-based Practice Center
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Appendix A. Summary of Key Studies

Antibiotic Treatment Decision Studies

Finkelstein et al: Reducing antibiotic use in children: a randomized trial in 12 practices (Pediatrics 2001; 108(1): 1-7)

This quasi-randomized controlled trial, conduced in 12 Managed Care Organizations (MCOs) in Massachusetts and Washington state, demonstrates the effectiveness of repeated, active clinician education in combination with parent education in reducing antibiotic prescribing to children.

In this trial, practices were randomly assigned to intervention or comparison groups (after stratification by size and baseline prescribing rate). The clinician intervention consisted of academic detailing sessions, led by a practicing pediatrician "peer leader"; at these interactive 90-minute small-group sessions, the groups engaged in discussions on potential ways to prevent overuse of antibiotics. Approximately 4 months later, the peer leaders conducted another educational session at which the groups received feedback on their practice- and clinician-specific prescribing practices. In the parent intervention (conducted contemporaneously), each family in the MCO was mailed CDC-produced pamphlets,[44] reinforced by pamphlets and posters in waiting rooms. The control groups did not receive either clinician or parent education.

During this trial, which was conducted in the late 1990s, there was a substantial secular trend toward reduced antibiotic prescribing; in the comparison groups, antibiotic prescribing declined by 0.17 – 0.33 prescriptions per person-year (for children 36 - 72 months old and 3 – 36 months old, respectively). Despite this, the intervention still achieved a 12 – 16% relative reduction in prescribing rates in the two groups. At the practice level, this resulted in absolute reductions of 0.23 fewer antibiotic courses per person-year for children aged 3 - 36 months, and 0.13 fewer antibiotic courses per person-year for children aged 36-72 months. To arrive at these results, the investigators carried out statistical analyses accounting for clustering of patients within clinics.

This study used an intensive clinician and patient education intervention to achieve significant reductions in antibiotic prescribing in a managed care setting. This trial clearly demonstrates the value of active, repeated clinician education. It also demonstrates that a quality improvement intervention can successfully reduce inappropriate prescribing even while prescribing rates are declining overall.

Gonzales et al: Decreasing antibiotic use in ambulatory practice: Impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults (JAMA 1999; 281: 1512-1519)

This study provides an example of a rigorously conducted, comprehensive intervention targeting clinicians and patients in a health maintenance organization (HMO). Conducted in Kaiser Permanente clinics in Denver, Colorado, this non-

randomized controlled trial targeted antibiotic prescribing for acute bronchitis in adults.

The study contained three sites: a “full intervention” site, a “limited intervention” site, and a control site. Before the trial, the investigators conducted preliminary studies to identify why clinicians prescribed antibiotics and why patients expected antibiotic treatment for bronchitis. The intervention was then targeted to specifically address these factors. In both intervention sites, each enrolled patient household received mailed educational materials (such as refrigerator magnets and pamphlets). Office-based educational materials directed at clinicians and patients included colorful posters and pamphlets placed in waiting rooms and examination rooms. The importance of reducing inappropriate antibiotic prescribing was emphasized through a letter to all patients from the medical director of the organization. The “limited intervention” site received only the office-based and household educational materials; the “full intervention” site received the office and household educational materials as well as a clinician education session, a one-time educational intervention conducted at regularly scheduled staff meetings. This intervention consisted of education on the evidence-based management of acute bronchitis, advice on communication skills to deal with patient expectations, and practice-specific feedback on baseline prescribing rates. This intervention was conducted by the medical director of the clinic.

The study was conducted in a methodologically rigorous fashion; in addition to conducting preliminary studies to identify a specific quality gap and target the intervention, the study used a comparable comparison group with contemporaneous measurements, with outcomes assessors blinded to treatment group assignment. The statistical analysis took into account potential clustering of clinician prescribing practices by site.

The full intervention significantly reduced antibiotic prescribing. At baseline, 74% of patients received antibiotics for acute bronchitis; this fell to 48% after the intervention. Little change in prescribing rates was seen in both the limited intervention site and control site (prescribing rates went from 78% to 76% and 82% to 77%, respectively). In addition to measuring prescribing rates, the investigators also assessed the safety of the intervention by measuring the percentage of patients diagnosed with pneumonia at a return visit (there was no difference between groups). They also addressed potential confounders such as “code shifting.” (Theoretically, an intervention to reduce antibiotic prescribing for bronchitis could have resulted in clinicians shifting diagnoses to conditions more likely to warrant antibiotics, such as acute sinusitis.) They found no evidence of it.

This study highlights several key intervention characteristics. First, the use of preliminary studies to identify reasons for inappropriate prescribing allowed the investigators to tailor their intervention appropriately. While the purely passive limited intervention had no effect, when the more active clinician education session was added (the full intervention), the results were striking. Pairing the focused clinician intervention with high-visibility strategies such as exam room posters likely helped reinforce the message to clinicians. The involvement of high-level management may also have helped the success of the intervention. Finally, the methodological rigor of the study as well as the attention paid to documenting the

absence of potentially harmful consequences of the intervention reinforces the conclusions.

Perz et al: Changes in antibiotic prescribing for children after a community-wide campaign (JAMA 2002; 287(23): 3103-3109)

This study demonstrates the effectiveness of a community-wide campaign to reduce inappropriate antibiotic prescribing to children for respiratory infections. The intervention in this non-randomized controlled trial took place in Knox County, Tennessee, with a control group consisting of three other Tennessee counties. The study measured the effect on antibiotic prescriptions for children under 15 years of age enrolled in the Tennessee Medicaid Managed Care Program (TennCare).

The intervention targeted clinicians, parents, and the general public through a multifaceted approach. The main goals of the intervention were to reduce antibiotic prescribing for non-bacterial illnesses, particularly acute respiratory infections (ARIs); and to increase the prescribing of narrow-spectrum antibiotics for bacterial illnesses. Clinicians received an intensive educational intervention consisting of lectures and presentations in a variety of settings (hospital staff meetings, grand rounds, CME seminars, and resident conferences). Prescribing guidelines for ARIs were distributed to clinicians, and articles on the campaign were mailed to all physicians in Knox County. Parent education pamphlets (developed by the CDC[44] were distributed to parents of all children in day care and grades K-3, as well as to parents of all newborns. Clinicians also received patient education materials to distribute in their offices. An effort to reach the entire population was made by distributing over 100,000 pamphlets to hospitals, clinics, dental offices, and pharmacies; the campaign was further publicized through mass media efforts such as television, radio, and newspaper public service announcements. The control counties engaged in no organized efforts to reduce or rationalize antibiotic prescribing during this time.

Investigators used negative binomial regression models to determine the effect of the intervention on adjusted prescription rates, with a random-effect model used to account for heterogeneity within the counties. The visit rates for respiratory illnesses was measured as well, to account for the possibility that changes in prescribing could be confounded by changes in visit rates. The rates of antimicrobial resistance among cases of invasive *Streptococcus pneumoniae* infection were also measured.

After the year-long intervention, an 11% intervention-attributable decline in total antibiotic prescriptions for children was found in the intervention county. This translates to an approximate savings of 23 antibiotic prescriptions per 1000 children per year. No change in respiratory illness visit rates was found, indicating that physicians were truly prescribing antibiotics to a smaller proportion of patients. Antimicrobial resistance rates were high at baseline (>50% for penicillin) and did not change over the 3-year study period.

The investigators multifaceted approach, targeting the general public, parents, and clinicians, achieved impressive reductions in antibiotic prescribing. This demonstrates the viability of a community-based campaign to reduce general antibiotic prescribing in an area where baseline prescribing rates were high. This study was one of the few to use mass media advertisements to educate the public

on the problem of inappropriate prescribing. The study was methodologically sound, using appropriate models to determine the effect of the intervention.

Antibiotic selection studies

Hux et al: Confidential prescriber feedback and education to improve antibiotic use in primary care: a controlled trial (Canadian Medical Association Journal 1999; 161: 388-92)

Conducted in Ontario in the mid-to-late 1990s, this randomized controlled trial provides a case example of the effectiveness of passively-delivered clinician feedback and education.

Study investigators provided mailed packages of feedback on antibiotic prescribing practices (based on claims data obtained from the province's prescription drug claims database), accompanied by brief educational bulletins to primary care physicians. These packages were sent every 2 months over a 6-month period. The goal of the intervention was to encourage use of first-line antibiotics as suggested by guidelines written by a provincial panel. The comparison group was consented but was provided no materials during the study period, although it was promised feedback information after completion of the study.

Among the 250 participating physicians, the proportion of visits in which a first-line antibiotic was prescribed was 67.2% in the intervention group and 68.5% in the comparison group at baseline. After implementation of the intervention, the proportion of visits involving first-line antibiotic prescriptions rose by 2.6% in the intervention group, compared with a 1.7% decline in the comparison group, a statistically significant difference.

This study highlights the general finding that passively-delivered feedback and education can result in statistically significant improvements in antibiotic selection, but that the magnitude of the change tends to be small.

MacCara et al: Impact of a limited fluoroquinolone reimbursement policy on antimicrobial prescription claims (Annals of Pharmacotherapy 2001; 35: 852-8)

This study is a case example of the potential power of regulatory interventions. In this interrupted time series analysis conducted in the mid-to-late 1990s in Nova Scotia, the investigators evaluated the impact of a change in provincial guidelines governing the reimbursement of fluoroquinolones for elders aged 65 and older enrolled in the province's pharmaceutical care program.

In early 1997, new guidelines were instituted that required completion of additional paperwork certifying that the drug was being prescribed for one of several guideline-approved uses, which was delivered with the prescription to the pharmacy. Data was obtained from the province's drug plan claims database.

In the 12 months before and after institution of the policy, fluoroquinolone use fell from 20.2% to 4.2% of antibiotic prescriptions for elders, a relative reduction of 80%.

This reduction was immediate. Use of other antibiotics rose, such that overall antibiotic use remained stable.

This study demonstrates the power of regulatory interventions, which in this case resulted in an immediate and dramatic decline in fluoroquinolone use. Like other research in this area, this study did not report the impact of the intervention on quality indicators or on potential patient harms, for example the number of patients whose clinical situation merited a fluoroquinolone but who did not receive the drug.

Schaffner et al: Improving antibiotic prescribing in office practice: a controlled trial of three educational methods. (JAMA 1983; 250: 1728-1732)

Conducted in the early 1980s in Tennessee, this non-randomized controlled study provides important insight into the relative value of different forms of educational outreach and mailed materials.

The investigators delivered three separate interventions to 300 physicians in geographically distinct areas of the state: (1) a mailed brochure; (2) visits by a pharmacist who was trained as a "drug educator," and (3) visits by physicians who were trained as "physician counselors." Each type of visit lasted less than 15 minutes. A fourth area of the state served as a comparison group. The goal of the interventions was to reduce use of non-recommended antibiotics, and to reduce use of the oral cephalosporins (as a cost-saving measure). Data on antibiotic utilization were measured using Medicaid claims data for the year before and after the intervention.

The prescribing practices of physicians receiving the mailed brochure were very similar to the comparison group, and the two groups were combined for analyses. In this combined comparison group, use of both types of medications declined substantially (41% relative reduction in prescriptions for non-recommended antibiotics, and 33% for oral cephalosporins). In the intervention arms, the use of physician counselors was the most effective intervention, resulting in an 85% relative reduction in non-recommended antibiotic use, and a 50% reduction in oral cephalosporin use. Pharmacist drug educators were less effective in reducing the use of non-recommended antibiotics (67% relative reduction); they were no more effective than mailed brochures in reducing the use of oral cephalosporins (35%).

This study highlights several important points. First, it exemplifies the general finding that active educational outreach is more effective than passive forms of education (such as mailed brochures). Second, it highlights that not all forms of outreach are equally effective; what is unclear is whether the differences were due to the relative effectiveness of a physician vs. a pharmacist in general, or due to individual characteristics of the persons conducting the outreach. Third, this study highlights the importance of controlling for secular trends in antibiotic use, which may be substantial. Finally, it provides a model for examining different types of interventions head-to-head, thereby addressing the problems intrinsic to inter-study comparisons.

Appendix B. Summaries of Included Studies, Grouped by Setting and Measured Population

Table 1. Antibiotic treatment studies conducted in the U.S.

