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QUERI

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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EXECUTIVE SUMMARY

BACKGROUND

The majority of antimicrobials prescribed to humans originate in outpatient settings. 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.

Antimicrobial stewardship programs (ASPs) are a focused effort by a health care system or a part of the system (*ie*, an outpatient clinic) to *optimize* the use of antimicrobial agents. The goals of an ASP are to improve patient outcomes, decrease adverse consequences including from adverse drug reactions and antimicrobial associated infections (*eg*, *Clostridium difficile* diarrhea), reduce or prevent antimicrobial resistance, and deliver cost-effective therapy. The emphasis is on appropriate use, selection, dosing, and duration of antimicrobial therapy.

The purpose of this review is to synthesize the evidence about the effectiveness of ASPs implemented in outpatient settings. We categorized ASPs based on the primary focus of the intervention as described by the study author. Our categories are: provider and/or patient education, provider feedback, guidelines, delayed prescribing, communications skills training, restriction, decision support, financial incentives, and laboratory testing. The topic was nominated by Matthew Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, on behalf of the VA Antimicrobial Stewardship Task Force, and is intended to provide a summary of the evidence on outpatient ASPs to guide clinical practice and policy within the Veterans Healthcare System. We developed the following key questions with input from a technical expert panel.

Key Question #1. What is the effectiveness of 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)?

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?

METHODS

We conducted an exploratory literature search that identified 2 relevant Cochrane reviews that partially addressed the key questions but were no longer current. We used a search strategy similar to those of the Cochrane reviews to search MEDLINE (Ovid) from 2000 through November 2013. We limited the search to studies published in English language and enrolling human subjects. The full search strategy is presented in Appendix A. Additional citations were identified from systematic reviews, reference lists of retrieved articles, and suggestions made by our technical expert panel members and peer reviewers.

STUDY SELECTION

Titles, abstracts, and articles were reviewed by investigators and research associates trained in the critical analysis of literature. Full text versions of potentially eligible articles were retrieved for review. We excluded studies done in settings or enrolling patient populations not relevant to the United States (*eg*, patients with infections unlikely in the United States; settings where antimicrobials are available without a prescription); studies not involving an intervention or not involving an intervention of interest (*eg*, studies of interventions involving only community education were excluded); studies describing an intervention with no assessment of the effects of the intervention; studies not reporting either prescribing outcomes, patient outcomes, microbial outcomes, costs, or harms; studies of antimicrobials for medical or surgical prophylaxis; studies of patients with viral or fungal infection, or tuberculosis; and studies other than randomized controlled trials (RCTs) or cluster randomized controlled trials (CRCTs), controlled clinical trials (CCTs), controlled before/after trials (CBAs), or interrupted times series (ITS) with at least 3 data points before and after implementation of the intervention.

To avoid duplication with a recent Agency for Healthcare Research and Quality (AHRQ) Technical Review titled "Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies, Volume 4 – Antibiotic Prescribing Behavior," which included a literature search through November of 2004, we included in our review only studies meeting our eligibility criteria as described above and not included in the AHRQ review or subsequent publications.

DATA ABSTRACTION

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

QUALITY ASSESSMENT

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

DATA SYNTHESIS

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

RATING THE BODY OF EVIDENCE

We rated overall strength of evidence for our primary outcome, antimicrobial prescribing, for each intervention category using methods developed by AHRQ and the Effective Health Care Program. The strength of the evidence was evaluated based on 4 domains: 1) risk of bias, 2) consistency, 3) directness, and 4) precision.

PEER REVIEW

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

RESULTS

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

The AHRQ 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. The publications based on the review focused on strategies to reduce unnecessary prescribing (with studies published to March 2007) and strategies to improve antimicrobial selection (with studies published to November 2004) There were limited data on our other outcomes of interest including duration of treatment, guideline concordant use, or patient centered, microbial, or cost outcomes.

Reducing Unnecessary Prescribing

For the review of interventions to improve the treatment decision, 30 trials (in 20 studies) were included in the median effect size analysis for the overall prescribing outcome. Interventions reduced the median absolute proportion of visits at which an antimicrobial was prescribed by -9.7% (IQR -6.6 to -13.7%) over 6 months median follow-up. Effect sizes could not be determined for an additional 18 trials from 16 studies. In those trials, 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 the other 14 trials (13 studies) with values ranging from 0.3% to 55.0% (median 12.0%); 9 of 14 trials reported a reduction of more than 10%. In 7 RCTs of delayed prescription, absolute reduction in antimicrobial prescriptions filled was reported in 6 studies with values ranging from 15% to 75% (median 35.5%). 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.

Few studies reported patient centered outcomes. Of those that did, most observed no increases in return office visits or telephone consultations and no differences between intervention and control groups in time to symptom resolution or patient satisfaction.

Three studies reported antimicrobial resistance. Only one of the studies reported a significant effect – a reduction in the incidence of colonization with penicillin-resistant *S. pneumoniae* over 6 months follow-up.

In 2 studies that reported costs, prescribing costs were decreased in the intervention groups (relative reductions of 18% and 31%). Both studies reported increased use of narrow-spectrum antimicrobials. No program costs were reported.

Improving Antimicrobial Selection

Of the 33 trials (in 26 studies), 22 reported changes in absolute volume of recommended antimicrobials and were included in the median effect size analysis. The overall median effect – an increase in recommended antimicrobial prescribing attributable to the intervention – was 10.6% (IQR 3.4 to 18.2%). Four studies evaluated duration of antimicrobial prescribing with one study reporting a 13 percentage point increase in short-course antimicrobial regimens, 2 reporting decreases in antimicrobial duration (1.89 days and 0.55 days) compared to the control group, and one reporting an increase in duration (0.06 days). Effect sizes could not be determined for 11 trials (in 6 studies) but the results were similar with increases in recommended antimicrobials (5% and 12%) and decreases in non-recommended antimicrobials (1.8% to 31.7%; median 16.7%).

No studies looked at patient outcomes or the effect of interventions on antimicrobial resistance. Three studies reported cost data finding that costs, either for individual prescriptions or for total antimicrobials within a health care system, decreased by approximately 20 to 30%.

Updated Evidence Newly Identified for this Evidence Report

We identified 50 unique trials meeting eligibility criteria that were not included in the existing AHRQ Technical Review. There were 17 RCTs, 18 CRCTs, 3 CCTs, 6 CBA trials, and 6 ITS studies. Twenty of the trials were conducted in the United States or Canada; 2 studies included data from VA Health Care Systems. Five trials enrolled only children or adolescents, 14 enrolled only adults, and 31 enrolled either all ages or did not specify age. Most of the studies enrolled patients with respiratory infections (29 trials). We report prescribing, patient, and cost outcomes. None of the studies reported microbial outcomes. Executive Summary Table 1 provides an overview of strength of evidence for prescribing, patient, and microbial outcomes.

Provider and/or Patient Education (5 RCTs, 6 CRCTs, 1 CCT, 4 CBAs)

> Provider and/or patient education interventions were associated with improved prescribing rate or use with mixed results for antimicrobial selection and no effect on patient outcomes. Interventions were directed at providers in 13 of 16 studies. (Executive Summary Tables 2a and 2b)

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

Patient outcomes were reported in 3 studies (2 RCT, 1 CRCT). One study 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.

Three studies reported drug costs with one finding a reduction in average drug costs in the intervention group, 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 not reporting the significance.

Provider Feedback (1 RCT, 2 CRCTs, 1 CCT, 1CBA)

> Individualized provider feedback on prescribing resulted in mixed findings for prescribing outcomes and possibly improved costs. No study reported patient centered outcomes. (Executive Summary Tables 2a and 2b)

Three studies reported significant decreases when individualized feedback was compared to more general feedback or 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 improvement for use of targeted antimicrobials. However, in the only study reporting 12-month outcomes, improvements were not sustained.

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.

Guidelines (1 CRCT, 1 CCT, 4 ITS)

> Limited data demonstrated that guidelines generally improved antimicrobial outcomes, with no difference in patient satisfaction and mixed results on antimicrobial costs. There were no data on other outcomes. (Executive Summary Tables 2a and 2b)

In 4 studies reporting antimicrobial use following introduction of guidelines, 3 found significant decreases post-intervention. One study of guidelines to improve antimicrobial selection reported mixed results across antimicrobials. A study focused on fluoroquinolone use observed improved selection. Two other studies found either no differences in selection post-intervention or differences with unclear interpretation. One study that assessed treatment duration reported no differences between intervention and control groups.

One study reported patient satisfaction with care and found no difference between those who received an antimicrobial and those who did not.

One study found significant decreases post-intervention for cephalosporins, fluoroquinolones, penicillins, and "other" antimicrobial costs with no significant change in overall antimicrobial costs or macrolide costs.

Delayed Prescribing (4 RCTs)

> Limited data suggest that delayed prescribing strategies may reduce antimicrobial use and return clinic visits with no major adverse events. No data on costs or other outcomes were reported. (Executive Summary Tables 2a and 2b)

Delayed prescribing is a strategy to reduce unnecessary antibiotic use by asking patients to fill a prescription only if symptoms persist or worsen. Two studies investigated delayed prescribing

strategies and 2 other studies included a delayed prescribing component. One study enrolling women with urinary tract infection found a significant reduction in antimicrobial use among patients receiving delayed prescriptions compared to immediate prescriptions. The 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) because it also included education and no education groups, observed a significant reduction in use of antimicrobials in the group assigned to delayed prescribing compared to the immediate antimicrobial group. Another study, summarized under Laboratory Tests (below) because it also included testing for C-reactive protein, 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 also given delayed prescriptions (22.7% intervention, 72.4% control, $p<0.001$).

One study reported patient outcomes, finding lower odds of return clinic visits 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 addition, the study described under Provider and/or Patient Education found return clinic visits did not differ between groups assigned to delayed or immediate antimicrobials.

Communication Skills Training (6 CRCTs)

> Communication skills training to enhance patient and provider communication, address patient expectations for antimicrobial treatment, and foster a more "patient-centered" approach to care reduced antimicrobial prescribing and/or use of antimicrobials. Limited evidence suggested that there was little impact on patient or cost outcomes. (Executive Summary Tables 2a and 2b)

Six cluster randomized trials with a primary focus on communication skills training were identified. Five of the 6 studies reported significantly reduced prescribing and/or use of antimicrobials following the intervention.

