



Antimicrobial Stewardship Programs in Outpatient Settings: A Systematic Review

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PREFACE

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

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

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

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

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

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EVIDENCE REPORT

INTRODUCTION

Several factors are contributing to the current antimicrobial crisis which has been labeled “an unfolding catastrophe.”¹ The greatest challenges are overuse of existing antimicrobials, increasing resistance to existing agents, the absence of new products, and changes in the types of organisms affected by new agents.

The majority of antimicrobials are prescribed to humans in outpatient settings. Three studies used combined data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Survey. Of these, 2 recent studies found that over 80% of adult outpatients with rhinosinusitis were prescribed antimicrobials.^{2,3} The third study reported that although adult primary care visits for sore throat decreased significantly between 1997 and 2010, antimicrobials were prescribed at 60% of the visits and the overall prescribing rate did not change.⁴ This is despite estimates that approximately 10% of patients with sore throat have group A *Streptococcus* infection, the only cause of pharyngitis benefitted by antimicrobials.

Several reasons for high prescribing rates for unneeded antimicrobials in outpatient settings have been suggested. In making prescribing decisions, primary care providers are faced with patient expectations, and with patient and provider lack of awareness of antimicrobial resistance and lack of understanding of the seriousness of the antimicrobial resistance problem.⁵

While increasing antimicrobial resistance is often thought of as a population-based problem, individual antimicrobial resistance has also been shown to be associated with prior exposure to antimicrobials. A recent systematic review focused on the effects of antimicrobial use on the emergence of resistance for individual patients.⁵ Twenty-four studies (5 RCTs and 19 observational studies) were eligible for the review. For urinary isolates, exposure to antimicrobials was associated with increased odds of resistance compared to no exposure. At 3 months, based on pooled data from 3 studies (4 comparisons) the odds ratio was 2.48 (95% CI 2.06, 2.98) with $I^2=0\%$. In 3 studies (5 comparisons) with data at 12 months, there was greater heterogeneity ($I^2=72\%$) but the odds of resistance associated with exposure to antimicrobials were still significant (OR 1.33 [95% CI 1.15, 1.53]). For respiratory isolates, the odds of resistance associated with exposure were significantly higher at 1 month (1 study; OR 2.10 [95% CI 1.04, 4.23]), 2 months (2 studies; OR 2.37 [95% CI 1.42, 3.95], $I^2=2\%$) and 12 months (3 studies; 6 comparisons, OR 2.7 [95% CI 1.25, 4.50], $I^2=57.3\%$) but not at 3 months (2 studies, 4 comparisons) or 6 months (1 study, 2 comparisons).

ANTIMICROBIAL STEWARDSHIP PROGRAMS

An antimicrobial stewardship program (ASP) is a focused effort by a healthcare organization or a portion of an organization (*ie*, a primary care clinic) to optimize antimicrobial use for the purposes of improving patient outcomes, reducing adverse consequences, and delivering cost-effective therapy.⁶⁻⁹ The emphasis is on appropriate selection, dosing, and duration of antimicrobial therapy.^{7,9}

In hospital settings, strategies for improving antimicrobial stewardship typically involve prospective audit and feedback, formulary restriction, pre-authorization of prescriptions, guidelines for prescribing and/or modifying therapy, and education.^{7,10} A comprehensive ASP may include some or all of the following:^{7,10,11}

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

Due to the nature of the patient encounter, ASPs in outpatient settings may emphasize additional elements (*eg*, patient education, communication skills training for providers, delayed prescribing, rapid testing). In many outpatient prescribing situations, the prescribing decision will be made without input from a team of specialists, the provider may not have an opportunity to modify the initial prescription, and provider may not receive feedback on the patient's progress.

PURPOSE AND SCOPE OF REVIEW

The purpose of this review is to synthesize the evidence about the effectiveness of ASPs implemented in outpatient settings. The topic was nominated by Matthew Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, on behalf of the VA Antimicrobial Stewardship Task Force, and the review is intended to provide a summary of the evidence on outpatient ASPs to guide clinical practice and policy within the Veterans Healthcare System. This review is a companion to a recently completed review on ASPs in inpatient settings.¹²

We focus on outpatient settings with patients of all ages and limit our review to randomized controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs), and interrupted time series (ITS) analyses with data for at least 3 time points before and after the intervention. Our main outcomes of interest for this review were antimicrobial prescribing outcomes (*ie*, the percentage of patient receiving antimicrobials after an initial consultation for a possible infectious condition in an outpatient setting and the selection of an appropriate antimicrobial). We also report patient-centered outcomes, microbial outcomes, costs, harms of stewardship programs, key intervention components, and barriers to implementation, sustainability, and scalability. We summarize the findings from a prior Agency for Healthcare Research and Quality (AHRQ) Technical Review that included studies published through 2004¹³ and focus on studies published since the time of that review or not included in the review.

METHODS

TOPIC DEVELOPMENT

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

The final key questions are:

Key Question 1. What is the effectiveness of antimicrobial stewardship programs in outpatient settings on the following:

a. Primary Outcome: Antimicrobial prescribing (decision to prescribe, selection of antimicrobial, duration of treatment, guideline concordant use)

b. Secondary Outcomes: 1) Patient centered outcomes (return clinic visit, hospital admission, adverse events, late antimicrobial prescription, patient satisfaction with care); 2) Microbial outcomes (resistance in study population); 3) Costs (program costs, drug costs)?

Key Question 2. What are the key intervention components associated with effective outpatient antimicrobial stewardship (*eg*, type of intervention; personnel mix; level of support)?

Key Question 3. Does effectiveness vary by a) clinic type or setting (primary care clinic vs emergency department or urgent care; VA, non-VA) or b) suspected patient condition (respiratory tract infections, urinary tract infections, soft-tissue infections)?

Key Question 4. What are the harms of antimicrobial stewardship programs in outpatient settings?

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

SEARCH STRATEGY

The literature search for this review was conducted concurrently with the literature search for our review of inpatient ASPs.¹² An exploratory search identified 2 relevant Cochrane reviews that partially addressed the key questions but were no longer current.^{14,15} We used a search strategy similar to that of the Cochrane reviews to search MEDLINE (Ovid) from 2000 through November 2013. We limited the search to studies in English language, and enrolling human subjects. Our search included terms for antimicrobial agents (*eg*, anti-bacterial agents, anti-infective agents), infection types, and program implementation (*eg*, guideline implementation, practice patterns). The full search strategy is presented in Appendix A. Additional citations were identified from systematic reviews, reference lists of retrieved articles, and suggestions made by our technical expert panel members and peer reviewers.

STUDY SELECTION

Titles, abstracts, and articles were reviewed by investigators and research associates trained in the critical analysis of literature. During title and abstract review, we identified studies conducted

in both inpatient and outpatient settings. We excluded studies for the following reasons and identified for full text review any articles that either did not fall into one of these categories or for which there was uncertainty about eligibility:

1. Study not published in English language;
2. Study done in nursing home (long-term care) setting;
3. Study not about antimicrobial stewardship;
4. Study of antimicrobials for medical or surgical prophylaxis;
5. Study of patients with viral or fungal infection or tuberculosis;
6. Study not involving an intervention or not involving an intervention of interest; patient education programs were included; community/public health campaigns were excluded;
7. Description of an intervention with no assessment of the effect of the intervention;
8. Study design OTHER THAN randomized, controlled trial (RCT), cluster randomized controlled trial (CRCT), controlled clinical trial (CCT), controlled before/after study (CBA), or interrupted time series (ITS) with at least 3 time points before and after implementation of the intervention; and
9. No outcomes of interest; outcomes of interest are a) antimicrobial prescribing (*eg*, decision to prescribe, selection of antimicrobial, duration of treatment, guideline concordant use), b) patient-centered outcomes (*eg*, return clinic visits, hospital admission, adverse events, late antimicrobial prescriptions, patient satisfaction with care), c) microbial outcomes (resistance in study population), d) cost (program costs, drug costs), and e) other (process, sustainability, scalability etc.).

We reviewed full text versions of potentially eligible articles and excluded studies that met any of the criteria outlined in items 1 to 9 above. We also added the following exclusion criterion: study done in setting not relevant to medicine in the United States or involving a population or infectious disease not relevant to United States population.

To avoid overlap with the existing AHRQ review, we excluded any studies cited in the full Technical Review¹³ or the related publications.^{16,17}

DATA ABSTRACTION

We categorized ASP interventions based on the primary emphasis of the intervention as described by the study author: provider and/or patient education, provider feedback, guidelines, delayed prescribing, communications skills training, restriction, decision support, financial incentives, and laboratory testing.

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

1. Study characteristics – study design, geographic region, intervention(s), comparator(s), intervention staff (to develop and implement the intervention), resources (*ie*, hardware or software used or purchased, staff hired), site,

- patient characteristics (number, age), exclusion criteria, recruitment, and randomization unit (for RCTs and CRCTs);
2. Antimicrobial prescribing outcomes – percent prescribed antimicrobial, selection, duration, guideline concordant use;
 3. Patient outcomes – return clinic visits, hospitalizations, adverse events, late antimicrobial prescriptions, patient satisfaction with care;
 4. Microbial outcomes – resistance in the study population;
 5. Costs – dispensing costs, program costs;
 6. Harms of stewardship program implementation; and
 7. Other – barriers to implementation, sustainability and scalability of intervention.

From each study, we extracted all data fitting the descriptions of the outcomes in the list above including multiple outcomes, if provided. For ITS studies, we report, where provided by study authors, level and trend (or slope) results. Level refers to the change in the value of the outcome measure from pre- to post-intervention. Trend refers to the change between the slope of the line through data points before the intervention and the line through data points after the intervention.

QUALITY ASSESSMENT

We assessed the risk of bias of individual studies using the criteria developed for use in Cochrane Effective Practice and Organization of Care (EPOC) reviews (Appendix B). There are 9 criteria for assessing risk of bias for studies with a separate control group (*ie*, RCTs, CCTs, and CBA studies) and 7 criteria for assessing risk of bias for ITS studies. Each element is scored as high, unclear, or low risk. A study was rated as low risk of bias if each of the individual criteria were scored as low risk, medium risk of bias if one or 2 criteria were scored as unclear or high risk, and high risk of bias if more than 2 criteria were scored as unclear or high risk.

Quality of systematic reviews was determined using the measurement tool for assessment of multiple systematic reviews (AMSTAR).¹⁸

DATA SYNTHESIS

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

RATING THE BODY OF EVIDENCE

We rated overall strength of evidence for our patient outcomes for each intervention category using methods developed by AHRQ and the Effective Health Care Program.¹⁹ The strength of

the evidence was evaluated based on 4 domains: 1) risk of bias (whether the studies for a given outcome or comparison have good internal validity); 2) consistency (the degree of similarity in the effect sizes, ie, same direction of effect, of the included studies); 3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and 4) precision (degree of certainty surrounding an effect estimate of a given outcome).

PEER REVIEW

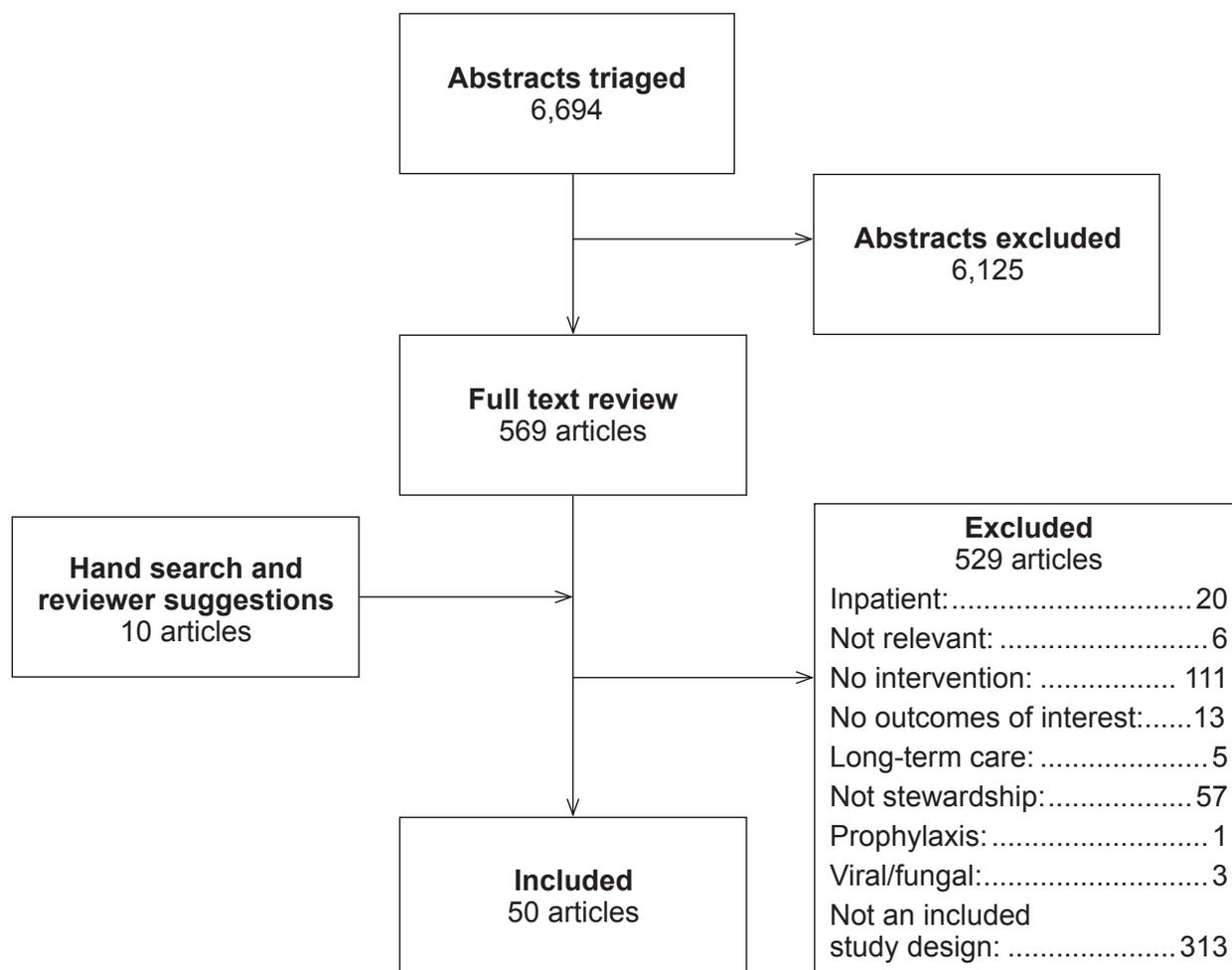
A draft version of this report was reviewed by technical experts as well as clinical leadership. Reviewer comments (Appendix C) were addressed and our responses incorporated in the final report.

RESULTS

LITERATURE FLOW

We reviewed 6,694 titles and abstracts from the electronic literature search. After applying inclusion/exclusion criteria at the abstract level, 6,125 references were excluded. We retrieved 569 full-text articles for further review and another 529 references were excluded. An additional 10 references were identified from reference lists of recent relevant systematic reviews or were suggested by peer reviewers for a total of 50 included articles reporting 50 trials (1 article reported 2 trials, 1 trial was reported in 2 articles). We grouped the studies by key question, type of intervention, hospital site, and clinical condition. Figure 1 details the exclusion process. We also summarized the results from 2 recent systematic reviews.

Figure 1. Literature Flow Diagram



KEY QUESTION 1

What is the effectiveness of antimicrobial stewardship programs in outpatient settings on the following:

- a. Primary Outcome: Antimicrobial prescribing (decision to prescribe, selection of antimicrobial, duration of treatment, guideline concordant use)
- b. Secondary Outcomes:
 - 1) Patient centered outcomes (return clinic visits, hospital admission, adverse events, late antimicrobial prescription, patient satisfaction with care);
 - 2) Microbial outcomes (resistance in study population);
 - 3) Costs (program costs, drug costs)?

Existing Systematic Review

A 2006 AHRQ Technical Review¹³ focused on quality improvement strategies to reduce inappropriate prescribing of antimicrobials in the outpatient setting (primary care clinics or urgent care/walk-in clinics). The review included randomized and quasi-randomized controlled trials, controlled before-after studies, and interrupted time series with at least 3 measurements before and after a clearly defined intervention. Included studies were required to report at least one measure of antimicrobial use. The literature search identified studies published through November 2004.

Interventions were categorized as strategies to influence a) the prescribing of antimicrobials for non-bacterial illnesses (*ie*, the decision to prescribe) or b) the prescribing of broad-spectrum antimicrobials when narrow-spectrum antimicrobials would be appropriate (*ie*, the selection decision). The quality improvement initiatives studied included clinician education, patient education, provision of delayed prescriptions, audit and feedback, clinician reminders, and financial or regulatory incentives. If a study involved more than one intervention arm compared with a control condition, the authors considered each comparison as a separate trial. Overall, the review included 54 articles with 74 comparisons. There were 28 articles (35 comparisons) addressing the decision to prescribe, 20 articles (27 comparisons) addressing the selection decision, and 6 studies (12 comparisons) addressing both the decision and the selection. A publication based on the review and focused on interventions to reduce unnecessary antimicrobial prescribing included an updated review of the literature (to March 2007).¹⁶ With the updated search, there were 43 articles (55 trials) addressing the decision to prescribe.

For studies of interventions focused on the decision to prescribe, the primary outcome of interest was the percentage of patients prescribed an antimicrobial. For studies of interventions focused on selection, the primary outcome of interest was the percentage of patients prescribed a recommended antimicrobial or guideline-concordant therapy. Secondary outcomes for the review included effects on antimicrobial resistance, safety (disease outcomes and adverse events), return visits or illness-related hospitalizations, prescribing costs, and patient satisfaction.

The authors calculated median effect sizes for studies that reported both pre- and post-intervention prescribing rates. In the treatment decision studies, a negative effect size indicated a reduction in prescribing in the intervention group following the intervention. In the treatment selection studies, a positive effect size indicated an increase in the prescription of recommended antimicrobials in the intervention group. The median effect was the median of the effect sizes from individual studies with common features.

Interventions to Improve the Treatment Decision

Of the 43 studies about improving the treatment decision, 19 were conducted in the United States or Canada and 13 in Europe or the United Kingdom. Fifteen targeted antimicrobial use in children, 5 targeted antimicrobial use in adults, and 22 targeted antimicrobial use in patients of all ages. Most of the studies (34) included patients with acute respiratory infections; 2 focused on acute diarrhea and 7 did not specify an infection site. The review included 22 RCTs, 3 quasi-RCTs, and 18 CBAs. The overall quality of the studies was rated as fair.

Antimicrobial Prescribing

Thirty trials (in 20 studies) were included in the median effect size analysis for prescribing. Effect sizes were calculated by subtracting the change in prescribing rate from pre- to post-intervention in the comparator group from the change from pre- to post-intervention in the intervention group. Interventions included clinician education, patient education, clinician and patient education, clinician and patient education combined with audit and feedback, and other strategies. The median absolute reduction in the proportion of visits at which an antimicrobial was prescribed was -9.7% (IQR -6.6 to -13.7%) over 6 months median follow-up.¹⁶ The ranges of effect sizes for specific interventions are presented in Table 1.

Table 1. Effect Sizes for Trials of Quality Improvement Strategies to Improve the Treatment Decision (Ranji 2008)¹⁶

Quality Improvement Strategy	Reduction in Prescribing Antimicrobials*	Significance
Clinician Education Alone (10 trials)	-6.5 to -28.6% (median -8.9%)	p=0.85 for comparison across quality improvement strategies
Clinician Education and Patient Education (5 trials)	-1.5 to -28.5% (median -12.0%)	
Clinician Education, Patient Education, and Audit and Feedback (3 trials)	-7.9 to -24% (median -12.0%)	
Patient Education Alone (6 trials)	-0.2 to -17.0% (median -7.5%)	
Other Strategies (alone or in combination) (6 trials) [†]	-2.0 to -15.0% (median -7.3%)	

*Negative effect sizes indicate a reduction in prescribing in the intervention group following the intervention; (Post-intervention - Pre-intervention)_{intervention group} - (Post-intervention - Pre-intervention)_{control group}

[†]Included audit and feedback, decision support, mass media campaign, financial disincentives

Effect sizes could not be determined for 18 trials from 16 studies. Included were 7 trials of community-based interventions (*ie*, mass media campaigns or audit and feedback with educational materials for clinicians and/or patients), 2 trials of non-community based interventions for clinicians and patients (audit and feedback and/or educational materials), 7 trials of non-community based interventions for clinicians (education, guideline distribution, reminders, audit and feedback, decision support), and 2 trials of non-community based interventions for patients (financial incentives and educational materials). Absolute reductions in post-intervention antimicrobial prescribing were reported for 4 trials (three studies) with values ranging from 0.2% to 10.5% (median 8.4%). Relative reductions in prescriptions were reported in 14 trials (13 studies). Values ranged from 0.3% to 55.0% (median 12.0%) with 9 of 14 trials reporting a reduction of more than 10%.