Studies targeting prescribing for children

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Finkelstein JA, Pediatrics, 2001	United States 12 practices affiliated with 2 managed care organizations (located in northwest Washington state and eastern Massachusetts)	Children in Managed Care Organizations with respiratory infections.	***Clinician education*** *(distribution of materials, education meetings),* ***Patient education*** *(distribution of materials),* ***Audit and feedback*** The intervention consisted of small group provider education sessions with a peer leader and a reinforcing visit four months after the start of the intervention. Providers also received feedback on practitioner and practice-level antibiotic prescribing rates. Parent education consisted of a mailed CDC-produced brochure with a cover letter signed by their pediatrician. Educational pamphlets and posters were also present in the waiting room and examination rooms of the intervention practices.	Overall antibiotic prescriptions were reduced by 0.08 courses per child per year for children aged 3-36 months, and 0.04 courses per child per year for children aged 36-72 months.
Belongia EA, Pediatrics, 2001	United States Multiple counties in Northern Wisconsin	Children in managed care and fee-for-service practices with respiratory infections.	***Clinician education*** *(distribution of materials, educational meetings, educational outreach),* ***Patient education*** *(distribution of materials)* This study was a community-based trial with patient and provider education targeting antibiotic prescribing for ARIs. Patient education involved distribution of educational materials to clinics, daycare facilities, and schools. Providers received academic detailing in small groups, led by study authors and lasting 30-60 minutes. At the meetings, clinical practice guidelines, educational materials from CDC (on appropriate antibiotic use), and parent education pamphlets were distributed. Project nurses visited each practice to educate office staff as well.	**Absolute effect size: 1.5%** The percentage of patients receiving antibiotics for ARIs declined by 3.6% in the intervention region. In the control region, the prescribing rate declined by 5.1%. Although the percentage of patients receiving antibiotics when seeing a physician was not statistically significantly changed, the total number of antibiotic prescriptions (for both solid and liquid antibiotics) decreased significantly in the intervention region compared to the control region.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Christakis DA, Pediatrics, 2001	United States Academic pediatric primary care clinic	Children receiving care at academic primary care clinic with otits media.	***Clinician reminder*** Providers received an electronic evidence-based reminder to avoid treating otitis media with antibiotics, and if using antibiotics to treat for less than 10 days. Reminder was electronic in nature, incorporated into existing electronic prescription program. When providers selected an antibiotic to prescribe, a pop-up screen displayed information on appropriate use and appropriate dosage. The pop-up window contained options for receiving more information.	There was no significant impact on the percentage of patients receiving antibiotics in either the intervention or control groups. A statistically significant increase in prescribing at the appropriate duration of therapy was found.
Mainous AG, Family Medicine, 2000 **[comparison 1]**	United States 8 Medicaid administrative regions in Kentucky	Children in Medicaid program with respiratory infections	***Patient education*** *(distribution of materials)* The intervention consisted of a statewide program that used direct patient education to reduce antibiotic prescribing for pediatric respiratory infections. Each physician received 25 pamphlets that they were to distribute themselves to patients with upper respiratory infections.	**Absolute effect size: -9.9%** In the intervention group, prescribing rates increased from 31.9% to 44.5% over the study period. The control group increased from 31.0% to 53.5%. This difference was not statistically significant.
Mainous AG, Family Medicine, 2000 **[comparison 2]**	United States 8 Medicaid administrative regions in Kentucky	Children in Medicaid program with respiratory infections	***Audit and feedback*** The intervention consisted of a statewide program that used physician feedback. Physicians received a prescribing profile, consisting of the percent of patients with pediatric respiratory conditions to whom they prescribed antibiotics and information on total and relative costs. It also contained their percentile ranking for antibiotics prescribing compared to peers.	**Absolute effect size: -7.3%** In the intervention group, prescribing rates increased from 28.4% to 43.6% over the study period. The control group increased from 31.0% to 53.5%. This difference was not statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Mainous AG, Family Medicine, 2000 **[comparison 3]**	United States 8 Medicaid administrative regions in Kentucky	Children in Medicaid program with respiratory infections	***Patient education*** *(distribution of materials),* ***Audit and feedback*** The intervention was a combination of physician feedback and patient education. Physicians received a prescribing profile, consisting of the percent of patients with pediatric respiratory conditions to whom they prescribed antibiotics and information on total and relative costs. It also contained their percentile ranking for antibiotic prescribing compared to peers. Physicians also received 25 patient education leaflets that they were to distribute themselves to patients with upper respiratory infections.	**Absolute effect size: -7.2%** In the intervention group, prescribing rates increased from 34.4% to 49.7%. The control group increased from 31.0% to 53.5%. This difference was not statistically significant.
Perz JF, JAMA, 2002	United States 4 counties in Tennessee	Children in Medicaid program	***Clinician education*** *(distribution of materials, educational meetings, educational outreach),* ***Patient education*** *(distribution of materials, mass media educational campaign)* A year long intervention targeting providers, parents, and the general public was performed. Provider education consisted of lectures from an expert, presentations at conferences, distribution of guidelines, and newsletters. Parent education consisted of distribution of pamphlets by mail, via the providers, to all parents of newborns. Public education consisted of mass media advertisements and distribution of pamphlets at hospitals, clinics, dental offices, and pharmacies.	The intervention achieved a reduction of about 0.16 antibiotic courses per child per year, an 11% intervention-attributable relative reduction in antibiotic prescriptions. This difference was statistically significant.

Studies targeting prescribing for adults

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Gonzales R, JAMA, 1999 **[comparison 1]**	United States 4 HMO primary care practices	Kaiser Permanente patients with acute bronchitis	***Patient education*** *(distribution of materials, other)* ***Clinician education*** *(distribution of materials, educational meetings),* ***Audit and feedback*** The study consisted of a multifaceted educational intervention provided to Kaiser patients and providers with the goal of reducing antibiotic use for acute bronchitis. Patients received mailed educational materials (refrigerator magnets, pamphlets, letters), and educational materials in the provider's office (posters). Providers received site-specific antibiotic prescription rates, education on evidence-based management of bronchitis. Provider education was carried out by the medical director of the facility in a one-time, 30-minute meeting.	**Absolute effect size: -24.0%** In the intervention group, the percentage of visits at which antibiotics were prescribed for acute bronchitis declined from 74% before the intervention to 48% after the intervention. In the control group, the prescribing rate declined from 78% to 76%. This difference was statistically significant.
Gonzales R, JAMA, 1999 **[comparison 2]**	United States 4 HMO primary care practices	Kaiser Permanente patients with acute bronchitis	***Patient education*** *(distribution of materials),* ***Clinician education*** *(other)* In this study arm, the intervention consisted of office-based patient educational materials only. These were colorful posters placed on the walls of each room, accompanied by information on the ineffectiveness of antibiotic for bronchitis, as well as information on antimicrobial resistance.	**Absolute effect size: -2.0%** In the intervention group, the percentage of visits at which antibiotics were prescribed for acute bronchitis declined from 82% to 78%. In the control group, the prescribing rate declined from 78% to 76%. This difference was not statistically significant.

Studies targeting prescribing for patients of all ages

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Hickman DE, Annals of Pharmacotherapy, 2003	United States Suburban community-based physician group	Patients enrolled in non-profit medical group (approximately 50% in capitated health plans) with acute bronchitis	***Patient education*** *(distribution of materials),* ***Clinician education*** *(distribution of materials, educational meetings, educational outreach),* ***Audit and feedback*** The intervention consisted of as patient education delivered via a newsletter and posters and pamphlets in the waiting room. Providers received pharmacist-led seminars, written materials, and provider-specific prescription profiling. This took place during a 20 minute presentation by a clinical pharmacist at regular staff meetings. Feedback was provided confidentially in a folder, which also contained educational materials.	**Absolute effect size: -9.7%** In the intervention group, the prescribing rate declined from 48.3% of visits to 38.6% after the intervention. There was no change in the prescribing rate in the control group (31.8% before and after the intervention.) This difference was statistically significant.
McConnell TS, Western Journal of Medicine, 1982	United States United States New Mexico Medicaid program	Medicaid patients with respiratory infections	***Clinician education*** *(distribution of materials, educational outreach),* ***Audit and feedback*** Physicians who were found on audit to be inappropriately prescribing tetracycline for acute respiratory infections (ARIs) received educational visits. Visits took about 30 minutes and occurred a single time. Information on their prescribing was presented, as well as educational materials. Visits were carried out by physician consultants in the physician's office.	The intervention achieved a reduction of 6.4 prescriptions for tetracycline per clinician per 6-month period. No change in prescribing was found in the control group. The investigators did not report if this difference was statistically significant.
Foxman B, Journal of Chronic Diseases, 1987	United States 6 cities: Dayton, OH; Seattle, WA; Fitchburg, MA; Franklin County, MA; Charleston, SC; Georgetown County, SC	Comparison of cost-sharing insurance plans (intervention) versus fee-for-service insurance (control)	***Financial or regulatory incentives for patients*** This study was the RAND health insurance experiment, where patients were randomized to insurance plans varying by level of cost-sharing. How antibiotic use varies by insurance plan, diagnosis and health status, geographic area, and demographic characteristics were also examined.	Antibiotic use declined by 0.43 courses per insured family per year in the intervention group compared to the control group. This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Hennessy TW, Clinical Infectious Diseases, 2002	United States 13 rural Alaskan villages	Patients receiving care through Indian Health Service with respiratory infections	***Patient education*** *(distribution of materials, mass media educational campaign),* ***Clinician education*** *(educational outreach, educational workshops)* The investigators described the intervention as a community-based educational intervention provided with the goal of reducing inappropriate antibiotic use for acute respiratory infections. Physicians and community health aides received workshops on antibiotic use. Residents received information at village-wide meetings, community fairs, and high school classrooms. Residents also received a total of four informational mailings.	**Absolute effect size: -12.0%** In the intervention villages, antibiotic prescribing declined from 64% of visits for ARIs to 47%. In control villages, prescribing declined from 54% to 49%. The investigators did not report if this difference was statistically significant.

* The measured population refers to the patient population in which prescribing data was measured. This population is the group to which the study results are most generalizable.

** The Absolute effect size is provided for studies that were used in the median effects analysis. These studies reported data as the percentage of visits at which patients received an antibiotic prescription. The individual study Absolute effect size was calculated as: $[(\text{Intervention})_{post} - (\text{Intervention})_{pre}] - [(\text{Control})_{post} - (\text{Control})_{pre}]$. A negative effect size means an overall reduction in the rate of antibiotic prescribing. The % sign refers to the percent of patients with a particular diagnosis.

Appendix B Table 2: Antibiotic treatment studies conducted outside the U.S.

Studies targeting prescribing for children

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Smabrekke L, Scandinavian Journal of Infectious Diseases, 2002	Norway Physicians and nurses at urgent care clinic	Children with otitis media	***Patient education*** *(distribution of materials****), Clinician education*** *(distribution of materials, educational meetings)* The intervention consisted of a symposium on evidence-based management of otitis media for physicians and nurses at an acute care clinic. Guidelines on appropriate treatment were distributed. The guideline recommended narrow-spectrum antibiotic use when necessary, and suggested use of delayed prescriptions. Pamphlets for patients were made available in exam rooms; the pamphlets stressed that most patients recover without antibiotic and indiscriminate use of antibiotic leads to resistance. This information was also provided to patients who called the clinic.	**Absolute effect size: -12.0%** The percentage of patients receiving antibiotics decreased 16.0% (from 90.0% before the intervention to 74.0% after). In the control group, the prescribing rate decreased 4.0% (from 95.0% to 91.0%). This difference was statistically significant.
Cates C, BMJ, 1999	UK General practitioners in outpatient clinics in Hertfordshire	Children with otitis media	***Patient education*** *(distribution of materials),* ***Delayed prescriptions*** Parents of children with acute otitis media who were "not particularly ill" were given a handout summarizing the limited benefit of antibiotics. Parents also received a delayed prescription for antibiotics with instructions to fill the script if the child did not improve in the next "day or two." The comparison was another nearby clinic that followed usual care.	In the intervention clinic, the number of amoxicillin prescriptions per month decreased from 75 to 47 (a 32% relative reduction.) In the control group, the number of amoxicillin prescriptions decreased from 72 to 66 per month (a 12% relative reduction.) This difference was statistically significant.
Little P, BMJ, 2001	UK General practices in southwest England	Children with otitis media	***Delayed prescriptions*** Children with otitis media were randomized to receive either immediate antibiotics or delayed treatment. Patients in the delayed treatment group were to receive antibiotics after 72 hours if their symptoms did not improve.	In the intervention group, 24.0% of patients used antibiotics, compared to 98.5% of patients in the control group. This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Gonzalez Ochoa E, Bulletin of the Pan American Health Organization, 1996 **[comparison 1]**	Cuba General practitioners in 4 areas of Havana	Children with respiratory infections	***Patient education*** *(group educational sessions, distribution of materials),* ***Clinician education*** *(distribution of materials, educational meetings, educational outreach visits, educational workshops)* The intervention consisted of education of health care providers and community education components. For education of health care providers, there was a special refresher course for family physicians which included videos and slide presentations on treatment of acute respiratory infections in children. There were also opportunities for provider group discussions. The community education program consisted of group discussions in the participants' homes and talks given to mothers in the clinics.	**Absolute effect size: -28.5%** The percentage of patients receiving antibiotics decreased 27.8% (from 36.6% before the intervention to 7.8% after). In the control group, the prescribing rate increased 0.7% (from 19.6% to 20.3%).
Gonzalez Ochoa E, Bulletin of the Pan American Health Organization, 1996 **[comparison 2]**	Cuba General practitioners in 4 areas of Havana	Children with respiratory infections	***Clinician education*** *(distribution of materials, educational meeting)* This study arm consisted of health care provider education. For education of health care providers, there was a special refresher course for family physicians which included videos and slide presentations on treatment of acute respiratory infections in children. There were also opportunities for provider group discussions.	**Absolute effect size: -9.6%** In the intervention group, prescribing decreased 8.9% (from 20.6% before the intervention to 11.7% after the intervention). In the control group, the prescribing rate increased 0.7% (from 19.6% to 20.3%). The investigators did not report if this difference was statistically significant.
Gonzalez Ochoa E, Bulletin of the Pan American Health Organization, 1996 **[comparison 3]**	Cuba General practitioners in 4 areas of Havana	Children with respiratory infections	***Patient education*** *(individual educational sessions, group educational sessions, distribution of materials)* This study arm consisted of a community education program. The community education program consisted of group discussions in the participants' homes and talks given to mothers in the clinics.	**Absolute effect size: 0.2%** In the intervention group, prescribing increased 0.9% (from 11.4% before the intervention to 12.3% after.) In the control group, the prescribing rate increased 0.7% (from 19.6% to 20.3%). The investigators did not report if this difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Pshetizky Y, Family Practice, 2003	Israel General practitioners	Children with otitis media	***Patient education*** *(individual educational sessions),* ***Delayed prescriptions*** The intervention targeted parents of children with acute otitis media. All patients were given an antibiotic prescription. Parents in the intervention group received instruction to only use antibiotics if the child's condition did not improve in 24- 48 hours. The intervention group also received a brief explanation from the physician, stressing that most patients recover regardless of whether antibiotics are used, and that serious complications of acute otitis media are not necessarily prevented by antibiotics.	In the intervention group, 37.0% of patients used antibiotics after the intervention. In the comparison group, 63.0% of patients used antibiotics. This difference was statistically significant.
Wilson EJ, Communicable Diseases Intelligence, 2003	Australia General practitioners in Canberra	Children with respiratory infections	***Clinician education*** *(distribution of materials, consensus building sessions),* ***Patient education*** *(distribution of materials),* ***Self-management*** Physicians participated in focus groups with parents of young children and workshops with other GP's; these were used to develop a practice guideline for antibiotic prescribing in upper respiratory infection. All intervention general practitioners then received a packet containing the guideline, information sheets on otitis media and sore throat for patient education, prescription pads for nonprescription medicines, patient self-management advice, and a poster advocating the guideline.	In the intervention group, prescriptions decreased by 0.78 prescriptions per 100 visits; in the control group, prescribing increased by 0.35 prescriptions per 100 visits. This difference was statistically significant.
Santoso B, Social Science & Medicine, 1996 **[comparison 1]**	Indonesia General practitioners in Yogyakarta and Java provinces	Children with diarrhea	***Clinician education*** *(distribution of materials, educational outreach, educational workshops)* The study consisted of a small group intervention designed to reduce antibiotic prescribing in cases of acute diarrhea. The small group meetings consisted of face-to-face, interactive discussions involving 8-12 providers at a health center. Discussions were led by a trained physician moderator, assisted by a pharmacologist or pediatrician. Each lasted approximately two hours. A booklet on appropriate management of diarrhea was also provided.	**Absolute effect size: -13.7%** In the intervention group, prescribing rates decreased by 17.0% (from 77.4% before the intervention to 60.4% after the intervention.) In the control group, prescribing rates decreased by 3.3% (from 82.6% before the intervention to 79.3% after the intervention.)