The return clinic visit rate did not differ between intervention and control (three studies). One study reported time to resolution of symptoms rated as moderate or worse was one day longer ($p=0.002$) in the communication skills group but no difference in new or worse symptoms or symptom severity at 2 to 4 days after the initial visit. Hospitalizations were infrequent. Patient satisfaction results were mixed with improvement satisfaction in the intervention group in one of 4 studies.

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.

Restriction Policies (2 ITS)

> Restriction policies resulted in little impact on prescribing, patient, or cost outcomes. (Executive Summary Tables 2a and 2b)

One study looked at the effects of a fluoroquinolone restriction policy. A second analyzed data from a government-funded insurance plan that limited reimbursement for ciprofloxacin,

ofloxacin, and levofloxacin to treatment of patients with specified conditions. Results were mixed for prescribing with a significant increase in the percentage of prescriptions consistent with formulary guidelines post-intervention.

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

One study reported antimicrobial costs with mixed results.

Computerized Clinical Decision Support (2 RCTs, 3 CRCTs, 1 CBA)

> Clinical decision support linked to the existing electronic health record generally improved prescribing outcomes with no change in patient outcomes. No data were provided on microbial or cost outcomes. (Executive Summary Tables 2a and 2b)

Computerized 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 with increased adherence to some of the 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.

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).

No study reported cost outcomes.

Financial Incentives (1 CBA)

> A single CBA study reported that financial incentives improved the volume of prescribing and adherence to recommended use for 2 of 7 antimicrobials studied though changes were not maintained at one year. Patient, microbial and cost outcomes were not reported. (Executive Summary Tables 2a and 2b)

Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (1 Systematic Review, 6 RCTs, 2 CRCTs, 1 CBA)

> Testing (procalcitonin, viral PCR, and C-reactive protein) generally improved prescribing outcomes, with no difference in patient outcomes and may be cost effective with regard to antimicrobial use. (Executive Summary Tables 2a and 2b)

A recent systematic review including 2 studies in outpatient settings found that procalcitonin testing in patients with acute respiratory tract infection was associated with decreased antimicrobial prescriptions. 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. 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. However, the use of the clinical score alone also was associated with decreased antimicrobial use. Five of 6 studies of C-reactive protein (CRP) testing in patients with acute respiratory tract infection or mixed infections (alone and in combination with communication skills training) showed decreased antimicrobial prescriptions and potentially avoidance of newer, broad spectrum antimicrobials in select patients.

There were no differences between groups receiving any of the tests studied and comparator groups in return clinic visits, hospitalizations, modification of initial treatment, duration of fever, or performance of further testing. CRP testing and communication skills training lead to at least equivalent, and possibly increased, patient satisfaction with care.

The single study that compared cost of care in patients with acute respiratory infection 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.

Executive Summary Table 1. Overview of Strength of Evidence - Antimicrobial Stewardship Interventions for Outpatients

ASP Intervention (# studies)*	Prescribing Outcomes	Patient Outcomes (Return Clinic Visits, Hospitalizations)	Microbial Outcomes
Provider and/or Patient Education (k=16)	Low (k=15)	Low for Return Clinic Visits (k=3) Low for Hospitalizations (k=2)	Insufficient (k=0)
Provider Feedback (k=5)	Low (k=5)	Insufficient for Return Clinic Visits and Hospitalizations (k=0)	Insufficient (k=0)
Guidelines (k=6)	Low (k=4)	Insufficient for Return Clinic Visits and Hospitalizations (k=0)	Insufficient (k=0)
Delayed Prescribing (k=4)	Low (k=4)	Low for Return Clinic Visits (k=1) Insufficient for Hospitalizations (k=0)	Insufficient (k=0)
Communication Skills Training (k=6)	Medium (k=6)	Low for Return Clinic Visits (k=2) Low for Hospitalizations (k=2)	Insufficient (k=0)
Restriction (k=2)	Low (k=2)	Low for Return Clinic Visits (k=1) Low for Hospitalizations (k=1)	Insufficient (k=0)
Decision Support (k=6)	Low (k=6)	Low for Return Clinic Visits (k=4) Low for Hospitalizations (k=2)	Insufficient (k=0)
Financial Incentive (k=1)	Low (k=1)	Insufficient for Return Clinic Visits and Hospitalizations (k=0)	Insufficient (k=0)
Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (k=9)	Medium (k=9)	Low for Return Clinic Visits (k=5) Low for Hospitalizations (k=4)	Insufficient (k=0)

***Number of studies is greater than 50; studies with multiple interventions are included under each intervention**

Executive Summary Table 2a. Overview of Prescribing Outcomes - Antimicrobial Stewardship Interventions for Outpatients

ASP Intervention (# studies)	Prescribing Rate/ Use	Selection	Duration	Guideline Concordant Use	Summary
Provider and/or Patient Education (5 RCT, 6 CRCT, 1 CCT, 4 CBA)	**Decreased: + 9 studies*^ ≈ 6 studies**	**+ 3 studies* ≈ 5 studies**	**≈ 1 study**	NR	Provider and/or patient education was associated with mixed results for prescribing outcomes.
Provider Feedback (1 RCT, 2 CRCT, 1 CCT, 1 CBA)	**Decreased: + 3 studies ≈ 2 studies**	**+ 2 studies* ≈ 1 study**	NR	**≈ 1 study**	Feedback on prescribing was associated with mixed results for prescribing outcomes.
Guidelines (1 CRCT, 1 CCT, 4 ITS)	**Decreased: + 3 studies ≈ 1 study**	**+ 3 studies* ≈ 1 study**	**≈ 1 study**	NR	Introduction of prescribing guidelines was associated with decreased use and improved selection with no difference in duration.
Delayed Prescribing (4 RCT)	**Decreased: + 3 studies ≈ 1 study**	NR	NR	NR	Delayed prescribing was associated with with decreased use of antimicrobials.
Communication Skills Training (6 CRCT)	**Decreased: + 5 studies ≈ 1 study**	NR	NR	NR	Communication skills training was associated with a decrease in antimicrobial use.
Restriction (2 ITS)	**Decreased: +/- 2 studies**	**+/- 2 studies**	NR	**+ 1 study**	Restriction policies had mixed results for antimicrobial use and selection.
Decision Support (2 RCT, 3 CRCT, 1 CBA)	**Decreased: + 4 studies* ≈ 2 studies**	**+ 2 studies**	NR	**+ 1 study**	Decision support systems were associated with reduced antimicrobial prescribing and improved selection.
Financial Incentive (1 CBA)	**Decreased: + 1 study***	NR	NR	NR	A financial incentive for providers was associated with mixed results across antimicrobials.
Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (6 RCT, 2 CRCT, 1 CBA)	**Decreased† + 8 studies ≈ 1 studies**	**+ 1 study**	NR	NR	Rapid antigen testing in patients with sore throat and C-reactive protein testing in patients with respiratory or unspecified infection were associated with decreased antimicrobial prescribing.

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

*Some studies with a "+" reported mixed results (*ie*, significant differences for some conditions or some age groups, no difference for others)

^Includes one study with significance not reported

†Two studies from an existing systematic review also reported decreased antimicrobial use

+ indicates statistically significant difference favoring antimicrobial stewardship intervention
≈ indicates no statistically significant difference between antimicrobial stewardship intervention and control
- indicates statistically significant difference favoring control
+ / - indicates mixed results across different antimicrobials studied or differences between level and trend outcomes in ITS analyses

Executive Summary Table 2b. Overview of Patient Outcomes - Antimicrobial Stewardship Interventions for Outpatients

ASP Intervention (# studies)	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescribing	Patient Satisfaction with Care	Summary
Provider and/or Patient Education (5 RCT, 6 CRCT, 1 CCT, 4 CBA)	**≈ 2 studies - 1 study**	**≈ 2 studies**	**≈ 1 study**	NR	**≈ 1 study**	Provider and/or patient education did not affect patient outcomes.
Provider Feedback (1 RCT, 2 CRCT, 1 CCT, 1 CBA)	NR	NR	NR	NR	NR	Patient outcomes were not reported.
Guidelines (1 CRCT, 1 CCT, 4 ITS)	NR	NR	NR	NR	**≈ 1 study**	One study of guideline implementation reported no difference in patient satisfaction with treatment.
Delayed Prescribing (4 RCT)	**+ 1 study ≈ 1 study**	NR	**≈ 1 study**	NR	NR	Two studies of delayed prescribing found mixed results for return clinic visits; no major adverse events were noted.
Communication Skills Training (6 CRCT)	**≈ 3 studies**	**≈ 1 study p=NR, 1 study**	**≈ 4 studies**	**+ 1 study**	**≈ 3 studies + 1 study**	Communications skills training did not affect patient outcomes.
Restriction (2 ITS)	**- 1 study**	**- 1 study**	**≈ 1 study**	NR	NR	In one study, a restriction intervention was associated with small but significant increases in return outpatient visits and all-cause (but not infection-related) hospitalization.
Decision Support (2 RCT, 3 CRCT, 1 CBA)	**≈ 4 studies**	**≈ 2 studies**	**p=NR, 1 study**	**≈ 2 studies**	NR	Decision support interventions did not affect patient outcomes.
Financial Incentive (1 CBA)	NR	NR	NR	NR	NR	Patient outcomes were not reported.
Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein (6 RCT, 2 CRCT, 1 CBA)	**≈ 4 studies**	**≈ 4 studies**	**≈ 6 studies**	**+ 2 studies ≈ 1 study**	**+ 1 study ≈ 2 studies**	None of the laboratory tests studied affected most patient outcomes; 2 of 3 studies found fewer late prescriptions with CRP testing.

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

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

KEY QUESTION 2

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

Limited evidence is available on key intervention components. Speculation by authors or information from focus group interviews suggests that leadership and use of a team approach, patient education materials, provider reminders, user friendly interfaces and evidence-based materials may be key.

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)?

Most studies included in the review were conducted in primary care clinics and enrolled patients with respiratory tract infections. With limited information from other settings or other suspected patient conditions, it is not possible to reach conclusions about whether effectiveness varies by clinic type or patient condition. Two studies were conducted at VA medical centers. Provider and patient education was found to decrease the percentage of patients presenting to emergency departments prescribed antimicrobials for respiratory tract infections without effecting patient outcomes and a computerized clinical decision support system was found to reduce the proportion of unwarranted prescriptions.