There were 7 RCTs of delayed prescription. Four enrolled children with otitis media, 2 enrolled adults with either acute cough or acute bronchitis, and one enrolled patients of any age with a “common cold.” Six studies reported the absolute reduction in antimicrobial prescriptions filled; values ranged from 15% to 75% (median 35.5%). In those studies, the median rate of antimicrobial use in the intervention groups was 37.5% compared with 75.0% in the control groups. One study reported a 20% relative reduction in prescriptions filled.

Other Outcomes

Few studies reported patient outcomes. In 9 studies (11 trials) reporting, no increases in return office visits or telephone consultations were observed. In 6 studies (7 trials) reporting, all but one trial found no difference between intervention and control groups in time to symptom resolution as documented in patient interviews or diaries. One study reported significantly less diarrhea in patients not receiving antimicrobials. Seven trials measured patient satisfaction with no differences observed in 6 trials; one trial reported fewer patients in the delayed prescribing group were “very satisfied.”

The review included 3 studies that reported antimicrobial resistance. The interventions included clinician and patient education. Prescribing was reduced in all 3 studies but only one study reported a reduction in the incidence of colonization with penicillin-resistant *S. pneumoniae* over 6 months follow-up among children in the intervention group compared to those in the control group.

In 2 studies that reported costs, prescribing costs were decreased in the intervention groups (relative reductions of 18% and 31%). In both studies, there was increased use of narrow-spectrum antimicrobials which the review authors reported were likely less expensive. No program costs were reported.

Interventions to Improve the Antimicrobial Selection Decision

Of the 26 studies (33 trials) that evaluated interventions to improve antimicrobial selection, 11 were conducted in Europe or the United Kingdom, 5 in the United States, 3 in Canada, and 4 in Australia.^{13,17} Most studies (16) did not specify the patient population; 3 enrolled children only and 7 enrolled adults only. Diseases studied included respiratory conditions and tonsillitis (13 studies), urinary tract infections (7 studies), and sexually transmitted diseases (1 study). The remaining 5 studies did not specify a disease focus. The interventions were intended to reduce the use of broad-spectrum or costly antimicrobials or improve the selection of recommended antimicrobials over others. There were 12 RCTs, 13 CBAs, and 1 ITS study. Overall study quality was fair.

Antimicrobial Prescription Selection

Twenty-two of the comparisons (trials) reported changes in absolute volume of recommended antimicrobials and were included in the median effect size analysis. Effect sizes were calculated by subtracting the pre-intervention difference between intervention and control groups from the post-intervention difference between groups. Interventions included clinician education alone, clinician education with audit and feedback, clinician education and patient education, and audit and feedback alone. The overall median effect – an increase in recommended antimicrobial

prescribing attributable to the intervention – was 10.6% (IQR 3.4 to 18.2%). The median follow-up for all studies of antimicrobial selection included in the review was 4 months. The median effect sizes for specific interventions are presented in Table 2.

Table 2. Effect Sizes for Trials of Quality Improvement Strategies to Improve the Antimicrobial Selection Decision (Ranji 2006, Steinman 2006)^{13,17}

Quality Improvement Strategy	Median Effect with Quality Improvement Strategy*	Significance
Clinician Education Alone (11 trials)	13.9% (8.6% to 21.6%)	p=0.182 for comparison across quality improvement strategies
Clinician Education with Audit and Feedback (8 trials)	3.4% (1.8% to 9.7%)	
Clinician Education with Patient Education (2 trials)	22.8% (2.4% to 43.1%)	p=0.028 for comparison of clinician education alone with clinician education and audit and feedback
Audit and Feedback Alone (1 trial)	13.9%	

*Positive effect sizes indicate an increase in the prescription of recommended antimicrobials in the intervention group

Antimicrobial Prescription Duration

Four studies evaluated duration of antimicrobial prescribing. All were studies of clinician education alone or clinician education with audit and feedback. Results were mixed. One study reported a 13% increase in the percentage of short-course antimicrobial regimens, 2 reported decreases in antimicrobial duration (1.89 days and 0.55 days) compared to the control group, and one reported an increase in duration (0.06 days).

Effect sizes could not be determined for 11 trials (6 studies). There were 7 trials (3 studies; 2 RCTs, 1 CBA) of clinician education alone (printed materials or educational outreach by pharmaceutical representatives, pharmacists educators, or physician counselors), 3 trials (2 studies; 1 RCT, 1 CBA) of clinician education with audit and feedback, and 1 trial (1 study; ITS) of a strategy limiting reimbursement for quinolone prescription. In the 3 studies of clinician education alone, one study reported a 31.7% reduction in cephalexin use (the non-recommended antimicrobial), the second study reported a 1.4% increase in the adjusted market share for amoxicillin (the recommended antimicrobial), and the third study reported 1.8% (pharmacist educator outreach) and 17.4% (physician counselor outreach) relative decreases in the number of prescriptions for non-recommended antimicrobials. Decreases in numbers of prescriptions were also reported for contraindicated antimicrobials (26.6% relative decrease with a pharmacist educator and 44.5% relative decrease with a physician counselor). In one study of clinician education with audit and feedback, increases in recommended generic amoxicillin (12%) and trimethoprim (5%) use were reported following introduction of group outreach by a pharmacy advisor with feedback but no change was observed when the education component was a workbook. The second study observed a 13.1% increase in antimicrobial courses of the recommended duration. The study of limited reimbursement found a 16.0% reduction in non-recommended antimicrobial use.

Other Outcomes

No studies looked at patient outcomes, including adverse events or health services utilization, or the effect of interventions on antimicrobial resistance. Three studies reported cost data in usable form. Costs, either the median prescription cost for individual physicians or total costs for antimicrobials, decreased by approximately 20% to 30% in intervention groups compared to control groups.

Updated Evidence Newly Identified for this Evidence Report

Overview of Studies

We identified 50 unique trials that were not included in the original AHRQ review¹³ or the updated review on the decision to prescribe.¹⁶ Study characteristics are presented in Appendix D, Tables 1 and 2. Twenty trials were conducted in the United States or Canada; 2 included data from VA Health Care Systems.^{30,62} There were 16 trials (5 RCTs, 6 CRCTs, 1 CCT, 4 CBAs) with provider and/or patient education as the primary intervention.²⁰⁻³⁶ Twelve of these trials involved multifaceted interventions. One of the trials included 3 arms and is also included under studies of laboratory testing interventions.^{23,24} There were 5 trials (1 RCT, 2 CRCTs, 1 CCT, 1 CBA) of feedback to providers (four with education components)^{21,27-40} and 6 studies (1 CRCT, 1 CCT, and 4 ITS) of guidelines (four with provider and/or patient information).⁴¹⁻⁴⁶ Six trials (all CRCTs) focused on communication skills training for providers;⁴⁹⁻⁵⁶ 2 also included decision support, 2 were 3-arm studies with laboratory testing and are also reported in the section on laboratory testing, and one included patient education components. Two trials (both RCTs) evaluated delayed prescribing (asking patients to fill the prescription only if symptoms persist or worsen).^{47,48} A study of provider and/or patient education and a study of laboratory testing also included delayed prescribing components. There were 6 studies (2 RCTs, 3 CRCTs, 1 CBA) of decision support each with supplemental components including clinician education, patient education, guidelines, and reminders.⁵⁹⁻⁶⁴ There were 2 studies (both ITS studies) of restriction policies^{57,58} and one (a CBA) of financial incentives for adherence to prescription guidelines.⁶⁵ Three trials, all RCTs, evaluated rapid testing⁶⁶⁻⁶⁸ and 6 (3 RCTs, 2 CRCTs, and 1 CBA, including the 3 studies mentioned previously) evaluated C-reactive protein (CRP) testing.^{23,24,52-54,49,69-71} Fourteen trials enrolled only adults, 5 enrolled only children or adolescents,^{20,25,28,34,55} and 31 either enrolled all ages or did not report patient age. Twenty-nine trials focused on patients with respiratory infection, one enrolled patients with dental pain,⁴⁵ 2 enrolled patients with urinary tract infection,^{42,47} one enrolled patients with sexually transmitted infection,⁴¹ and 17 either included more than one type of infection or did not specify.

Outcomes Reported

Prescribing Outcomes (Appendix D, Table 3)

Forty-seven trials reported rate of antimicrobial prescribing. Twenty trials reported selection, 2 reported duration, and 4 reported guideline concordant antimicrobial use.

Patient Outcomes (Appendix D, Table 4)

Fifteen studies reported return clinic visits, 10 reported hospitalizations, 11 reported adverse events, 6 reported late antimicrobial prescription, and 8 reported patient satisfaction with care.

Microbial Outcomes

No studies reported antimicrobial resistance outcomes.

Cost Outcomes (Appendix D, Table 5)

Seven studies reported antimicrobial costs and 3 reported program or intervention costs.

Provider and/or Patient Education (k=16 trials)

Key Findings

Prescribing Outcomes: Fifteen studies reported on antimicrobial use with 6 finding decreased use of antimicrobials following an education intervention and 6 finding no difference. Of the 3 remaining studies, one reported decreased use for lower respiratory tract infections but not acute rhinosinusitis, one reported decreased use for acute respiratory tract infections but not diarrhea, and significance could not be determined for one. Antimicrobial selection was reported in 8 studies with 3 reporting increased prescribing of targeted antimicrobials and 5 reporting no difference.

Patient Outcomes: Three studies reported patient outcomes. One of the 3 studies observed a higher number of return clinic visits per patient during the month after the initial visit in the group receiving the patient education leaflet. No differences in hospitalizations (2 studies), adverse events (1 study), or satisfaction with care (1 study) were observed.

Microbial Outcomes: No study reported microbial outcomes.

Prescribing Outcomes: Two studies reported drug costs with one finding a non-significant reduction in the intervention group and one finding reduced costs in a continuous intervention group compared to a seasonal intervention group but the significance was not reported.

Sixteen trials were eligible for inclusion. Six were conducted in North America,^{20,21,28,30,35,36} 4 in Europe,^{23,24,27,31,32} 2 in the United Kingdom,^{22,33} 3 in the Middle East,^{25,26,29} and one in the Asia/Pacific region.³⁴ There were 6 cluster randomized trials,^{20,25,26,28,30,31} 5 randomized controlled trials,^{22,29,32,33,34} one controlled clinical trial,³⁵ and 4 controlled before and after studies.^{21,24,25,27,36} Most of the cluster randomized trials and randomized controlled trials randomized providers or practices; the exceptions were one study that randomized geographic regions,²⁶ one that randomized metropolitan areas within geographic regions,³⁰ one that randomized communities,²⁸ and one that randomized patients.³³ Risk of bias was medium for 7 studies and high for 9 studies (Appendix D, Table 6).

In all but one study,³² the purpose was to reduce the use of antimicrobials. Eight studies also reported antimicrobial selection.^{21,25,27-29,31,32,36} One study assessed the effect of the intervention on duration of treatment;³² no studies reported on guideline concordance. There were 9 studies of respiratory infection, one with children only,²⁰ 2 with adults only,^{30,35} and 6 that enrolled patients of all ages or did not specify.^{21,23,24,27,31-33} One study enrolled children 5 years or younger with acute respiratory infection or diarrhea.³⁴ The remaining 6 studies either included all infection types or did not report infection type. Two of these enrolled children only^{25,28}; the other 4 did not specify an age range for inclusion.^{22,26,29,36}

Interventions were directed at health care providers in 13 of the 16 trials. Training ranged from a single session to multiple sessions over the study period. Most of the interventions were multifaceted and included discussion of current guidelines,^{20,22-25,27,29,31,34,36} feedback (either individual or site specific),^{20,22-25,27,30,34} patient education,^{23,24,27,28,30,31,36} communication skills training,^{25,27,36}

or C-reactive protein testing.^{23,24} Five studies involved local clinician leaders in the education sessions.^{27,30,31,32,36} In 7 studies, the comparator was usual care,^{20,22,25,27,28,30,36} in 4 studies the comparator was education delivered in an alternative format,^{26,29,31,32} and in one study there were 2 comparator groups – education (without CRP testing) or active control (development of a patient registry).^{23,24} For this study, we summarize findings from the education intervention group in this section and the findings from the CRP testing group in the Laboratory Tests section.

Three trials focused on patient education.^{21,33,35} In one CBA study, an educational brochure and an explanatory letter were sent to patients with a diagnosis of upper respiratory infection in the prior 2 years (first mailing) or one year (second mailing).²¹ In addition, providers were given patient education materials to distribute to patients. Another study used a factorial design to assign patients to either an patient education brochure or no brochure and then to a prescribing strategy (immediate, delayed, or no offer of antimicrobials).³³ The third study, a controlled clinical trial, compared findings from a group of patients that received patient education materials (at home and in clinic) to a group where providers were issued guidelines for diagnosis and treatment of bronchitis in adults and received performance feedback.³⁵ A summary of outcomes reported is presented in Table 3.

Table 3. Outcomes Reported in Studies of Provider and/or Patient Education

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Gerber 2013 ²⁰	✓			
Vinnard 2013 ²¹	✓			
Butler 2012 ²²	✓	✓		✓
Llor 2012 ^{23,24} (see also C-Reactive Protein testing)	✓			
Regev-Yochay 2011 ²⁵	✓			
Esmaily 2010 ²⁶	✓			
Smeets 2009 ²⁷	✓			
Finkelstein 2008 ²⁸	✓			
Chazan 2007 ²⁹	✓			✓
Metlay 2007 ³⁰	✓	✓		
van Driel 2007 ³¹	✓			
Varonen 2007 ³²	✓			
Little 2005 ³³ (see also Delayed Prescribing)	✓	✓		
Pagaiya 2005 ³⁴	✓			✓
Gonzales 2004 ³⁵	✓			
Stewart 2000 ³⁶	✓			

Prescribing Outcomes (Appendix D, Table 3)

Fifteen studies reported on antimicrobial use with 9 reporting decreased use^{20,22-25,28-30,34,36} and 6 reporting no differences between groups.^{21,26,27,31,33,35} Specifically, in studies of adults or patients of all ages, a provider education program, which included reflection on one’s practice, new research evidence, communications skills training, shared experiences, practice in usual clinical contexts, significantly reduced oral antimicrobial dispensing for all diagnoses (4.2% [95% CI

0.6, 7.7]; $p=0.02$).²² Provider education (including discussion of baseline prescribing findings and training on diagnosis and treatment of lower respiratory tract infections and acute rhinosinusitis) and patient information leaflets were found to decrease antimicrobial prescriptions for lower respiratory tract infections compared to usual care control (56.2% vs 76.6%; OR 0.42 [95% CI 0.22, 0.82]; $p=0.01$).²³ For acute rhinosinusitis, the prescription rates were not significantly different between intervention and control (82.9% vs 86.7%; OR 0.65 [95% CI 0.21, 1.06]; $p=0.06$).²⁴ Continuing medical education with monthly interactive sessions designed to improve diagnostic skills and antimicrobial prescribing combined with guidelines for antimicrobial treatment in primary care and seasonal medical education during September and October (with emphasis on antimicrobials for respiratory infections) was observed to decrease defined daily doses of antimicrobials significantly more than the seasonal education program alone (20.0% reduction vs 16.5% reduction, $p<0.0001$).²⁹ Guideline-based continuing medical education sessions for health professionals and pharmaceutical representatives along with a “local champion” physician, newsletters to physicians, and community education were associated with a 9.4% decrease in antimicrobial claims (significance not reported). The values were derived from an analysis of pre- to post-intervention data from a controlled before and after study, but the authors did not report this outcome for the control location.³⁶

In one study, emergency department education sessions led by clinician leaders and supplemented with site-specific data on use of antimicrobials for acute respiratory tract infections during the pre-intervention year and patient education materials were associated with a significant decrease in antimicrobial prescribing compared to usual care (adjusted differences of 10% at the intervention sites and 0.5% at the control sites). No difference was observed in antimicrobial use for antimicrobial-responsive respiratory infections.³⁰ Half of the included emergency departments were located in VA hospitals.

In studies with children, clinician education with personalized audit and feedback every 4 months significantly reduced the proportion of broad spectrum antimicrobials prescribed to children for any indication ($p=0.01$) or for pneumonia ($p<0.001$) compared to usual care.²⁰ No significant differences were noted for antimicrobial prescriptions for acute sinusitis, streptococcal pharyngitis, or viral infections. An education session on reducing non-judicious use of antimicrobials for respiratory tract infections supplemented with focus groups on guidelines, improving diagnosis, promoting awareness of antimicrobial resistance, patient education, and parent-physician communication, was found to significantly reduce antimicrobial prescribing compared to usual care (40% reduction vs 22% reduction; RR 0.76 [95% CI 0.75, 0.78]).²⁵ The reduction was maintained over the three-year study period; a workshop was held at the start of each year. It was noted that the health maintenance organization introduced a campaign to reduce antimicrobial use concurrently with the first year of the study intervention. An intervention that combined physician education and parent education was observed to significantly decrease antimicrobial prescribing for children ages 24 to less than 48 months ($p<0.01$) and for children age 48 to less than 72 months ($p<0.0001$) but not for children age 3 to less than 24 months compared to usual care.²⁸ A three-day training course for nurses from nurse-directed primary health centers in Thailand and based on clinical guidelines for acute respiratory infection or diarrhea was associated with a significant reduction in antimicrobial prescribing for acute respiratory infection (14.6% reduction in intervention group vs 2.8% increase in control group; $p=0.02$) with no change in antimicrobial prescribing for diarrhea (1.8% reduction in intervention

group vs 2.1% reduction in control group; $p=0.31$) at 6 months after the training.³⁴ An educational outreach visit with audit and feedback took place 3 to 4 months after the training.

In 6 studies, the interventions were not associated with reduced prescribing. A patient education mailing directed at patients with a recent history of upper respiratory infection did not significantly reduce antimicrobial prescribing for acute bronchitis or upper respiratory infection compared to usual care.²¹ Neither an outcome-based education program nor the comparator (usual continuing medical education) significantly reduced antimicrobial prescribing.²⁶ An educational program based on guidelines for management of respiratory tract infections and skills training in patient education that also included patient educational materials and audit and feedback after the first year of the study was not associated with a reduction in antimicrobial prescriptions for acute respiratory tract infections compared to usual care.²⁷ A peer-led discussion section on a new rhinosinusitis guideline (where the discussion leader was trained by a member of the research team and provided with supporting evidence, patient leaflets, research on patient expectations, and clinical case vignettes) was comparable to a group meeting about the guideline without the supplemental materials. A national public campaign on rational use of antimicrobials was instituted at the same time.³¹ Patient education leaflets were not associated with a significant reduction in self-reported use of antimicrobials compared to no leaflets (55% vs 57%, $p=0.58$).³³ In this factorial design study, there was a significant reduction in use of antimicrobials associated with delayed prescribing. For treatment of elderly patients with acute respiratory tract infections, patient education materials mailed to households and available in clinics were no more effective than a comparator of guidelines for diagnosis and management of bronchitis and performance feedback measures based on aggregated claims data.³⁵

Of 8 studies reporting on antimicrobial selection, 3 observed significant changes post-intervention. In one study, after one year of a three-year intervention, there was a significant reduction in prescriptions for penicillins (RR 0.84 [95% CI 0.82, 0.87]), cephalosporins (RR 0.77 [95% CI 0.73, 0.82]), and macrolides (RR 0.58 [95% CI 0.55, 0.62]) in the intervention group (workshops and focus groups) relative to the control group (usual care).²⁵ The reductions were maintained over the 3 year intervention and one year follow-up, especially for cephalosporins and macrolides. The study of physician and parent education observed significant reductions in second-line penicillins in the 2 older age groups (age 24 to <48 months: -9.2%, $p=0.03$; age 48 to <72 months: -21.3%, $p<0.0001$) but not in the younger age group (age 3 to <24 months: -2.2%, $p=0.48$). The intervention was associated with a reduction in broad-spectrum antimicrobials for all age groups (range -6.7% to -22.5%).²⁸ In the study comparing on-going medical education plus seasonal medical education to seasonal education alone (control), a significant difference between groups was noted in the reduction in broad-spectrum antimicrobial use (-17.6% intervention vs -4.5% control, $p<0.0001$) with no significant difference between groups in the reduction in narrow-spectrum antimicrobial use (-21.2% intervention vs -20.6% control).²⁹

Five studies reported no differences in antimicrobial selection post-intervention. Mailing educational materials to patients did not change the use of broad versus narrow-spectrum antimicrobials.²¹ The educational program with guidelines for management of respiratory tract infections and skills training in patient education supplemented by patient educational materials and audit and feedback after the first year of the study was not associated with differences in the percentage of antimicrobial prescriptions that were second-choice antimicrobials (amoxicillin-

clavulanate, macrolides, fluoroquinolones) compared to usual care.²⁷ The peer-led discussion section on a new rhinosinusitis guideline was not associated with a change in the proportion of prescriptions for first-choice antimicrobials.³¹ In the third study, although the 5 year trend data showed increased use of amoxicillin as first-line treatment for acute sinusitis in the problem-based learning group (OR 1.10 [95% CI 1.02, 1.20]) but not for the academic detailing group (OR 1.11 [95% CI 0.99, 1.24]), there was no significant difference between the groups. There was also no significant difference between groups for use of macrolides as first-line treatment.³² No change in prescribing of “first-line” antimicrobials (defined as “drugs of choice”) was noted following an intervention of education programs for health professionals, pharmaceutical representatives, and the community. There was a reduction in prescriptions for “second-line” antimicrobials (not defined) among the intervention providers relative to providers in the rest of the province (control group). The authors calculated an odds ratio for the control period compared with the study period but also reported the inverse of the odds ratio (0.71 [95% CI 0.62, 0.81] to convey the reduced likelihood of prescribing “second-line” antimicrobials after the intervention.³⁶ There was also an increase in “first-line” prescribing relative to “second-line” prescribing (OR 1.75 [95% CI 1.55, 1.97]).