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Santoso B, Social Science & Medicine, 1996 **[comparison 2]**	Indonesia General practitioners in Yogyakarta and Java provinces	Children with diarrhea	***Clinician education*** *(distribution of materials, educational meetings)* The study consisted of a two hour seminar on appropriate prescribing for acute diarrhea targeted at physicians and paramedical personnel. The goal was to reduce antibiotic use and encourage use of oral rehydration solution. The presentation was by two physicians from the district office and the university. Question-and-answer sessions followed the seminar. Written materials on management of diarrhea were also provided.	**Absolute effect size: -6.7%** In the intervention group, prescribing rates decreased by 10.0% (from 82.3% to 72.3%.) In the control group, prescribing rates decreased by 3.3% (from 82.6% before the intervention to 79.3% after the intervention.)

Studies targeting prescribing for adults

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
McIsaac WJ, Medical Decision Making 1998	Canada Family physicians in Ontario	Adults with sore throat	***Clinician reminder*** Physicians received a mailing containing both a modified scoring system to help guide antibiotic prescribing and management recommendations. The intervention group also received an encounter form for a specific patient visit with the scoring system and recommendations for testing or treating based on the score. The control group received a similar encounter form without the scoring system or treatment recommendations.	In the intervention group, 27.8% of patients received antibiotics, compared to 35.7% in the comparison group. This difference was not statistically significant.
Coenen SJ, Antimicrobial Agents and Chemotherapy, 2004	Belgium General practitioners	Adults with respiratory infections	***Clinician education*** *(distribution of materials, educational outreach)* Physicians received a mailed guideline for treatment of patients with acute cough, which was followed by a reminder phone call. Provides also received an educational outreach visit from a pharmacist and "former medical representative", which focused on guideline adherence and dialogue with the provider to overcome barriers to appropriate prescribing. Following this, the providers received a mailing with the key messages from the guideline.	**Absolute effect size: 6.5%** The percentage of patients receiving antibiotics decreased 15.6% (from 43.0% before the intervention to 27.4% after). In the control group, the prescribing rate decreased 9.1% (from 37.8% to 28.7%). This difference was statistically significant.
Macfarlane J, BMJ, 2002	UK General practices	Adults with acute bronchitis	***Patient education*** *(distribution of materials),* ***Delayed prescriptions*** Patients with acute bronchitis not requiring immediate treatment received a delayed prescription for antibiotics. They also were given a patient information leaflet about symptoms and the advantages/disadvantages of antibiotic use. The leaflet described when to fill the prescription and methods of self-treatment.	Patients in the intervention group used antibiotics in 47.0% of cases, compared to 62.0% in the comparison group. This difference was statistically significant.

Studies targeting prescribing for patients of all ages

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
McNulty CA, Journal of Antimicrobial Chemotherapy, 2000	UK General practices in Gloucester-shire	All patients	***Clinician education*** *(educational workshops),* ***Audit and feedback*** General practitioners received twelve antibiotic educational workshops, which were delivered over a seven week period. Workshops focused on promoting antibiotic guidelines, reducing antibiotic use for unnecessary conditions and making better prescribing decisions.	In the intervention group, the number of antibiotic prescriptions per provider per year declined from 395.9 before the intervention to 382.3 after the intervention. In the control group, prescriptions declined from 356.7 per provider per year to 348.7. This difference was not statistically significant.
Melander E, Scandinavian Journal of Primary Health Care, 1999 **[comparison 1]**	Sweden General practitioners	All patients with respiratory infections	***Clinician education*** *(educational workshops),* ***Audit and feedback*** The intervention consisted of an audit of physician's antibiotic prescribing behavior. Based on the results of this audit, group discussions on appropriate management of ARIs were held, and an educational program was developed using local opinion leaders. Prescribing data was fed back to the individual physicians.	**Absolute effect size: -2.0%** The percentage of patients receiving antibiotics for ARIs decreased 4.0% (from 13.0% before the intervention to 9.0% after). In the control group, the prescribing rate decreased 2.0% (from 37.0% to 35.0%). The investigators did not report if this difference was statistically significant.
Molstad S, Family Practice, 1989	Sweden General practitioners at community health centers	All patients with respiratory infections	***Clinician education*** *(consensus building sessions)* Physicians designed and administered an educational program consisting of developing indications for antibiotic treatment and reviewing regional resistance patterns. Physicians were encouraged to use rapid streptococcal assays when warranted.	**Absolute effect size: -23.3%** The percentage of patients receiving antibiotics decreased 23.7% (from 67.6% before the intervention to 43.9% after). In the control group, the prescribing rate decreased 0.4% (from 71.5% to 71.1%). The investigators did not report if this difference was statistically significant.
Zwar N, Family Practice, 1999	Australia General practitioner trainees in New South Wales	All patients with respiratory infections	***Clinician education*** *(distribution of materials, educational outreach, other),* ***Audit and feedback*** The intervention consisted of a mailed packet of individualized feedback to providers, management guidelines, and patient handouts. Providers who exceeded thresholds for inappropriate prescriptions based on feedback data also received an academic detailing session, in person or over the telephone.	**Absolute effect size: -15.0%** The percentage of patients receiving antibiotics decreased 5.3% (from 25.0% before the intervention to 19.7% after). In the control group, the prescribing rate increased 9.7% (from 22.0% to 31.7%). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Angunawela I, International Journal of Epidemiology, 1991 **[comparison 1]**	Sri Lanka General practitioners at rural primary care clinics	All patients	***Clinician education*** *(distribution of materials)* The intervention consisted of newsletters mailed fortnightly to providers, which covered topics about treatment of common infections, encouraged use of penicillin, discouraged use of antibiotics in viral infections and tetracycline to children.	**Absolute effect size: -7.0%** The percentage of patients receiving antibiotics decreased 7.4% (from 31.5% before the intervention to 24.1% after). In the control group, the prescribing rate decreased 0.4% (from 32.2% to 31.8%). This difference was not statistically significant.
Angunawela I, International Journal of Epidemiology, 1991 **[comparison 2]**	Sri Lanka General practitioners at rural primary care clinics	All patients	***Clinician education*** *(distribution of materials, educational meetings)* In addition to the newsletters described above, providers participated in a seminar conducted by two clinical pharmacologists, one microbiologist, and one general physician. The seminar reinforced the information in the newsletter.	**Absolute effect size: -6.9%** The percentage of patients receiving antibiotics decreased 7.3% (from 38.8% before the intervention to 31.5% after). In the control group, the prescribing rate decreased 0.4% (from 32.2% to 31.8%). This difference was not statistically significant.
Arroll B, Journal of Family Practice, 2002	New Zealand General practitioners	All patients with common cold	***Delayed prescriptions*** Patients with the common cold who requested antibiotics were given a prescription with instructions to fill it only if their symptoms did not improve after 3 days. The comparison group was given antibiotics immediately.	In the intervention group, 48% of patients used antibiotics; in the comparison group, 89% of patients used them. This difference was statistically significant.
Bexell A, Journal of Clinical Epidemiology, 1996	Zambia General practices in	All patients with diarrhea and respiratory infections	***Clinician education*** *(educational meetings)* The intervention consisted of three 2-day seminars for providers on rational drug prescribing. Educational content consisted of standardized guidelines for managing "common conditions seen in primary care." Seminars were led by pharmacists, clinical officers, medical officers, and a nurse. Specific diseases discussed included diarrheal diseases and acute respiratory infections.	**Absolute effect size: -8.1%** The percentage of patients receiving antibiotics decreased 7.0% (from 41.2% before the intervention to 34.2% after). In the control group, the prescribing rate increased 1.1% (from 41.0% to 42.1%). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Flottorp S, BMJ, 2002	Norway 142 General practices	All patients with sore throat	***Patient education*** *(distribution of materials, other),* ***Clinician education*** *(distribution of materials, other),* ***Clinician Reminders, Organizational change, Regulatory changes for providers, Financial or regulatory incentives for patients*** The investigators conducted a multifaceted intervention to improve management of sore throat. Providers received guidelines on sore throat management, in electronic and poster format. Computer based decision support, reminders, and interactive courses were offered to providers. Patients received electronic and paper-based educational materials. Patients had to pay an increased fee for a telephone consult (but not for office visit.) Only practices using an electronic medical records system were eligible.	**Absolute effect size: -3.0%** The percentage of patients receiving antibiotics decreased 4.3% (from 48.1% before the intervention to 43.8% after). In the control group, the prescribing rate decreased 1.3% (from 50.8% to 49.5%). This difference was statistically significant.
Gutierrez G, Medical Care, 1994	Mexico General practitioners at health care clinics of the Mexican Social Security Institute	All patients with diarrhea	***Clinician education*** *(distribution of materials, educational workshops, consensus building session),* ***Audit and feedback*** Physicians received an educational workshop on treatment of acute diarrhea for physicians. They received literature and had group discussions to develop a treatment algorithm and discuss management of simulated cases. Five months after the workshops, physicians' practice habits were audited and reviewed by a committee including study physicians.	After the intervention, the prescribing rate in the intervention group was 20.2%, compared to 35.4% before the intervention. Corresponding comparison group values were not provided.
McIsaac WJ, Journal of Family Practice, 2002	Canada Family physicians in Ontario	All patients with sore throat	***Clinician reminder*** Physicians received a sample encounter form for patients with sore throat, which explicitly described a scoring system (to help guide antibiotic prescribing) and provided management recommendations. The form also had space to record the score. The control group did not receive the sticker, and the encounter form did not have the prompt to record the score.	The prescribing rate in the intervention group was 28.1%, compared to 27.9% in the comparison group. This difference was not statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Meyer JC, Medical Education, 2001	South Africa Nurses at primary health clinics	All patients with diarrhea	***Clinician education*** *(educational workshops)* Nurses in primary health care centers received training focused on teaching rational drug prescribing, conducted during a 4-day workshop. A World Health Organization manual was used as the framework for the training course. The target was reducing antibiotic prescribing for ARIs.	**Absolute effect size: -28.6%** The percentage of patients receiving antibiotics decreased 36.9% (from 66.3% before the intervention to 29.4% after). In the control group, the prescribing rate decreased 8.3% (from 53.9% to 45.6%). This difference was statistically significant.
O'Connell DL, BMJ, 1999	Australia General practitioners in rural area	All patients	***Clinician education*** *(distribution of materials),* ***Audit and feedback*** Physicians received a graphical display of their level of prescribing of five different drug groups (including oral antibiotics) over the past eight quarters. These data were provided as graphs displaying the individual physician's prescribing in comparison to all physicians. This intervention was repeated twice, six months apart. The first intervention was accompanied by a general prescribing educational letter. The second was accompanied by a letter with specific antibiotic prescribing information.	In the intervention group, median antibiotic prescribing rates changed from 10.7 prescriptions per 100 patients before the intervention to 10.5 prescriptions per 100 patients after the intervention. Corresponding comparison group values were 10.7 prescriptions per 100 patients before the intervention and 10.1 after the intervention. This difference was not statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Welschen I, BMJ, 2004	The Netherlands General practitioners in Utrecht	All patients with respiratory infections	***Patient education*** *(distribution of materials),* ***Clinician education*** *(distribution of materials, educational meetings, educational workshops, consensus building sessions),* ***Audit and feedback*** Physicians attended a group educational meeting, at which feedback data on antibiotic prescribing was provided, evidence on the effectiveness of antibiotic for upper respiratory infections was presented, and used to develop consensus on indications for antibiotic use and choice. These were formalized into guidelines that were mailed to participations. Six months later physicians received repeat feedback on their prescribing. Physician assistants and pharmacists also received a 2 hour session on antibiotic prescribing guidelines. Physicians, assistants, and pharmacists also received communication skills training. Patient education materials, consisting of brochures and posters, were provided in offices, pharmacies, and municipal health services.	**Absolute effect size: -12.0%** The percentage of patients receiving antibiotics decreased 4.0% (from 27.0% before the intervention to 23.0% after). In the control group, the prescribing rate increased 8.0% (from 29.0% to 37.0%).

* The measured population refers to the patient population in which prescribing data was measured. This population is the group to which the study results are most generalizable.

** The Absolute effect size is provided for studies that were used in the median effects analysis. These studies reported data as the percentage of visits at which patients received an antibiotic prescription. The individual study Absolute effect size was calculated as: $[(\text{Intervention})_{post} - (\text{Intervention})_{pre}] - [(\text{Control})_{post} - (\text{Control})_{pre}]$. A negative effect size means an overall reduction in the rate of antibiotic prescribing. The % sign refers to the percent of patients with a particular diagnosis.

Appendix B Table 3: Antibiotic selection studies conducted in the U.S.

Studies targeting prescribing for children

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Bush PJ, Medical Care, 1979 **[comparison 1]**	United States Pediatricians at 3 HMO sites in Washington, DC	Children enrolled in HMO with otitis media	***Clinician education*** *(distribution of materials, consensus building session)* The intervention consisted of a drug therapy protocol for otitis media, which specified drugs, doses, and days of therapy by patient age. The protocol was developed and implemented by a physician group at one site. The intervention encouraged use of ampicillin or penicillin. The control group received no intervention.	**Absolute effect size: 22.7%** In the intervention group, the prescribing rate for recommended antibiotics increased 0.1% (from 87.7% before the intervention to 87.8% after). In the control group, the prescribing rate for recommended antibiotics decreased 22.6% (from 89.6% to 67.0%). The investigators did not report if the difference between groups was statistically significant.
Bush PJ, Medical Care, 1979 **[comparison 2]**	United States Pediatricians at 3 HMO sites in Washington, DC	Children enrolled in HMO with otitis media	***Clinician education*** *(distribution of materials)* In this study, the drug therapy protocol (above) was implemented at a separate site from the one that created the protocol.	**Absolute effect size: 35.6%** In the intervention group, the prescribing rate for recommended antibiotics increased 13.0% (from 64.3% before the intervention to 77.3% after). In the control group, the prescribing rate decreased 22.6% (from 89.6% to 67.0%). The investigators did not report if the difference between groups was statistically significant.

Studies targeting prescribing for adults

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Klein LE, Journal of Medical Education, 1981	United States Residents in academic emergency room and primary care center	Adults with urinary tract infections	***Clinician education*** *(educational meetings)* The intervention consisted of an educational tutorial that addressed four misconceptions about the treatment of urinary tract infection. This tutorial aimed to encourage use of sulfisoxazole or tetracycline, and discourage use of ampicillin or trimethoprim-sulfamethoxazole. The tutorial was presented to each participant for 15 minutes. In addition to the tutorial, the authors gave a ten minute talk just before the post-intervention data collection period on options for treating urinary tract infection.	**Absolute effect size: 48.0%** In the intervention group, the prescribing rate for recommended antibiotics increased 65.0% (from 12.0% before the intervention to 77.0% after). In the control group, the prescribing rate increased 17% (from 22.0% to 39.0%). This difference was statistically significant.