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: a study of antimicrobial prescribing for acute dental pain was conducted in general dental practices; a study of changes in fluoroquinolone use for gonorrhea where 35% of patients were treated in sexually transmitted disease clinics, 24% in primary care, 16% in emergency departments or urgent care centers, 12% in a hospital, and 7% in family planning clinics; a study that enrolled providers from a group practice that was also the sole provider of care at the urgent care clinic and the emergency department; and a study of rapid viral PCR testing that enrolled patients from 8 primary care clinics and 4 outpatient departments of infectious diseases. With so few exceptions, it is impossible to comment on the effectiveness of interventions in sites other than primary care.

Respiratory infections were most commonly studied (29 of 50 trials). Seventeen studies included more than one type of infection or did not report infection site. We identified one study of antimicrobial prescribing for acute dental pain, 2 studies of prescribing for urinary tract infections, and one study of prescribing for sexually transmitted infections. With so few studies of any infection other than respiratory, it is impossible to determine whether the effectiveness of interventions varies by infection site.

One study was conducted exclusively in emergency departments, half of which were at VA Medical Centers. This study of provider and patient education found a significant reduction in the percentage of patients prescribed antimicrobials for upper respiratory tract infections and acute

bronchitis in the intervention group but not the control group, with no effect on return visits, hospitalization, or patient satisfaction with care. Another study analyzed outpatient visits to 2 VA Medical Centers – one serving as the intervention site and the other as the control site. There was a significant decrease in the proportion of unwarranted prescriptions for targeted antimicrobials associated with the clinical decision support system at the intervention site and no significant change at the usual care control site.

KEY QUESTION 4

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

None of the recent eligible studies reported possible harms of outpatient ASP implementation. There was limited reporting of return clinic visits, hospitalizations, and adverse events (including mortality). 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?

Limited data suggest that scalability and sustainability outside of the studied settings may be difficult. Implementation facilitators include convenience of interventions and access to training sessions and efforts to include patients in self-care.

Implementation Facilitators

Several studies reported on facilitators to implementation of stewardship efforts. Providers would be more likely to utilize a computer-based intervention if the intervention was easy to access, similar to existing software, and not too complex. Providers would be more likely to attend training sessions if the location and scheduling were convenient, if the sessions were interactive, if the information was evidence-based, if the topics were of interest and relevant to their practice, and if the intervention included efforts to get patients involved in their own care.

Scalability/Applicability

Most of the recent studies were multisite studies but only 3 studies provided any information related to implementing an intervention on a larger scale. One of the studies was an effort to implement an intervention on a larger scale. In the original study, involving 12 peer review groups and 100 general practitioners, the intervention (provider and patient education, communication skills training, and provider feedback) was associated with reduced prescription rates for acute respiratory symptoms. However, when a similar intervention was implemented with over 300 providers, no difference in prescription rate was noted between intervention and control. It was speculated that the intervention was less rigorously applied in the second study.

In another study, the authors reported that a weakness of the study was the need to train 13 peer academic detailers to reach the 79 practice groups enrolled in the trial. The authors suggested that the different personalities of the individuals could have influenced the success of the intervention.

In the third study, the intervention was an internet-based training program providing general practitioners with information about CRP testing and enhancing communications skills. In interviews with providers from 5 different European countries who were exposed to a pilot version of the training, there were 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 their 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 studies done in other countries.

Sustainability

Seven studies reported follow-up data ranging from one to 4 years post-intervention. Results were mixed. The study comparing postal prescribing feedback plus an academic detailing visit to postal prescribing feedback alone found immediate improvements in prescribing but by 12 months post-intervention, both groups had returned to pre-intervention prescribing patterns with no differences between groups. A financial incentive to encourage adherence to prescribing guidelines was associated with improvements in prescribing for 3 of 7 antimicrobials at 3 months post-intervention but the improvements were not maintained at one year.

However, several studies did report sustained benefits. An educational intervention to reduce antimicrobial use in children found reductions in total antimicrobial use and use of cephalosporins and macrolides relative to the control group that were maintained over the 3 year study period. In this study, the intervention was on-going but became less intensive over the course of the study. Distribution of guidelines with voluntary education sessions was associated with a significant change for use of antimicrobials overall and for each class of antimicrobials studied that was maintained over 36 months. A one-time visit by a peer general practitioner with a focus on the "antibiotic misunderstanding" and communication with patients was associated with decreased odds of antimicrobial prescribing that was significant at both 6 weeks and 12 months post-intervention. The effect was slightly attenuated at 12 months. A VA study of a computerized clinical decision support system to improve congruence with guideline recommendations for acute respiratory infections reported that the increase in congruence at the intervention site (but not the control site) was sustained for 4 years post-intervention. Medical records for 87.9% of patients enrolled in a CRCT study of provider training in CRP testing and/or communication skills were accessed at a mean follow-up of 3.7 years. The number of office visits for respiratory tract infections during follow-up did not differ significantly between intervention and control groups. However, communication skills training was associated with a reduction in use of respiratory tract infection antimicrobial treatments (corrected difference -10.4%, p=0.02). There was no difference between groups for patients in the CRP testing arm.

DISCUSSION AND CONCLUSIONS

KEY FINDINGS

Medium strength of evidence for association of communication skills training and laboratory testing with reduction in use of antimicrobials; low strength of evidence that other ASP interventions are associated with changes in prescribing.

Patient outcomes, where reported, were not adversely affected.

Few studies reported cost outcomes; no studies reported microbial outcomes.

There are limited data on effectiveness of ASPs in outpatient settings other than primary care clinics; most studies are of patients with respiratory infections.

There are limited data on sustainability and scalability of interventions.

Our review of recent evidence found generally low strength evidence (Executive Summary Table 1) 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. Many of the interventions evaluated in the included studies 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.

Most of the included studies were conducted in primary care clinics with patients with respiratory infections. There is little information about whether the stewardship interventions would be effective in other settings or with other infectious conditions. There was also limited information on scalability and sustainability of interventions. Future research should focus on assessment of clinically-meaningful outcomes.

Our findings update and generally are consistent with an existing AHRQ Technical Review of studies published to 2007. The AHRQ report found quality improvement strategies (including clinician education, patient education, audit and feedback, and delayed prescribing) to be moderately effective in reducing inappropriate antimicrobial prescribing and improving appropriate antimicrobial selection. Their findings encompass a broad range of interventions evaluated in studies of adults and children with acute infection.

ABBREVIATIONS

Abbreviation	Definition
ARI	acute respiratory infection
ARS	acute rhinosinusitis
ARTI	acute respiratory tract infection
ASP	antimicrobial stewardship program
CAP	community-acquired pneumonia
CBA	controlled before and after study
CCT	controlled clinical trial
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRCT	cluster randomized, controlled trial
CRP	C-reactive protein
DDD	defined daily dose
ED	emergency department
EPOC	Effective Practice and Organization of Care
GP	general practitioner
ITS	interrupted time series
LRTI	lower respiratory tract infection
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NP	nurse practitioner
PA	physician assistant
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
URTI	upper respiratory tract infection
UTI	urinary tract infection
VA	Department of Veterans Affairs
€	euro, currency used by the Institutions of the European Union
£	pound sterling, currency of the United Kingdom

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 2004[13] 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 Review[13] 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

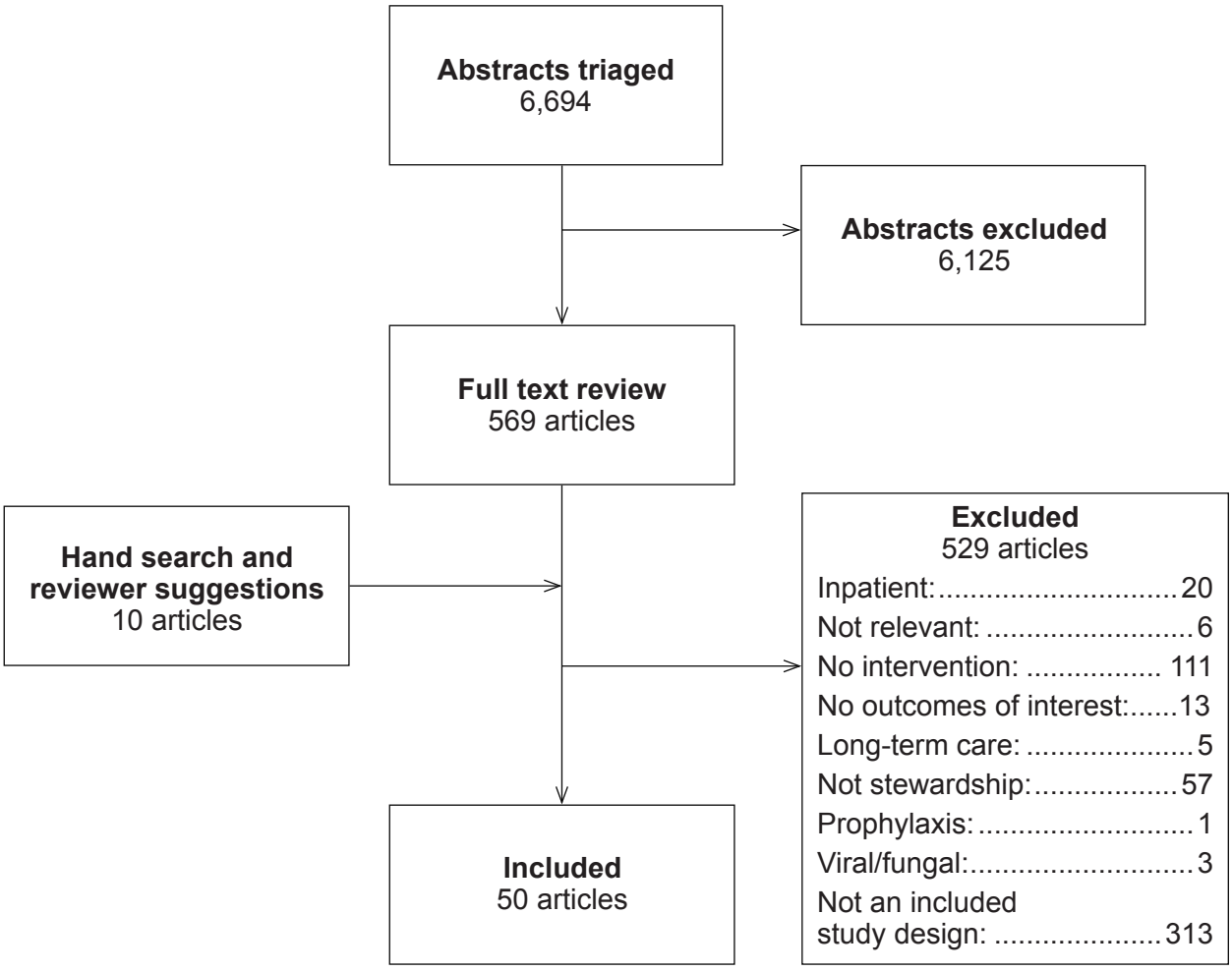
A draft version of this report was reviewed by technical experts as well as clinical leadership. Reviewer comments (Appendix C) were addressed and our responses incorporated in the final report.