One study reported on use of 7-day courses of antimicrobials.³² In both the problem-based learning group and the academic detailing group, there was increased likelihood of use of 7-day courses (ORs 1.18 and 1.17) and decreased use of longer courses. The difference between the 2 groups was not significant.

Patient Outcomes (Appendix D, Table 4)

Three studies reported return clinic visits. In one study, return clinic visit rates for respiratory tract infections were documented within 7 days and within 31 days of the initial visit.²² No significant differences in median number of patients with a return clinic visit were observed between intervention (provider education) and control (usual care) groups at either time point. A second study, comparing provider and patient education with usual care, also found no difference in return emergency department visits within 2 weeks after the initial emergency department visit.³⁰ The factorial study with a patient education leaflet and alternative prescribing strategies observed fewer patients in the no-leaflet group with return visits within one month of the initial visit (mean attendance of 0.11 vs 0.17; IRR 1.63 [95% CI 1.07, 2.49]; p=0.02). Patients who received immediate antimicrobials were less likely to have a return visit within one month than those who received no antimicrobials (IRR 0.55 [95% CI 0.33, 0.91]; p=0.02). The results were not significantly different from immediate prescribing for patients receiving a delayed prescription (IRR 0.65 [95% CI 0.40, 1.04]; p=0.08). There was no significant difference in return clinic visit with cough between 1 month and 1 year after the initial visit for patients who received the leaflet compared to those who did not (adj IRR 1.27 [95% CI 0.86, 1.87]) and no difference between those who received a delayed prescription (adj IRR 0.81 [95% CI 0.51, 1.28]) or no prescription (adj IRR 1.05 [95% CI 0.68, 1.63]) and those who received an immediate prescription.^{33,72}

Two of the studies reported hospitalizations. In the study comparing provider education with usual care, the percent reduction (intervention relative to control) in episodes for possible respiratory tract infection and complications of common infections was not significant (-1.9%

[95% CI -13.2, 8.2]; $p=0.72$).²² The study of provider and patient education versus usual care found the differences in hospitalizations between the intervention and control sites over time was not significant.³⁰

The factorial study reported adverse events.³³ There were no significant differences between groups in pneumonia or diarrhea episodes. Numbers of episodes were not reported.

One study reported patient satisfaction. There was no difference in self-reported satisfaction with the initial visit in patients at intervention sites compared to control sites (site by time interaction $p=0.71$).³⁰

Microbial Outcomes

None of the studies reported microbial outcomes.

Costs (Appendix D, Table 5)

Three studies reported cost outcomes.^{22,29,34} In one study, there was a 5.5% reduction in drug costs in the intervention group relative to the control group but the finding was not significant (95% CI -0.4, 11.4; $p=0.07$).²² The second study reported greater savings in total antimicrobial costs in the group that underwent continuous medical education (\$330 per 1000 patients/season) than in the group that underwent seasonal medical education (\$186 per 1000 patients/season).²⁹ In the third study, average drug cost per patient decreased in the intervention group and increased in the control group, resulting in a significant difference between groups ($p=0.002$).³⁴

One of the studies reported program costs with a mean cost per practice of £2,923 in the intervention group.²²

Provider Feedback (k=5 trials)

Key Findings

Prescribing Outcomes: Findings for prescribing outcomes were mixed, with 2 trials of individualized feedback reporting significant decreases compared to more general feedback and one reporting a significant decrease compared to usual care. There were no differences in prescribing when postal feedback plus academic detailing was compared to postal feedback alone or when an electronic health record component was compared to usual care. Three studies reported on antimicrobial selection with 2 reporting significant changes for targeted antimicrobials. In one study reporting 12 month outcomes, the changes were not sustained.

Patient Outcomes: No study reported patient outcomes.

Microbial Outcomes: No study reported microbial outcomes.

Cost Outcomes: In one study, an individualized feedback program was associated with reduced prescribing costs compared to a minimal intervention. In a second study, a postal prescribing feedback program was associated with improved prescribing at a lower cost than a pharmacist-led advisor service.

We identified 5 trials that used feedback as the primary intervention component.^{21,37-40} The studies were conducted in either North America^{21,38} or Europe.^{37,39,40} One was a randomized controlled trial,³⁹ 2 were cluster randomized trials with physician groups or clinics as the unit of randomization,^{37,38} one was a controlled clinical trial,⁴⁰ and one was a controlled before and after study.²¹ All 5 studies aimed to reduce antimicrobial use; 3 also reported on antimicrobial selection.^{37,39,40} One study was rated as medium risk of bias⁴⁰ and 4 as high risk of bias (Appendix D, Table 6).

In each study, the setting was primary care. Three studies included patients with respiratory conditions^{21,37,38} and 2 studies either did not report or included patients with any infection.^{39,40} Three studies did not report whether adults and children were included^{21,38,40} although in one study the mean age of patient was 49 years.³⁸ Two studies reported including patients of all ages.^{37,39}

The intervention in all of the studies involved individualized feedback on prescribing. Three studies also included provider education,^{37,39,40} and one study included patient education materials.²¹ In one study, the feedback was integrated into the electronic health record.³⁸ In another study, the feedback was provided through the mail and by an academic detailer.³⁹ In the remaining 3 studies, feedback was provided by an academic detailer,³⁷ a pharmacist,⁴⁰ or a pharmacist and an opinion leader in antimicrobial use.²¹ Comparators included an intervention similar in design to the antimicrobial intervention but targeting appropriate use of drugs other than antimicrobials (*eg*, strong analgesics, long-acting benzodiazepines) in patients over age 70 years,³⁷ postal feedback only,³⁹ a minimal intervention (public health announcements and group prescribing data),⁴⁰ or usual care.^{21,38} Table 4 provides an overview of outcomes reported in the trials.

Table 4. Outcomes Reported in Studies of Provider Feedback

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Gjelstad 2013 ³⁷	✓			
Vinnard 2013 ²¹	✓			
Linder 2010 ³⁸	✓			
Naughton 2009 ³⁹	✓			✓
Madrdejos-Mora 2004 ⁴⁰	✓			✓

Prescribing Outcomes (Appendix D, Table 3)

Significant decreases in antimicrobial prescribing were reported in 3 studies. An intervention that involved individual reports of prescriptions rates and distribution of different antimicrobials for acute respiratory tract illness along with national guidelines, educational seminars, and an emphasis on delayed prescribing found a reduced odds of prescribing an antimicrobial in the intervention group than the control (feedback on drug treatment for the elderly) (OR 0.72 [95% CI 0.61, 0.84]).³⁷ Presentation of published literature and a provider-specific evaluation by a pharmacist and an antimicrobial stewardship advocate was associated with a significant reduction in antimicrobial prescribing for respiratory infections compared to usual care (Ratio of Odds Ratios 2.60 [95% CI 1.23, 5.48]).²¹ The intervention also included patient education materials to distribute during the office visit. No significant reduction in prescribing was observed in the group receiving the education materials alone. Individualized feedback along with pharmacist-

led education and a leaflet providing an anonymous comparison with other providers was associated with a significant reduction in over prescription of antimicrobials in the intervention group (-2.0 DDD x 1000 inhabitant x day, $p=0.006$).⁴⁰ There was no change in prescribing in the comparator group, minimal intervention (*ie*, prescribing data for practice groups as a whole). Post intervention prescribing was significantly different for the 2 groups ($p=0.026$).

Two other studies found no significant changes in prescribing. An Acute Respiratory Infection Quality Dashboard (a display of a clinician's prescribing performance and billing practices for acute respiratory infection visits compared to peers and national benchmarks that was integrated into the electronic health record) along with monthly reminders about the Dashboard did not significantly change the odds of prescribing an orally administered antimicrobial within 3 days of a visit for acute respiratory infection (OR 0.97 [95% CI 0.07, 1.14]; $p=0.87$).³⁸ It was noted that only 28% of providers used the Dashboard; the antimicrobial prescribing rate for acute respiratory infections was lower in those who used the Dashboard (42%) than those who did not (50%, $p=0.02$). In the second study, postal prescribing feedback (an individual's prescribing for the 12 months prior to the intervention compared to Health Authority averages) along with an academic detailing visit to review the postal feedback and discuss ways to reduce prescribing was associated with changes in prescribing comparable to those with postal prescribing feedback alone.³⁹ Overall prescribing in the 2 groups was compared immediately post intervention ($p=0.26$) and at 12 months ($p=0.33$).

Three studies reported on selection of antimicrobials. The study comparing individual feedback on antimicrobial prescribing to individual feedback on other (non-antimicrobial) prescribing reported a significant increase in episodes of acute respiratory tract infection for which penicillin V (the recommended treatment) was prescribed in the intervention group (45.0% pre intervention vs 53.8% post intervention; $p<0.05$) and a decrease in the control group (45.2% pre intervention vs 43.2% post intervention; $p<0.05$).³⁷ There was a significant reduction in the odds of prescribing a non-penicillin V when an antimicrobial was issued in the intervention group compared to the control group (OR 0.64 [95% CI 0.49, 0.82]). In the study comparing postal feedback plus academic detailing to postal feedback alone, there was a significant difference ($p=0.04$) in narrow-spectrum penicillin prescribing between the 2 groups with greater prescribing in the combined feedback group.³⁹ There were significant decreases in co-amoxiclav and cephalosporin prescribing but no differences between groups. During the 12 months post-intervention no differences were observed between group for narrow-spectrum penicillin, co-amoxiclav, or cephalosporins. Prescribing patterns tended to return to pre-intervention patterns. The study comparing individual feedback to practice group feedback observed a significant decrease in third generation cephalosporin use in the intervention group (28.0% pre intervention vs 22.4% post intervention, $p=0.017$) but no change in the control group and no significant difference between groups post intervention ($p=0.338$).⁴⁰ Both groups increased use of broad spectrum quinolones but neither the changes within groups nor the difference between groups post intervention were significant.

One study reported antimicrobial prescribing based on diagnosis.³⁸ No differences were observed between intervention (the feedback Dashboard) and control (usual care) in antimicrobial prescribing for antimicrobial-appropriate diagnoses (65% intervention vs 64% control; $p=0.68$) or non-antimicrobial-appropriate diagnoses (38% intervention vs 40% control; $p=0.70$).

Patient Outcomes

No study reported patient outcomes.

Microbial Outcomes

No study reported microbial outcomes.

Costs (Appendix D, Table 5)

Two studies reported cost outcomes. A significant decrease ($p=0.004$) in drug costs was reported following introduction of an individualized feedback program.⁴⁰ There was a non-significant increase in drug costs in the comparator group – minimal intervention. The groups were significantly different post-intervention (2.49 euros/inhabitant in the intervention group vs 3.25 euros/inhabitant in the comparator group; $p=0.013$).

The second study reported program costs.³⁹ The estimated cost for the initial year of the postal prescribing feedback program evaluated in the study was €175 per general practice. The authors also estimated the first year costs of establishing a pharmacist-led prescriber advisor service. That cost was €1,556 per general practice.

Guidelines (k=6 trials)

Key Findings

Prescribing Outcomes: Four studies reported antimicrobial use with 3 finding significant decreases post-intervention. Two studies of guidelines to improve antimicrobial selection reported mixed results across antimicrobials; a study focused on fluoroquinolone use observed improved selection. One study that assessed treatment duration reported no differences between intervention and control groups.

Patient Outcomes: One study reported patient satisfaction with care finding no difference between those who received an antimicrobial and those who did not.

Microbial Outcomes: No study reported microbial outcomes.

Cost Outcomes: One study reported prescription costs finding significant decreases post-intervention for cephalosporins, quinolones, penicillins, and “other” antimicrobials with no significant change in overall antimicrobial costs or macrolide costs. Lower costs were maintained for cephalosporins, quinolones, and “other” antimicrobials.

Six studies met inclusion criteria.⁴¹⁻⁴⁶ Two studies were conducted in North America,^{41,44} 3 in Europe,^{42,43,46} and one in the United Kingdom.⁴⁵ There was one cluster randomized trial,⁴⁵ one controlled clinical trial,⁴⁶ and 4 interrupted time series studies.⁴¹⁻⁴⁴ In the cluster randomized trial, the unit of randomization was practices. Risk of bias was rated as medium for 5 studies and high for one study⁴⁶ (Appendix D, Table 6 and Table 7).

Three studies evaluated interventions designed to reduce antimicrobial use⁴⁴⁻⁴⁶ while 2 focused on antimicrobial selection^{41,42} and one assessed both.⁴³ Infectious conditions varied with one study of

a respiratory condition (acute rhinosinusitis),⁴³ one study of urinary tract infections,⁴² one study of sexually transmitted infections (gonorrhea),⁴¹ one study of acute dental pain,⁴⁵ and 2 that did not specify a condition.^{44,46} The study of urinary tract infections enrolled only women (ages 15 to 65 years old).⁴² The studies of dental pain⁴⁵ and rhinosinusitis⁴³ also enrolled only adults; the remaining studies did not specify the patient population.^{41,44,46} A summary of outcomes reported is presented in Table 5.

Table 5. Outcomes Reported in Studies of Guidelines

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Dowell 2012 ⁴¹	✓			
Slekovec 2012 ⁴²	✓			
Venekamp 2012 ⁴³	✓			
Weiss 2011 ⁴⁴	✓			✓
Seager 2006 ⁴⁵	✓	✓		
Marten 2006 ⁴⁶	✓			

Prescribing Outcomes (Appendix D, Table 3)

Four studies reported on antimicrobial use. The introduction of guidelines for acute rhinosinusitis (with discussions about the guidelines at medical education sessions) was associated with a significant change in the slope of the prescription rate data before and after the intervention ($p < 0.05$).⁴³ A guideline addressing common infectious conditions accompanied by promotion of the guideline at continuing medical education meetings was associated with a level change of -4.1 prescriptions per 1000 inhabitants monthly (95% CI -6.6, -1.6, $p = 0.002$).⁴⁴ The decrease was maintained during the 36 month follow-up. There were similar results for all classes of antimicrobial studied – cephalosporins, macrolides, penicillins, fluoroquinolones, and “others.” The odds of being prescribed an antimicrobial for acute dental pain decreased relative to usual care (OR 0.63 [95% CI 0.41, 0.95]) following the introduction of printed educational materials (including guidelines and patient brochures) and an academic detailing visit.⁴⁵ The odds of being prescribed antimicrobials inappropriately (*ie*, in the absence of a pre-defined set of signs and symptoms) also decreased in the intervention group (OR 0.33 [95% CI 0.21, 0.54]). There were no differences from usual care in either prescribing outcome for the group that received the guideline alone.

One study failed to show an association with the intervention.⁴⁶ The introduction of a guideline for antimicrobials did not significantly reduce the total number of antimicrobial prescriptions per general practitioner per year relative to the usual care control group.

Several studies reported on antimicrobial selection. A reduction in fluoroquinolone use for treatment of gonorrhea decreased following introduction of revised guidelines from the Centers for Disease Control and Prevention.⁴¹ The overall decrease was 21.5% with a range of 7.9% to 48.3% across the 5 metropolitan areas where the guideline was introduced. The greatest decreases were observed in sexually transmitted diseases clinics; the smallest in emergency department/urgent care/hospital settings. A guideline for management of urinary tract infections accompanied by voluntary training sessions was associated with significant increases in slope for prescriptions for nitrofurantoin and fosfomycin-trometamol and a significant decrease in slope for prescriptions for norfloxacin.⁴² However, there was a significant level change

post-intervention for single-dose fluoroquinolones only. In the study of a guideline about antimicrobial use for dental pain, there was a significantly higher percentage of prescriptions for amoxicillin in the intervention group than the usual care control group, a significantly lower percentage of prescriptions for penicillin in the intervention group than in the usual care or guidelines only groups, and a significantly higher percentage of prescriptions for metronidazole in the intervention group than in the guideline only group (all $p < 0.05$).⁴⁵ It was unclear whether these changes were in the direction of a desired prescribing pattern. The study of guidelines for acute rhinosinusitis reported no change in the type of antimicrobial prescribed over time.⁴³

One study reported on treatment duration. The study of interventions to improve antimicrobial prescribing for dental pain found no significant difference across the 3 study groups (guidelines and educational materials plus academic detailing visit, guidelines only, or usual care) in the percentages of patients receiving antimicrobials for less than 3 days, 3 or 4 days, 5 days, or more than 5 days.⁴⁵

Patient Outcomes (Appendix D, Table 4)

One study commented on patient satisfaction with care.⁴⁵ Data were available for patients in the usual care and educational materials groups only; no data were available for the intervention group (educational materials plus academic detailing visit). The authors reported that patients who did not receive an antimicrobial were no more likely than those who did receive an antimicrobial to feel that the treatment they received had been ineffective.

Microbial Outcomes

None of the studies reported microbial outcomes.

Costs (Appendix D, Table 5)

One study reported prescription costs.⁴⁴ The intervention addressed common infectious conditions. Significant decreases were reported post-intervention for cephalosporins, fluoroquinolones, penicillins, and “other” antimicrobials with no significant change in overall antimicrobial costs or macrolide costs. Lower costs were maintained over the 36 month post-intervention period for cephalosporins, quinolones, and “other” antimicrobials

Delayed Prescribing (k=4 trials)

Key Findings

Prescribing Outcomes: One study enrolling women with urinary tract infection found a significant reduction in antimicrobial use among patients receiving delayed prescriptions compared to immediate prescriptions. A second study found no significant difference in prescriptions filled when patients were given a post-dated (two day delay) or a same day prescription. One additional study, summarized under Provider and/or Patient Education (above), observed a significant reduction in use of antimicrobials in the group assigned to delayed prescribing compared to the immediate antimicrobial group.³³ Another study, summarized under Laboratory Tests (below), found fewer patients in the intervention group who were given delayed prescriptions by their provider filled the prescriptions compared to patients in the

control group who were given delayed prescriptions (22.7% intervention, 72.4% control, $p < 0.001$).⁷¹

Patient Outcomes: One study reported patient outcomes finding lower odds of return clinic visit in the delayed prescription group compared to immediate prescription for women with urinary tract infection. There were no major adverse events in either group. In the study described under Provider and/or Patient Education return clinic visits did not differ between groups assigned to delayed antimicrobials or immediate antimicrobials.³³

Microbial Outcomes: No study reported microbial outcomes.

Cost Outcomes: No study reported cost outcomes.