Studies targeting prescribing for patients of all ages

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Avorn J, New England Journal of Medicine, 1983 **[comparison 1]**	United States Physicians in 4 state Medicaid programs (Arkansas, New Hampshire, Vermont, and the District of Columbia)	Medicaid patients	***Clinician education*** *(distribution of materials)* Physicians received an office-based education program consisting of a visit from a clinical pharmacist to discuss ways to reduce prescribing of targeted drugs. Physicians also received mailed educational materials, including drug information letters and "unadvertisements" (specially designed brochures with colorful illustrations on appropriate prescribing practices.) These materials were distributed eight times over a period of four months. The objective was to reduce the prescribing of oral cephalosporins.	In the intervention group, the number of non-recommended antibiotic prescriptions was reduced by 31% relative to the control group. This difference was statistically significant.
Avorn J, New England Journal of Medicine, 1983 **[comparison 2]**	United States Physicians in 4 state Medicaid programs (Arkansas, New Hampshire, Vermont, and the District of Columbia)	Medicaid patients	***Clinician education*** *(distribution of materials)* In this study, physicians received only the mailed drug information letters and "unadvertisements" described above.	In the intervention group, the number of non-recommended antibiotic prescriptions was reduced by 10% relative to the control group. This difference was not statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Farris KB, Pharmaceutical Research, 1996	United States Family physicians in HMO in southeastern Michigan	HMO patients with respiratory infection	***Clinician education*** *(distribution of materials, educational meetings, educational outreach, educational workshops),* ***Audit and feedback*** The intervention consisted of face to face group detailing sessions involving opinion leaders with written presentation summaries placed in physicians clinic mailboxes 3-6 weeks after the detailing session. Physicians also received personal and peer comparison feedback on prescribing trends for target medications, periodic posted reminders, summary poster displays, and a report of program results at the end of the intervention.	**Absolute effect size: 7.2%** In the intervention group, the prescribing rate for recommended antibiotics increased 8.0% (from 58.9% before the intervention to 66.9% after). In the control group, the prescribing rate increased 0.8% (from 58.9% to 59.7%). The investigators did not report if the difference between groups was statistically significant.
Schaffner W, JAMA, 1983 **[comparison 1]**	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	***Clinician education*** *(distribution of materials, educational outreach)* Physicians received an educational visit from a drug educator, who went over a brochure that discussed the reasons not to use contraindicated antibiotics (chloramphenicol, clindamycin, and tetracycline for children under age 8) and provided reasonable alternatives. The drug educator was a trained clinical pharmacist.	In the intervention group, the number of prescriptions for contraindicated antibiotics was reduced by 35% relative to the pre-intervention period. In the control group, prescribing was reduced by 33% relative to the pre-intervention period. This difference was not statistically significant.
Schaffner W, JAMA, 1983 **[comparison 2]**	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	***Clinician education*** *(distribution of materials, educational outreach)* Physicians received an educational visit from a physician counselor, who went over a brochure that discussed the reasons not to use the contraindicated antibiotics (chloramphenicol, clindamycin, and tetracycline for children under age 8) and provided reasonable alternatives. The physician counselors were three senior physicians in part-time practice recruited by study advisory committee.	In the intervention group, the number of prescriptions for contraindicated antibiotics was reduced by 50% relative to before the intervention. In the control group, prescribing was reduced by 33% relative to the pre-intervention period. This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Schaffner W, JAMA, 1983 **[comparison 3]**	United States Physicians participating in Tennessee Medicaid program	Medicaid patients	***Clinician education*** *(distribution of materials, educational outreach)* Physicians received an educational visit from a drug educator who went over a brochure that discussed the reasons not to use the oral cephalosporins and provided reasonable alternatives. The drug educator was a trained clinical pharmacist.	In the intervention group, the number of prescriptions for cephalosporins was reduced by 67% relative to the pre-intervention period. In the control group, prescribing was reduced by 41% relative to the pre-intervention period. This difference was not statistically significant.
Schaffner W, JAMA, 1983 **[comparison 4]**	Physicians participating in Tennessee Medicaid program	Medicaid patients	***Clinician education*** *(distribution of materials, educational outreach)* Physicians received an educational visit from a physician counselor, who went over a brochure that discussed the reasons not to use oral cephalosporins counselors were three senior physicians in part-time practice recruited by study advisory committee.	Prescribing of cephalosporins was reduced by 85% in the intervention group in the follow-up period relative to before the intervention. In the control group, prescribing was reduced by 41% relative to the pre-intervention period. This difference was statistically significant.

* The measured population refers to the patient population in which prescribing data was measured. This population is the group to which the study results are most generalizable.

** The Absolute effect size is provided for studies that were used in the median effects analysis. These studies reported data as the percentage of visits at which patients received an antibiotic prescription. The individual study Absolute effect size was calculated as: $[(\text{Intervention})_{post} - (\text{Intervention})_{pre}] - [(\text{Control})_{post} - (\text{Control})_{pre}]$. A negative effect size means an overall reduction in the percentage of patients receiving a recommended antibiotic.

Appendix B Table 4: Antibiotic selection studies conducted outside the U.S.

Studies targeting prescribing for children

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Dolovich L, Drug Information Journal, 1999	Canada Family physicians in Southern Ontario	Children with otitis media	***Clinician education*** *(distribution of materials, educational outreach)* The intervention consisted of verbal and written evidence-based academic detailing on prescribing for acute otitis media. The academic detailers were pharmaceutical sales representatives that were asked to promote the message that physicians use amoxicillin as the first line drug. (The sales representatives worked for a company that sold a different second-line agent, pivampicillin.) Commission-based financial incentives tied to the volume of products sold were eliminated in the intervention region. Each physician had at least two follow up visits during the six month intervention period.	The primary outcome was the percentage "market share" for amoxicillin, defined as the percentage of all antibiotic prescriptions written for amoxicillin. Amoxicillin's market share increased by 1.4% compared to the control group after the intervention. This difference was not statistically significant.
Smabrekke L, Scandinavian Journal of Infectious Diseases, 2002	Norway Physicians at an acute care center	Children with otitis media	***Patient education*** *(distribution of materials),* ***Clinician education*** *(distribution of materials, educational meetings)* The intervention was a symposium on evidence-based management of otitis media for physicians and nurses at an acute care clinic. Guidelines on appropriate treatment were distributed. The guideline recommended Penicillin V use when antibiotics were necessary. Pamphlets for patients were made available in exam rooms; the pamphlets stressed that most patients recover without antibiotic and indiscriminate use of antibiotic leads to resistance. This information was also provided to patients who called the clinic.	**Absolute effect size: 2.4%** In the intervention group, the prescribing rate for recommended antibiotics increased 12.2% (from 72.3% before the intervention to 84.5% after). In the control group, the prescribing rate for recommended antibiotics increased 9.8% (from 68.2% to 78%). This difference was not statistically significant.

Studies targeting prescribing for adults

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Coenen SJ, Antimicrobial Agents and Chemotherapy, 2004	Belgium General practitioners	Adults with acute cough	***Clinician education*** *(distribution of materials, educational outreach)* The intervention consisted of a mailed guideline for treatment of patients with acute cough, which was delivered to physicians by mail and followed by a reminder phone call. Provides also received an educational outreach visit from a pharmacist and "former medical representative", which focused on guideline adherence and dialogue with the provider to overcome barriers to appropriate prescribing. Following this, the providers received a mailing with the key messages from the guideline. The recommended antibiotics were amoxicillin and doxycycline.	**Absolute effect size: 13.9%** In the intervention group, the prescribing rate for recommended antibiotics increased 13.7% (from 40.10% before the intervention to 53.8% after). In the control group, the prescribing rate decreased 0.2% (from 37.5% before to 37.3% after). This difference was statistically significant.
Dowell J, British Journal of General Practice	UK General practitioners in Scotland	Adults with cough	***Delayed prescriptions*** Patients presenting with acute cough were given an antibiotic prescription, but asked to wait one week before using the prescription.	In the intervention group, 45.0% of patients used antibiotics after the intervention. In the comparison group, 100% of patients used antibiotics. This difference was statistically significant.
Harrison A, AIDS, 2000	South Africa Practitioners in 10 primary care clinics in rural KwaZulu - Natal	Adults with sexually transmitted diseases	***Clinician education*** *(distribution of materials, educational outreach, educational workshops),* ***Patient education*** *(distribution of materials)* The intervention was a training and supervision program for health care workers. The training was an initial two day workshop attended by a senior primary health care nurse from each clinic. Three follow up sessions were held in each clinic. There were also monthly follow up visits to each clinic by a member of the district STD team. The intervention also included the development and implementation of syndrome packets, including recommended drug treatment information, condoms, partner cards and patient information leaflet.	**Absolute effect size: 43.1%** In the intervention group, the prescribing rate for recommended antibiotics increased 47.7% (from 36.3% before the intervention to 84.0% after). In the control group, the prescribing rate increased 4.6% (from 45.4% before to 50.0% after). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Veninga CC, Journal of Clinical Epidemiology, 2000	Netherlands General practitioners	Adults with urinary tract infection	***Clinician education*** *(educational workshops, other),* ***Audit and feedback*** The intervention was a series of meetings constituting a self-learning auditing program for providers. These meetings took place two times over a four month period. The first consisted of reviewing a guideline for urinary tract infection treatment and going over case vignettes. Decision strategy feedback was given on the provider's responses to the vignettes. At the second meeting, providers received individualized feedback on their prescribing behavior over the previous six months. The goals of the intervention were to increase prescription of recommended antibiotics (trimethoprim, nitrofurantoin, and sulfamethoxazole), and to encourage short courses of treatment.	**Absolute effect size: -1.0%** In the intervention group, the prescribing rate for recommended antibiotics remained unchanged at 0.0% (from 89.0% before the intervention to 89.0% after). In the control group, the prescribing rate decreased 1.0% (from 86.0% before to 85.0% after). This difference was not statistically significant.
Lagerlov P, Quality in Health Care, 2000	Norway General practitioners	Adults with urinary tract infections	***Clinician education*** *(distribution of materials, educational workshops, consensus building sessions),* ***Audit and feedback*** The intervention consisted of two group meetings in which the doctors (with the help of guidelines, and review of their own prescribing habits) established their own criteria for inappropriate and appropriate prescribing for urinary tract infection. The goal was to encourage treatment of urinary tract infection with 4 or fewer days of antibiotics.	The intervention resulted in a 13% relative increase in the proportion of UTI treatments of appropriate duration in the intervention group. This change was statistically significant.
Lundborg CS, Journal of Clinical Epidemiology, 1999	Sweden 36 General practitioner groups	Adults with urinary tract infections	***Clinician education*** *(distribution of materials, educational workshops),* ***Audit and feedback*** The intervention was a two-part educational session based on national treatment guidelines for urinary tract infection, which recommended the use of first-line antibiotics with a treatment duration of 3-7 days. Sessions, which were run by an external GP-pharmacist team, involved feedback on simulated written cases and on actual physician-level prescriptions.	**Absolute effect size: 17.0%** In the intervention group, the prescribing rate for recommended antibiotics increased 18% (from 52.0% before the intervention to 70.0% after). In the control group, the prescribing rate increased 1.0% (from 57.0% before to 58.0% after). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Rokstad K, Journal of Clinical Epidemiology, 1995	Norway General practitioners in 2 counties	Adults with urinary tract infection	***Audit and feedback*** The intervention consisted of a one time report sent by mail that included a prescription profile for treatment of urinary tract infection, for both the individual physician and the total sample of general practitioners in the study.	**Absolute effect size: 13.9%** In the intervention group, the prescribing rate for recommended antibiotics increased 7.2% (from 22.8% before the intervention to 30.0% after). In the control group, the prescribing rate decreased 6.7% (from 21.1% before to 14.4% after). The study did not report if this difference was statistically significant.
MacCara ME, Annals of Pharmacotherapy, 2001	Canada General practitioners	Adults over age 65 enrolled in Nova Scotia Seniors' Pharmacare Program	***Regulatory changes for providers, Financial and regulatory incentives for patients*** A policy change which limited reimbursement of the fluoroquinolones and other antimicrobials was instituted. In order to prescribe fluoroquinolones, the physician filled out a special form and a pharmacist determined whether the request was within the established criteria. Flouroquinolones use was limited to treatment of infections due to *Pseudomonas* and infections resistant to other drugs.	After instituting the policy, flouroquinolone use declined from 20.2% of all antibiotic prescriptions to 4.2% of all prescriptions. This change was statistically significant.
Hux JE, CMAJ, 1999	Canada Family physicians in Ontario	Adults with respiratory infections or urinary tract infections	***Clinician education*** *(distribution of materials),* ***Audit and feedback*** The intervention consisted of mailings with prescribing feedback and targeted educational bulletins stressing the use of less expensive first-line antibiotics, which took place every 2 months over 6 month period.	**Absolute effect size: 4.3%** In the intervention group, the prescribing rate for recommended antibiotics increased 2.6% (from 67.2% before the intervention to 69.8% after). In the control group, the prescribing rate decreased 1.7% (from 68.5% before to 66.8% after). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Peterson GM, Journal of Clinical Pharmacy & Therapeutics, 1997	Australia General practitioners in Southern Tasmania	Adults with urinary tract infection	***Clinician education*** *(distribution of materials, educational outreach)* The investigators described the intervention as educational mailings sent to general practitioners. The materials were designed to encourage rational prescribing of antibiotics in the management of acute, uncomplicated urinary tract infection. After two weeks, each general practitioner was contacted by telephone to confirm receipt of materials and to set up an appointment with a pharmacist to discuss materials.	**Absolute effect size: 8.8%** In the intervention group, the prescribing rate for recommended antibiotics increased 11.0% (from 73.5% before the intervention to 84.5% after). In the control group, the prescribing rate increased 2.2% (from 81.1% before to 83.3% after). This difference was statistically significant.