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 Review[13] 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; $(\text{Post-intervention - Pre-intervention})_{\text{intervention group}}$ - $(\text{Post-intervention – Pre-intervention})_{\text{control group}}$
†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 p=0.028 for comparison of clinician education alone with clinician education and audit and feedback
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%)	
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 review[13] 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 testing[66-68] 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 multi-faceted 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 between1 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 bias[40] 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]	✓			✓
Madridejos-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 study[46] (Appendix D, Table 6 and Table 7).

Three studies evaluated interventions designed to reduce antimicrobial use[44-46] 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 pain[45] and rhinosinusitis[43] 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 Kingdom[47] or Canada.[48] One study was rated as medium risk of bias[47] and one as high risk of bias[48] (Appendix D, Table 6). In each of the studies the goal was to reduce prescribing of antimicrobials for respiratory infections[48] 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 Education[33] 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 States[59-63] 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 study[60] 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 rules[61] and a decision support tool to use when interviewing and evaluating patients[63] found no significant differences in return clinic visits at either 2 weeks[61] or 30 days[63] 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)	✓	✓		
Diederischsen 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 $\geq 9x10^9$ /l), cefcapene pivoxil was started in 51% of patients receiving antimicrobials compared to patients without elevated WBC count (WBC $\leq 9x10^9$ /l) (26%) (p=0.025); of patients receiving antimicrobials, macrolides were prescribed in 50% of patients with WBC $\leq 9x10^9$ /l compared to 7.7% of patients with WBC $\geq 9x10^9$ /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% CI1.0, 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 CRCT[52] 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 study[37] 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 authors[37] 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	*Proportion of unwarranted prescriptions* 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, 09.95]
Slekovec 2012[42] ITS	Guideline (with voluntary training sessions)	Appropriate selection	UTI Women 15 to 65 years old	*Slope* Post intervention: Increased for nitrofurantoin, fosfomycin-trometamol; decreased for norfloxacin (all p<0.001); unchanged for fluoroquinolones *Level* 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 training[52] 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 2nd-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, mupriocin 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	
Diederischsen 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[52]	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
Diederischsen 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	
Takemura 2005[70]	RCT	Effect of WBC and CRP results on prescribing for ARTI	High	Hospitalization	0.7% intervention, 0% control; p=ns	Low for Hospitalizations
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 Review[13] 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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APPENDIX A. SEARCH STRATEGY

Database: Ovid MEDLINE(R)

1 antibiot$.mp. or exp antibiotics/
2 antimicrob$.mp.
3 exp Anti-Bacterial Agents/
4 exp Anti-Infective Agents, Urinary/
5 exp Cross Infection/
6 exp Community-Acquired Infections/
7 exp Respiratory Tract Infections/
8 exp Wound Infection/
9 exp Catheter-Related Infections/
10 exp Vancomycin Resistance/ or exp Vancomycin/ or vancomycin.mp.
11 aminoglycosides.mp. or exp Aminoglycosides/
12 fluoroquinolones.mp. or exp Fluoroquinolones/
13 broad spectrum antibiotics.mp.
14 carbapenems.mp. or exp Carbapenems/
15 exp Cephalosporins/ or broad spectrum cephalosporins.mp.
16 or/1-15
17 exp Education/ or education.mp.
18 information campaign.mp.
19 audit.mp.
20 feedback.mp. or exp Feedback/
21 dissemination.mp. or exp Information Dissemination/
22 provider reminders.mp.
23 computerized medical records.mp. or exp Medical Records Systems, Computerized/
24 exp Physician Incentive Plans/ or financial incentives.mp.
25 discharge planning.mp.
26 guideline implementation.mp.
27 guideline adherence.mp. or exp Guideline Adherence/
28 exp Quality Assurance, Health Care/ or quality assurance.mp.
29 program evaluation.mp. or exp Program Evaluation/
30 exp Practice Guideline/
31 exp Physician's Practice Patterns/
32 exp Drug Prescriptions/
33 exp Drug Utilization/
34 or/17-33
35 randomized controlled trial.mp. or exp Randomized Controlled Trial/
36 controlled clinical trial.mp. or exp Controlled Clinical Trial/
37 intervention study.mp. or exp Intervention Studies/
38 Comparative Study/
39 experiment.mp.
40 time series.mp.
41 pre-post test.mp.
42 (randomized controlled trial or controlled clinical trial).pt.
43 (randomized controlled trials or random allocation or clinical trial or double blind method or single blind method).sh.
44 exp clinical trial/
45 (clin$ adj25 trial$).ti,ab.
46 ((singl$ or doubl$ or trebl$ or trip$) adj25 (blind$ or mask$)).ti,ab.
47 (research design or placebos).sh.
48 (placebo$ or random$).ti,ab.
49 exp Double-Blind Method/
50 exp cohort studies/ or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study

or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or comparative study/ or follow-up studies/ or prospective studies/ or cohort.mp. or compared.mp. or multivariate.mp. (4148897)
51 ("time series" or pre-post or "Before and after" or intervention).tw.
52 or/35-51
53 16 and 34 and 52
54 limit 53 to english language
55 limit 54 to humans
56 limit 55 to yr="2000 -Current"
57 (influenza$ or antimalar$ or malaria$ or prophylax$).mp.
58 56 not 57

APPENDIX B. RISK OF BIAS CRITERIA*

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

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

Was the allocation sequence adequately generated?

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

Was the allocation adequately concealed?

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

Were baseline outcome measurements similar?[1,2]

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

Were baseline characteristics similar?

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

Were incomplete outcome data adequately addressed?[1]

Score "Low risk" if missing outcome measures were unlikely to bias the results (*eg* the proportion of missing data was similar in the intervention and control groups or the proportion of missing data was less than the effect size *ie* unlikely to overturn the study result). Score "High risk" if missing outcome data was likely to bias the results. Score "Unclear risk" if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

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

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

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

Was knowledge of the allocated interventions adequately prevented during the study? [1]

Score "Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, *eg* length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.

Was the study adequately protected against contamination?

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

Was the study free from selective outcome reporting?

Score "Low risk" if there is no evidence that outcomes were selectively reported (*eg* all relevant outcomes in the methods section are reported in the results section). Score "High risk" if some important outcomes are subsequently omitted from the results. Score "Unclear risk" if not specified in the paper.

Was the study free from other risks of bias?

Score "Low risk" if there is no evidence of other risk of biases

II. Risk of bias for interrupted time series (ITS) studies

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

Was the intervention independent of other changes?

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

Was the shape of the intervention effect pre-specified?

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

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

Was the intervention unlikely to affect data collection?

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

Was knowledge of the allocated interventions adequately prevented during the study?[3]

Score "Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, *eg* length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.

Were incomplete outcome data adequately addressed?[3]

Score "Low risk" if missing outcome measures were unlikely to bias the results (*eg* the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size *ie* unlikely to overturn the study result). Score "High risk" if missing outcome data was likely to bias the results. Score "Unclear risk" if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

Was the study free from selective outcome reporting?

Score "Low risk" if there is no evidence that outcomes were selectively reported (*eg* all relevant outcomes in the methods section are reported in the results section). Score "High risk" if some important outcomes are subsequently omitted from the results. Score "Unclear risk" if not specified in the paper.

Was the study free from other risks of bias?

Score "Low risk" if there is no evidence of other risk of biases. *eg* should consider if seasonality is an issue (*ie* if January to June comprises the pre-intervention period and July to December the post, could the "seasons' have caused a spurious effect).

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes. Very thoroughly described objectives and methodology. They have used strict criteria on randomized controlled trials, cluster randomization and interval time series analysis studies, Excluding retrospective analyses with all their flaws and bias with these studies is appropriate. The studies are mostly current (<10 years old) which is critical for determining relevance to current clinical practice. Breaking down the studies into their purpose, outcomes and strength in the tables makes it easier to review than the long discussions. Another strength is also grouping studies on type of intervention (lab, provider education etc) can really relate the type of studies to likely clinical outcomes.	Thank you.
Yes	
Yes. The review is extremely well-organized, with clear objectives and scope. Methods are also transparent, particularly in how the prior AHRQ review is discussed in relation to the data the authors find that correspond to each category of analysis. I particularly appreciated the authors separating out communication skills training as a category of analysis; this may be a particularly fruitful area for further research in antimicrobial stewardship.	Thank you.
Yes	
Yes. Well structured and organized	Thank you.
Yes	
2. Is there any indication of bias in our synthesis of the evidence?	
No. All studies selected are appropriate. I performed a current pubmed search and saw no papers missing from this analysis. Knowing some of these papers from having reviewed them for journals, you have identified the critical issues (Legare especially – several papers of this author have not been published I have reviewed due to errors you have identified). The evidence is as you state – limited for all types of interventions and with end points that are short term. There are no data on how these interventions look one-2 years later. Defining the optimal intervention is also limited by lack of data strength especially for scalability and mostly sustainability of the intervention.	Thank you. Please note that we have updated our literature search and added 3 references.
No	
No. I continue to be surprised at the rather high level of bias present in the majority of the studies analyzed, as assigned by the authors of the review. I am also surprised that only 2 studies that addressed formulary restriction were of significant quality to include in the review.	We, too, are disappointed in the high level of bias. Of note, the AHRQ review also identified only one study of a restrictive intervention.
Yes. Not including studies that were in the AHRQ review and only including recent studies (noting, however, the older Cochrane review studies that were analyzed separately) may have biased the outcomes.	We attempted to provide sufficient information about the studies included in the AHRQ review (and the findings). The 2 Procalcitonin studies from the Cochrane review on that topic were also fairly recent studies (2008 and 2010).
No. Comments: p. 26, line 28-31: “It is unlikely that there will be a team of specialists involved in the prescribing decision, unlikely the provider will have an opportunity to modify the initial prescription, and unlikely the provider will receive feedback on the patient’s progress.” The above statement does not reflect the recognition that experts can deliver evidence-based recommendations at the point-of-service through electronic means, or that automated surveillance methods can follow the progress of individual patients. In general, the review could expand its underlying vision of how a team of specialists could deliver effective, sustainable and scalable outpatient antibiotic stewardship.	Thank you. We have modified the statement cited to reflect that in “many outpatient situations” these factors may apply and included a sentence about improving prescribing and monitoring in the Future Research section.