Two studies investigated delayed prescribing strategies as the primary intervention.^{47,48} Both were randomized controlled trials conducted in the United Kingdom⁴⁷ or Canada.⁴⁸ One study was rated as medium risk of bias⁴⁷ and one as high risk of bias⁴⁸ (Appendix D, Table 6). In each of the studies the goal was to reduce prescribing of antimicrobials for respiratory infections⁴⁸ or urinary tract infections.⁴⁷ The studies were conducted in family or general practice settings and enrolled only adults.

Both studies randomized patients. In one study, women with urinary tract infections were randomized to either immediate antimicrobials (usual care), delayed antimicrobials, or antimicrobials offered based on a) symptom, b) dipstick test, or c) midstream urine analysis.⁴⁷ The second study randomized patients to either usual care (a prescription dated the day of the visit) or post-dated prescription (a prescription dated 2 days after the office visit).⁴⁸ Patients in both groups were asked to use the prescription only if symptoms had not improved or had worsened after 2 days. Both studies included a patient education component for all groups.

Two additional studies included a delayed prescribing component. One study is described under Provider and/or Patient Education³³ and the other under C-Reactive Protein testing.⁷¹ Outcomes reported in all 4 studies are summarized in Table 6.

Table 6. Outcomes Reported in Studies of Delayed Prescribing

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Little 2010 ⁴⁷	✓	✓		
Worrall 2010 ⁴⁸	✓			
Cals 2010 ⁷¹ (see also C-Reactive Protein)	✓			
Little 2005 ³³ (see also Provider and/or Patient Education)	✓	✓		

Prescribing Outcomes (Appendix D, Table 3)

In the study of women with urinary tract infections, the odds of using antimicrobials were significantly lower in the delayed prescribing group (77% vs 97% in the immediate prescribing group; OR 0.12 [95% CI 0.03, 0.59]).⁴⁷ Fifty-three percent in the delayed prescribing group reported waiting at least 48 hours prior to taking antimicrobials compared to 8% of the

immediate prescribing group. In the study of post-dated prescriptions, there was no difference in the percentage of prescriptions filled (44.0% vs 43.2% in the usual date group, $p=0.92$).⁴⁸ Two other studies provided data on delayed prescribing. One study, summarized under the section on Provider and/or Patient Education found significantly lower ($p<0.001$) self-reported use of antimicrobials in the delayed prescribing group (20%) compared to the immediate antimicrobial group (90%).³³ Another study, summarized under Laboratory Tests (below), randomized patients to either CRP testing prior to prescription or no CRP testing prior to prescription. Providers in each group were allowed to select delayed, immediate, or no prescription. There was no significant difference in the percentage of patients who received delayed prescriptions but significantly fewer patients in the intervention group filled those prescriptions (22.7% intervention vs 72.4% control, $p<0.001$).⁷¹

Patient Outcomes (Appendix D, Table 4)

The study of women with urinary tract infections reported patient outcomes.⁴⁷ The authors reported a lower odds of return clinic visit within one month in the delayed prescribing strategy (OR 0.44 [95% CI 0.21, 0.95]). No major illnesses, hospital admissions, or deaths were reported for either group. In addition, the study described under Provider and/or Patient Education found return clinic visits during the month after the initial visit (IRR 0.65 [95% CI 0.40, 1.04]) or return clinic visits with cough between one month and one year after the initial visit (IRR 0.81 [95% CI 0.51, 1.28]) did not differ between groups assigned to delayed antimicrobials or immediate antimicrobials.³³

Microbial Outcomes

None of the studies reported microbial outcomes.

Costs

No study reported cost outcomes.

Communication Skills Training (k=6 trials)

Key Findings

Prescribing Outcomes: Five of the 6 cluster randomized trials of training to enhance communication skills as the primary component in multifaceted interventions reported significantly reduced prescribing and/or use of antimicrobials following the intervention.

Patient Outcomes: The return clinic visit rate did not differ between intervention and control (reported in three studies). One study reported resolution of symptoms rated as moderately bad or worse was one day longer ($p=0.002$) in the communication skills group, but no difference was reported for new or worse symptoms or symptom severity at 2 to 4 days after the initial visit. Hospitalizations were infrequent. Patient satisfaction did not differ between intervention and control conditions in 3 of 4 studies reporting that outcome.

Microbial Outcomes: No study reported microbial outcomes.

Cost Outcomes: Cost data were reported in one study with the lowest per patient

costs for patients in the communication skills training group but the significance was not reported.

Six studies with a primary focus on communication skills training met eligibility criteria.⁴⁹⁻⁵⁶ The goal of the training was to improve provider and patient communication to allow for a more “patient-centered” approach to care and to address patient expectations for antimicrobial treatment. One study was a factorial design with a second focus on CRP testing.⁵² Another randomized practices to either communication training, CRP training, communication and CRP training, or usual care.⁴⁹ All were cluster randomized trials; 2 from Canada,^{50,51} 2 from Europe,^{52,56} one from the United Kingdom,⁵⁵ and one multi-national study from Europe and the United Kingdom.⁴⁹ In 4 studies, the unit of randomization was practices;⁴⁹⁻⁵² in the other 2 studies, general practitioners were randomized.^{55,56} The study risk of bias was medium for 4 studies and high for 2 studies (Appendix D, Table 6). The purpose of the intervention in each study was to reduce prescribing. All of the studies focused on respiratory conditions and all were conducted in general or family practice clinics. Two studies enrolled patients of any age,^{50,51} 2 enrolled patients 18 years of age and older,^{49,52} one enrolled patients 16 years of age and older,⁵⁶ and one enrolled children 6 months to 14 years of age.⁵⁵

All of the studies were of multifaceted interventions. In one study, internet-based training focused on enhanced communication skills and/or use of a point-of-care test for C-reactive protein.⁴⁹ Other elements were an interactive booklet to use during consultations, video demonstrations of consultation techniques, and lead physicians to organize provider meetings on prescribing issues. A second study also evaluated point-of-care testing for C-reactive protein.⁵² One study supplemented on-line tutorials with on-site interactive workshops about shared decision making, diagnosis and treatment of acute respiratory tract infections, and effective communication of risks and benefits.⁵⁰ Decision support tools were available in the consultation rooms. An earlier study from this group involved interactive workshops focused on shared decision making, reminders about expected shared decision making behaviors, feedback to providers about agreement with patient perspective, local opinion leaders, and decision support tools.⁵¹ In both studies, the comparator was usual care. The fifth study provided on-line training for clinicians on how to use an interactive booklet developed for the study.⁵⁵ The sixth study involved general practitioner peers who provided instruction on antimicrobial misunderstanding during the consultation, patient expectations, and pressures on providers.⁵⁶ Patient education leaflets and a poster in the waiting room were also part of the intervention. A summary of outcomes reported is presented in Table 7.

Table 7. Outcomes Reported in Studies of Communication Skills Training

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Little, 2013 ⁴⁹	✓	✓		
Légaré 2012 ⁵⁰	✓	✓		
Légaré 2010 ⁵¹	✓	✓		
Cals 2009, ⁵² Cals 2011, ⁵³ Cals 2013 ⁵⁴	✓	✓		✓
Francis 2009 ⁵⁵	✓	✓		
Altiner 2007 ⁵⁶	✓			

Prescribing Outcomes (Appendix D, Table 3)

The study of C-reactive protein and communication skills training reported significantly lower antimicrobial prescribing among patients from sites where providers received communication skills training (adj RR 0.69 [95% CI 0.53, 0.87]; $p < 0.0001$).⁴⁹ Similarly, there was lower antimicrobial prescribing among patients from sites that received training in use of C-reactive protein testing (adj RR 0.54 [95% CI 0.42, 0.69]; $p < 0.0001$). The interaction term was not significant. Prescribing decreased the most in the combination intervention group (RR 0.38 [95% CI 0.25, 0.55]; $p < 0.0001$).

In the factorial study, practitioners who received communications skills training prescribed fewer antimicrobials than those who did not (27.4% vs 53.5%, $p < 0.01$).⁵² There was also lower antimicrobial prescribing among practitioners who received devices to test for CRP (30.8% vs 52.9%, $p = 0.02$). An interaction analysis was not significant. Over a mean follow-up of 3.67 years, there were fewer episodes of respiratory tract infections treated with antimicrobials among providers who received communication skills training (26.3% intervention vs 39.1% control, $p = 0.02$).⁵⁴ There was no significant difference among providers who received C-reactive protein test devices (30.7% intervention vs 35.7% control, $p = 0.36$).

The 2 studies from the same group reported the percentage of patients who decided to use antimicrobials following consultation with a physician. In the more recent study, significantly fewer patients used antimicrobials in the intervention group than in the control group following the intervention. The absolute difference was 25% (adj RR 0.5 [95% CI 0.3, 0.7]).⁵⁰ The finding was similar when only data from adults were included (absolute difference=24.1%, adj RR 0.5 [95% CI 0.4, 0.8]). In the earlier study, the absolute difference was 16% ([95% CI -31, 1.0], $p = 0.08$).⁵¹

In the study of children, an interactive booklet used during the consultation and then taken home by parents was associated with significantly fewer antimicrobial prescriptions at the index consultation (19.5% vs 40.8%, OR 0.29 [95% CI 0.14, 0.60]).⁵⁵

The sixth study reported a significant reduction in prescribing at 6 weeks post-intervention associated with the provider peer training and patient education materials (29% intervention vs 59% control; adj OR 0.38 [95% CI 0.26, 0.56]; $p < 0.001$). The improvement was maintained at 1 year post-intervention (37% intervention vs 65% control; adj OR 0.55 [95% CI 0.38, 0.80]; $p = 0.002$).⁵⁶

Patient Outcomes (Appendix D, Table 4)

Five studies reported patient outcomes. One study used a telephone interview 2 weeks after the index visit to gain information about return clinic visits for the same condition.⁵⁰ No difference was found between the intervention and control sites (absolute difference 7.5%; adj RR 1.3 [95% CI 0.7, 2.3]). A similar method was used in the pediatric study.⁵⁵ There was also no difference in return clinic visits within 2 weeks (12.9% intervention vs 16.2% control; OR 0.75 [95% CI 0.41, 1.38]).

The factorial study reported non-significant differences in return clinic visit within 28 days associated with either communication skills training (27.9% intervention vs 37.0% control,

p=0.14) or CRP test availability (34.8% intervention vs 30.4% control, p=0.50).⁵² When antimicrobial prescriptions during the 28 day follow-up were added to the initial prescriptions, differences between intervention and control groups in antimicrobial prescription remained significant for both communication skills training (37.8% intervention vs 63.0% control, p<0.001) and CRP testing (44.9% intervention vs 58.3% control, p<0.01).

Two studies reported all-cause hospitalization. In one study, there were 6 hospitalizations in the enhanced communication group, 12 in the combined enhanced communication/CRP group, 10 in the CRP group, and 2 in the usual care group.⁴⁹ The authors did not report whether there were significant differences between the groups. Another study reported 3 patients in the intervention group and 4 patients in the control group were hospitalized or observed in a pediatric assessment unit.⁵⁵

Three studies reported adverse events. The study of C-reactive protein training and communication skills training reported no deaths during the study period. There was a significant decrease in number of days to resolution of symptoms rated moderately bad or worse in the groups receiving communication skills training (6 days vs 5 days; adj HR 0.83 [95% CI 0.74, 0.93]; p=0.002). There were no significant differences between groups for new or worse symptoms or symptom severity scores 2 to 4 days after initial consultation.⁴⁹ A second study reported no significant difference in the percentage of patients who felt they had stable, a little better, or much better health 2 weeks after the initial visit.⁵¹ The third study reported that there were no adverse events.⁵²

Four studies reported patient satisfaction with care. In 2 of the studies, the authors assessed patients' intention to participate in the future in shared decision making regarding acute respiratory tract infections. There were no differences between intervention and control sites following the intervention.^{50,51} Patient regret over decision making was also assessed. One study reported no difference in the percentage of patients expressing regret over decision making (7% intervention vs 9% control, p=0.91).⁵¹ The second study found a significant difference between intervention and control sites with a score of 12.4 among intervention site patients and 7.6 among control site patients (mean difference 4.8 [95% CI 0.9, 8.7]). Possible scores ranged from 0 (very low regret) to 100 (very high regret).⁵⁰

In the factorial study, there were no significant differences in percentage of patients "at least very satisfied" associated with either communication skills training (78.7% intervention, 74.4% control, p=0.88) or CRP testing (76.8% intervention, 76.0% control, p=0.53).⁵² No differences in satisfaction with the consultation (90.2% intervention, 93.5% control, OR 0.64 [95% CI 0.33, 1.22]) or usefulness of information received during the consultation (85.4% intervention, 85.2% control, OR 1.01 [95% CI 0.60, 1.68]) were observed between parents receiving an information booklet or usual care.⁵⁵

Microbial Outcomes

None of the studies reported microbial outcomes.

Costs (Appendix D, Table 5)

The factorial study reported costs.⁵³ The mean direct health care cost (medications, physician visits, diagnostic testing) per patient for providers who received communication skills training was

€20.27, with an additional cost of €5.34 for the communication skills training intervention, for a total of €25.61. For providers who received C-reactive protein testing devices, the direct health care costs were €32.86, with an additional €4.72 for the intervention, for a total of €37.58. In the usual care group, the direct health care costs were €35.96 and there were no intervention costs.

Restriction Policies (k=2 trials)

Key Findings

Prescribing Outcomes: Data from 2 interrupted time series reporting on insurance claims data before and after restriction policies found mixed results with decreases in some, but not all targeted antimicrobials. One study reported on appropriate prescribing with a significant increase in the percentage of prescriptions consistent with formulary guidelines post-intervention.

Patient Outcomes: One study reported patient outcomes finding no change in mortality or infection-related hospitalizations and small but statistically significant increases in return clinic visit and all-cause hospitalization.

Microbial Outcomes: Neither study reported microbial outcomes or harms associated with the interventions.

Cost Outcomes: One study reported antimicrobial costs with mixed results.

We identified 2 studies, both from Canada, where the primary intervention was a restriction policy.^{57,58} Both were interrupted time series studies. One was rated as low risk of bias and one as medium risk of bias (Appendix D, Table 7). The focus was on antimicrobial selection.

One study looked at the effects of a policy that restricted fluoroquinolone use.⁵⁷ The authors analyzed insurance claims data from 170,247 patients age 65 and older who had an outpatient primary care visit for acute exacerbation of chronic bronchitis, CAP, URTI, or UTI. They excluded claims for the same infection within a 30 day period. In addition, a convenience sample of physicians was invited for a chart review to assess appropriateness of prescribing. The second study analyzed data from a government-funded insurance plan, focusing on 20 antimicrobial drug categories prescribed for patients 65 years of age or older or recipients of social assistance.⁵⁸ The restriction policy switched ciprofloxacin, ofloxacin, and levofloxacin to “limited use” which limited reimbursement to treatment of patients with specified conditions.

One of the studies reported additional elements of the stewardship effort.⁵⁷ During the study period, 2 new fluoroquinolones were added to the formulary (gatifloxacin, moxifloxacin) and a guide for prescribing restrictions and an educational packet was mailed to all physicians. Table 8 presents an overview of outcomes reported.

Table 8. Outcomes Reported in Studies of Restriction Policies

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Manns, 2012 ⁵⁷	✓	✓		
Marshall, 2006 ⁵⁸	✓			✓

Prescribing Outcomes (Appendix D, Table 3)

Both studies reported prescribing outcomes. In the fluoroquinolone restriction study, there was no significant change in the rate (level) or slope (trend) of fluoroquinolone use following the implementation of the restriction policy.⁵⁷ Among those receiving an antimicrobial, there were significant decreases ($p < 0.001$) in the rate of use of ciprofloxacin for UTIs and levofloxacin for acute exacerbations of chronic bronchitis, URTI, and pneumonia. In the sample of prescriptions assessed for appropriateness, the percentage of prescriptions consistent with formulary guidelines increased from 42.5% before the restriction to 58.5% after ($p = 0.002$).

The “limited use” policy study reported no change in the level of total antimicrobial prescribing but a decreasing trend.⁵⁸ Decreases in the level of use were reported for the fluoroquinolone group (six antimicrobials, 3 of which were restricted) and ciprofloxacin, but not levofloxacin. Non-significant changes in trend were reported for the fluoroquinolone group and ciprofloxacin with a significant increasing trend for levofloxacin. Increases in level of use were reported for TMP/SMX and nitrofurantoin; the trend for use of TMP/SMX was decreasing while the trend for nitrofurantoin was increasing.

Patient Outcomes (Appendix D, Table 4)

The fluoroquinolone restriction study reported patient outcomes.⁵⁷ There was a small but statistically significant increase in claims for an outpatient visit in the 30 days following the index visit (55.6% before restriction vs 56.5% after, $p < 0.001$). There was also a small increase in all-cause hospitalization within 30 days (4.9% before restriction vs 5.2% after, $p = 0.0001$) but no change in hospitalization related to the 4 infections of interest (1.4% before restriction vs 1.4% after, $p = 0.20$). Mortality was unchanged.

Microbial Outcomes

Neither study reported microbial outcomes.

Costs (Appendix D, Table 5)

The study of a “limited use” policy reported cost data.⁵⁸ There was no significant change in either the level or trend of total antimicrobial costs following implementation of the policy. There were significant decreases ($p < 0.0001$) in the level for costs of the fluoroquinolone group and ciprofloxacin but no significant changes in the trend for costs. There was no change in the level of levofloxacin costs but a significant change in trend (increasing). The level for costs of TMP/SMX and nitrofurantoin increased significantly ($p < 0.0001$) with a decreasing trend for TMP/SMX and an increasing trend for nitrofurantoin.

Computerized Clinical Decision Support (k=6 trials)

Key Findings

Prescribing Outcomes: Clinical decision support was associated with decreased prescribing in 4 of the 6 studies. One study found no difference but also reported that the intervention was rarely used by providers. Another study reported mixed results – reminders were associated increased adherence to only some prescribing

recommendations. For antimicrobial selection, one study found significantly reduced use of broad-spectrum antimicrobials post-intervention. A second study found clinical prediction rules associated with changes in prescribing for some, but not all, antimicrobials.

Patient Outcomes: No significant differences between intervention and control were reported for return clinic visits (4 studies), hospitalization (2 studies), late antimicrobial prescriptions (2 studies), or adverse events (1 study).

Microbial Outcomes: No study reported microbial outcomes.

Cost Outcomes: No study reported cost outcomes.

In 6 studies, the primary intervention was clinical decision support.⁵⁹⁻⁶⁴ Two were RCTs,^{60,61} 3 were CRCTs,^{59,63,64} and one was a CBA study.⁶² Five studies were conducted in the United States⁵⁹⁻⁶³ and one in the Netherlands.⁶⁴ All of the studies involved primary care clinics; one study was conducted at VA facilities.⁶² Risk of bias was medium for one study⁶⁰ and high for 5 studies (Appendix D, Table 6). All of the studies focused on reducing antimicrobial use; 2 studies also addressed antimicrobial selection.^{60,61} One study included clinical decision support pathways for 8 outpatient infections,⁶⁰ one included all antibiotic prescriptions,⁶⁴ and the remaining studies focused only on respiratory conditions. One study included adults and adolescents,⁵⁹ one study included adults,⁶² and 4 studies did not report inclusion or exclusion criteria based on age. Each of the studies involved the use of an electronic health record (already in place at the facilities).

For the RCTs and CRCTs, the unit of randomization was practices/clinics in 4 studies^{59,60,63,64} and providers in one study.⁶¹ All of the studies involved a computerized decision support system. One study evaluated both printed decision support (patient brochures, posters) and computer-assisted decision support.⁵⁹ In another study, the decision support included reminders for alternative medications, no prescriptions, alternative approaches, and specialist referral.⁶⁴ A third developed a “Smart Form” to be used when interviewing and evaluating patients.⁶³ Supplemental components included clinician education,⁵⁹ instruction on use of the system,^{61,63,64} advice to providers on maintaining patient satisfaction,⁶² information on individual or clinic performance,^{59,63} patient education,^{59,60} a peer champion,⁶⁰ bundled order sets,⁶¹ and guidelines.⁶⁴ The comparator was usual care in 5 studies with one study also providing the usual care group with background information on the clinical prediction rules used in the intervention.⁶¹ In the sixth study, the comparator was reminders about cholesterol prescriptions.⁶⁴ Outcomes reported are summarized in Table 9.