Studies targeting prescribing for patients of all ages

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Braybrook S, Journal of Clinical Pharmacy & Therapeutics, 1996 **[comparison 1]**	UK 66 family health practices in Wales	All patients with urinary tract infections	***Clinician education*** *(educational outreach),* ***Audit and feedback, Regulatory changes for providers*** Intervention practices received visits from a pharmaceutical prescribing adviser to discuss rational antibiotic use and to give feedback on current antibiotic use. This information was presented in a graphical computer slide show. Participating physicians received postgraduate education credit	Prescribing of generic amoxicillin (the recommended antibiotic) increased by 21 items per 1000 patients in the control group. In the intervention group, prescribing of generic amoxicillin increased by 33 items per 1000 patients. The study did not report if this difference was statistically significant.
Braybrook S, Journal of Clinical Pharmacy & Therapeutics, 1996 **[comparison 2]**	UK 66 family health practices in Wales	All patients with urinary tract infections	***Clinician education*** *(distribution of materials),* ***Audit and feedback, Regulatory changes for providers*** The intervention consisted of practice-specific feedback on prescribing practices (identical in layout to the information given in comparison 1 above) contained within a workbook and accompanied with a series of discussion questions. One general practitioner within each practice received the workbook and organized discussion sessions on rational prescribing. Participating physicians received postgraduate education credit.	Prescribing of generic amoxicillin (the recommended antibiotic) increased by 21 items per 1000 patients, in both the control and intervention groups.
De Santis G, Medical Journal of Australia, 1994	Australia General practitioners in 8 rural and metropolitan Victorian Health Department regions	All patients with tonsillitis	***Clinician education*** *(distribution of materials, educational outreach)* The intervention consisted of a 3-month educational campaign directed at providers. The campaign was initiated with a mailed brochure, which contained the recommended guidelines. These guidelines encouraged use of penicillin V or erythromycin to treat tonsillitis. The brochure was used as a focus of discussion by an academic detailer (project pharmacist) who visited doctors to discuss the campaign messages. Providers received five additional mailings, reiterating key messages.	**Absolute effect size: 8.4%** In the intervention group, the prescribing rate for recommended antibiotics increased 27.2% (from 60.5% before the intervention to 87.7% after). In the control group, the prescribing rate increased 18.8% (from 52.9% before to 71.7% after). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Friis H, Danish Medical Bulletin, 1991 **[comparison 1]**	Denmark General practitioners in 5 counties	All patients with respiratory infections or skin or soft tissue infections	***Clinician education*** *(distribution of materials, educational meetings)* An informational campaign stressed the importance of reducing ampicillin and co-trimoxazole, while increasing penicillin usage. Written materials were distributed and a series of ten lectures were held. In this comparison, the meetings were arranged by the department of clinical microbiology.	**Absolute effect size: 5.1%** In the intervention group, the prescribing rate for recommended antibiotics increased 19.1% (from 56.9% before the intervention to 76.0% after). In the control group, the prescribing rate increased 14.0% (from 58.0% before to 72.0% after). This difference was statistically significant
Friis H, Danish Medical Bulletin, 1991 **[comparison 2]**	Denmark General practitioners in 5 counties	All patients with respiratory infections or skin or soft tissue infections	***Clinician educatio****n (distribution of materials, educational meetings)* An informational campaign stressed the importance of reducing ampicillin and co-trimoxazole, while increasing penicillin usage. Written materials were distributed and a series of ten lectures were held. In this comparison, the meetings were sponsored by a pharmaceutical company and held free of charge.	**Absolute effect size: 3.1%** In the intervention group, the prescribing rate for recommended antibiotics increased 17.1% (from 56.9% before the intervention to 74.0% after). In the control group, the prescribing rate increased 14.0% (from 58.0% before to 72.0% after). This difference was not statistically significant.
Ilett KF, British Journal of Clinical Pharmacology, 2000	Australia General practitioners in the Perth metropolitan area	All patients with respiratory infections or urinary tract infections	***Clinician education*** *(distribution of materials, educational outreach)* The investigators described the intervention as a one time visit by an academic detailer to providers. The visit consisted of a brief discussion of best practice guidelines and included the distribution of a laminated copy of a chart summarizing prescribing guidelines. The recommended antibiotics were amoxicillin and doxycycline for ARIs, and penicillin for UTIs.	**Absolute effect size: 14.9%** In the intervention group, the prescribing rate for recommended antibiotics increased 10.0% (from 30.6% before the intervention to 40.6% after). In the control group, the prescribing rate decreased 4.9% (from 38.6% before to 33.7% after). The investigators did not report if this difference was statistically significant.
McNulty CA, Journal of Antimicrobial Chemotherapy, 2000	UK 84 general practices in Gloucester-shire	All patients with respiratory infections or urinary tract infections	***Clinician education*** *(educational workshops),* ***Audit and feedback*** The intervention consisted of twelve antibiotic educational workshops, which were delivered to providers over a seven week period. Workshops focused on promoting antibiotic guidelines, reducing antibiotic use for unnecessary conditions and making better prescribing decisions.	**Absolute effect size: 2.5%** In the intervention group, the prescribing rate for recommended antibiotics increased 0.6% (from 21.1% before the intervention to 21.7% after). In the control group, the prescribing rate decreased 1.9% (from 19.8% before to 17.9% after). The investigators did not report if this difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Melander E, Scandinavian Journal of Primary Health Care, 1999 **[comparison 2]**	Sweden General practices in 3 communities	All patients with respiratory infections	***Clinician education*** *(educational workshops),* ***Audit and feedback*** Physician's antibiotic prescribing behavior was audited and fed back to the individual physicians. Group discussions and an educational program were based on the results of these data. Physicians were encouraged to use penicillin V as the first choice drug.	**Absolute effect size: -7.7%** In the intervention group, the prescribing rate for recommended antibiotics increased 4.1% (from 61.4% before the intervention to 65.5% after). In the control group, the prescribing rate increased 12.8% (from 37.1% before to 49.9% after). This difference was not statistically significant.
Molstad S, Family Practice, 1989	Sweden General practitioners at 3 community health centers	All patients with respiratory infections	***Clinician education*** *(consensus building sessions)* Clinicians received an educational program consisting of reviewing regional resistance patterns and indications for antibiotic treatment. Phenoxypenicillin was agreed upon as the first-choice antibiotic, with amoxicillin or pivampicillin for treatment failures and erythromycin for penicillin-allergic patients.	**Absolute effect size: 20.0%** In the intervention group, the prescribing rate for recommended antibiotics increased 16.2% (from 62.3% before the intervention to 78.5% after). In the control group, the prescribing rate decreased 4.2% (from 57.3% before to 53.1% after). The investigators did not report if this difference was statistically significant.
Raz R, Israel Journal of Medical Sciences, 1995	Israel Physicians and nurses at 3 community outpatient clinics	All patients with pharyngitis	***Clinician education*** *(distribution of materials, educational meetings)* Two 1-hour educational sessions on antibiotic prescribing for pharyngitis were given by the study physicians to the entire medical staff (physicians, nurses and pharmacists.) Written handouts were distributed recommending treatment with penicillin V for streptococcal pharyngitis.	**Absolute effect size: 12.5%** In the intervention group, the prescribing rate for recommended antibiotics increased 11.5% (from 57.5% before the intervention to 69.0% after). In the control group, the prescribing rate decreased 1.0% (from 44.4% before to 43.4% after). This difference was statistically significant.

STUDY	SETTING AND TARGET	MEASURED POPULATION AND CONDITION*	INTERVENTION DESCRIPTION AND QUALITY IMPROVEMENT STRATEGIES	RESULTS**
Sondergaard J, Scandinavian Journal of Primary Health Care, 2003	Denmark 181 general practices	All patients with respiratory infections	***Clinician education*** *(distribution of materials),* ***Audit and feedback*** The intervention consisted of mailed information to general practitioners on their prescribing practices combined with a clinical guideline on the diagnosis and treatment of respiratory tract infections. The feedback provided some aggregate data so the general practitioner could compare the prescription rates of their own practice to other local practices. The clinical guidelines recommended restricting antibiotics used for respiratory tract infections to the lowest justifiable level, and that narrow-spectrum antibiotics (e.g. penicillin V) should be preferred to broad-spectrum antibiotics.	**Absolute effect size: 2.0%** In the intervention group, the prescribing rate for recommended antibiotics decreased 7.0% (from 52.0% before the intervention to 45.0% after). In the control group, the prescribing rate decreased 9.0% (from 52.0% before to 43.0% after). This difference was not statistically significant.
Zwar N, Family Practice, 1999	Australia General practitioner trainees in New South Whales	All patients with pharyngitis	***Clinician education*** *(distribution of materials, educational outreach, other),* ***Audit and feedback*** The intervention consisted of a mailed packet of individualized feedback to providers, management guidelines, and patient handouts. Providers also received an academic detailing session, in person or over phone, for doctors who exceeded thresholds for inappropriate prescriptions based on feedback data. Providers were encouraged to use narrow-spectrum penicillin or erythromycin for streptococcal pharyngitis.	**Absolute effect size: 18.6%** In the intervention group, the prescribing rate for recommended antibiotics increased 17.5% (from 55.5% before the intervention to 73.0% after). In the control group, the prescribing rate decreased 1.1% (from 59.6% before to 58.5% after). This difference was statistically significant.

* The measured population refers to the patient population in which prescribing data was measured. This population is the group to which the study results are most generalizable.

** The Absolute effect size is provided for studies that were used in the median effects analysis. These studies reported data as the percentage of visits at which patients received an antibiotic prescription. The individual study Absolute effect size was calculated as: $[(\text{Intervention})_{post} - (\text{Intervention})_{pre}] - [(\text{Control})_{post} - (\text{Control})_{pre}]$. A negative effect size means an overall reduction in the percentage of patients receiving a recommended antibiotic.

Appendix C. EPOC and Medline Search for Antibiotic QI Articles

We conducted two searches to identify relevant articles.

1. EPOC Databases Search: The EPOC, Medline and HealthSTAR search strategy (see below) was combined with the antiobiotic terms search strategy (see below) to identify relevant articles from the EPOC databases upto October 2004.

2. Medline Search: To identify more recent articles that may not have been indexed in the EPOC databases, we searched Medline from June 2004 to November 2004 using the search below.

1. EPOC Databases Search

EPOC MEDLINE and HealthSTAR * Search Strategy

1. exp *education,continuing/
2. (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw.
3. (behavio?r$ adj2 intervention?).tw.
4. *pamphlets/
5. (leaflet? or booklet? or poster or posters).tw.
6. ((written or printed or oral) adj information).tw.
7. (information$ adj2 campaign).tw.
8. (education$ adj1 (method? or material?)).tw.
9. *advance directives/
10. outreach.tw.
11. ((opinion or education$ or influential) adj1 leader?).tw.
12. facilitator?.tw.
13. academic detailing.tw.
14. consensus conference?.tw.
15. *guideline adherence/
16. practice guideline?.tw.
17. (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw.
18. ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw.
19. *reminder systems/
20. reminder?.tw.
21. (recall adj2 system$).tw.
22. (prompter? or prompting).tw.
23. algorithm?.tw.
24. *feedback/ or feedback.tw.
25. (feedback adj1 (loop? or control? or regula$ or mechanism? or inhib$ or system? or circuit? or sensory or visual or audio$ or auditory)).tw.
26. 23 not 24
27. chart review$.tw.
28. ((effect? or impact or records or chart?) adj2 audit).tw.
29. compliance.tw.
30. marketing.tw.
31. or/1-22,26-30
32. exp *reimbursement mechanisms/
33. fee for service.tw.
34. *capitation fee/
35. *"deductibles and coinsurance"/
36. cost shar$.tw.
37. (copayment? or co payment?).tw.
38. (prepay$ or prepaid or prospective payment?).tw.
39. *hospital charges/
40. formular$.tw.
41. fundhold$.tw.
42. *medicaid/

43. *medicare/
44. blue cross.tw.
45. or/32-44
46. *nurse clinicians/
47. *nurse midwives/
48. *nurse practitioners/
49. (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw.
50. *pharmacists/
51. clinical pharmacist?.tw.
52. paramedic?.tw.
53. *patient care team/
54. exp *patient care planning/
55. (team? adj2 (care or treatment or assessment or consultation)).tw.
56. (integrat$ adj2 (care or service?)).tw.
57. (care adj2 (coordinat$ or program$ or continuity)).tw.
58. (case adj1 management).tw.
59. exp *ambulatory care facilities/
60. *ambulatory care/
61. or/46-60
62. *home care services/
63. *hospices/
64. *nursing homes/
65. *office visits/
66. *house calls/
67. *day care/
68. *aftercare/
69. *community health nursing/
70. (chang$ adj1 location?).tw.
71. domiciliary.tw.
72. (home adj1 treat$).tw.
73. day surgery.tw.
74. *medical records/
75. *medical records systems, computerized/
76. (information adj2 (management or system?)).tw.
77. *peer review/
78. *utilization review/
79. exp *health services misuse/
80. or/62-79
81. *physician's practice patterns/
82. quality assurance.tw.
83. *process assessment/ [health care]
84. *program evaluation/
85. *length of stay/
86. (early adj1 discharg$).tw.
87. discharge planning.tw.
88. offset.tw.
89. triage.tw.
90. exp *referral/ and consultation/
91. *drug therapy,computer assisted/
92. near patient testing.tw.
93. *medical history taking/
94. *telephone/
95. (physician patient adj (interaction? or relationship?)).tw.
96. *health maintenance organizations/
97. managed care.tw.
98. (hospital? adj1 merg$).tw.
99. or/81-98
100. ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw.
101. (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw.
102. (program$ adj1 (health or care or intervention?)).tw.
103. ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw.
104. ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw.

105. ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw.
106. ((effect? or impact or evaluat$ or introduc$ or compara$) adj2 prevent$ program$).tw.
107. (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw.
108. ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw.
109. ((effect? or impact or introduc$) adj2 (legislation or regulations or policy)).tw.
110. or/100-109
111. 31 or 45 or 61 or 80 or 99 or 110
112. randomized controlled trial.pt.
113. controlled clinical trial.pt.
114. intervention studies/
115. experiment$.tw.
116. (time adj series).tw.
117. (pre test or pretest or (posttest or post test)).tw.
118. random allocation/
119. impact.tw.
120. intervention?.tw.
121. chang$.tw.
122. evaluation studies/
123. evaluat$.tw.
124. effect?.tw.
125. comparative studies/
126. animal/
127. human/
128. 126 not 127
129. or/112-125
130. 129 not 128
131. 111 and 130

*insert :
(randomised or randomized).tw.
(random$ adj1 (allocat$ or assign$)).tw.