No	
3. Are there any published or unpublished studies that we may have overlooked?	
No	
Yes. Cals JW et al. Point-of-Care C-Reactive Protein Testing and Antibiotic Prescribing for Respiratory Tract Infections: A Randomized Controlled Trial Ann Fam Med March 1, 2010 vol. 8 no. 2 124-133	Thank you. This trial was already included in the review.
No. The studies that I previously suggested for inclusion appear to have been considered by the authors. I have no new studies to suggest.	Thank you.
No. None that met the strict criteria for entry.	Thank you.
No. The review's choice to leverage existing reviews and focus on the latest additions to the literature is both wise and well implemented. I am not aware that the evidence review has missed a meaningful entry. The following are a few note/errors noted in the reference section: p. 85, line 7: I cannot find this reference in PubMed p. 85, line 29: Labracque should read Labrecque p. 88, line 41: Blair should read Blais	Thank you. The reference noted on page 85, line 7 (the Godlee 2013 reference) is correct but is not cited in PubMed. We have corrected the typographical errors on the other 2 references.
No. Not that I am aware of although I did not review the literature comprehensively.	Thank you.
4. Please write any additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.	
None, very thorough review and conclusions. Areas that should have been also considered for future evaluation include routine urine cultures and treatment of asymptomatic bacteruria in outpatient settings and pre-operative clinics (See Drekonja JAMA 2013) as a future intervention and target for stewardship. As this is in the outpatient setting the data is limited compared to the vast inpatient literature where there is more "control" for antibiotic use in larger centers	Thank you. This may be a topic for future intervention but, at present, we found no studies. The reference cited (actually in Archives of Internal Medicine) would not have been eligible for inclusion in the review.
Executive Summary table 2a: what does "+-/-" signify – this is not defined in the table legend Page 39, line 28: agree that the duration of follow-up and sustainability of the cited 9.7% reduction of antimicrobial use should be provided	Executive Summary Table 2a: We have added the definition of +/- to the table legend. Page 39: We have added the follow-up information for this outcome.
Page 4, lines 2-6, 28, 29: When ranges are presented (*ie* "ranging from 0.2% to 10.5%" (line 2), "ranging from 0.3% to 55.0%" (line 3), "ranging from 15-75%" (lines 5-6), "1.4%-13.1%" (line 28), "10.4%-44.5% (line 29)), would suggest including medians if possible. Page 34, lines 27-28: Agree that duration of followup and sustainability be addressed if possible. Perhaps give a range/median of duration of followup from the studies in which it was reported. How many studies actually addressed sustainability, though? If not many, maybe it's not worth including. Page 35, line 32: *pneumonia* should be *pneumoniae* Page 44, line 16: "twol" should be "two" Page 61, line 43: I'd specifically say here that no other studies addressing procalcitonin beyond the two discussed in the Cochrane review met criteria for inclusion in the current review	Page 4: Thank you. We have added medians. Page 34: We have reported the median length of follow-up. The AHRQ report did not provide information on follow-up in individual studies. It is not possible to determine whether the studies were addressing sustainability. Page 35 and Page 44: we have corrected these errors Page 61: We have added this statement.

I think the rationale for not including studies from the AHRQ review is troublesome to explain; if their methodology otherwise met the criteria of this systematic review, why not include them?	We decided that including the studies cited in the AHRQ review was a duplication of effort and therefore elected to summarize the findings from that review.
Given the population of patients served through the VA system, excluding studies primarily focused on pediatric patient populations would have seemed reasonable.	In a conference call with our Operational Partners and Technical Expert Panel it was agreed that the pediatric studies should be included because the interventions were relevant to all populations
The tables in Appendix D are superb.	
Please discuss the role of the risk of adverse drug effects, particularly the risk of C. difficile colitis, in projects involving provider and patient education. Was the inclusion of these effects effective in reducing overall antibiotic use?	We mentioned the potential for adverse drug effects especially C. difficile colitis. These adverse effects were extracted if reported.
I think the authors should discuss the limitations of this systematic review. In the limitations paragraph on page 82, comments are primarily made towards the limitations of the studies included in the review. The methods of a systematic review may not be the optimal way to address the primary outcomes (key questions) sought for assessing the available literature on outpatient antimicrobial stewardship programs. For instance, a comment is made "most of the interventions were multifaceted making specific recommendations about key components difficult." The authors seem to fault the studies for this, rather than question whether trying to assess the various outcomes measurements of the studies through a systematic review is the most appropriate venue to assess these studies.	We recognize the reviewer's concern and agree that systematic reviews have limitations. Systematic reviews are intended to summarize and synthesize the available evidence on a topic and are therefore limited by the study methods, selected outcomes and outcomes reporting of the original research. Our intention is to highlight for researchers how the design of the existing research (multifaceted interventions, short follow-up periods, etc.) limits what can be concluded about specific interventions, sustainability, etc.
Another limitation to address is the methods of the electronic literature search. Despite a thorough vetting of 559 full-text articles, Fifteen (43%) of the 35 studies ultimately included did not come from the electronic literature search, implying that there were possibly flaws in the methods of the literature search. In addition, there are no comments on whether any other studies reviewed outside of the electronic literature search (ie, suggested by reviewers) were excluded from the analysis.	At present, there are no Medical Subject Headings (MeSH) terms for searching in MEDLINE that directly pertain to antimicrobial stewardship. We modeled our search after searches in existing reviews. We also reviewed reference lists of existing reviews and included studies. For this review, only one reference was suggested by reviewers and this reference was already included in the review.
I'm concerned that some interventions in certain studies that demonstrated statistically significant improvements in outcomes were dismissed by the authors due to the extent of the improvement rather than the four domains described the section "rating the body of evidence" (page 31). For instance, many studies showed statistically significant improvements in prescribing habits but since the size of the difference was ~10% it was subjectively characterized by the authors. I think the interpretation of the extent of statistically significant improvements in an effect should be left to the readers opinion.	We have provided the reader with the findings from the individual studies and then determined an overall strength of evidence (Executive Summary Table 3a) taking into account risk of bias, consistency, directness and precision.
Finally, a limitation that systematic reviews often have is coming to a conclusion about an outcome without discussing the possibility that certain excluded studies may have added important and valid variables to affect the outcome. It is likely that with over 90% of the full-text articles excluded, at least some of these data would have important findings that would affect the answers to the key questions. This limitation is probably slight in systematic reviews that assess the objective, clear comparative outcomes of "drug A" versus "drug B" for a given disease state, but is probably more important for the key questions addressed in this review.	Certainly there is a large body of literature on antimicrobial stewardship that was excluded from our review. The most common reason for excluding studies was the study design. We chose to focus on the studies with the lowest potential for bias and therefore believe we have captured the most important evidence on the topic.

1) The review categorizes stewardship interventions in a manner that more or less follows precedent reviews. The rationale for this categorization is not given. Many of the interventions involve the delivery of guideline-derived education to providers and/or patients. There is no systematic attempt to abstract information about the nature, format, intermediary, timing and periodicity of this education in relation to the provision of care. 2) Labeling of the "Laboratory Testing" category is not informative. Category label should reflect what is being introduced to the antibiotic prescribing logic: rapid laboratory evidence of either specific infection, or of systemic inflammation. 3) Evaluation of the evidence supporting an intervention is limited to biases inherent to study design. The review could attempt to better abstract and synthesize other potentially significant markers of intervention utility, such as effect size and sustainability. For example, a VA study that reports a 4-year intervention is not mentioned in the "Sustainability" section.	1) We attempted to categorize studies by the primary intervention based on the study authors' description of the intervention. We have noted where the interventions were multifaceted. We agree that the factors listed are potentially important in evaluating the effectiveness of the intervention and have attempted to highlight these factors in the report. There is limited information provided on this and goes beyond the scope of our review and input we received from our Technical Expert Panel when constructing the key questions, outcomes and protocol. 2) We have modified the "Laboratory Testing" section to better characterize the interventions. 3) We used standard methods (the approach used in the Cochrane Effective Practice and Organization of Care reviews) to evaluate the risk of bias of individual studies. Overall strength of evidence for the interventions was determined based on risk of bias of individual studies plus the consistency and precision of the findings across the studies. We have added the VA study to the sustainability section.
I know there was some discussion of this, but I don't find studies of children relevant to the VA population. On page 34 there is a comment in the 3rd full paragraph that looks like an unfinished question I still find the format somewhat confusing in differentiating information from the old reviews (AHRQ and Cochrane) versus results from this review. In addition, it would be nice to see a summary including the overall result combining the two for the main outcomes. I said this on the inpatient review as well, but I find the tables very difficult to follow. It would be nice to have a visual summary somewhere – either a boxed off area with summary results or a Forrest plot to see the outcomes in a way that is easy to follow. I find this very useful in the Cochrane analyses which are also very long and comprehensive, but allows for a quick review of the data. I know it is a lot of information, but I wish tables 1-5 were combined. It's difficult to flip back and forth between study design and outcomes for a clinician trying to use this information	As noted above, it was agreed that pediatric studies should be included. Pg. 34 – this has been corrected We chose to categorize interventions somewhat differently than in the AHRQ review therefore it wasn't possible to seamlessly combine the older studies and the newer studies. We have added a summary of the AHRQ review to the Discussion section of both the Executive Summary and full report. Due to the variety of ways the outcomes were reported across studies, we were unable to create forest plots. We have added a key findings section to the Discussion section of the Executive Summary. It would be difficult if not impossible to put sufficient information about study characteristics AND outcomes on a single table. We have considered alternative options but given the volume of information believe the current Tables 1-5 are preferred.
5. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	
Most of studies are on URTI. Would have table showing the data/patient outcomes of not treating versus treating from all the randomized studies. End points may be different but populations wlll be similar. Also would break out (Looks like one asymptomatic bacteruria) study. This is a detailed report and the tables are excellent for reviewing.	Thank you. We included a table that highlighted the non-respiratory infections because they were so few in number. A table of studies with respiratory infections would comprise the bulk of the studies already displayed. Similarly, a table of outcomes of not treating versus treating would be largely duplicative. We believe that additional Tables would not add much value especially for the length and resources involved.
This is a nicely written report. I have no further suggestions	Thank you.
All in all, this report does a nice job of directly addressing implementation needs. I do not think major revisions are necessary.	Thank you.
The authors might expand upon their ideas for future research recommendations.	We have added some additional information to this section.
Again – a clearer visual demonstration of key results.	We have added a key findings section to the Discussion section in the Executive Summary.