Table 9. Outcomes Reported in Studies of Clinical Decision Support

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Gonzales 2013 ⁵⁹	✓	✓		
Jenkins 2013 ⁶⁰	✓	✓		
McGinn 2013 ⁶¹	✓	✓		
Rattinger 2012 ⁶²	✓			
Linder 2009 ⁶³	✓	✓		
Martens 2007 ⁶⁴	✓			

Prescribing Outcomes (Appendix D, Table 3)

The study of paper and computer-assisted decision support found differences in prescribing rates from baseline to intervention to differ significantly when both paper ($p=0.003$) and computer-assisted ($p=0.01$) systems were compared to usual care.⁵⁹ Paper decision support was associated with a 12% decrease in prescriptions, computer-assisted decision support was associated with a 13% decrease in prescriptions, and usual care with a nearly 2% increase.

In the study of multiple infection sites, over 70% of the visits were for respiratory infections.⁶⁰ The authors reported a significant reduction in prescribing at the intervention sites (11.2%, $p<0.0001$) but not at the control sites (2.8%, $p=0.25$). A trend analysis showed greater decline in use in the intervention group.

Clinical prediction rules were associated with a significant reduction in overall prescribing in the intervention group (adj RR 0.74 [95% CI 0.60, 0.92]; $p=0.008$) with a reduction in prescriptions for pneumonia but not pharyngitis.⁶¹

In the VA study, a clinical decision support system for azithromycin and gatifloxacin was associated with a decrease in the proportion of unwarranted prescriptions for these antimicrobials at the intervention site (22% baseline vs 3.3% post-intervention; $p<0.0001$) but not the control site.⁶² There was no significant change in other antimicrobials at either site. The proportion of visits where antimicrobial use was congruent with guidelines increased significantly at the intervention sites (63% baseline, 72% post-intervention; $p=0.0001$) but not at control sites (74% baseline vs 69% post-intervention; $p=0.69$).

The “Smart Form” was not found to effect prescribing patterns.⁶³ It was noted that the form was used for only 6% of patient visits (742/11,954) for acute respiratory infection.

The study of reminders looked at situations where no prescribing of a particular drug was advised and found few differences in prescribing between intervention and control.⁶⁴ Of 8 prescribing recommendations, there were significant ($p<0.05$) reductions in prescriptions of first-line drugs for acute sore throat (0.2 per practitioner per 1000 enlisted patients intervention vs 0.8 control) and quinolones for cystitis in women age 12 and older (1.5 per practitioner per 1000 enlisted patients intervention, 4.6 control). In situations where prescribing of a particular drug was advised, only one finding was significant – appropriate prescriptions for cystitis in women age 12 and older (73% intervention vs 57% control; $p<0.05$).

Two studies reported on antimicrobial selection. The study of multiple infection sites also reported on the proportion of all clinical pathway conditions for which a broad-spectrum antimicrobial was prescribed and found a significant reduction from baseline to post-intervention at the intervention sites (26.4% to 22.6%, $p<0.0001$) but not at the control sites (20.0% to 19.4%, $p=0.35$). The trend analysis showed a greater decline in broad-spectrum use in the study group ($p=0.001$).⁶⁰ In the study of clinical prediction rules, there was a significant difference between intervention and control in quinolone prescriptions following the intervention (9.9% intervention vs 19.6% control, $p=0.02$) but no differences for penicillins, cephalosporins, and macrolides.⁶¹

Patient Outcomes (Appendix D, Table 4)

Four studies reported patient outcomes. The study comparing paper decision support, computer-assisted decision support, and usual care found no difference between study arms for return clinic visits or hospitalizations for bronchitis, pneumonia, or COPD.⁵⁹ Between 0.5% and 1.5% of patients were initially diagnosed with uncomplicated acute bronchitis and subsequently diagnosed with pneumonia on the return visit. Differences between study arms were not reported.

Studies of a decision support tool with clinical prediction rules⁶¹ and a decision support tool to use when interviewing and evaluating patients⁶³ found no significant differences in return clinic visits at either 2 weeks⁶¹ or 30 days⁶³ after the initial visit. One study also reported no difference in return visits attributable to acute respiratory infections.⁶³ One study reported antimicrobial prescriptions 2 weeks after the initial visit with no significant difference between intervention and control.⁶¹

The study enrolling patients with any of 8 outpatient infections found a significant increase in return clinic visits in the control sites (3.3% baseline vs 4.2% post-intervention; $p=0.02$) but not at the intervention sites (3.7% baseline vs 3.0% post-intervention; $p=0.13$).⁶⁰ There were no significant changes in hospitalizations or late antimicrobial prescriptions (8 to 30 days after the initial visit) in either group.

Microbial Outcomes

None of the studies reported microbial outcomes.

Costs

No study reported cost outcomes.

Financial Incentives (k=1 trial)

Key Findings

Prescribing Outcomes: In one study of financial incentives, immediate changes in prescribing were observed in the intervention group for 2 of 7 antimicrobials studied. The changes were not maintained at one year.

Patient Outcomes: Patient outcomes were not reported.

Microbial Outcomes: Microbial outcomes were not reported.

Cost Outcomes: Cost outcomes were not reported.

One study meeting eligibility criteria examined the effect of financial incentives to modify general practitioner prescribing behavior (volume and quality of prescriptions).⁶⁵ The controlled before and after study was conducted in the Netherlands and was of high risk of bias (Appendix D, Table 6). The focus was on 7 antimicrobials or antimicrobial classes 1) quinolones for urinary tract infection (decrease expected), 2) nitrofurantoin as an alternative to fluoroquinolones (increase expected), 3) trimethoprim as an alternative to quinolones (increase expected), 4) amoxicillin plus clavulanic acid (decrease expected), 5) amoxicillin (decrease expected), 6) doxycycline for sinusitis (decrease expected), and 7) mupirocin for skin infections (decrease

expected). The analysis also included gastric drugs and newly introduced drugs. The financial incentive was a bonus that was independent of performance. Providers were expected to adhere to prescription guidelines and formulary recommendations. The usual care providers were not provided with the formulary and were not aware that their performance was being evaluated. It was assumed that both groups were familiar with the national guidelines and attended medical education sessions. No information was provided about the patient population.

Prescribing Outcomes (Appendix D, Table 3)

Significant improvements immediately post-intervention (three months prior to the intervention compared to 3 months after the start of intervention) were noted in the intervention group for 2 of the 7 antimicrobials studied: trimethoprim (7% intervention vs 0% control, $p=0.006$) and amoxicillin+clavulanic acid (17% intervention vs 0% control, $p=0.008$).⁶⁵ For doxycycline, there was a significantly greater improvement in the control group (2% intervention vs 14% control, $p=0.01$). Long-term, comparing findings from April, May, and June prior to the intervention with the same months the following year, no differences between the intervention and control groups were noted.

Patient Outcomes

Patient outcomes were not reported.

Microbial Outcomes

Microbial outcomes were not reported.

Costs

Costs were not reported.

Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (Findings from a Systematic Review and 9 Recent Trials)

Key Findings

Prescribing Outcomes: A recent systematic review including 2 studies in outpatient settings found that procalcitonin testing leads to decreased antimicrobial prescriptions in patients with ARTI. In a recent study, viral PCR testing in patients with acute respiratory tract infection was associated with an initial decrease in antimicrobial prescriptions in the intervention group but this was not sustained through the study period, while testing for Group A β -hemolytic *Streptococcus* antigen was associated with decreased antimicrobial prescriptions in patients with sore throat compared to usual care. A second study of rapid antigen testing for patients with sore throat found that rapid testing combined with a clinical score was associated with decreased antimicrobial use compared to delayed prescribing. Five of 6 studies of CRP testing in patients with ARTI or mixed infections (alone and in combination with communication skills training) show decreased antimicrobial prescriptions and potentially avoidance of newer, broad spectrum antimicrobials in select patients.

Patient Outcomes: The use of procalcitonin, rapid antigen testing, or CRP testing did not lead to increased mortality. Studies showed no difference in return clinic visits, hospitalizations, modification of initial treatment, duration of fever, or performance of further testing. CRP testing and communication skills training was associated with at least equivalent, and possibly increased, patient satisfaction with care.

Microbial Outcomes: Microbial outcomes were not reported.

Cost Outcomes: The single study that compared cost of care in patients with ARTI managed with CRP testing and communication skills training compared to no CRP testing or communication skills training showed that these both were, alone and in combination, cost-effective methods to decrease antimicrobial use.

Procalcitonin Testing – Systematic Review

A recent high quality Cochrane systematic review and meta-analysis examined studies of the use of procalcitonin, a laboratory marker associated with bacterial infections.⁷³ The review included only prospective RCTs in which procalcitonin cut-off ranges were used to guide initiation and discontinuation of antimicrobial therapy in one study group. Studies were eligible for inclusion if the control group received antimicrobials without the use of procalcitonin levels. Two of the trials included in the review were performed in primary care settings. A total of 1008 patients with acute respiratory tract infections were enrolled. No other studies were identified that addressed the use of procalcitonin testing and were eligible for inclusion in the current review.

Rapid Testing (k=3 trials)

We identified 3 studies that examined the use of rapid testing in helping guide antimicrobial therapy in patients with ARTI or sore throat. One study was a non-blinded RCT performed in Swedish outpatients (median age 39 years) that evaluated the effect of rapid viral PCR testing with rapid (within 1 day) versus delayed (8-12 days after visit) test reporting in patients presenting during usual business hours Monday-Thursday with ARTI with symptom duration less than 2 weeks.⁶⁷ Notably, patients with confirmed bacterial infection (positive rapid test for Group A *Streptococcus* and clinical findings corresponding to bacterial tonsillitis, perforated acute otitis media, high suspicion of lobar pneumococcal pneumonia or severe septicemia, positive blood culture for clinically significant bacterial pathogen and clinical findings corresponding to septicemia) were excluded. Two studies evaluated the use of rapid antigen testing for patients with sore throat. In one three-arm RCT, patients (age 3 years and older) were evaluated with a clinical score based on symptoms, the clinical score plus the rapid antigen test, or delayed prescribing (usual care).⁶⁶ The second study was an RCT in Canadian family physician practices that compared sore throat decision rules (STDR), rapid testing for Group A β -hemolytic *Streptococcus* antigen, or both to usual care in patients presenting with sore throat.⁶⁸ Thirty 7 physicians were randomized. Two studies were rated medium risk of bias^{67,68} and one high risk of bias (Appendix D, Table 6).⁶⁶ Table 10 summarizes outcomes reported in these studies.

C-Reactive Protein Testing (k=6 trials)

We identified 6 studies that examined the effect of testing of C-reactive protein (a non-specific inflammatory marker that is elevated in bacterial infections) alone or combination with other tests or interventions.^{23,24,49,52,53,69-71} There were 3 RCTs,⁶⁹⁻⁷¹ 2 CRCTs,^{49,52,53} and one CBA.^{23,24} Four of the studies were conducted in Europe,^{23,24,52,53,69,71} one in the United Kingdom and Europe,⁴⁹ and one in Japan.⁷⁰ Risk of bias was rated medium for 4 studies^{23,24,49,58,71} and high for 2 studies (Appendix D Table 6).^{52,70} All of the studies reported use; one study also reported antimicrobial selection outcomes.⁷⁰ Five of the studies included patients with respiratory infections;^{23,24,52,53,49,69,71} one did not specify the infection type.⁷⁰ Two studies included only adult patients;^{49,52,53} the other studies included all ages or did not specify. Most studies did not use strict cut-off levels for initiating antimicrobial therapy. In general, providers were provided with the results of the CRP test prior to making a decision about antimicrobial prescription. The amount of provider education about CRP testing and communication skills training varied across studies.

One RCT compared adding rapid CRP testing to usual care to usual care alone in patients presenting with a respiratory infection. The first 1-2 patients each day during the study period were invited to participate.⁶⁹ Another RCT was performed in a Japanese general medicine clinic and enrolled patients presenting with fever and symptoms of suspected infection; antimicrobial selection was also analyzed in this study and, in addition to CRP level, white blood cell count (WBC) was measured and reported to the provider.⁷⁰ The third RCT was performed in Netherlands family practice centers and analyzed the effect of POC CRP testing in combination with education about delayed antimicrobial prescribing in patients presenting for their first consultation for a LRTI or ARS.⁷¹ Of note, providers were advised not to prescribe antimicrobials when the CRP level was less than 20 mg/L, to prescribe immediate antimicrobials for CRP greater than 100 mg/L, and to consider a delayed prescription (patient informed about this strategy and given an information sheet about this strategy, and a prescription given to the patient).

One of the cluster RCTs was performed in Netherlands general practitioner clinics and enrolled patients with suspected LRTI (cough, one focal symptom, and one systemic symptom) and symptom duration less than 4 weeks.^{52,53} As noted in the section on Communication Skills Training, this study used a factorial design and analyzed the effect of enhanced communication skills training alone and in combination with CRP testing. The cost effectiveness of these interventions alone and in combination has also been reported.⁵³

The second CRCT, conducted in multiple European countries and the United Kingdom, aimed to determine the effect of internet-based trainings about POC CRP testing and enhanced communication skills (each training alone or in combination and compared to usual care) on antimicrobial prescribing and symptom control.⁴⁹ The patients presented with LRTI or URTI and were 18 years or older.

The CBA trial was conducted in Spanish general practitioner clinics and was part of the multinational HAPPY AUDIT study. Spain was the only country in which 2 levels of intervention (feedback for providers after chart audit, courses and guidelines on rational diagnostics and treatment of RTI, patient information leaflet alone or in combination with POC CRP testing and workshops about CRP testing, all compared to usual care) were performed.^{23,24}

The study analyzed 836 patients with ARS before and after the study intervention. A summary of outcomes reported is presented in Table 10.

Prescribing Outcomes (Appendix D, Table 3)

Procalcitonin

The 2 studies of procalcitonin testing in primary care clinics included in the Cochrane review showed a decrease in the rate of initiation of antimicrobials in the procalcitonin testing group compared to the non-testing groups (23% procalcitonin vs 63% no procalcitonin, $p < 0.001$).⁷³ There was also a decrease in the duration of antimicrobials between the groups (median 7, IQR 5-8 days procalcitonin vs median 7, IQR 6-8 days no procalcitonin, difference -0.6 days, $p = 0.04$) as well the total exposure of antimicrobials (median 0, IQR 0 to 0 days procalcitonin vs median 6, IQR 0-7 days no procalcitonin, difference -3.6 days, $p < 0.001$).

Table 10. Outcomes Reported in Studies of Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein

Study, Year	Prescribing Outcomes	Patient Outcomes	Microbial Outcomes	Costs
Little 2013 ⁶⁶ (Rapid Antigen Detection Test)	✓	✓		
Brittain-Long 2011 ⁶⁷ (Rapid Antigen Detection Test)	✓	✓		
Worrall 2007 ⁶⁸ (Polymerase Chain Reaction Assay)	✓			
Little 2013 ⁴⁹ (CRP) (see also Communication Skills Training)	✓			
Llor 2012 ^{23,24} (CRP) (see also Provider and/or Patient Education)	✓			
Cals 2010 ⁷¹ (CRP) (see also Delayed Prescribing)	✓	✓		
Cals 2009 ⁵² , Cals 2011 ⁵³ (CRP) (see also Communication Skills Training)	✓	✓		✓
Takemura 2005 ⁷⁰ (CRP)	✓	✓		
Diederichsen 2000 ⁶⁹ (CRP)	✓	✓		

CRP = C-reactive protein

Rapid Testing

One study of viral PCR testing in patients with respiratory infection showed a decrease in initial prescription rate (4.5% early test result vs 12.3% late test result, $p = 0.005$). However, this effect was not sustained at follow-up in the study period, 8-12 days after initial consultation, when no difference in prescription rates between the early result and late result groups was observed (13.9% early result vs 17.2% late result).⁶⁷

A study of rapid testing for Group A, C, and G *Streptococci* antigen found the use of the rapid test in combination with a clinical score was associated with a significant reduction in antimicrobial use compared to the control condition, delayed prescribing (35% vs 46%, $p=0.03$).⁶⁶ Use of the clinical score, alone, was also associated with a reduction in antimicrobial use (37% vs 46%, $p=0.02$). A second study of rapid testing for Group A β -hemolytic *Streptococcus* antigen showed a decrease in antimicrobial prescription rate with use of rapid antigen testing alone (26.7%) and in combination with sore throat decision rules (STDR) (38.2%) when compared to usual care (58.2%, $p<0.001$ for both comparisons).⁶⁸ Use of STDR alone did not result in decreased antimicrobial prescription rates compared to usual care (55.3% STDR vs 58.2% usual care).

C-Reactive Protein Testing

Five of the 6 studies showed decreased antimicrobial prescribing associated with CRP testing. One study showed a decrease in antimicrobial prescription rates with advance testing of CRP and WBC count (51.7%) compared to usual care (87.6%) ($p<0.001$).⁷⁰ A CRCT found a decrease in antimicrobial prescription rate with CRP testing (30.8%) compared to no CRP testing (52.9%) ($p=0.02$). As noted in the section on Communication Skills Training, there was also a decrease in the group that received communication skills training (27.4%) compared to no communication skills training (53.5%) ($p<0.01$).⁵² Overall, among patients treated with antimicrobials, 67% received amoxicillin or doxycycline, the Dutch guideline recommended first line therapy for LRTI. Another CRCT with a communication skills training component, reported a decrease in antimicrobial prescription rate in patients treated by physicians randomized to the CRP training compared to those with no CRP training (33% CRP vs 48% no CRP, adj RR 0.54 [95% CI 0.42, 0.69]; $p<0.0001$) as well as those randomized to enhanced communication skills training compared to no communication skills training (36% training vs 45% no training, adj RR 0.69 [95% CI 0.53, 0.87]; $p<0.001$). The antimicrobial prescription rate was lowest in the group of patients treated by providers that were randomized to both CRP and enhanced communication skills training (RR 0.38 vs control, [95% CI 0.25, 0.55]; $p<0.0001$). A RCT reported a decrease in overall antimicrobial prescription rate with CRP testing (43.4% CRP vs 56.6% usual care, RR 0.77 [95% CI 0.56, 0.98]).⁷¹ In this study, providers in both groups were allowed to recommend delayed prescribing. As noted in the section on Delayed Prescribing (above), there was no significant difference in the percentage of patients who received delayed prescriptions (17.1% in the intervention group vs 22.5% in the control group) but significantly fewer patients in the intervention group filled those prescriptions (22.7% intervention vs 72.4% control, $p<0.001$). The CBA study showed a significant decrease in the rate of antimicrobial prescription in the full intervention group compared to control for acute rhinosinusitis (56.7% vs 86.7%; OR 0.12 [95% CI 0.01, 0.32])²⁴ and lower respiratory tract infections (43.9% vs 76.6%); OR 0.22 [95% CI 0; .12, 0.38]; $p=0.000$).²³ Of acute rhinosinusitis patients in the full intervention group for whom CRP testing was available, 46.7% of patients who were tested received antimicrobials compared to 82.9% of those in whom CRP testing was not performed ($p<0.001$).²⁴ Similar findings were reported for patients with lower respiratory tract infections (43.9% vs 61.8%, $p<0.001$).²³

One study showed no change in antimicrobial prescription rate between the CRP testing group (43%) and the usual care group (46%) (OR=0.9 [95% CI 0.7, 1.2]).⁶⁹

One study reported on antimicrobial selection. In the study from Japan, the absolute number of prescriptions for newer antimicrobials (cefcapene pivoxil [not FDA-approved] or clarithromycin)

was decreased in patients with non-pneumonic infections compared to other antimicrobials in the advance testing group, although the rate increased due to the smaller number of total patients receiving antimicrobial prescriptions in the advance testing group (67% advance testing vs 45% , $p=0.0031$). Among patients in the advance testing group with elevated WBC count ($WBC \geq 9 \times 10^9 /l$), cefcapene pivoxil was started in 51% of patients receiving antimicrobials compared to patients without elevated WBC count ($WBC \leq 9 \times 10^9 /l$) (26%) ($p=0.025$); of patients receiving antimicrobials, macrolides were prescribed in 50% of patients with $WBC \leq 9 \times 10^9 /l$ compared to 7.7% of patients with $WBC \geq 9 \times 10^9 /l$ ($p < 0.001$).⁷⁰

Patient Outcomes (Appendix D, Table 4)

Procalcitonin

In the Cochrane review, mortality in patients in the 2 studies conducted in primary care settings was 0% in the procalcitonin testing group and 0.2% in the control group ($p=ns$).⁷³ There was no difference in the rate of treatment failure between the groups (31.4% procalcitonin vs 32.7% control, $p=ns$). The number of days with restricted activities was also not different between the groups (median 9 days, IQR 6 to 14, procalcitonin vs median 9 days, IQR 5 to 14, control, $p=ns$).