Antibiotics Terms Search Strategy
antibiotic*
Amoxicillin
Azithromycin
Cephalosporin*
Cephalexin
Ciprofloxacin
Clarithromycin
Clindamycin
Doxycycline
Erythromycin
Flouroquinolone*
Fluconazole
Levofloxacin
Macrolide*
Metronidazole
Nitrofurantoin
Penicillin
Tetracycline
Trimethoprim

2. Medline Search

#1 Targets clinical conditions	"Community-Acquired Infections"[MeSH] OR "Respiratory Tract Infections"[MeSH] OR "Bronchitis"[MeSH] OR "Pneumonia, Bacterial"[MeSH] OR Sinusitis[MeSH] OR Common Cold[MeSH] OR Influenza[MeSH] OR "Urinary Tract Infections"[MeSH] OR Sexually Transmitted Diseases[MeSH] OR Vaginitis[MeSH] OR Candidiasis, Vulvovaginal[MeSH] OR Pelvic Inflammatory Disease[MeSH]	365549
#2 Targets antibiotics and prescribing	Anti-Bacterial Agents[MeSH] OR Antibiotic[ti] OR Anti-Infective Agents, Urinary[MeSH] OR Antibiotics[ti] OR Prescriptions, Drug[MeSH] OR Drug Utilization[MeSH] OR Physician's Practice Patterns[MeSH] OR Attitude of Health Personnel [MeSH] OR Prescribing[ti] OR Prescription[ti]	255351
#3 Targets QI strategies that tend to be multi-factorial using relevant MeSH terms and title words	Disease Management [mh] OR Patient Care Planning [mh] OR Patient-Centered Care [mh] OR Primary Health Care [mh] OR Progressive Patient Care [mh] OR Critical Pathways [mh] OR Delivery of Health Care, Integrated [mh] OR Health Services Accessibility [mh] OR Managed Care Programs [mh] OR Product Line Management [mh] OR Patient Care Team [mh] OR Patient-Centered Care [mh] OR Behavior Control [mh] OR Counseling [mh] OR Health Promotion [mh] OR Patient Compliance [mh] OR After-Hours Care [mh] OR ((coordination [ti] OR coordinated [ti] OR Multifactorial [ti] OR Multi-factorial [ti] OR Multicomponent [ti] OR Multi-component [ti] OR multidisciplinary [ti] OR multi-disciplinary [ti] OR interdisciplinary [ti] OR inter-disciplinary [ti] OR integrated [ti] OR community-based [ti] OR organized [ti]) AND (care [ti] OR approach [ti] OR intervention [ti] OR strategy [ti] OR strategies [ti] OR management [ti] OR managing [ti] OR center* [ti] OR clinic*[ti])) OR Organization and Administration [mh]	735481
#4 Targets TQM and CQI	Total Quality Management [mh] OR Quality control [mh] OR TQM [ti] OR CQI [ti] OR (quality [ti] AND (continuous [ti] OR total [ti]) AND (management [ti] OR improvement [ti]))	31249
#5 Targets provider education	Education, Continuing [mh] OR (Education [ti] AND Continuing [ti] AND (medical [ti] OR professional* [ti] OR nursing [ti] OR physician* [ti] OR nurse* [ti])) OR (outreach [ti] AND (visit*[ti] OR educational [ti]) OR (academic [ti] AND detailing [ti]))	36,929
#6 Targets diffusion of innovation	Diffusion of Innovation [mh] OR (Diffusion [ti] AND (Innovation [ti] OR technology [ti]))	5519
#7 Targets audit and feedback, reminder systems, and financial incentives	Medical audit [mh] OR ((Audit [ti] OR feedback [ti] OR compliance [ti] OR adherence [ti] OR training [ti]) AND (improvement* [ti] OR improving [ti] OR improves [ti] OR improve [ti] OR guideline* [ti] OR practice* [ti] OR medical [ti] OR provider* [ti] OR physician* [ti] OR nurse* [ti] OR clinician* [ti] OR practice guidelines [mh] OR academic [ti] OR visit* [ti])) OR Reminder Systems [mh] OR Reminder* [ti] OR ((financial [ti] OR economic [ti] OR physician* [ti] OR patient*) AND incentive* [ti]) OR Reimbursement Mechanisms [mh]	40,152
#8 Targets informatics and telemedicine	Medical Informatics [mh] OR computer [ti] OR (decision [ti] AND support [ti]) OR Telemedicine[mh] OR Telemedicine [ti] OR telecommunication* [ti] OR Internet [mh] OR web [ti] OR modem [ti] OR telephone* [ti] OR telephone [mh]	339608
#9 Overall set of articles relating to QI	#3 OR #4 OR #5 OR #6 OR #7 OR #8	1072468

#10 Combines QI strategies search terms with ABX search	#9 AND (#1 OR #2)	75,957
#11 Systematic review search string	(meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti] OR Decision Support Techniques [mh]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case reports [pt] OR case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt]	46,865
#12 Original research search string	Randomised [ti] OR Randomized [ti] OR Controlled [ti] OR intervention [ti] OR evaluation [ti] OR impact [ti] OR effectiveness [ti] OR Evaluation [ti] OR Studies [ti] OR study [ti] Comparative [ti] OR Feasibility [ti] OR Program [ti] OR Design [ti] OR Clinical Trial [pt] OR Randomized Controlled Trial [pt] OR Epidemiologic Studies [mh] OR Evaluation Studies [mh] OR Comparative Study [mh] OR Feasibility Studies [mh] OR Intervention Studies [mh] OR Program Evaluation [mh] OR Epidemiologic Research Design [mh]	2394801
#13 Subset of #10 likely to include original research or systematic reviews	#10 AND (#11 OR #12)	21,936
#14 Supplementary search results	[See supplement below]	25,569
#15	#13 OR #14	42317
#16	#15 BUTNOT (editorial [pt] OR comment [pt] OR letter [pt] OR news [pt] OR newspaper article [pt] OR case reports[pt])	36850
#17	#14 limit to Human and English	31200
#18	#15 limit to June 2004 – November 2004	846

Supplemental search:

#1	(Drug Therapy [mh] OR Drug Utilization [mh] OR Drug Utilization Review [mh] OR Drug Therapy, Combination [mh] OR Decision Support Techniques [mh] OR Drug Information Services [mh] OR Decision Making [mh] OR Attitude of Health Personnel [mh] OR Attitude to Health [mh] OR Clinical Competence [mh] OR Education, Continuing [mh] OR Education, Medical, Continuing [mh] OR Guideline Adherence [mh] OR Practice Guidelines [mh] OR guideline [ti] OR Health Education [mh] OR "Health Knowledge, Attitudes, Practice" [mh] OR Health Personnel [mh] OR Health Promotion [mh] OR Health Services Misuse [mh] OR Medical Audit [mh] OR Models, Educational [mh] OR Counseling [mh] OR Patient Education [mh] OR Patient Participation [mh] OR Patient Satisfaction [mh] OR Physician-Patient Relations [mh] OR Physician's Practice Patterns [mh] OR Point-of-Care Systems [mh] OR Prescribing [ti] OR Prescription* [ti] OR Prescriptions, Drug [mh])	887970
#2	(Anti-Infective Agents [mh] OR Drug Resistance, Microbial [mh] OR Disease Transmission [mh] OR Infection/ drug therapy [mh] OR antibiotic* [ab] OR antimicrobial* [ab] OR anti-infective [ab] OR Cephalexin [ab] OR Cephalosporin* [ab] OR Chloramphenicol [ab] OR Clindamycin [ab] OR Cephalexin [mh] OR Cephalosporin* [mh] OR Chloramphenicol [mh] OR Clindamycin [mh] Common Cold/ drug therapy [mh] OR Community-Acquired Infections/drug therapy [mh] OR Cough/drug therapy [mh] OR Cystitis/drug therapy [mh] OR Diarrhea/drug therapy [mh] OR Diarrhea/chemically induced [mh] OR Erythromycin [ab] OR Erythromycin [mh] OR Fluoroquinolone* [ab] OR Fluoroquinolone* [mh] OR Otitis Media/ drug therapy [mh] OR Penicillin* [mh] OR penicillin* [ab] OR Pharyngitis [mh] OR Pneumococcal Infections [mh] OR Respiratory Tract Infections [mh] OR Rhinitis [mh] OR Streptococcal Infections [mh] OR Streptococcus [ab] OR Tetracycline [ab] OR Tonsillitis [mh] OR Trimethoprim [ab] OR Tetracycline [mh] OR Trimethoprim [mh] OR Urinary Tract Infections [mh] OR Virus Diseases [mh] OR Anti-Infective [ti] OR Antiinfective [ti] OR antibiotic* [ti] OR antimicrobial* [ti] OR Cephalosporin* [ti] OR Chloramphenicol [ti] OR Clindamycin [ti] OR infection* [ti] OR Cystitis [ti] OR Diarrhea [ti] OR Erythromycin [ti] OR macrolide* [ti] OR Fluoroquinolone* [ti] OR "Otitis Media" [ti] OR Pharyngitis [ti] OR throat [ti] OR cough [ti] OR Pneumococcal [ti] OR "Respiratory Tract" [ti] OR Streptococcal [ti] OR Tetracycline [ti] OR Tonsillitis [ti] OR Trimethoprim [ti])	948535
#3	#1 AND #2	73845
#4	(systematic [sb] OR Randomised [ti] OR Randomized [ti] OR Controlled [ti] OR intervention [ti] OR evaluation [ti] OR impact [ti] OR effectiveness [ti] OR Evaluation [ti] OR Studies [ti] OR study [ti] Comparative [ti] OR Feasibility [ti] OR Program [ti] OR Design [ti] OR Clinical Trial [pt] OR Randomized Controlled Trial [pt] OR Epidemiologic Studies [mh] OR Evaluation Studies [mh] OR Comparative Study [mh] OR Feasibility Studies [mh] OR Intervention Studies [mh] OR Program Evaluation [mh] OR Epidemiologic Research Design [mh])	2394833
#5	#3 AND #4	25,569

Appendix D. Antibiotic Abstraction Forms for Screening and Full-Text Review

Stage 1

1. Does this article report or evaluate the results of an intervention (whether performed by the investigators or not)?
   - o Yes
   - o No ***[exclusion]***
   - o Can't tell

2. Does the article involve quality improvement or a QI strategy?
   - o Yes - involves quality improvement or a QI strategy
   - o Yes - systematic review of evaluations of a QI strategy
   - o No ***[exclusion]***
   - o Can't tell

Only answer questions 3-5 if questions 1-2 were answered "Yes"

3. Should this article proceed to full text review for this topic?
   - o Yes - evaluates a QI strategy involving microbial use
   - o No - ineligible topic (focussed on inpatient care, antimicrobial use in chronic disease, not related to antimicrobial use) ***[exclusion]***
   - o No - not an evaluation or not QI ***[exclusion]***
   - o Can't tell - need article
   - o No - foreign language ***[exclusion]***

4. What type of study design was used?
   - o RCT or quasi-RCT
   - o CBA* or ITS**
   - o Cohort study; before-after or time series not meeting CBA* or ITS** definitions ***[exclusion]***
   - o Observational (e.g.,cross-section, case-control) ***[exclusion]***
   - o Systematic review or meta-analysis
   - o Economic or decision analysis, modeling ***[exclusion]***
   - o Non-research (commentary, review, news) ***[exclusion]***
   - o Qualitative research (e.g.,focus groups) ***[exclusion]***
   - o Guideline or consensus statement ***[exclusion]***
   - o Can't tell (need article)

* CBA: Controlled Before After requires contemporaneous observation periods for control and intervention groups AND judgement that control represents a comparable group or setting.

** ITS: Interrupted Time Series requires statement of well-defined time period for intervention implementation AND data measurement for at least three time points before and after intervention.

NOTE: At this stage of triage, err on the side of inclusion if there is a reasonable chance the study is an RCT, CBA or ITS. Similarly, if there is a reasonable chance that the article is a systematic review, designate it as such so the article can be pulled.

5. What category of study question is addressed by the article?
   - o Can antimicrobial prescribing for illnesses not requiring antimicrobial therapy be reduced?
   - o Can the selection of antimicrobials for illnesses requiring antimicrobials be improved?
   - o Can prescribing antimicrobials at the appropriate dose or duration of treatment be improved?
   - o Unclear
   - o Other (explain)
   - o None of the above

Stage 2

1. Does this article merit full text abstraction?
   - o Yes
   - o No – not QI or not an evaluation of a QI strategy ***[exclusion]***
   - o No – ineligible study design (i.e., not RCT, CBA, or ITS) ***[exclusion]***
   - o No - excluded topic (focused only on inpatient care, antimicrobial use in chronic disease) ***[exclusion]***
   - o No – no eligible outcomes* ***[exclusion]***
   - o No- other ***[exclusion]***

*Eligible outcomes include measures of antimicrobial prescribing, antimicrobial resistance, or health services utilization (as a marker of prescription use).

2. Does this article present data overlapping with another article?
   - o Exclude this article as a duplicate publication (identify included citation being duplicated) ***[exclusion]***
   - o Include this article, but obtain listed citation to help with abstraction (e.g., separate methods paper; identify required citation)
   - o No or N/A

3. Does abstraction of this study require information from methods or results reported in other citations?
   - o Yes (specify)
   - o No

4. Does the article report data for more than one comparison (i.e., should it be abstracted as more than one study)?
   - o Yes (specify which comparison is being abstracted here and which others will be abstracted elsewhere)
   - o No

5. What category of study question is addressed by the article?
   - o Can antimicrobial prescribing for illnesses not requiring antimicrobial therapy be reduced?
   - o Can the selection of antimicrobials for illnesses requiring antimicrobials be improved?
   - o Can prescribing antimicrobials at the appropriate dose or duration of treatment be improved?
   - o Can antimicrobial resistance be reduced?
   - o Can adverse effects of antimicrobial prescribing (i.e., adverse drug events or clinical consequences) be reduced?
   - o Can the costs associated with antimicrobial prescribing be reduced?
   - o Can health services utilization be reduced via improving the antimicrobial prescribing process?
   - o Other

6. Describe the QI strategy used and its salient features. **[text box]**

A) Study Setting and Participants

7. In what country did the study take place?
   - o US
   - o non-US (specify)

8. When did the study take place?
   - o If supplied, give exact dates of study period (beginning to end of intervention period)
   - o Not reported

9. Who or what was targeted by the intervention? (check all that apply)
   - o Patients
   - o Providers (i.e., individual clinicians)
   - o Entire population of a geographic area
   - o Other (describe)

10. If the intervention targeted providers, in what setting did they practice? (check all that apply)
   - o Outpatient primary care clinic (specify type of clinic, e.g.,academic, VA, HMO)
   - o Urgent care or walk-in clinic

- o Emergency department
- o Other (describe)
- o Not stated or not clear

12. Which specific disease process was the target of the antimicrobial intervention? (check all that apply)
    - o Respiratory tract infection (specify)
    - o Urinary tract infection
    - o Sexually transmitted disease (e.g.,gonorrhea/chlamydia, syphilis)
    - o Gynecologic infection (e.g.,vaginitis)
    - o Other infection(s) (describe)
    - o No specific disease targeted

13. Were patients in the study selected on the basis of specific demographic or clinical characteristics? (check all that apply)
    - o Children (specify age groups)
    - o Elderly (specify age groups)
    - o Immunocompromised patients (specify)
    - o Specific type of insurance (i.e., patients within a particular HMO) (describe)
    - o Other demographic or clinical characteristic (describe)
    - o No specific patient population targeted