APPENDIX D. EVIDENCE TABLES

Table 1. Study Characteristics

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Provider and Patient Education						
Gerber 2013[20] North America (US) CRCT	Reduce inappropriate antimicrobial prescribing for common ARTIs in pediatric primary care	Clinician education (1 hour) addressing study goals, current prescribing guidelines, practice specific baseline antimicrobial prescribing data related to the guidelines	Personalized audit and feedback: guideline-based prescribing rates for individual clinician, practice, and network every 4 months	No intervention but were aware of participation in study and tracking of prescribing patterns	Clinicians	Electronic health record
Vinnard 2013[21] North America (US) CBA	Effect of a provider-approved patient education mailing on prevalence of antimicrobial prescribing	Educational brochure and explanatory letter signed by provider mailed to patients	Intervention providers also received "Prescription Pad" and patient education sheets	Usual care	Primary care providers	Brochures, "Prescription Pad" and patient education sheets
Butler 2012[22] United Kingdom STAR Educational Program RCT	Reduce antimicrobial dispensing for all causes without increasing reconsultations, hospital admissions for selected causes, and costs	Blended learning experience (reflection on own practice, new research evidence and guidelines, communication skills with motivational interviewing, practice in usual clinical contexts, sharing experiences, facilitator-led practice-based seminar)	NR	Control (usual care)	General practitioners and nurse practitioners	NR
Llor 2012[23,24] Europe (Spain) CBA HAPPY AUDIT SEE Laboratory Tests	Lower prescriptions of antimicrobials for respiratory infections	Full-intervention Group (FIG): POC CRP Test plus provider education (discussion of findings from baseline period, training on diagnosis and treatment of respiratory infections, discussion of guidelines, patient information leaflets, workshop on rapid tests, introduction of CRP test)	NR	1) Partial-intervention Group (PIG): Provider education without CRP 2) Control: usual care (providers created registry of patients during intervention period)	General practitioners	POC CRP testing, courses, workshops, guidelines, patient information leaflets

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Regev-Yochay 2011[25] Middle East (Israel) CRCT	Reduce prescription rates for antimicrobials known to be promoters of antimicrobial resistance	3 workshops 1) Start of Year 1: determinants of non-judicious use of antimicrobials; potential intervention to reduce non-judicious use 2) Start of Year 2: Parent-physician communication 3) Start of Year 3: antimicrobial prescription rate feedback	Focus groups (each participating physician joined one group) 1) Develop local guidelines for diagnosis and management of RTIs 2) Lead seminar on Improving RTI diagnosis 3) Distribute leading articles on promoting awareness of antimicrobial resistance 4) Develop campaign for parents and children (posters, pamphlets, coloring books) 5) Develop seminar on parent-physician communication	Usual care	5 physicians allocated to intervention group were asked to serve as local leaders based on leadership skills, low prescribing rate, and consent; participated in preparing the intervention	
Esmaily 2010[26] Middle East (Iran) CRCT	Decrease use of antimicrobials	Outcome-based education (OBE) for general practitioners (principles of prescription writing, adverse reactions to drugs, drug interactions, injections, antimicrobial therapy, anti-inflammatory therapy); used interactive and learner-centered teaching techniques; included self-learning materials after the program	NR	Continuing medical education (CME) program with same topics; lecture based	1) General practitioners 2) Experienced CME trainers (medical specialists and pharmacists	
Smeets 2009[27] Europe (Netherlands) CBA	Reduce antimicrobial prescribing for ARTIs	Educational outreach based on guideline for respiratory tract infections (initial group education meeting, academic detailing at start of intervention, second group meeting about guideline plus skills training in patient education)	1) Communication skills training 2) Patient education material 3) Audit and feedback on prescriptions after 1 year 4) Regional expert general practitioners	Usual care	1) General practitioners (194 intervention, 188 control enrolled; 131 intervention and 127 control analyzed) 2) Collaborating pharmacists 3) Staff members of Institute for Proper Use of Medicine (organized group meetings)	NR

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Finkelstein 2008[28] North America (US) CRCT REACH Mass study	Reduce unnecessary antimicrobial use in children (overall and broad-spectrum)	1) Physician: Kick-off dinner (study information, educational materials); bi-monthly "briefs" on topic; visit from educational coordinator; reinforcing education session prior to 3rd season* 2) Parents: brochure titled "Kids and Antibiotics;" newsletters; Web site; posters and other materials in provider offices; displays at pharmacies; training (in 3rd year of study) of child care directors	"Prescription" pad with symptom treatment recommendations	Usual care	Pediatricians and family physicians	Web site, brochures, newsletters, posters, and other materials with REACH Mass logo
Chazan 2007[29] Middle East (Israel) RCT	Effect of 2 education programs on appropriate use of antimicrobials	Continuing medical education (aimed at improving diagnostic skills in infectious diseases and appropriate antimicrobial treatment); monthly interactive teaching sessions	1) Guidelines for antimicrobial treatment in primary care 2) Seasonal medical education (Sept-Oct for 2 consecutive winters; interactive meeting on judicious use of antimicrobials for respiratory infections; reminders and patient leaflets)	Seasonal medical education only	Family physicians, pediatricians, nurses, pharmacists	Patient leaflets
Metlay 2007[30] North America (US) IMPAACT trial CRCT	Reduce antimicrobial overuse for acute respiratory tract infections in the emergency department	Educational – clinician leaders conducted education sessions in clinics	1) Clinician leaders – trained on judicious antimicrobial use 2) Aggregate site-specific data on antimicrobial use for ARTIs in pre-intervention year 3) Patient education – posters, brochures, video kiosk	Control (usual care)	Emergency department staff (including attending physicians, fellows, residents, medical students, RNs, PAs, and NPs)	NR
van Driel 2007[31] Europe (Belgium) CRCT	Implementation of a new guideline for rational use of antimicrobials for acute rhinosinusitis	Peer-led discussion session on the new guideline; trained academic detailer from research team met with leader of discussion session prior to the session to present material for the discussion (main recommendations and supporting evidence, patient information leaflets, research on patient expectations, clinical case vignettes)	1) National public campaign addressing rational use of antimicrobials, in general 2) Rhinosinusitis guideline disseminated by mail to all general practitioners	Group meeting on the guideline (without supplemental materials)	Trained academic detailer	Presentation materials, patient leaflets

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Varonen 2007[32] Europe (Finland) RCT	Effect of different education strategies for guideline introduction on prescribing patterns for acute maxillary sinusitis	Problem-based learning (PBL): group work facilitated by a local GP tutor; used case scenarios, information retrieval, and reflection; sessions led by GP facilitators in each health center using materials provided by the research group	NR	Academic detailing (AD): use of information sources, feedback of own practices, visits from external experts; education sessions led by GP facilitators in each health center	GP facilitators	Presentation materials, patient leaflets
Little 2005[33] United Kingdom RCT	Estimate effectiveness of 3 prescribing strategies and an information leaflet	Patient education (leaflet with natural history of condition, response to major patient worries, advice about when to seek further help)	Prescribing strategy (Immediate antimicrobials, no offer of antimicrobials, or delayed antimicrobials) NOTE: factorial design – 1st factor was leaflet/no leaflet, 2nd factor was prescribing strategy	No leaflet, alternative prescribing strategy(all patients were given brief information about natural history, analgesics, and support for the proposed prescribing strategy)	General practitioners	Patient diaries
Pagaiya 2005[34] Asia/Pacific (Thailand) RCT	Examine whether guidelines improve quality of care (Note: study conducted in nurse-led health centers)	Nurse training (3-day interactive training on guidelines and related content including conduct of the physical examination, rational drug use, and use of effective communications skills)	1) Thai national clinical guidelines for acute respiratory infection and diarrhea in children 2) One educational outreach visit	Usual care	Nurses	Guidelines (laminated)
Gonzales 2004[35] North America (US) CCT	Improve antimicrobial use for ARTIs in the elderly	Patient education materials mailed to households and placed in offices	NR	1) Guidelines for diagnosis and treatment of bronchitis in adults 2) Performance feedback measures based on aggregated managed care organization claims data	NR	Educational materials (brochures, refrigerator magnets, reference cards, posters)

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Stewart 2000[36] North America (Canada) CBA	Improve antimicrobial use	1) Health Professionals and Pharmaceutical Representatives Small group, guideline-based CME sessions 2) Community Education including town hall meeting; handouts distributed in physician offices, walk-in clinic, and pharmacies in conjunction with counseling; presentations to school and community groups; articles by lead physician for local media	1) Lead "local champion" physician 2) Support for the program from local physicians and pharmacists 3) "Non-drug prescription pad" to use during patient visits 4) Newsletters to update physicians on program activities	Usual care - prescription claims from rest of province (study was conducted in one community)	Lead physician, research pharmacists, pharmaceutical industry	Educational handouts
Provider Feedback						
Gjelstad 2013[37] Europe (Norway) CRCT	Reduce antimicrobial prescribing for ARTIs and reduce use of broad-spectrum antimicrobials	Individual report of GP prescription rates and distribution of different antimicrobials for ARTI diagnoses; findings compared to averages from participating GPs; presented during 2nd group session with academic detailer	1) National guidelines and recent research evidence presented by academic detailer (1st group session) 2) Emphasis on delayed prescribing (some GPs had pop-up reminder) 3) Additional 1-day educational seminar	Same intervention components but focus on more appropriate drug treatment (not including antimicrobials) in patients over age 70 years	Trained GPs who were peer academic detailers	Software to capture data from GP's electronic health record and generate prescribing reports
Vinnard 2013[21] North America (US) CBA	Impact of intensive academic detailing for providers with high rates of antimicrobial prescribing for URTIs	1) Intensive Intervention: Academic detailing (pharmacist and opinion leader in antimicrobial use met with provider; presented published literature and provider-specific results 2) Mild Intervention: See Supplements to Core	1) "Prescription Pad" for symptom relief modalities 2) Patient information sheets	Usual care	Primary care providers; pharmacist and opinion leader in antimicrobial use	"Prescription Pads" and patient education sheet
Linder 2010[38] North America (US) CRCT	Reduce inappropriate prescribing and improve quality of care for ARIs	*ARI Quality Dashboard* integrated into electronic health record; displays a clinician's prescribing performance and billing practices for ARI visits against peers and national benchmarks	Monthly e-mails reminding clinicians about the *ARI Quality Dashboard*	Usual care	Physicians, residents, fellow, NPs, PAs (258 at intervention sites, 315 at control sites), research team (application and user support)	1) Electronic health record (already in place) 2) *ARI Quality Dashboard report*