Rapid Testing

In the study of rapid viral PCR testing it was reported that there were no cases of death, life-threatening events, hospitalization or events resulting in, or threatening to result in, persistent or significant disability.⁶⁷ In one study of a rapid streptococcal antigen detection test, no significant differences were noted between the clinical score plus rapid test group and the usual care (delayed prescribing) group for return clinic visits, adverse events, or patient satisfaction with care.⁶⁶

C-Reactive Protein Testing

Four studies reported on return clinic visits. One study reported no difference between the CRP testing and control groups in subsequent contact with the health service.⁶⁹ The study of CRP and WBC count testing found no differences between the CRP testing group and the control group among patients who returned a follow-up questionnaire (38% of the CRP group, 29% of the control group) with respect to return clinic visits (74.5% CRP vs 80% control, $p=0.2$).⁷⁰ In the CRCT with CRP testing and communications skills training, there was no difference between the CRP testing group and the non-CRP testing group, nor between the communication skills training group and the group without communication skills training, with respect to return clinic visits (34.8% CRP vs 30.4% no CRP, 27.9% communication training vs 38% no training).⁵² A second study from this group also found no difference between the CRP testing and control groups in return clinic visits (25.6% CRP vs 17.8% control).⁷¹

Two studies reported no hospitalizations and no adverse events.^{52,71} The study of CRP and WBC count testing also found no differences in patients who reported fever more than 3 days after starting treatment (45.7% CRP+WBC vs 42.2% usual care, $p=0.72$).⁷⁰ There was also no difference between groups in modification of initial treatment (4.7% CRP+WBC vs 7.1% usual care) or further testing performed at follow-up (12.2% CRP+WBC vs 11.6% usual care). In another study, there were a total of 22 hospitalizations in the CRP testing groups versus 8 hospitalizations in the no CRP groups (OR=2.61, [95% CI 1.07, 6.35]; $p=0.034$).⁴⁹ However, when controlled for all potential confounders the difference was not significant (OR 2.92 [95%

CI 0.96, 8.85]; $p=0.06$). There was no difference between CRP groups in days of symptoms rated moderately bad or worse (median 5, IQR 3-9 for both groups). The median days of symptoms rated moderately bad or worse was higher in the communication skills training groups compared to the no communication skills training groups (median 5, IQR 3-7 days, no communication skills training vs median 6, IQR 3-10 days, communication skills; adj HR 0.83 [95% CI 0.74, 0.03]; $p=0.002$). There were no significant differences between the groups in new or worsening symptoms or the symptom severity scores 2-4 days after the index consultation

One study reported “increased or unchanged morbidity” more frequently after one week in the CRP group (12%) compared to the control group (8%) (OR=1.6 [95% CI 1.0, 2.6]; $p=0.05$).⁶⁹ In this open-label study, a greater number of patients not receiving antimicrobials reported “increased or unchanged morbidity” (13%) compared to those receiving antimicrobials (7%) (OR=2.0 [95% CI 1.2, 3.1]; $p=0.006$). Among patients not receiving antimicrobials, the study reported “increased or unchanged morbidity” more in patients in the CRP group (16%) compared to the control group (10%) (OR=1.7 [95% CI 1.0, 2.8]; $p=0.04$). The study also reported “increased or unchanged morbidity” more frequently in patients with CRP levels less than 11 mg/l (16%) than in patients with CRP levels greater than 11 mg/l (8%) (OR 2.2 [95% CI 1.1, 4.4]; $p=0.03$).

Patient satisfaction was reported in 2 studies. The study with CRP testing and communication skills training reported the proportion of patients “at least very satisfied” with care was not significantly different between the groups (76.8% CRP vs 76% no CRP, 78.7% communication training vs 74.4% no training).⁵² A second study found the proportion of patients “at least very satisfied” with care was higher in the CRP testing group (76.3% CRP vs 63.2% control, $p=0.03$).⁷¹

Microbial Outcomes

No study reported microbial outcomes.

Cost Outcomes (Appendix D, Table 5)

C-Reactive Protein Testing

A cost analysis was done using data from the CRCT⁵² that showed, as discussed above, a decrease in antimicrobial prescription rate with CRP testing compared to no CRP testing and with communication skills training compared to no communication skills training. Medication costs (mean cost per patient) were lower in the 3 intervention groups (CRP €16.89, communications skills training €10.47, and CRP + communication skills training €12.54) than in the usual care group (€18.18). Total costs (including intervention costs) were lowest in the communication skills training group (€25.62 compared to €37.58 in the CRP group, €37.78 in the CRP + communications skills training group, and €36.96 in the usual care group). The cost-effectiveness analysis showed that both the communication skills training and CRP testing, alone and in combination, are cost effective means to reduce antimicrobial prescription for LRTI at no, or low, willingness-to-pay.⁵³

KEY QUESTION 2

What are the key intervention components associated with effective outpatient antimicrobial stewardship (eg, type of intervention; personnel mix; level of support)?

Existing Systematic Review

The AHRQ review of studies focused on the decision to treat compared studies with interventions of provider education alone to studies with both provider and patient education.¹³ Among studies included in the effect size analysis, there was no reduction in prescribing in studies with a patient education component. However, 2 studies not included in the effect size analysis, both of which were large population-based studies conducted in the United States, did report a benefit of a combined intervention. In studies focused on treatment selection, the authors were able to compare provider education to provider education with audit and feedback. Interventions with audit and feedback were less effective than education alone although caution was advised in interpreting this finding due to potential confounding factors. There was some evidence that inclusion of more active education elements (eg, consensus-building sessions, educational outreach visits) may be associated with improved prescribing outcomes compared to passive education interventions (eg, distribution of educational materials, lectures).

Updated Evidence Newly Identified for this Evidence Report

Several of the recent studies meeting eligibility for inclusion in the review provided information about key components of the interventions studied. The study conducted in emergency departments,³⁰ half of which were VA sites, incorporated several elements that allowed for an evaluation of the organizational factors associated with the intervention outcomes.⁷⁴ Included were telephone interviews with local project leaders during each year of the 3-year intervention, “stealth observers” who visited sites to assess intervention implementation, and site visits after the intervention period (which included focus groups, personal interviews, an educational seminar where study results were presented, and a structured discussion following the seminar). Three “organizational effect modifiers” were identified. The first was leadership. Passionate and knowledgeable project leaders (physician champions) were viewed as critical. The second was “quality improvement history and approach.” Different sites reported different approaches to quality improvement ranging from a teamwork approach (involving staff at all levels in determining appropriate quality improvement measures) to a “top-down” approach where directions were issued from the central office. Involvement of the whole team with opportunities for non-physician involvement was recommended. Prior experience with quality improvement was also cited as a factor in implementation success. The third modifier was institutional priorities. Some sites focused heavily on patient satisfaction surveys and there were concerns about poor satisfaction ratings if patient expectations for antimicrobials were not met. There was also a sense that if the institution did not prescribe antimicrobials, patients would go elsewhere to get the prescription. Use of personal or departmental consequences for low patient satisfaction scores was perceived as a barrier to successful implementation. Of the 7 intervention sites, 4 were rated as “responders” (ie, prescription rates for acute respiratory syndrome were less than 20% of all visits or prescription rate decreased more than 20% during a 2 year follow-up period). The overall *implementation rating* was excellent for 2 of the 4 sites and fair for the remaining 2 sites. The rating was based on local opinion leader feedback, observations, and focus group discussions. A rating

of excellent meant that all the components of the intervention were implemented and the majority of the providers were aware of the goal. A rating of poor meant that none or almost none of the components were implemented. Other implementation achievements were rated as fair. Of the 3 non-responder sites, 2 were rated at poor and one as fair.

Another study used a provider questionnaire and provider interviews to gain insight into the intervention. The intervention focused on patient and provider education regarding antimicrobial use for children 6 years of age and younger.²⁸ Included were patient newsletters, a website, materials placed in offices and pharmacies, practice-level feedback to providers, bi-monthly information sheets for providers on antimicrobial use and respiratory tract infections, and a visit to practices by the education coordinator. A questionnaire was distributed to all providers in the participating communities interviews were conducted with a convenience sample of the providers.⁷⁵ The questionnaire focused on attitudes about antimicrobial resistance and prescribing patterns. The interviews, with 20 providers from intervention communities and 16 from control communities, included questions about the intervention. Physicians were asked to identify what caused them to change their prescribing patterns. Most responded that the major influence was either the intervention program used in the study or elements similar to those in the intervention (*ie*, the messages, methods). Other factors cited were journal articles and guidelines from professional organizations. Providers in the intervention group were asked to specify which of the intervention elements were most useful. The 2 key elements were “frequent, brief reminders to be careful about antibiotic use” and patient education brochures and office posters. Providers also offered suggestions for future interventions including a) repeated, consistent, brief reminders about antimicrobials to parents and providers, b) annual repetition of messages before the cold season, c) campaigns on television, in the lay press, and in other mass media formats, d) using principals of academic detailing and direct-to-consumer advertising to education parents about judicious use of antimicrobials, and e) education in schools.

A third study³⁷ conducted focus group interviews with providers and peer tutors who participated in the study.⁷⁶ The core of the intervention was individual feedback of prescription rates for antimicrobials used for acute respiratory tract infections. Other elements of the intervention included a comparison of individual prescribing data to data from other participating practitioners, a presentation on national guidelines and recent evidence, emphasis on delayed prescribing, and a 1-day educational seminar. Tutors – experienced general practitioners specifically trained for the role – led the educational sessions and feedback reporting. Providers were recruited to participate in the study according to the continuing medical education group in which they participated. Interviews were completed with 39 general practitioners (of 489 representing 80 medical education groups) and 20 tutors (of 27 who participated in the intervention).⁷⁶ The general practitioners viewed “peer group academic detailing” to be a suitable method for learning although some viewed it as time-consuming. They thought the learning sessions allowed them to become more reflective when making decisions about prescribing. The general practitioners were more accepting of peer tutors who were independent of “the pharmaceutical industry and the health authorities.” They were more comfortable discussing reasons for inappropriate prescribing with peers who “shared an understanding of the complex decision-making involved in prescribing in general practice.” The tutors and the practitioners also appreciated the “sense of security” among participants in the group sessions and thought that led to “open and constructive discussion.” Tutors noted that practitioners would try to justify

and explain cases of inappropriate prescribing brought to their attention. Practitioners generally thought that the feedback was incentive to reflect, learn, and change prescribing practices. Most openly shared their prescription results but the experience was stressful for some and some were unwilling to share. Practitioners also commented on the patient role in the prescribing process, noting patient demands for certain drugs and the difficulty experienced convincing patients of the appropriate care pathway. The study authors³⁷ identified the following key components associated with the success of the intervention in significantly reducing acute respiratory tract infection episodes with an antimicrobial prescription: a) the comfort of practitioners discussing prescribing practices with peers within their continuing medical education group, b) provider willingness to reflect on baseline reports of their prescribing practice, and c) use of tutors who were general practitioner colleagues and who had a high level of enthusiasm and dedication.

Other studies commented on factors they perceived to be related to success of the interventions. A study that assigned practices to internet-based CRP training, communications skills training, CRP and communications skills training, or usual care, considered the interactive nature of the intervention to be a key factor in the effectiveness of the intervention.⁴⁹ Physicians in the communications skills training groups were given an interactive booklet to use during patient consultations and video demonstrations of consultation approaches were part of the training.

The authors of a study evaluating educational interventions for health professionals, pharmaceutical representatives, and the general public thought that synchronizing the professional and public education components was a key feature of their intervention.³⁶ They noted that during the educational sessions, providers commented on improving their diagnostic accuracy (viral vs bacterial infection) and greater willingness of patients to accept the diagnosis of viral infection. At the professional level, they cited leadership by local health professionals, providing leaders with high quality materials, operational support, and compensating leaders for their time as important. In addition, they noted the use of user-friendly and credible educational materials. For the public campaign, leadership of local health professionals was critical to heightening public awareness. Understandable key messages were disseminated to the public. Finally, the formation of working alliances between the pharmaceutical industry, government, and providers allowed for delivery of consistent educational messages.

A study of an educational intervention for primary care pediatricians that included workshops on antimicrobial prescribing and parent-physician communication, feedback on prescribing rates, and provider participation in focus groups, reported that the emphasis on physician engagement and commitment to the educational process was a key factor associated with the success of the intervention.²⁵ Local leaders were involved in development of the intervention.

The success of guidelines distributed to physicians and pharmacists, with voluntary educational events for promotion of the guidelines, was attributed, in part, to their “user-friendly” and “concise and attractive” format.⁴⁴ The guidelines were prepared by a credible organization and had a strong evidence base. In addition, professional associations endorsed the guidelines and they were actively promoted and disseminated.

Several steps were taken to ensure successful integration of clinical prediction rules for pharyngitis and pneumonia into an electronic health record.^{61,77} Usability testing (including both simulated patient encounters and staged patient encounters) preceded the study period.

Additionally, a rapid response team (with informatics and clinical expertise) was available during the first week of software use, an option to send messages to the software team was included in the design, a lead clinician was present at the practice to address any frustration or problems with the software, and focus groups were held to capture user feedback.⁷⁷ Providers in the intervention groups completed a 1-hour training session that included the evidence supporting the prediction rules and study protocols, a demonstration of how to use the tool within the electronic health record, and a video of a simulated patient encounter.⁶¹ It was reported that 62.8% of providers in the intervention group opened the tool with 57.5% of providers accepting it. The pharyngitis tool was more widely used than the pneumonia tool.⁶¹

A study of sore throat decision rules and/or rapid antigen detection tests for Group A β -hemolytic *Streptococcus* found lower antimicrobial prescribing for sore throat in the groups randomized to either rapid testing or rapid testing plus decision rules when compared to usual clinical practice.⁶⁸ The authors concluded a negative rapid antigen test result might have allowed providers to be more confident in rationalizing the decision not to prescribe antimicrobials.

One study speculated on why an electronic health record component, the “*ARI Smart Form*,” when used, *did not* reduce prescribing.⁶³ Among the reasons given were diagnostic uncertainty, patient desire, fear of complications, lack of time, lack of compelling reason to change practice patterns, competing and conflicting guidelines for some ARIs, and concern that recommendations might not be applicable to specific patients (*ie*, patients with comorbid conditions or contraindications to recommended therapies). It was also noted that the “*Smart Form*” addressed errors of commission for an acute problem (*ie*, asking providers *not* to do something). Most decision support tools have been focused on errors of omission for chronic conditions. The authors recommended usability testing and refinement of the tool prior to system-wide implementation and more intensive training on the use of the tool once it is introduced to providers.

KEY QUESTION 3

Does effectiveness vary by a) clinic type or setting (primary care clinic vs emergency department or urgent care; VA, non-VA) or b) suspected patient condition (respiratory tract infections, urinary tract infections, soft-tissue infections)?

Clinic Type or Setting

Existing Systematic Review

The AHRQ Technical Review did not report findings for different clinic types or settings.¹³

Updated Evidence Newly Identified for this Evidence Report

The majority of studies included in this review were conducted in primary care settings (including general practice, family practice, and pediatric clinics). Two studies did not specify the location.^{44,58}

The exceptions were as follows. A study of antimicrobial prescribing for acute dental pain was conducted in general dental practices.⁴⁵ A study of changes in fluoroquinolone use for

gonorrhea included patients from multiple practice settings (with only 26% of patient seen in primary care).⁴¹ The largest percentage of patients was treated in sexually transmitted disease clinics (35%) with 16% treated in emergency departments or urgent care centers, 12% treated in a hospital, and 7% in family planning clinics. Another study enrolled providers from a group practice that was the sole provider of care at the urgent care clinic and the emergency department.³⁶ A study of rapid viral PCR testing enrolled patients from 8 primary care clinics and 4 outpatient departments of infectious diseases.⁶⁷

One study was conducted exclusively in emergency departments, half of which were at VA Medical Centers.³⁰ Another study analyzed outpatient visits to 2 VA Medical Centers – one serving as the intervention site and the other as the control site.⁶² Results from these 2 studies are summarized in Table 11.

Table 11. Studies Conducted in VA Medical Centers

Author, year Study design	Intervention type	Goal	Infection site, Patients	Antimicrobial Prescribing	Patient Outcomes
Metlay 2007 ³⁰ CRCT	Education (with clinician leaders, site-specific antimicrobial use data, patient education)	Reduce antimicrobial overuse in the emergency department	Acute respiratory tract infection Adults at 8 VA Medical Centers and 8 non-VA academic medical centers	Percent prescribed antimicrobials for URTIs and acute bronchitis (adjusted differences from baseline) Intervention sites: -10% [95% CI -18%, -2%] Control sites: 0.5% [95% CI -3%, 5%]	No significant site by time interaction for a) return emergency department visits during 2 week follow-up (p=0.48) b) hospitalizations during 2 week follow-up (p=0.51) c) self-reported satisfaction with visit (p=0.71)
Rattinger 2012 ⁶² CBA	Clinical decision support system for azithromycin and gatifloxacin	Minimize unnecessary use	Respiratory infection Adults at 2 VA Medical Centers	<i>Proportion of unwarranted prescriptions</i> Targeted antimicrobials Intervention site: significant decrease from 22% to 3.3%, p<0.0001; no significant change for other antimicrobials Control site: no significant change for targeted or other antimicrobials	NR

CBA = controlled before and after; CRCT = cluster randomized controlled trial; URTI = upper respiratory tract infection; VA = Veterans Affairs; NR = not reported

Suspected Patient Condition

Existing Systematic Review

The AHRQ Technical Review did not find evidence of differential effects for interventions directed at different patient populations.¹³

Updated Evidence Newly Identified for this Evidence Report

Respiratory infections were most commonly studied (29 trials). Seventeen studies included more than one type of infection or did not report infection site.^{22,25,26,28,29,34,36,39,40,44,46,57,58,60,64,65,70} We identified one study of antimicrobial prescribing for acute dental pain,⁴⁵ 2 studies of prescribing for urinary tract infections,^{42,47} and one study of prescribing for sexually transmitted infections.⁴¹ With numerous studies of respiratory infection, the findings would likely mirror those of the total body of included studies. We summarized results from the 4 unique infection studies in Table 12.

Table 12. Summary of Results from Studies of Dental Pain, Urinary Tract Infection, and Sexually Transmitted Infections

Author, year Study design	Intervention type	Goal	Infection site, Patients	Antimicrobial Prescribing	Patient Outcomes
Seager 2006 ⁴⁵ CRCT	Guidelines (with patient leaflets, academic detailing)	Reduce unnecessary and inappropriate prescribing	Dental Age 16 and older	Odds of being prescribed an antimicrobial (vs control) OR 0.63 [95% CI 0.41, 0.95] Odds of being prescribed inappropriate antimicrobial OR 0.33 [95% CI 0.21, 0.54]	NR
Little 2010 ⁴⁷ RCT	Delayed prescribing	Reduce antimicrobial use	UTI Non-pregnant women, uncomplicated UTI	Odds of using antimicrobials if assigned to delayed prescribing group (vs immediate antimicrobials) OR 0.12 [95% CI 0.03, 0.59]	Return clinic visit within 1 month (delayed vs immediate) OR 0.44 [95% CI 0.21, 0.95]
Slekovec 2012 ⁴² ITS	Guideline (with voluntary training sessions)	Appropriate selection	UTI Women 15 to 65 years old	<i>Slope</i> Post intervention: Increased for nitrofurantoin, fosfomycin-trometamol; decreased for norfloxacin (all p<0.001); unchanged for fluoroquinolones <i>Level</i> Post intervention: Decreased for single-dose fluoroquinolone (p=0.002); unchanged for all others studied	NR
Dowell 2012 ⁴¹ ITS	Guideline	Decrease use of fluoroquinolones	Sexually transmitted Infection Gonorrhea	Post-intervention: proportion of gonorrhea cases treated with fluoroquinolones decreased by 21.5%	NR

CRCT = cluster randomized controlled trial; RCT = randomized controlled trial, ITS = interrupted time series; UTI = urinary tract infection; OR = odds ratio; NR = not reported

KEY QUESTION 4

What are the harms of antimicrobial stewardship programs in outpatient settings?