14. What type of intervention was provided to the control population?
    - o No intervention or usual care
    - o Some form of low intensity intervention (describe)
    - o No true control - just two or more different types of intervention (discuss with other reviewers; study may need to be excluded)

B) Study Design

15. What was the study design?
    - o Randomized trial (state method of randomization if described)
    - o Quasi-randomized trial (state basis for treatment allocation, e.g.,alternating patients, calendar date, even or odd identification numbers)
    - o Controlled before-after study*
    - o Interrupted time series**

*Controlled Before After (CBA) requires contemporaneous observation periods for control and intervention groups AND judgment that control represents a comparable group or setting

** Interrupted time series (ITS) requires statement of well-defined time period for intervention implementation AND measurement of data at three or more time points both before and after intervention

16. What was the unit of randomization or treatment allocation?
    - o Patient
    - o Episode of care
    - o Clinic day
    - o Provider
    - o Clinic or practice
    - o Firm (describe)
    - o Institution
    - o Community
    - o Other
    - o Not applicable—ITS study (skip to question 27)

17. For the unit of treatment allocation above, state sample size in each group (If sample size differs for outcomes, detail differences in "Not stated or not clear" text box):
    - o control group
    - o intervention group
    - o Not stated or not clear (explain)

18. If unit of analysis differed from unit of treatment allocation (e.g., providers randomized, but patient outcomes analyzed), state sample size in each group: (Use text box for "Not applicable" if sample size for any outcomes reported is different-give details)
- o control group
- o intervention group
- o Not stated or not clear
- o Not applicable (unit of analysis same as unit of treatment allocation above)

19. If unit of analysis differed from unit of treatment allocation, did authors acknowledge this issue and/or make appropriate adjustments?
- o Yes (describe)
- o No
- o Not applicable (unit of analysis did not differ from unit of treatment allocation)

20. Was there adequate concealment of treatment allocation?
- o Yes (unit of allocation was institution, team or professional and randomization process explicity described, OR unit of allocation was patient or episode of care and some form of centralized randomization scheme or sealed envelopes used)
- o Not clear (only partially meets above criteria) or not stated - specify which
- o No inadequate concealment (enrollment of patients in alternation or through use of even/odd identifying numbers OR unit of allocation was patient or episode of care and reported use of any allocation process that is entirely transparent before assignment (e.g., open list of random numbers) OR allocation was altered by investigators, professionals or patients)

21. Was informed consent obtained? (check all that apply)
- o Obtained from patients
- o Obtained from providers
- o Not obtained or not stated (specify)

22. Was IRB approval obtained by investigators?
- o Yes
- o No or not stated (specify)

Design criteria for randomized and quasi-randomized trials
(If study is a CBA, skip to question 27; if ITS, skip to question 33)

23. Did the study have a cross over design? (Patients randomized to a sequence of interventions such as treatment A followed by treatment B in one group and treatment B followed by treatment A in the other group).
- o Yes (describe)
- o No
- o Not sure - clarify with other reviewers before proceeding

24. Were patients blind to intervention/treatment allocation?
- o Yes
- o No
- o Not sure (explain)
- o Not applicable (patients not actively involved in study - e.g., provider-focused intervention with patient level data obtained retrospectively from charts)

25. Were providers blind to intervention/treatment allocation?
- o Yes
- o No
- o Not sure (explain)
- o Not applicable (explain)

26. Were outcomes assessors blinded to intervention/treatment allocation?
- o Yes
- o No
- o Not sure (explain)
- o Not applicable (explain)

Design criteria for CBA trials

27. Were measurements in the control group performed at the same time as the intervention group?
    - o Yes
    - o No
    - o Unclear

28. Were the criteria used for selecting the control site explained?
    - o Yes (describe)
    - o No

29. Was the control site comparable (in both patients and providers)?
    - o Yes
    - o No (explain why not)
    - o Unclear (describe)

Design criteria for ITS trials

30. Was the intervention performed independent of other quality improvement efforts or other changes?
    - o Yes
    - o No
    - o Unclear

31. Was the intervention unlikely to affect data collection?
    - o Yes
    - o No
    - o Unclear

32. Was the data analyzed using a formal test for trend (time series ANOVA or regression)?
    - o Yes
    - o No
    - o Unclear

33. (For all studies) Do any methodologic aspects of the study design not captured above seriously undermine appropriateness of inclusion?
    - o Yes (explain)
    - o No (use text box to document any non-fatal, but still noteworthy methodological features)

C) Quality Improvement Attributes of Intervention

34. Did the investigators identify a specific quality gap (a difference between optimal and actual care) in the study population?
    - o Yes (describe)
    - o No

35. Did the investigators cite previous literature to describe the evidence base for their proposed intervention?
    - o Yes
    - o No

36. Did the QI strategy involve PATIENT EDUCATION?
    - o Yes
    - o No patient education (skip to question 36)

37. Which of the following educational strategies was used? (check all that apply)
    - o One-on-one session, in person or via telephone
    - o Group session (e.g.,classes)
    - o Distribution of printed or audiovisual materials (e.g.,pamphlets or poster in waiting room)
    - o Community-wide mass media efforts (e.g.,television advertisements or billboards)
    - o Interactive computer-based learning
    - o Provision of clinical data to patient (e.g.,test results)
    - o Not sure or other (describe)

38. In what setting was the educational content delivered? (check all that apply)
- o Clinical setting (e.g.,office or emergency department)
- o Home (in person, by phone, mail or internet)
- o School or workplace
- o Other community setting (e.g.,church, community center) (describe)
- o Mass media exposure
- o Other or unclear (describe)

39. Who was responsible for delivery of the educational content? (check all that apply)
- o Physician
- o Nurse or nurse practitioner
- o Pharmacist
- o Other ancillary health provider (describe)
- o Health educator
- o No specific delivery person (e.g.,entirely mailed, computer-based, or passively distributed content)
- o Other (describe)

40. Did the intervention include access to a resource that promoted PATIENT SELF- MANAGEMENT?
- o Delayed prescriptions or other therapy based on patient self-monitoring of symptoms (describe)
- o Decision support for patient to use before seeing health care provider (e.g.,access to a call center) (describe)
- o Other type of decision support (describe)
- o No

41. Did the QI strategy involve PROVIDER EDUCATION?
- o Yes
- o No (skip to question 42)

42. Which of the following educational strategies was used? (check all that apply)
- o Distribution of educational materials (published or printed recommendations for clinical care, including clinical practice guidelines, audio-visual materials and electronic publications)
- o Meetings or lectures (e.g.,traditional CME)
- o Educational outreach visits (e.g.,"academic detailing"—a trained person who met with providers in their practice settings to give information with the intent of changing the provider's practice)
- o Interactive in-person education (e.g.,workshops or role-playing)
- o Computer- or internet-based interactive tutorials
- o Consensus-building sessions (e.g.,for development of guideline)
- o Not sure or other (describe)

43. In what setting was the educational content delivered? (check all that apply)
- o Office, emergency department, or other clinical setting
- o Off-site meeting (e.g.,CME)
- o Other (describe)

44. Who was responsible for delivery of the educational content? (check all that apply)
- o Expert opinion leader (describe how selected)
- o Other physician (including colleagues)
- o Pharmacist
- o Pharmaceutical sales representative
- o Other (describe)
- o Not clear or not specified

45. Did the QI strategy involve a PROVIDER REMINDER system*?
- o Chart based decision support or reminder system*
- o Computer based reminder* or decision support*
- o Not sure
- o No or N/A

* Patient or provider encounter specific information, provided verbally, on paper or on a computer screen, which is intended to prompt provider to recall information at the time of the patient encounter (e.g., reminder that antibiotics are ineffective for the common cold)

46. Did the QI strategy involve provider AUDIT AND FEEDBACK*? (check all that apply)
- o feedback to individual provider (state if confidential)
- o feedback about clinic or practice performance only
- o Public reporting of performance data (state if individual data or data for a group or institution)
- o Benchmarking**
- o Not sure or other
- o No or N/A

*Any summary of clinical performance of health care over a specified period of time. E.g., the number of times over the last year a provider prescribed antimicrobials for bronchitis.

**Benchmarking refers to the provision of performance data from institutions or providers regarded as "leaders in the field." These data provide targets for other providers and institutions to emulate.

47. Did the QI strategy involve ORGANIZATIONAL CHANGE?
- o Adding new members to team (e.g., adding a clinical pharmacist to clinic, or creation of a call center for patients) or creating multidisciplinary teams for patient care
- o Revision of professional roles among health professionals (e.g., nurse practitioner or pharmacist given prescribing authority)
- o Increased staffing without changes in roles (e.g., adding more nurses)
- o TQM/CQI - cycles of measurement of quality problems, design of interventions, implementation and re-measurement
- o Changes in medical records systems -- e.g.,changing from paper to computerized records, patient tracking systems
- o Communication and case discussion between distant health professionals (e.g., telemedicine)
- o Not sure or other (describe)
- o No or N/A

48. If the intervention involved changes to medical record systems, what type of change was instituted?
- o Change from paper to computerized records
- o Implementation of computerized provider order entry (CPOE)
- o New patient tracking system
- o Other (describe)
- o Not applicable - No change to medical record system

49. Did the intervention involve FINANCIAL INCENTIVES DIRECTED AT PROVIDERS?
- o Financial incentives for achievement of performance goals
- o Change in reimbursement system (i.e., capitation)
- o Other (describe)
- o No component of provider-directed financial incentives

50. Did the intervention involve REGULATORY CHANGES DIRECTED AT PROVIDERS?
- o Restriction of formulary to cover only certain antimicrobials
- o Authorization from another physician required to prescribe antimicrobial
- o Authorization from health plan required to prescribe antimicrobial
- o Restriction of access to pharmaceutical sales representatives
- o Other (describe)
- o No component of provider-directed regulatory changes

51. Did the intervention involve FINANCIAL OR REGULATORY INCENTIVES DIRECTED AT PATIENTS?
- o Additional charge (copayment) for specific antimicrobials
- o Additional charge (copayment) for visits or phone calls
- o Change in health insurance premiums
- o Other (describe)
- o No component of patient-directed financial or regulatory incentives

52. Did the intervention involve FINANCIAL OR REGULATORY INCENTIVES DIRECTED AT A PRACTICE OR HEALTH SYSTEM?
- o Yes (describe)
- o No component of health-system-directed financial or regulatory incentives

53. Did a clinical information system play a role in design or implementation of the intervention?
- o Identification and/or group allocation of eligible patients or providers
- o Reminders generated by existing clinical information system
- o Decision support at point of care (e.g., for provider order entry)
- o Facilitated communication between providers (e.g., generated emails between members of care team)
- o Audit data gathered from clinical information system to design QI strategy (e.g., audit and feedback, TQM, provider education, financial incentives)
- o Other
- o No role for a clinical information system

54. Use textbox to state any important study features or concerns not captured above.

D) Results

55. For unit of treatment allocation (e.g., clinics, providers, patients), were results reported for at least 80% of participants?
- o Yes (state %)
- o No (state %)
- o Not stated

56. If unit of analysis differed from unit of treatment allocation (e.g., providers randomized, but patient level outcomes analyzed), were results reported for at least 80% of participants?
- o Yes (state %)
- o No (state %)
- o Not stated or not clear
- o Not applicable (unit of analysis same as unit of treatment allocation)

57. What was the length of the study follow-up period? (describe)

58. What were the outcome types? (check all that apply)
- o Measure of antimicrobial use
- o Measure of antimicrobial resistance
- o Measure of clinical outcome of disease
- o Health services utilization (when used as a marker of antimicrobial use)
- o Adverse drug events
- o Cost
- o Patient or provider satisfaction with plan of care
- o Not sure or other

Measures of antimicrobial use

59. For studies reporting measures of antimicrobial use, what specific outcomes were measured? (check all that apply)
- o Total prescriptions for antimicrobials (overall and/or a specific antimicrobial or class) by an individual provider, practice or health care system
- o Total volume of antimicrobials used by a provider, practice, or health care system (e.g.,number of defined daily doses of an antibiotic prescribed by a physician)
- o Percentage of patient visits resulting in an antimicrobial prescription (overall and/or use of a specific antimicrobial or class)
- o Rate of compliance to clinical guideline for antimicrobial prescription (including decision to prescribe antimicrobial, choice of antimicrobial, or dose/duration of therapy)
- o Other (describe)
- o No measurement of antimicrobial use (skip to question 69)

60. For studies reporting data in the form of total prescriptions for antimicrobial use, provide the following data for the CONTROL group; if data is missing, record “NR”
- o Exact units of measurement
- o Number of prescriptions prior to intervention
- o Number of prescriptions after intervention
- o Percentage change in number of prescriptions

61. For studies reporting data in the form of total prescriptions for antimicrobial use, provide the following data for the INTERVENTION group; if data is missing, record “NR”
- o Exact units of measurement
- o Number of prescriptions prior to intervention
- o Number of prescriptions after intervention
- o Percentage change in number of prescriptions

62. For studies reporting data in the form of total volume of antimicrobial prescribed, provide the following data for the CONTROL group; if data is missing, record “NR”
- o Exact units of measurement
- o Volume of antibiotic used prior to intervention
- o Volume of antibiotic used after intervention
- o Percentage change in volume of antibiotic used

63. For studies reporting data in the form of total volume of antimicrobial prescribed, provide the following data for the INTERVENTION group; if data is missing, record “NR”
- o Exact units of measurement
- o Volume of antibiotic used prior to intervention
- o Volume of antibiotic used after intervention
- o Percentage change in volume of antibiotic used

64. For studies reporting data in the form of percentage of visits resulting in an antimicrobial prescription, provide the following data for the CONTROL group; if data is missing, record “NR”
- o Percentage of visits resulting in an antimicrobial prescription prior to intervention
- o Percentage of visits resulting in an antimicrobial prescription after intervention
- o Absolute change in percentage (after – prior)

65. For studies reporting data in the form of percentage of visits resulting in an antimicrobial prescription, provide the following data for the INTERVENTION group; if data is missing, record “NR”
- o Percentage of visits resulting in an antimicrobial prescription prior to intervention
- o Percentage of visits resulting in an antimicrobial prescription after intervention
- o Absolute change in percentage (after – prior)

66. For studies reporting data in the form of adherence to a guideline for antimicrobial prescribing, provide the following data for the CONTROL group; if data is missing, record “NR”
- o Percent adherence prior to intervention
- o Percent adherence after intervention
- o Absolute change in percentage (after – prior)

67. For studies reporting data in the form of adherence to a guideline for antimicrobial prescribing, provide the following data for the INTERVENTION group; if data is missing, record “NR”
- o Percent adherence prior to intervention
- o Percent adherence after intervention
- o Absolute change in percentage (after – prior)