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Naughton 2009[39] Europe (Ireland) RCT	Effect of interventions on reducing overall antimicrobial prescribing and second-line prescribing (co-amoxiclav and cephalosporins)	1) Postal prescribing feedback (individual prescribing feedback for 12 months prior to intervention – rate of overall antimicrobial prescribing compared with Health Authority average, proportion of first-line antimicrobial prescribing compared with second line co-amoxiclav and cephalosporins 2) Academic detailing (15-20 minute outreach visit from research coordinator with information from postal bulletin and discussion of ways to reduce prescribing)	NR	Postal prescribing feedback	General practitioners; research coordinator for academic detailing visits	NR
Madridejos-Mora 2004[40] Europe (Spain) CCT	Improve quality of prescribing in general practice; 3 quality levels 1) reduced prescribing of drugs with low pharmacological intrinsic value, 2) excessive drug prescribing, or 3) improved drug selection	Individualized feedback (n=195 practitioners): 45 minute team education session with pharmacist; individual feedback; recommendations to improve quality of prescribing (directed to 1 of 3 quality levels)	Leaflet with indicators and anonymous comparison to other providers	Minimal intervention (n=87 practitioners): usual information provided by public health organization (prescribing data for practice group as a whole; no individual data)	General practitioners and pharmacists	Computerized prescribing data (already in place)
Guidelines						
Dowell 2012[41] North America (US) ITS	Assess impact of revised guidelines on fluoroquinolone use	Revised guidelines from Centers for Disease Control and Prevention (sent to state and local health departments, national press conference, *Morbidity and Mortality Weekly Report* article)	NR	Usual care (pre-intervention)	NR	NR
Slekovec 2012[42] Europe (France) ITS	Effect of guidelines and educational session on prescribing (especially fluoroquinolones)	Guideline for management of UTIs mailed to all GPs and available on website	Voluntary training sessions (lecture, clinical examples, general and local information on antimicrobial use and resistance)	Usual care (pre-intervention)	General practitioners	

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Venekamp 2012[43] Europe (Netherlands) ITS	Effect of a revised guideline on prescription rates for ARS	Guideline, revised to advocate more judicious use of antimicrobials (*ie*, use only if severe illness, fever recurring after fever-free period within 1 ARS episode, symptoms lasting >14 days, recurrent ARS episodes [>3/yr], immunodeficiency)	1) Guidelines posted on open access Web site and abstract distributed to physician 2) Guidelines discussed as part of medical educational sessions required for re-registration of family physicians	Usual care (pre-intervention period)	Family physicians	
Weiss 2011[44] North America (Canada) ITS	Assess effect of guidelines on antimicrobial use	Guidelines issued addressing most common infectious conditions in outpatient setting; sent to all physicians and pharmacists; emphasis on proper regimens, not using antimicrobials for viral infections, using for shortest duration possible.	1) Letter from key stakeholders accompanied initial mailing 2) Promotion of guidelines by experts at CME meetings 3) Encouragement to include proper prescribing in medical school curriculum	Usual care (pre-intervention)	Physicians, pharmacists	
Seager 2006[45] United Kingdom CRCT	Assess effect of educational outreach visits on prescribing for dental conditions in the primary care setting	Printed educational material sent by mail (guidelines for management of acute dental pain, 1 page summary, and patient information leaflets)	Academic detailing visit by pharmacist who had been involved in development of guidelines; discussed guideline content and encouraged rational use of antimicrobials	1) Printed educational material sent by mail 2) Usual care (no intervention)	General dental practitioners	
Martens 2006[46] Europe (Netherlands) CCT	Effect of guidelines on volume of prescriptions	Guideline for antimicrobials	NR	Usual care	General practitioners	
Delayed Prescribing						
Little 2010[47] United Kingdom RCT	Assess impact of management strategies in women with urinary tract infection	1) delayed antimicrobials 2) antimicrobials offered based on symptoms 3) antimicrobials offered based on dipstick test 4) antimicrobials offered based on midstream urine test	Structured advice sheet for patients (for each strategy)	Immediate antimicrobials (usual care)	Physicians and nurses	Midstream urine and dipstick testing

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Worrall 2010[48] North America (Canada) RCT	To determine whether delayed prescribing reduces antimicrobial use for ARTIs	Post-dated prescription (dated 2 days after office visit); asked to use prescription only if symptoms had not improved or worsened after 2 days	Standardized explanation of likely viral, benign, and self-limiting nature of acute upper respiratory tract infections	Usual prescription (dated day of office visit); asked to use prescription only if symptoms had not improved or worsened after 2 days	Family practice physicians and nurse practitioners	NR
Communication Skills Training						
Little 2013[49] UK and Europe (multi-national) GRACE consortium CRCT SEE CRP testing	Effects of internet-based training tool on antimicrobial prescribing and symptom control (LRTI and URTI)	Internet-based training of physicians for: a. use of a point-of-care CRP test and b. enhanced communication skills	1) Interactive booklet to use during consultations (symptoms, use of antimicrobials and antimicrobial resistance, self-help measures, when to re-consult) 2) Video demonstrations of consultation techniques 3) Lead physician (at group practices) to organize a structured meeting on prescribing issues	1) Internet-based training for use of point-of-care CRP test 2) Internet-based training for enhanced communication skills 3) Usual care	Clinicians (and nurse prescribers in the UK)	POC CRP testing, internet training modules
Légaré 2012[50] North America (Canada) DECISION+2 CRCT	Reduce overuse of antimicrobials for ARTIs with focus on percentage of patients who decided to take antimicrobials after physician consultation	2-hour on-line tutorial followed by 2-hour on-site interactive workshop (included information on shared decision-making, diagnosis of ARTIs, treatment of ARTIs, effective communication of risks and benefits, and promoting active patient participation)	Decision support tools available in consultation rooms of intervention sites	Usual care	Family practice physicians	1) On-line tutorial 2) Facilitator to lead on-site workshops
Légaré 2010[51] North America (Canada) DECISION+ CRCT Feasibility study for Légaré 2012	Reduce overuse of antimicrobials for ARTIs with focus on decision whether to use antimicrobials	1) 3 3-hour interactive workshops and related materials; focus on shared decision-making 2) Reminders of expected shared decision-making behaviors 3) Feedback to physicians on agreement between their decisional conflict and that of their patients	1) Local opinion leaders 2) Decision support tools	Usual care (delayed exposure to the intervention)	Family practice physicians	

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Cals 2009[52] Cals 2011[53] Cals 2013[54] Europe (Netherlands) CRCT SEE CRP Testing	Determine the effect of CRP testing and communication skills training for practitioners on antimicrobial prescribing for LRTI	1) POC CRP testing AND 2) Training in enhanced communication skills	NR	1) Usual care 2) Training in enhanced communication skills 3) CRP testing.	Treating physician, Educators	POC CRP testing
Francis 2009[55] United Kingdom CRCT	Reduce reconsultation & antimicrobial use while maintaining parental satisfaction with care	Interactive 8 page booklet on RTIs in children to be used during the consultation and then provided to parents as a take-home resource	On-line training for clinicians on use of the booklet to facilitate communication skills (*eg*, parent main concerns, expectations, treatment options)	Usual care	Clinicians	Interactive booklet
Altiner 2007[56] Europe (Germany) CRCT	Reduce unnecessary antimicrobial prescribing for acute cough	General practitioner peers (teachers who were trained specifically for the outreach visit on antimicrobial misunderstanding during consultation-patient expectations, provider pressures)	Patient education leaflet and poster for waiting room	Usual care	General practitioners (n=104 with baseline data were randomized; n=86 completed 6 week documentation, n=61 completed 12 month documentation)	NR
Restriction						
Manns 2012[57] North America (Canada) ITS	Assess effect of formulary policy restricting quinolone use	Restriction policy (physicians could voluntarily enroll and become a designated quinolone prescriber)	1) Addition of 2 new quinolones to formulary (gatifloxacin, moxifloxacin) 2) Guide to prescribing restriction for quinolones and educational package mailed to all physicians (with a "consent to participate" form)	Pre-restriction period	NR	Prescription data from insurance company database
Marshall 2006[58] North America (Canada) ITS	Assess effect of formulary policy restricting fluoroquinolone (ciprofloxacin, ofloxacin, and levofloxacin) reimbursement	Ciprofloxacin, ofloxacin, and levofloxacin changed to "Limited Use" listing in formulary limiting reimbursement to treatment of patients with specified conditions	NR	Pre-restriction period	NR	Prescription data from government-funded drug insurance program