Existing Systematic Review

The AHRQ Technical Review did not report on harms of ASPs.¹³

Updated Evidence Newly Identified for this Evidence Report

None of the recent studies reported possible harms of implementing ASPs in outpatient settings. As reported under Key Question #1, there was limited reporting of return clinic visits, hospitalizations, and adverse events (including mortality). Those studies that did report generally found no significant differences between intervention and control groups.

KEY QUESTION 5

Within the included studies, what are the barriers to implementation, sustainability, and scalability of antimicrobial stewardship programs in outpatient settings?

Implementation Facilitators

A decision support study offered several possible ways to increase the use of an electronic medical record component - the “*ARI Smart Form*.”⁶³ First, it was recommended that clinical decision support applications be built into the provider workflow rather than additional step. Second, it was suggested that the link between the “*Smart Form*” and the electronic health record be the same as the link to other forms in the system. Again, a seamless fit with provider workflow was recommended. Third, the “*Smart Form*” included formats (*ie*, drop-down lists, radio buttons) that were not present in other parts of the electronic health record. Minimizing new, more complex, features was recommended. Fourth, the “*Smart Form*” was designed to be used with acute respiratory infection and providers were required to determine at the beginning of documentation whether they were going to call up the form. Providers may have chosen not to use the form because they were unsure whether the patient visit would include other medical problems. An estimated 25% of providers did not use the electronic health record during patient visits.

An intervention to train family physicians in shared decision making (DECISION+) was piloted in 4 family medicine groups with 33 family practitioners.⁵¹ The reduction in prescribing was not significant but it was noted that the study was underpowered. A feasibility analysis showed that 46% of physicians attended all 3 of the training workshops and that overall satisfaction with the workshops was high (94%).⁷⁸ Prior to initiating a second, larger trial, a study of barriers and facilitators to physician participation in a continuing professional development program was completed.⁷⁹ The program evaluation included a fifth medical group (with 6 physicians) that joined the pilot study after randomization and was assigned to the control group. The evaluation included semi-structured focus groups (23 physicians from 4 medical groups) and a self-administered questionnaire completed 2 years after the end of the pilot study. There were responses related to the practice environment. Location of the program (nearer to the practice was better), time of the week (daytime preferred), scheduling (easier to fit into schedule if

announced in advance; better to have a fixed period of time during the work schedule for development programs), and time of the year (avoiding summer) all influenced participation. There were also responses related to the program. Providers would be more willing to participate if the program was interesting, fun, motivating, and relevant to improving practice; encouraged patient involvement in care; was recommended by a professional association or by colleagues; and provided continuing medical education credits. Others commented on the DECISION+ training describing it as interactive, stimulating of learning, comprehensive, and evidence-based, although there were also concerns about the length of the program. The decision support tools were described as simple and accurate but it was noted that the method would not work with all patients.

Scalability

All but four^{36,61,62,70} of the recent studies included in the review implemented a stewardship intervention in more than one practice. However, few provided information about issues related to implementing a program in multiple sites.

One of the included studies was an effort to implement an intervention on a larger scale.²⁷ The original study (reported in the AHRQ review) involved 12 peer review groups representing 100 general practitioners.⁸⁰ The intervention included group education and communication skills training, feedback on prescribing behavior 6 months after the intervention, education for assistants to the general practitioners, and education materials for patients. Prescription rates for acute respiratory tract symptoms decreased in the intervention group and increased in the usual care control group (mean difference in change -12% [95% CI -18.9, -4.0]) with no difference in patient satisfaction.⁸⁰ The expanded study enrolled 141 intervention practices (194 general practitioners) from 25 peer review groups and 141 control practices (188 general practitioners).²⁷ Final data were available from 131 intervention and 127 control practices. The intervention was similar with group education and communication skills training, education for assistants, and patient education. The audit and feedback was conducted at one year. In the expanded study, no difference in prescription rate was noted between intervention and control. The authors speculated that the “intervention was not applied as rigorously” as in the original study, perhaps due to greater involvement of researchers in implementing the intervention in the original study and greater involvement of regional expert general practitioners in the expanded study. Less frequent monitoring was also cited as a factor.

Two other studies provided some insight into difficulties with multi-site interventions. In one study, the authors reported that a weakness of their study was the need to train 13 peer academic detailers to reach the 79 practice groups enrolled in the trial.³⁷ The authors suggested that the different personalities of the individuals could have influenced the success of the intervention.

Another study used an internet-based training program to provide general practitioners with information about CRP testing and enhancing communications skills.⁴⁹ Prior to using the training program in the study, feedback about an early version of the program was obtained from interviews with 30 general practitioners in 5 European countries.⁸¹ Respondents expressed their thoughts about the intervention while viewing the intervention materials and during a semi-structured interview following the interactive session. Providers expressed concerns about how the consultation style presented in the training materials would translate to their practices.

Specifically, providers from some countries noted that the length of the consultation and the nature of the patient/provider communication were not reflective of their practice. Some thought the suggestion that patients be asked to summarize what they learned during the consultation would not be accepted by patients. It was also noted that patients see providers sooner in some countries (*ie*, after having symptoms for one or 2 days vs over a week). There were concerns about loss of income in fee for service systems if antimicrobial prescriptions were reduced. There were also concerns about the relevance of evidence from other countries. The authors concluded that interventions need to be tailored to different contexts by including local information and allowing practitioners to choose the communication skills they would use in their practice.

Sustainability

Several studies presented findings over follow-up periods of one year or more. The study comparing postal prescribing feedback plus an academic detailing visit to postal prescribing feedback alone also reported outcomes over a one-year period after the academic detailing visit.³⁹ Overall prescribing and use of co-amoxiclav and cephalosporins decreased comparably for both groups immediately after the intervention; there was a significant increase in narrow-spectrum penicillin in the academic detailing group. By 12 months post-intervention, both groups had returned to pre-intervention prescribing patterns with no differences between groups.

An educational intervention to reduce antimicrobial use in children was implemented over 3 years (the first year was the most intensive) with an additional follow-up year.²⁵ Reductions in total antimicrobial use and use of cephalosporins and macrolides relative to the control group were maintained over the follow-up period. The authors attributed the success of the intervention to “physician engagement and commitment to the educational process.”

The effect of guidelines, distributed to physicians and pharmacists and accompanied by voluntary educational events for promotion of the guidelines, was assessed over 36 months following guideline dissemination.⁴⁴ For antimicrobials overall and for each class of antimicrobials studied, there was a significant level change following guideline dissemination that was maintained over 36 months.

The VA study of a computerized clinical decision support system to improve congruence with guideline recommendations for acute respiratory infections reported data for 4 years post-intervention.⁶² Congruence increased significantly at the intervention site but not at the control site. The increase at the intervention site was sustained over the follow-up period. The proportion of acute respiratory infection visits where antimicrobial use was congruent with guideline recommendations increased from 0.63 before the intervention to 0.72 at year 1 with values of 0.73 at year 2, 0.72 at year 3, and 0.73 at year 4.

A one-time visit by a peer general practitioner with a focus on the “antibiotic misunderstanding” and communication techniques (supplemented by patient education materials in the waiting room) was associated with decreased odds of antimicrobial prescribing relative to baseline.⁵⁶ The decrease was significant at both 6 weeks and 12 months post-intervention. The between groups odds ratios (intervention compared to control) were also significant at 6 weeks (OR 0.38 [95% CI 0.26, 0.56]; $p < 0.001$) and 12 months (OR 0.55 [95% CI 0.38, 0.80]; $p = 0.002$), indicating a sustained but slightly attenuated effect.

The study of a financial incentive to encourage adherence to prescribing guidelines reported outcomes during the 3 months following the intervention and one year later.⁶⁵ The bonus payment was given to all providers independent of performance. Although post-intervention improvements in prescribing were noted for 3 of the 7 antimicrobials, the improvements were not maintained at one year. Providers in one region of the country agreed to participate in the incentive program by a democratic majority decision (*ie*, individual providers were not approached).

Medical records of patients enrolled in a study of CRP testing and communication skills training⁵² were accessed at a mean follow-up of 3.7 years.⁵⁴ Data on the outcomes of interest, episodes of contact with a provider for respiratory tract infection and the proportion of episodes that results in an antimicrobial prescription, were available for 379 of the 431 patients enrolled (87.9%). The number of respiratory tract infections during follow-up did not differ significantly between intervention and control groups for patients in the CRP testing arm of the study (corrected difference -0.10 episodes per patient per year favoring the intervention group, $p=0.12$) or for patients in the communication skills training arm of the study (corrected difference -0.11 episodes per patient per year favoring the intervention group, $p=0.09$). The percentage of episodes of respiratory tract infection treated with antimicrobials during follow-up was not significantly different between intervention and control for patients in the CRP testing arm of the study (corrected difference -4.1% favoring the intervention group, $p=0.36$) but was significantly different between intervention and control for patients in the communication skills training arm (corrected difference -10.4% favoring the intervention group, $p=0.02$). It was noted that CRP testing was rarely used during the follow-up (3.7% of episodes of respiratory tract infection); no data were available on use of communication skills. The authors commented that the lack of effect on office visits would support broader use of either CRP testing or communication skills training (scalability). The findings suggest that training in communication skills may have a longer lasting effect.

SUMMARY AND DISCUSSION

SUMMARY OF RESULTS BY KEY QUESTION

Key Question 1

What is the effectiveness of antimicrobial stewardship programs in outpatient settings on the following:

- a. Primary Outcome: Antimicrobial prescribing (decision to prescribe, selection of antimicrobial, duration of treatment, guideline concordant use)
- b. Secondary Outcomes:
 - 1) Patient centered outcomes (return clinic visits, hospital admission, adverse events, late antimicrobial prescription, patient satisfaction with care);
 - 2) Microbial outcomes (resistance in study population);
 - 3) Costs (program costs, drug costs)?

Existing Systematic Review

An existing systematic review and 2 publications based on the review included studies of quality improvement strategies (*ie*, clinician education, patient education, education combined with audit and feedback, etc) to improve antimicrobial prescribing.¹³ For interventions aimed at reducing unnecessary prescribing, the median reduction in the proportion of subjects receiving antimicrobials was 9.7% (median follow-up of 6 months). The interventions were largely educational and directed toward clinicians and/or patients. There was no clear advantage to any of the interventions. For interventions aimed at improving antimicrobial selection the median improvement in recommended prescribing was 10.6%. Although clinician education with audit and feedback was less effective than clinician education alone, potential confounders were identified. Overall, the quality improvement interventions did not adversely impact patient outcomes.

Updated Evidence Newly Identified for this Evidence Report

We identified 50 trials meeting eligibility criteria that were not included in the systematic review. There were 17 RCTs, 18 CRCTs, 3 CCTs, 6 CBA studies, and 6 ITS studies. Sixteen trials focused on provider and/or patient education, 5 on provider feedback, 6 on guideline implementation, 4 on delayed prescribing, 6 on communication skills training, 2 on formulary restriction, 6 on decision support, one on financial incentives, and 9 on laboratory testing (*ie*, rapid antigen testing, PCR, and C-reactive protein). Two studies included data from VA Health Care Systems. Prescribing, patient, and cost outcomes were reported; none of the studies reported microbial outcomes.

Provider and/or patient education, guideline implementation, delayed prescribing, communication skills training, decision support, and laboratory testing interventions (rapid antigen testing, a PCR assay, and C-reactive protein testing) were generally associated with significant reductions in antimicrobial use (Table 13). Results were less conclusive for provider feedback, formulary restriction, and financial incentives due to either mixed results across studies

or few studies of the intervention type. Few interventions provided sufficient information to reach conclusions about antimicrobial selection. Similarly, there was limited reporting for the outcomes duration of therapy and guideline concordant use of antimicrobials.

For patient outcomes, where reported, there were few differences between intervention and control or from pre- to post-intervention in return clinic visits, hospitalizations, adverse events, late antimicrobial prescribing, or patient satisfaction (Table 14). Few studies reported cost data but in those that did, interventions were typically associated with lower drug costs.

Key Question 2

What are the key intervention components associated with effective outpatient antimicrobial stewardship (eg, type of intervention; personnel mix; level of support)?

Consistent findings across studies that surveyed intervention participants or speculated on effective components were the importance of leadership (ideally with peers as local champions, instructors, and/or discussion leaders) and use of a team approach (with input from health care professionals at all levels), patient education materials (ideally linked with provider materials on the same topic), provider reminders, user-friendly interfaces, and evidence-based materials.

Key Question 3

Does effectiveness vary by a) clinic type or setting (primary care clinic vs emergency department or urgent care; VA, non-VA) or b) suspected patient condition (respiratory tract infections, urinary tract infections, soft-tissue infections)?

The majority of studies included in this review were conducted in primary care settings (including general practice, family practice, and pediatric clinics). The exceptions were studies in dental clinics, sexually transmitted disease clinics, emergency departments, and outpatient infectious disease clinics. It is impossible to comment on the effectiveness of interventions in sites other than primary care.

Similarly, respiratory infections were most commonly studied (29 of 50 trials). We also identified one study of patients with acute dental pain, 2 studies in patients with urinary tract infections, and one study of patients with sexually transmitted infections. The remaining studies did not specify an infection site. With so few studies of any infection other than respiratory, it is impossible to determine whether the effectiveness of interventions varies by infection site.

Two studies included patients from VA Medical Centers. Both reported improved prescribing outcomes. One study reported no difference in patient outcomes.

Table 13. Strength of Evidence for Outpatient Antimicrobial Stewardship Studies, Antimicrobial Prescribing

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation (or as noted)	Strength of evidence, by outcome
A. Provider and/or Patient Education Studies (k=16)						
Gerber 2012 ²⁰	CRCT	Reduce inappropriate antimicrobials for pediatric acute RTIs	Medium	Proportion of broad-spectrum antimicrobials	Intervention: 12.5% decrease Control: 5.8% decrease Treatment by time interaction: p=0.01	Low For Antimicrobial Prescribing
Vinnard 2013 ²¹	CBA	Reduce antimicrobials for upper respiratory infection	High	Antimicrobial use	Intervention: 4.7% decrease Control: 1.2% increase; p=0.133	
Butler 2012 ²²	RCT	Reduce antimicrobials for all causes	Medium	Oral antimicrobial dispensing	% reduction: 4.9 [95% CI 0.5, 7.7]; p=0.02	
Llor 2012 ^{23,24}	CBA	Reduce antimicrobials for lower RTIs	Medium	Antimicrobial prescription rate	LRTI: OR 0.42 [95% CI 0.22, 0.82]; p=0.01*	
Regev-Yochay 2011 ²⁵	CRCT	Reduce prescription rates (pediatric)	High	Antimicrobial prescription rate	RR 0.76 [95% CI 0.75, 0.78]	
Esmaily 2010 ²⁶	CRCT	Decrease use of antimicrobials	High	% of prescriptions with antimicrobial	NS	
Smeets 2009 ²⁷	CBA	Reduce antimicrobials for acute RTIs	High	Number of antimicrobial prescriptions	NS	
Finkelstein 2008 ²⁸	CRCT	Reduce unnecessary antimicrobial use (pediatric)	Medium	Adjusted % change in prescribing	Change between intervention and control communities Age 3 to <24 mos: -0.5%; p=0.69 Age 24 to <48 mos: -4.2%; p<0.01 Age 48 to <72 mos: -6.7%; p<0.0001	
Chazan 2007 ²⁹	RCT	Increase appropriate use of antimicrobials	High	Total antimicrobial use	Continuous intervention group: 20.0% reduction Seasonal intervention group: 16.5% reduction p<0.0001	
Metlay 2007 ³⁰	CRCT	Reduce antimicrobial use for acute RTIs in the emergency department	Medium	Antimicrobials for URTIs and acute bronchitis	Adjusted differences (intervention year – baseline year) Intervention sites: -10% [95% CI -18%, -2%] Control sites: 0.5% [95% CI -3%, 5%]	
van Driel 2007 ³¹	CRCT	Increase rational use of antimicrobials for acute rhinosinusitis	High	Antimicrobial prescriptions	OR _{adj} 0.63 [95% CI 0.29, 1.37]	
Little 2005 ³³	RCT	Effectiveness of 3 prescribing strategies and an information leaflet (see delayed prescribing)	Medium	Self-reported use of antimicrobials	Leaflet: 55% No leaflet: 57%; p=0.58†	

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation (or as noted)	Strength of evidence, by outcome
Pagaiya 2005 ³⁴	RCT	Improve quality of care	Medium	Antimicrobial prescribing	ARTI Intervention: mean change -14.6% Control: mean change 2.8%; p=0.022 Diarrhea Intervention: mean change -1.8% Control: mean change -2.1%; p=0.308	Low For Antimicrobial Prescribing
Gonzales 2004 ³⁵	CCT	Improve antimicrobial use for acute RTIs (elderly)	High	Prescription rate for ARTIs	NS	
Stewart 2000 ³⁶	CBA	Improve antimicrobial use	High	Total antimicrobial claims	Analysis of before and after data: 9.4% decrease in claims; p=NR	
B. Provider Feedback (k=5)						
Gjelstad 2013 ³⁷	CRCT	Reduce antimicrobial prescribing for acute RTIs and reduce use of broad-spectrum antimicrobials	High	ARTI episodes with antimicrobial prescription	OR 0.72 [95% CI 0.61, 0.84]	Low For Antimicrobial Prescribing
Vinnard 2013 ²¹	CBA	Reduce antimicrobial prescribing for URTIs	High	Antimicrobial prescribing	Change in prescribing relative to control Intensive intervention: ROR 2.60 [95% CI 1.23, 5.45] Mild intervention: ROR 1.67 [95% CI 0.74, 3.79]	
Linder 2010 ³⁸	CRCT	Reduce inappropriate prescribing for acute respiratory infections	High	Oral antimicrobial within 3 days of ARI visit	OR 0.97 [95% CI 0.7, 1.4]; p=0.87	
Naughton 2009 ³⁹	RCT	Reduce overall antimicrobial prescribing and 2 nd -line prescribing	High	Antimicrobial prescribing	NS	
Madridejos 2004 ⁴⁰	CCT	Improve quality of prescribing	Medium	Over prescription of antimicrobials	Change in intervention group pre to post intervention: p=0.006 Difference between intervention and control groups post-intervention: p=0.026	
C. Guidelines (k=6)						
Venekamp 2012 ⁴³	ITS	Change prescription rates for acute rhinosinusitis	Medium	Prescription rate	Post-intervention slope significantly different from pre-intervention slope (p<0.05)	Low For Antimicrobial Prescribing
Weiss 2011 ⁴⁴	ITS	Effect of guidelines on antimicrobial use	Medium	Difference in prescribing	Significant level change after guideline dissemination (p=0.002)	
Seager 2006 ⁴⁵	CRCT	Assess effect of education outreach visits on prescribing for dental pain	Medium	Odds of prescription; odds of inappropriate prescription	Prescription: OR 0.63 [95% CI 0.41, 0.95]; p<0.05 Inappropriate prescription: OR 0.33 [95% CI 0.21, 0.54]; p<0.05	
Martens 2006 ⁴⁶	CCT	Effect of guidelines on volume of prescriptions	High	Total antimicrobial prescriptions per GP per year	NS	