68. Provide the following data for other types of measurements of antibiotic use not abstracted above:
- o Type of measurement and units of measurement
- o Value in CONTROL group before intervention
- o Value in CONTROL group after intervention
- o Value in INTERVENTION group before intervention
- o Value in INTERVENTION group after intervention

Measures of antimicrobial resistance

69. For studies reporting measures of antimicrobial resistance, what specific outcomes were measured? (check all that apply)
- o Percentage of isolates of an organism resistant to an antimicrobial or class of antimicrobials
- o Percentage of patients infected with a resistant organism
- o Rate of treatment failure for a specific antimicrobial used to treat a specific condition
- o Other (describe)
- o No measurement of antimicrobial resistance (skip to question 79)

70. For studies reporting the percentage of isolates resistant to an antimicrobial, record the following data; if data is missing, record “NR”
- Type(s) of organism
- Active infection or colonizer
- Antimicrobial (or class of antimicrobial) for which resistance was assessed

71. For studies reporting the percentage of isolates resistant to an antimicrobial, record the following data for the CONTROL group; if data is missing, record “NR”
- Number of isolates before intervention
- Percentage of isolates resistant to antimicrobial BEFORE intervention
- Number of isolates after intervention
- Percentage of isolates resistant to antimicrobial AFTER intervention
- Change in percentage of resistant isolates (after – before)

72. For studies reporting the percentage of isolates resistant to an antimicrobial, record the following data for the INTERVENTION group; if data is missing, record “NR”
- Number of isolates before intervention
- Percentage of isolates resistant to antimicrobial BEFORE intervention
- Number of isolates after intervention
- Percentage of isolates resistant to antimicrobial AFTER intervention
- Change in percentage of resistant isolates (after – before)

73. For studies reporting the percentage of patients infected with a resistant organism, record the following data for the CONTROL group; if data is missing, record “NR”
- Number of patients evaluated before intervention
- Percentage of patients with resistant organism BEFORE intervention
- Number of patients evaluated after intervention
- Percentage of patients with resistant organism AFTER intervention
- Change in percentage of resistant isolates (after – before)

74. For studies reporting the percentage patients infected with a resistant organism, record the following data for the INTERVENTION group; if data is missing, record “NR”
- Number of patients evaluated before intervention
- Percentage of patients with resistant organism BEFORE intervention
- Number of patients evaluated after inervention
- Percentage of patients with resistant organism AFTER intervention
- Change in percentage of resistant isolates (after – before)

75. For studies reporting the rate of treatment failure for a specific antimicrobial used to treat a specific condition, record the following data:
- Type of condition
- Antimicrobial or class of antimicrobial

76. For studies reporting the rate of treatment failure for a specific antimicrobial used to treat a specific condition, record the following data for the CONTROL group;
- Number of treated patients before intervention
- Rate of treatment failure (as a percentage) before intervention
- Number of patients after intervention
- Rate of treatment failure (as a percentage) after intervention
- Change in rate of treatment failure (after – before)

77. For studies reporting the rate of treatment failure for a specific antimicrobial used to treat a specific condition, record the following data for the INTERVENTION group;
- Number of treated patients before intervention
- Rate of treatment failure (as a percentage) before intervention
- Number of treated patients after intervention
- Rate of treatment failure (as a percentage) after intervention
- Change in rate of treatment failure (after – before)

78. Provide the following data for other types of measurements of antimicrobial resistance not abstracted above:
- Type of measurement and units of measurement
- Value in CONTROL group before intervention

- o Value in CONTROL group after intervention
- o Value in INTERVENTION group before intervention
- o Value in INTERVENTION group after intervention

Measures of disease outcomes
Note: measures of disease outcomes should be abstracted only if the study also has usable data for one of the primary outcomes (antimicrobial usage or antimicrobial resistance).

79. For studies reporting clinical disease outcomes, what specific outcomes were measured?
- o Subjective measure of disease severity (e.g.,time to symptom resolution)
- o Objective measure of disease severity (e.g.,symptom score)
- o Other (describe)
- o No measurement of disease outcomes (skip to question 82)

80. For studies reporting disease outcomes as subjective measures of disease severity, record the following data:
- o Definition of clinical outcome as supplied in article, including unit of measurement
- o Value for CONTROL group
- o Value for INTERVENTION group

81. For studies reporting disease outcomes as objective measures of disease severity, record the following data:
- o Definition of clinical outcome as supplied in article
- o Value for CONTROL group
- o Value for INTERVENTION group

Measures of health services utilization
Note: measurements of health services utilization should be abstracted only if the study also has usable data for one of the primary outcomes (antimicrobial usage or antimicrobial resistance).

82. For studies reporting on health services utilization, what specific outcomes were measured?
- o Percentage of patients requiring an initial visit with a health care provider
- o Percentage of patients requiring a follow-up visit with a health care provider (may include return visit to clinic or emergency department, or hospitalization)
- o Other (describe)
- o No measurement of health services utilization (skip to question 86)

83. For studies reporting the percentage of patients requiring an INITIAL visit with a health care provider, record the following data:
- o Percentage in CONTROL group
- o Percentage in INTERVENTION group
- o Absolute difference (intervention – control)

84. For studies reporting the percentage of patients requiring a FOLLOW-UP visit with a health care provider, record the following data:
- o Type of health care setting(s) at follow-up visit
- o Percentage in CONTROL group
- o Percentage in INTERVENTION group
- o Absolute difference (intervention – control)

85. For studies measuring health services utilization not captured above, record the measurement and results:

Measures of adverse events
Note: adverse events should be abstracted only if the study also has usable data for one of the primary outcomes (antimicrobial usage or antimicrobial resistance).

86. For studies reporting measures of adverse events related to antimicrobial use, how were the adverse events assessed?
- o Rate of adverse drug events (i.e., *clostridium dificile* colitis, rash or other allergic reaction)
- o Incidence of severe infections possibly due to undertreatment (e.g.,bacteremia)
- o Other (describe)
- o No measurement of adverse events (skip to question 90)

87. For studies reporting the rate of adverse drug events, record the following data:
    - o Specific type of ADE measured
    - o Rate in CONTROL group
    - o Rate in INTERVENTION group
    - o Absolute difference (intervention – control)

88. For studies reporting the rate of severe infections possibly due to undertreatment, record the following data:
    - o Specific type of infection measured
    - o Rate in CONTROL group
    - o Rate in INTERVENTION group
    - o Absolute difference (intervention – control)

89. For studies reporting measurement of adverse events not captured above, record the measurement and results:

Measures of costs

Note: cost outcomes should be abstracted only if the study also has usable data for one of the primary outcomes (antimicrobial usage or antimicrobial resistance).

90. For studies reporting cost outcomes, what specific measures were used?
    - o Total cost of antimicrobials to a practice, hospital, or health system
    - o Cost of health services utilization
    - o Other (describe)
    - o No measurement of costs (skip to question 94)

91. For studies reporting the total cost of antimicrobials, record the following data:
    - o Exact units of measurement
    - o Total costs in CONTROL group before intervention
    - o Total costs in CONTROL group after intervention
    - o Total costs in INTERVENTION group before intervention
    - o Total costs in INTERVENTION group after intervention
    - o Cost difference before intervention (intervention – control)
    - o Cost difference after intervention (intervention – control)
    - o Net change in costs attributable to intervention (cost difference after – cost difference before)

92. For studies reporting the total cost of health services utilization, record the following data:
    - o Exact units of measurement
    - o Total costs in CONTROL group before intervention
    - o Total costs in CONTROL group after intervention
    - o Total costs in INTERVENTION group before intervention
    - o Total costs in INTERVENTION group after intervention
    - o Cost difference before intervention (intervention – control)
    - o Cost difference after intervention (intervention – control)
    - o Net change in costs attributable to intervention (cost difference after – cost difference before)

93. For studies reporting cost measurements not abstracted above, record the units of measurement and results:

Patient or provider satisfaction with care

Note: patient/provider satisfaction should be abstracted only if the study also has usable data for one of the primary outcomes (antimicrobial usage or antimicrobial resistance).

94. For studies reporting data on PATIENT satisfaction with care, provide the following data; if data is missing, record “NR”
    - o No measurement of patient satisfaction
    - o Percent satisfaction in CONTROL group after intervention
    - o Percent satisfaction in INTERVENTION group after intervention
    - o Absolute difference (intervention – control)

95. For studies reporting data on PROVIDER satisfaction with care, provide the following data; if data is missing, record “NR”

- No measure of provider satisfaction
- Percent satisfaction in CONTROL group after intervention
- Percent satisfaction in INTERVENTION group after intervention
- Absolute difference (intervention – control)

96. Use textbox to state any important results or study concerns not captured above.

Appendix E. Random Effects Meta-Analysis of Included Trials

A. Methods

For our initial analytic approach, we identified studies that supplied information on the post-intervention rate of antibiotic use in both intervention and control groups. The primary outcomes were the same as used in the main report (for treatment articles, the percentage of visits at which an antibiotic was prescribed; for selection articles, the percentage of patients receiving a recommended antibiotic or the percentage compliance with a clinical guideline for antibiotic prescribing). We used the pooled risk difference as the summary statistic; the risk difference for each individual study was equal to ($intervention_{post}$ - $control_{post}$). Thus, for the treatment articles, the risk difference indicates the reduction in antibiotic prescribing in the intervention group compared to control. In the selection articles, the risk difference indicates the improvement in prescribing of a recommended antibiotic in the intervention group compared to control. We performed meta-analysis using the random effects model of DerSimonian and Laird on these data. In order to be suitable for meta-analysis, included studies were required to report the number of patients in each group (intervention and control). Analyses were performed using Stata version 8.2 (Stata Corp. College Station, TX).

B. Results

Antibiotic treatment decision studies. Twenty-one articles reporting a total of 26 comparisons met the inclusion criteria. The pooled risk difference across all studies was -13.8% (95% CI -17.7% to -9.9%,) indicating a significant reduction in antibiotic prescribing, as illustrated in the Figure below. However, significant heterogeneity was present, with the chi-squared test of heterogeneity significant at $p < 0.001$. The I^2 value, which indicates the percentage of the variance in the risk difference attributable to heterogeneity, was 96.2%.

We performed stratified analyses to investigate potential sources of heterogeneity. Having identified delayed prescribing studies as a unique subset of interventions, we repeated the analyses without these studies. The results continued to show a statistically significant reduction in prescribing (pooled RD -9.6%, 95% CI -12.6% to -6.9%,) but the tests of heterogeneity remained significant ($p<0.001$ for chi-squared test, I^2 92.9%). We found consistent evidence for high levels of heterogeneity when analyses were further restricted to randomized controlled trials ($p<0.001$, I^2 86.4%), interventions targeting ARIs only ($p<0.001$, I^2 93.8%), or studies with baseline prescribing rates above the median ($p<0.001$, I^2 92.3%) or below the median ($p<0.001$, I^2 97.1%). Heterogeneity was present for studies using each specific QI strategy as well, with $p<0.001$ for all individual QI strategies and combinations of strategies.

Heterogeneity may always be present in a meta-analysis, and finding heterogeneity generally warrants a search for potential sources of heterogeneity via stratified analyses. However, we recognize that pooling studies of quality improvement strategies of necessity involves combining studies across a broad range of target populations, target conditions, baseline care practices, and interventions. Although we selected articles reporting a common outcome, the outcome itself may have been measured in different ways (e.g., direct measurement of prescribing by chart review, versus measurement of actual antibiotic use by patient interview or pharmacy records).

Antibiotic selection decision studies. For the selection decision studies, an additional potential complication was induced by combining articles with an explicit clinical guideline for prescribing and those with recommendations but no defined guideline. Thus, we did not feel that stratified analyses alone could identify any factors responsible for heterogeneity, and this was borne out by the results in stratified analyses of the treatment studies.

Based on these results, we did not feel that performing random-effects meta-analysis would be appropriate for either the treatment studies or the selection studies, and opted to use the median effects approach as described in the Methods section.

Figure. Forest plot showing risk differences for treatment studies by random effects meta-analysis.

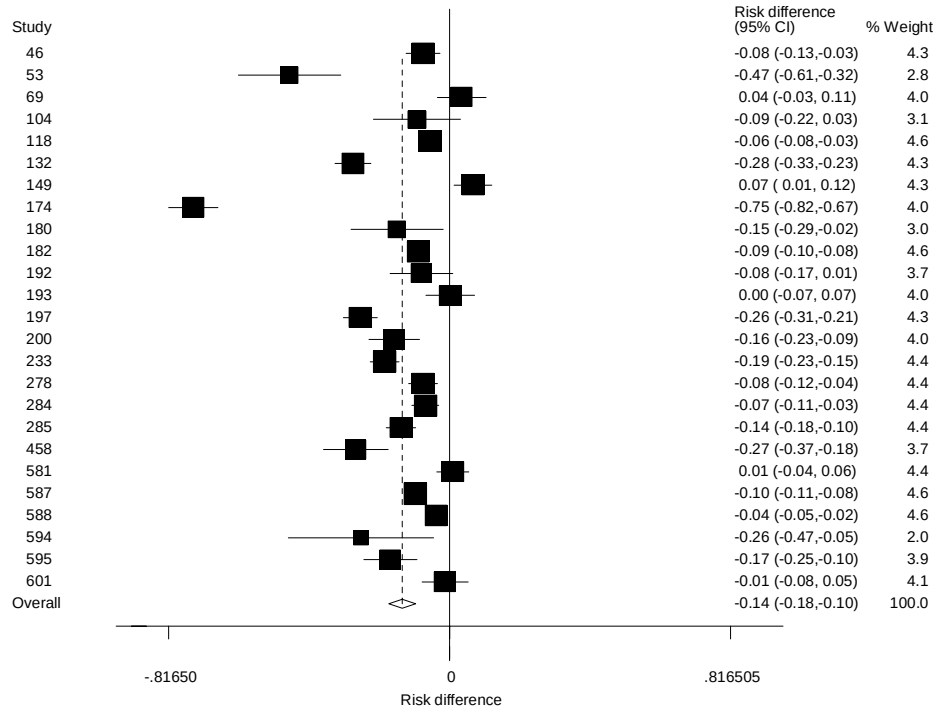

Figure Legend

Forest plot for the risk difference for antibiotic prescribing in intervention groups post-intervention as compared with comparison groups post-intervention. Negative numbers indicate reductions in antibiotic use.

Appendix F. Technical Expert Panel and Peer Reviewers

Technical Expert Panel

Jeremy Grimshaw, MBChB, PhD, University of Ottawa, Cochrane Collaboration Effective Practice and Organisation of Care Group (EPOC)
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