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation (or as noted)	Strength of evidence, by outcome
D. Delayed Prescribing (k=4)						
Cals 2010 ⁷¹	RCT	Effect on management of lower RTI and rhinosinusitis	Medium	Filled delayed prescription	Intervention 23%, Control 72%; p<0.001	Low For Antimicrobial Prescribing
Little 2010 ⁴⁷	RCT	Effect of management strategies for UTI	Medium	Antimicrobial use	Delayed group vs control: OR 0.12 [95% CI 0.03, 0.59]	
Worrall 2010 ⁴⁸	RCT	Reduce antimicrobial use for ARTIs	High	Prescriptions filled	Usual date 43%, Post date 44%, p=0.924	
Little 2005 ³³	RCT	Effectiveness of 3 prescribing strategies and an information leaflet (see education)	Medium	Self-reported use of antimicrobials	No antimicrobials 16%, delayed 20%, immediate 96%; p<0.001	
E. Communication Skills Training (k=6)						
Little 2013 ⁴⁹	CRCT	Effects of internet-based training on antimicrobial prescribing for lower and upper RTIs	Medium	Antimicrobial use	Communication training vs no communication training: RR _{adj} 0.69 [95% CI 0.53, 0.87]; p<0.0001	MEDIUM For Antimicrobial Prescribing
Légaré 2012 ⁵⁰	CRCT	Reduce overuse of antimicrobials for acute RTIs	Medium	Patient decision to use antimicrobials after consultation	RR _{adj} 0.50 [95% CI 0.3, 0.7]	
Légaré 2010 ⁵¹	CRCT	Reduce overuse of antimicrobials for acute RTIs	Medium	Patient decision to use antimicrobials after consultation	Absolute difference 16% [95% CI -31, 1]; p=0.08	
Cals 2009 ⁵²	CRCT	Effect of skills training on prescribing	High	Antimicrobials at index consultation	Communication training 27%, no training 54%; p<0.01	
Francis 2009 ⁵⁵	CRCT	Reduce use and return clinic visit (pediatric)	Medium	Antimicrobials at index consultation	OR 0.29 [95% CI 0.14, 0.60]	
Altiner 2007 ⁵⁶	CRCT	Reduce unnecessary antimicrobial prescribing for acute cough	High	Antimicrobials prescribed	At 6-weeks post-intervention OR _{adj} 0.38 [95% CI 0.26, 0.56]; p<0.001	
F. Formulary Restriction (k=2)						
Manns 2012 ⁵⁷	ITS	Restrict quinolone use	Medium	Quinolone use	NS (level and slope)	Low For Antimicrobial Prescribing
Marshall 2006 ⁵⁸	ITS	Restrict fluoroquinolone reimbursement	Low	Prescriptions per week for fluoroquinolone group (3 of 6 antimicrobials restricted)	p<0.0001 for level NS for trend	

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation (or as noted)	Strength of evidence, by outcome
G. Decision Support (k=6)						
Gonzales 2013 ⁵⁹	CRCT	Reduce use of antimicrobials for acute bronchitis	High	Antimicrobial prescriptions	Intervention period vs baseline Printed decision support: OR _{adj} 0.57 [95% CI 0.40, 0.82] Computer-assisted decision support: OR _{adj} 0.64 [95% CI 0.45, 0.91] Usual care: NS	Low For Antimicrobial Prescribing
Jenkins 2013 ⁶⁰	RCT	Decrease prescribing for non-pneumonia acute respiratory infection	Medium	Antimicrobials for ARIs	Significant time trend (p<0.0001); significant difference in trend between intervention and control (p<0.0001)	
McGinn 2013 ⁶¹	RCT	Effect on management of respiratory tract infections	High	Antimicrobial prescriptions	ARD 0.82, RR _{adj} 0.74 [95% CI 0.60, 0.92]; p=0.008	
Rattinger 2012 ⁶²	CBA	Minimize unnecessary use of antimicrobials	High	Proportion of unwarranted prescriptions	Intervention period vs baseline Targeted antimicrobials; p<0.0001 at intervention sites, p=ns at control sites	
Linder 2009 ⁶³	CRCT	Reduce inappropriate prescribing	High	Prescriptions to patients with ARI diagnosis	OR 0.80 [95% CI 0.6, 1.2]; p=0.30	
Martens 2007 ⁶⁴	CRCT	Change prescribing behavior	High	Prescriptions	NS	
H. Financial Incentive (k=1)						
Martens 2007 ⁶⁵	CBA	Reduce volume of prescriptions and improve quality of prescribing	High	Prescriptions	NS for Quinolones, nitrofurantoin, amoxicillin, mupirocin p<0.05 for trimethoprim, amoxicillin + clavulanic acid, doxycycline	Low For Antimicrobial Prescribing

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation (or as noted)	Strength of evidence, by outcome
I. Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (k=9)						
Little 2013 ⁶⁶	RCT	Effect of rapid streptococcal antigen detection test on prescribing for sore throat	High	Antibiotic use	Compared to delayed prescribing (control) Clinical score + RADT: RR 0.73 [95% CI 0.52, 0.98]; p=0.03 Clinical score: RR0.71 [95% CI 0.50, 0.95]; p=0.02	MEDIUM For Antimicrobial Prescribing
Brittain-Long 2011 ⁶⁷	RCT	Effect of rapid test for respiratory virus	Medium	Prescriptions (early result vs late result)	Early: 4.5% Late: 12.3%; p=0.005	
Worrall 2007 ⁶⁸	RCT	Compared clinical judgment, rapid antigen detection test, and decision rules for patients with sore throat	High	Prescriptions	p<0.001 for rapid antigen test vs usual care	
Diederichsen 2000 ⁶⁹	RCT	Effect of CRP testing on prescribing for RTI	Medium	Prescriptions	OR 0.90 [95% CI 0.7, 1.2]	
Takemura 2005 ⁷⁰	RCT	Effect of immediate availability of WBC and CRP results on prescribing for any infection	High	Prescriptions	CRP+WBC: 52% Usual care: 88%; p<0.001	
Cals 2009 ⁶²	CRCT	Effect of CRP and communication skills training for lower RTI	High	Prescriptions	CRP: 31% No CRP: 53%; p=0.02	
Cals 2010 ⁷¹	RCT	Effect of CRP testing on prescribing for lower RTI and rhinosinusitis	Medium	Prescriptions	CRP vs No CRP: RR 0.77 [95% CI 0.56, 0.98]	
Llor 2012 ^{23,24}	CBA	Effect of CRP testing on prescribing for lower RTI or acute rhinosinusitis	Medium	Prescriptions	Full intervention vs usual care LRTI: OR 0.22 [95% CI 0.12, 0.38]; p=0.00 ARS: OR 0.12 [95% CI 0.01, 0.32]; p=0.01	
Little 2013 ⁴⁹	CRCT	Effects of internet-based training for CRP for patients with lower or upper RTI	Medium	Prescriptions	CRP training vs no CRP training RR _{adj} 0.54 [95% CI 0.42, 0.69]; p<0.0001	

RCT = randomized controlled trial; CRCT = cluster randomized controlled trial; ITS = interrupted time series; CCT = controlled clinical trial; CBA = controlled before and after study; RTI = respiratory tract infection; UTI = urinary tract infection; RADT = rapid antigen detection test; CRP = C-reactive protein; WBC = white blood cell count; NS = not statistically significant; OR = odds ratio [95% confidence interval]; RR = rate ratio [95% confidence interval]; IRR = incidence rate ratio [95% confidence interval]; HR = hazard ratio [95% confidence interval]; WMD = weighted mean difference; ROR = ratio of odds ratios

*Partial intervention (education without CRP) vs usual care; see Laboratory Test section for full intervention results (including CRP test)

†Education component only (see delayed prescribing)

Table 14. Strength of Evidence for Outpatient Antimicrobial Stewardship Studies, by Patient Outcome

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
A. Provider and/or Patient Education Studies (k=14)						
Butler 2012 ²²	RCT	Reduce antimicrobial dispensing for all causes	Medium	Return clinic visit	Within 31 days (intervention – control): -2.32 [95% CI -4.76, 1.95]; p=0.50	Low for Return Clinic Visits
Metlay 2007 ³⁰	CRCT	Reduce antimicrobial overuse for ARTIs in the emergency department	Medium	Return clinic visit	Within 2 weeks: site by time interaction p=0.48	
Little 2005 ³³	RCT	Effectiveness of 3 prescribing strategies and an information leaflet	Medium	Return clinic visit	Within 1 month (patient leaflet vs no leaflet): IRR 1.63 [95% CI 1.07, 2.49]; p=0.02	
Butler 2012 ²²	RCT	Reduce antimicrobial dispensing for all causes	Medium	Hospitalization	% reduction (intervention relative to control): -1.9 [95% CI -13.2, 8.2]; p=0.72	Low for Hospitalizations
Metlay 2007 ³⁰	CRCT	Reduce antimicrobial overuse for ARTIs in the emergency department	Medium	Hospitalization	Within 2 weeks: site by time interaction p=0.51	
D. Delayed Prescribing (k=2)						
Little 2010 ⁴⁷	RCT	Effectiveness of management strategies for women with urinary tract infection	Medium	Return clinic visit	Within 1 month (delayed prescribing vs control [immediate prescribing]): OR 0.44 [95% CI 0.21, 0.95]	Low for Return Clinic Visits
E. Communication Skills Training (k=6)						
Légaré 2012 ⁵⁰	CRCT	Reduce overuse of antimicrobials for acute RTIs	Medium	Return clinic visit	RR 1.3 [95% CI 0.7, 2.3]	Low for Return Clinic Visits
Cals 2009 ⁵²	CRCT	Effect of skills training on prescribing	High	Return clinic visit	NS	
Francis 2009 ⁵⁵	CRCT	Reduce return clinic visit and antimicrobial use	Medium	Return clinic visit	Within 2 weeks (intervention vs control): OR 0.75 [95% CI 0.41, 1.38]	
Little 2013 ⁴⁹	CRCT	Effect of internet-based training on prescribing for LRTI and URTI	Medium	Hospitalization	NR (2 patients in usual care group, 6 patients in enhanced communication group)	Low for Hospitalizations
Cals 2009 ⁵²	CRCT	Effect of skills training on prescribing	High	Hospitalization	NS (no hospitalizations reported)	
F. Formulary Restriction (k=2)						
Manns 2012 ⁵⁷	ITS	Effect of policy restricting quinolone use	Medium	Return clinic visit	Within 30 days: 55.6% before restriction, 56.5% after restriction (p<0.001) (NOTE: overall n=170,247)	Low for Return Clinic Visits
Manns 2012 ⁵⁷	ITS	Effect of policy restricting quinolone use	Medium	Hospitalization	All-cause: 4.9% before restriction, 5.2% after restriction (p=0.0001)	Low for Hospitalizations

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
G. Decision Support (k=6)						
Gonzales 2013 ⁵⁹	CRCT	Reduce use of antimicrobials for acute bronchitis	High	Return clinic visit	NS	Low for Return Clinic Visits
Jenkins 2013 ⁶⁰	RCT	Decrease prescribing for non-pneumonia ARI	Medium	Return clinic visit	8 to 30 days after initial visit: significant increase for control sites (p=0.02); non-significant decrease for intervention sites	
McGinn 2013 ⁶¹	RCT	Effect on management of respiratory tract infections	High	Return clinic visit	Within 2 weeks: NS	
Linder 2009 ⁶³	CRCT	Reduce inappropriate prescribing	High	Return clinic visit	Within 30 days: 23% intervention 26% control; p=0.32	
Gonzales 2013 ⁵⁹	CRCT	Reduce use of antimicrobials for acute bronchitis	High	Hospitalization	NS	Low for Hospitalizations
Jenkins 2013 ⁶⁰	RCT	Decrease prescribing for non-pneumonia ARI	Medium	Hospitalization	NS	
I. Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (k=9)						
Little 2013 ⁶⁶	RCT	Effect of rapid streptococcal antigen detection test on prescribing for sore throat	High	Return clinic visit	Within 1 month with sore throat (compared to delayed prescribing control) Clinical score + RADT: RR 0.74 [95% CI 0.36, 1.47]; p=0.40 Clinical score: RR 0.91 [95% CI 0.47, 1.72]; p=0.78	Low for Return Clinic Visits
Diederichsen 2000 ⁶⁹	RCT	Effect of CRP testing on prescribing for RTI	Medium	Return clinic visit	No differences in contact with health service	
Takemura 2005 ⁷⁰	RCT	Effect of WBC and CRP results on prescribing for ARTI	High	Return clinic visit	30% intervention, 23% control; p=0.20	
Cals 2009 ⁵²	CRCT	Effect of CRP and communication skills training for lower RTI	High	Return clinic visit	35% CRP, 30% no CRP; p=ns	
Cals 2010 ⁷¹	RCT	Effect of CRP testing on prescribing for lower RTI and rhinosinusitis	Medium	Return clinic visit	26% CRP, 18% Usual care; p=ns	Low for Hospitalizations
Takemura 2005 ⁷⁰	RCT	Effect of WBC and CRP results on prescribing for ARTI	High	Hospitalization	0.7% intervention, 0% control; p=ns	
Cals 2009 ⁵²	CRCT	Effect of CRP and communication skills training for lower RTI	High	Hospitalization	NS (no hospitalizations reported)	
Cals 2010 ⁷¹	RCT	Effect of CRP testing on prescribing for lower RTI and rhinosinusitis	Medium	Hospitalization	NS (no hospitalizations reported)	
Little 2013 ⁴⁹	CRCT	Effects of internet-based training for CRP for patients with lower or upper RT	Medium	Hospitalization	CRP group vs no CRP group: OR 2.92 [95% CI 0.96, 8.85]; p=0.06	

RCT = randomized controlled trial; CRCT = cluster randomized controlled trial ITS = interrupted time series; CCT = controlled clinical trial; CBA = controlled before and after study; ARI = acute respiratory infection; ARTI = acute respiratory tract infection; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection; CRP = C-reactive protein; WBC = white blood cell; NS = not statistically significant; OR = odds ratio [95% confidence interval]; RR = rate ratio [95% confidence interval]; IRR = incidence rate ratio [95% confidence interval]; HR = hazard ratio [95% confidence interval]; WMD = weighted mean difference

Key Question 4

What are the harms of antimicrobial stewardship programs in outpatient settings?

None of the recent studies eligible for inclusion in the review reported possible harms of implementing ASPs in outpatient settings. There was only limited reporting of return clinic visits, hospitalizations, and adverse events (including mortality), with studies generally finding no significant differences between intervention and control groups.

Key Question 5

Within the included studies, what are the barriers to implementation, sustainability, and scalability of antimicrobial stewardship programs in outpatient settings?

Implementation Facilitators

Familiar and simple applications were recommended for computer-based interventions. For education sessions, providers commented on location, scheduling, type of education, content, relevance, and focus of the training.

Scalability

Although most studies were conducted at multiple centers, little information was provided about implementation of interventions across centers. Three studies provided some insight. In one study, providers expressed concerns about how materials from one country would apply to their practice, specifically in consultation style, length of consultations sessions, nature of the patient/provider communication, fee structure, and relevance of evidence from studies done in other countries. The other 2 studies commented on consistency of application of the intervention and differences in personalities when multiple academic detailers are involved.

Sustainability

Follow-up periods ranged from one to 4 years post-intervention. Two studies found post-intervention gains were lost by 12 months while 4 studies found improvements that were maintained for as long as 4 years. One study with a mean follow-up of 3.7 years found sustained benefit of communication skills training but not CRP testing.

DISCUSSION

Our review of recent evidence found generally low strength evidence that stewardship interventions (including provider and/or patient education, guidelines, delayed prescribing, and computerized clinical decision support) are associated with changes in antimicrobial prescribing. The exceptions were medium strength of evidence for the association of communications skills training and laboratory testing with reduced antimicrobial use. Changes in prescribing did not adversely affect patient outcomes or drug costs, where reported. Strength of evidence was low for patient outcomes (return clinic visits and hospitalizations) for provider and/or patient education, delayed prescribing, communications skills training, formulary restriction, decision support, and laboratory testing with insufficient evidence for provider feedback, guidelines, and financial incentives. There was insufficient evidence for the effect of outpatient stewardship interventions on microbial outcomes as no study reported these outcomes (Tables 13 and 14).

Our findings update and generally are consistent with an existing AHRQ Technical Review^{13,16,17} of studies published to 2007. The AHRQ review found that quality improvement strategies were moderately effective in decreasing inappropriate antimicrobial prescribing and improving appropriate antimicrobial selection. The review included studies of adults and children with any acute infection. The focus was on 6 quality improvement strategies: clinician education, patient education, delayed prescription, audit and feedback, clinician reminders and decision support systems, and financial and regulatory incentives or disincentives. The authors found no definitive evidence of one strategy being superior to another although in studies focused on reducing unnecessary prescribing, “active” education (*ie*, academic detailing and consensus building) interventions were more effective than “passive” education (*ie*, distribution of educational materials, lectures) interventions and for studies focused on improving the selection of an antimicrobial, the addition of audit and feedback was less effective than clinician education alone. The authors identified potential confounding factors and noted that the overall quality of the studies was fair.

Many of the interventions evaluated in the recent evidence and the AHRQ review were multifaceted. Although a few studies provided separate results for different intervention components, in most studies, the effects of different intervention components could not be distinguished. An analysis of data from 12 studies that looked at general practitioners’ views of antimicrobial prescribing and/or interventions directed at improving prescribing, several of which were related to intervention studies included in our review, provides insight on several elements of intervention programs.⁸² Providers thought that management of acute respiratory tract infection was complex. Their perceptions of the importance of antimicrobial resistance, past experience with withholding antimicrobials, external pressure to reduce prescribing, and potential conflicts with patients were noted. Providers recognized the potential value of guidelines but were not always trusting of the information contained in the guidelines and the relevance to their patients. Antimicrobial stewardship interventions were viewed as opportunities to reflect on prescribing patterns (through personal and local feedback), aids to decrease uncertainty (through guidelines for diagnosis and/or management), opportunities for learning (particularly discussions with peers creating a uniform practice), facilitators of more patient-centered care (through opportunities to educate patients and better understanding of patient wishes), and ways to possibly reduce workload (although there were concerns about the possibility of additional costs and longer consultation times). For an intervention to change prescribing behavior, it must be acceptable to providers and it must be feasible to put into practice.⁸²

A report from the 2002 International Forum on Antibiotic Resistance (IFAR) colloquium concluded that interventions should focus on changing behavior rather than simply providing information.⁸³ One of the key features of an intervention considered likely to improve antimicrobial use was planning and stakeholder support. This included baseline assessment of provider and public knowledge, attitudes and behaviors; information directed to health professionals, parents, educators, and day-care providers; stakeholder involvement in developing the intervention; and timing the intervention to coincide with peak infection season (*ie*, for respiratory tract infections). Another feature was the message. The information should be clear, consistent, and positive (*eg*, bacterial vs viral infections, treatment of symptoms). The third feature was communication. A multi-media and multicultural approach was recommended

with focus groups to help refine the educational materials, use of spokespersons to deliver the messages, and academic detailing for healthcare providers. The final feature was evaluation. It was suggested that an intervention project have realistic endpoints, use an appropriate study design, and provide feedback to health care professionals.

A recent invited commentary offered suggestions for changing prescribing behaviors for patients with acute respiratory infections and advancing knowledge about effectiveness of interventions.⁸⁴ It was suggested that communication with patients emphasize benefits and risks of antimicrobial use. Specifically, the benefits gained (a short reduction in symptoms) must be weighed against the risks (adverse reaction to medication with possible serious adverse event requiring an emergency department visit). It was also suggested that continuous quality improvement approaches might provide more valuable information than randomized trials. With continuous measurement of results, interventions could be modified or new components added in an attempt to improve the prescribing outcomes. Physicians should also explore types of interventions used to effect change in business or psychology.

LIMITATIONS

The AHRQ Technical Review¹³ identified limitations of the studies included in the review. Our update of the literature confirms that many of the limitations remain unaddressed. Harms associated with antimicrobial stewardship efforts, including additional utilization of healthcare services and adverse events due to under-treatment, were rarely reported. Few studies reported patient satisfaction with care. We found no studies that reported microbial outcomes. Reporting of costs was limited and typically included only drug costs rather than costs associated with implementation of the intervention and a cost-benefit analysis. As noted above, most of the interventions were multifaceted making specific recommendations about key components difficult. Resources required for program implementation were not reported. Little information was available about stewardship programs in outpatient settings other than primary care or for patient conditions other than respiratory infections. Although several studies provided follow-up data, findings were mixed and conclusions about long-term effects of interventions are not possible. Similarly, the ability to implement interventions on a wide scale has not been addressed.

FUTURE RESEARCH RECOMMENDATIONS

Our review highlights reduced prescribing associated with stewardship interventions. Future research might look at ways to enhance outpatient antimicrobial stewardship by involving infectious disease specialists and clinical pharmacists in the prescribing decision at the point-of-service via electronic interface or using automated surveillance techniques to monitor patient progress. Future studies should also focus on differences in clinically-meaningful endpoints such as return clinic visits, emergency department visits, adverse drug events, and duration of illness. Large healthcare systems might introduce new stewardship programs in a staggered manner, randomizing facilities to different roll-out times and collecting data as the roll-out proceeds, allowing for a block-randomized trial while instituting a stewardship program. To achieve large sample sizes needed to adequately assess patient outcomes, we recommend a collaborative approach with large healthcare institutions working together.

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