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Decision Support						
Gonzales 2013[59] North America (US) CRCT	Reduce use of antimicrobials for acute bronchitis	1) Printed decision support (patient brochures, posters) 2) Computer-assisted decision support (prompts for history and exam elements, order sets)	1) Clinician education 2) Information on clinic performance given to clinic champions 3) Patient education	Control (usual care)	All clinicians caring for patients diagnosed with acute bronchitis (MDs, NPs, PAs, RNs)	Computerized algorithms and order sets Electronic health record (already in place)
Jenkins 2013[60] North America (US) RCT	Decrease prescribing for non-pneumonia acute respiratory infections; decrease overall use of broad-spectrum antimicrobials	Clinical decision support pathways for 8 outpatient infections (non-specific upper respiratory, acute bronchitis, acute rhin osinusitis, pharyngitis, acute otitis media, urinary tract, skin and soft tissue, CAP)	1) Patient education 2) Peer champion	Control (usual care)	NR	Electronic health record (already in place)
McGinn 2013[61] North America (US) RCT	Assess effect of clinical decision support tool integrating clinical prediction rules (CPRs) for management of respiratory tract infections	1) One-hour training (overview of CPRs and supporting evidence, study protocols, demonstration of tool in electronic health record, video of simulated patient encounter using tool) 2) CPR tool	Bundled order sets	Control (usual care) with background information on the CPRs	Attendings, residents, fellows, and NPs	Electronic health record (already in place)
Rattinger 2012[62] North America (US) CBA	Minimize unnecessary use of antimicrobials	Clinical decision support system emphasizing azithromycin and gatifloxacin; treatment paths for CAP, acute bronchitis, acute sinusitis, non-specific upper respiratory infection, exacerbations of COPD	Advice to providers on maintaining patient satisfaction when withholding antimicrobials	Control (usual care)	NR	Electronic health record (already in place)
Linder 2009[63] North America (US) CRCT	Reduce inappropriate prescribing	*ARI Smart Form* used when interviewing and evaluating patients; decision support so antimicrobial treatment matches diagnosis; access to appropriate patient handouts	1) Visit from co-investigator to introduce *ARI Smart Form* 2) Monthly e-mail reminders to clinicians with summary info on usage of *ARI Smart Form*	Control (usual care)	NR	Electronic health record (already in place)

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Martens 2007[64] Europe (Netherlands) CRCT	Effect on drug-prescribing behavior	Reminders (reactive) about antimicrobials and asthma/COPD prescriptions as part of decision support system; included reminders for alternative type of drug, other doses, other routes of administration, other duration, no prescription, alternative approach, specialist referral	1) Guidelines 2) Instruction on use of guideline/reminder system	Reminders about cholesterol prescriptions	General practitioners	Electronic health record (already in place), automated feedback system
Financial Incentive						
Martens 2007[65] Europe (Netherlands) CBA	Effect of financial incentive on volume of prescriptions and quality of prescribing behavior	Financial incentive – bonus independent of performance; in exchange, practitioners expected to adhere to prescription guidelines (abstracted to a 1 page formulary with recommendations on frequently prescribed drugs and less expensive alternatives for a few expensive new drugs - drugs where "improvement seemed possible and necessary")	1) National evidence-based guidelines 2) Medical education 3) Awareness of performance being evaluated	Control (usual care) – providers were also likely aware of national evidence-based guidelines and likely attended medical education sessions but did not get 1 page formulary and were not aware that performance was being evaluated	General practitioners (n=119 from intervention region, n=118 from control region)	Prescription data from regional health insurance company
Rapid Testing						
Little 2013[66] United Kingdom RCT	Effect of rapid streptococcal antigen detection test or clinical prediction scores on prescribing for sore throat	Rapid antigen detection test (RADT) if clinical score ≥ 3; offered antimicrobials if positive results	NA	1) Clinical score (Fever PAIN) Score 0 or 1: no antimicrobials Score 2: delayed antimicrobials Score ≥3: immediate antimicrobials 2) Delayed antimicrobials	General practitioners, triage practice nurses	IMI test pack RADT
Brittain-Long 2011[67] Europe (Sweden) RCT	Determine whether access to a rapid PCR assay for respiratory viruses impacts antimicrobial prescription rates in patients with ARTI	Rapid (day after visit) reporting of PCR results to treating clinician	NA	Delayed (8-12 days after visit) reporting of PCR results to treating clinician	Treating physician	RT-PCR laboratory

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Worrall 2007[68] North America (Canada) RCT	Compare rates of antimicrobial prescription for GABHS infection using clinical judgment, STDR, RADT, or both STDR and RADT in patients with sore throat	STDR, RADT, or both	NA	Usual clinical judgment	Treating Physician	RADT laboratory
C-Reactive Protein						
Diederischsen 2000[69] Europe (Denmark) RCT	Determine whether frequency of prescriptions for respiratory infections is reduced with CRP testing and the effect on morbidity	POC CRP testing	NA	Usual clinical judgment	Treating physician	CRP testing laboratory
Takemura 2005[70] Asia/Pacific (Japan) RCT	Determine the effect of immediate availability of WBC and CRP results on antimicrobial prescribing for ARTI	Immediate reporting of CRP and WBC (performed prior to physician consultation)	NA	Usual clinical judgment (no advance testing)	Treating physician	CRP and WBC testing laboratory
Cals 2009[52] Cals 2011[53] Cals 2013[54] Europe (Netherlands) CRCT SEE Communication Skills Training	Determine the effect of CRP testing and communication skills training for practitioners on antimicrobial prescribing	POC CRP testing	Enhanced communication skills training	1) Usual care 2) Communication skills training 3) CRP only	Treating physician Educators	POC CRP testing
Cals 2010[71] Europe (Netherlands) RCT	Determine if POC CRP testing affects antimicrobial prescriptions for LRTI and rhino-sinusitis	POC CRP testing	Delayed prescription education for patients (both groups)	Usual care	Treating physician	POC CRP testing

Author Year Geographic Area Study Design	Purpose of Intervention	Core Intervention(s)	Supplements to Core	Comparator(s)	Intervention Staff	Resources
Llor 2012[23,24] Europe (Spain) CBA HAPPY AUDIT SEE Provider and Patient Education	Determine if POC CRP testing affects antimicrobial prescriptions	Full Intervention Group (FIG): POC CRP testing plus provider and patient education, provider feedback	NR	1) Partial Intervention Group (PIG): Same as FIG except no CRP 2) Usual care	Treating physician	POC CRP testing, courses, workshops, guidelines, patient information leaflets
Little 2013[49] UK and Europe (multi-national) GRACE consortium CRCT SEE Communication Skills Training	Effects of internet-based training tool on antimicrobial prescribing and symptom control (LRTI and URTI)	Internet-based training of physicians for: a. use of a point-of-care CRP test and b. enhanced communication skills	1) Interactive booklet to use during consultations (symptoms, use of antimicrobials and antimicrobial resistance, self-help measures, when to re-consult) 2) Video demonstrations of consultation techniques 3) Lead physician (at group practices) to organize a structured meeting on prescribing issues	1) Internet-based training for use of point-of-care CRP test 2) Internet-based training for enhanced communication skills 3) Usual care	Clinicians (and nurse prescribers in the UK)	POC CRP testing, internet training modules

US = United States; NA = not applicable; NR = not reported; CBA = controlled before and after; CRCT = cluster randomized controlled trial; RCT = randomized controlled trial; GP = general practitioner; MD = physician; NP = nurse practitioner; PA = physician assistant; RN = registered nurse; ARS = acute rhinosinusitis; ARI = acute respiratory infection; ARTI = acute respiratory tract infection; CAP = community acquired pneumonia; COPD = chronic obstructive pulmonary disease; LRTI = lower respiratory tract infection; URTI = upper respiratory infection; CRP = C-reactive protein; CME = continuing medical education; PCR = polymerase chain reaction; GABHS = Group A β-hemolytic streptococcus; STDR = sore throat decision rules; RADT = rapid antigen detection tests; CEA = cost-effectiveness analysis; POC = point-of-care; RTI = respiratory tract infection
*Study was conducted during 3 successive cold and influenza seasons (October through March)

Table 2. Study Characteristics, Continued

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Provider and Patient Education					
Gerber 2013[20] CRCT	Community-based practices from a pediatric primary care network (18 of 20 eligible practices with 170 clinicians randomized)	-Diagnostic code for acute sinusitis, streptococcal pharyngitis, pneumonia or viral ARTI* -Median age 5 years, 51% male	1) Excluded academic practices 2) Excluded preventive encounters, ARTI encounters with an additional bacterial infection, encounters with children with complex conditions, allergy to antimicrobials, or with antimicrobial prescription in prior 3 months	Data obtained from electronic health record	Practices
Vinnard 2013[21] CBA	University-affiliated clinical practices (included faculty and non-faculty providers)	-Visit for URTI (ICD-9-CM for acute bronchitis, bronchitis, cough, acute pharyngitis, and acute URTI not otherwise specified) during non-intervention months (February through August for 4 years – 2 pre-intervention years, 2 post-intervention years) NOTE: Intervention period defined as time when materials were mailed to patients (between September 1 and January 1) Included 1344 patient visits	Diagnosis of chronic bronchitis or emphysema in recorded history; study diagnosis within 60 days prior to index visit; diagnosis of acute or chronic sinusitis or pneumonia within 60 days prior to index visit	*Providers:* Intervention providers were faculty providers in practice for all 4 study years and had the highest number of visits for the inclusion diagnoses; also required to be in practice subgroup that used the electronic medical record system; control providers were affiliated non-faculty providers with highest number of inclusion diagnoses visits; intervention group had 48 providers from 2 practices; control group had 22 providers from 13 practices† *Patients:* Study authors randomly selected 15 patients from specified study periods (or included as many as available if fewer than 15); excluded patients if selected visits included providers in both intervention and control groups	NA
Butler 2012[22] RCT	68 general medical practices	NR	NR	NR	Practices
Llor 2012[23,24] CBA	Primary care physicians invited to participate in study and assigned to full intervention (n=235) or partial intervention (n=97) 60 physicians from other communities provided control data	Lower respiratory tract infections (LRTI) Acute Sinusitis	NR	Patients recruited by participating clinicians during 3 week period of winter months of baseline year and intervention year	NA

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Regev-Yochay 2011[25] CRCT	Primary care pediatric solo practices (52 pediatricians randomized)	Children (<18 years) registered at the participating practices Median age 5.0 years	Excluded practices with 800 or fewer children treated per year and with low availability of the physician (open 3 or fewer days per week and less than 15 hours per week)	NR Data obtained from retail central pharmacies in HMO; for non-HMO physicians only crude data from last 4 years of study only (6 year study)	Pediatricians (solo practices)
Esmaily 2010[26] CRCT	General practitioners from 6 cities in Iran	NR	Excluded GPs who did not have contracts with the 3 major social insurance organizations	Collected 10% of each randomized GPs total number of prescriptions for individual patients from the insurance organizations	Regions (northern and southern), each with 3 cities
Smeets 2009[27] CBA	General practice peer review groups	Adults and children	NR	84 peer review groups invited; 25 (with 141 practices) agreed to participate in intervention; control group of 141 practices selected from remaining peer review groups matching for type of practice and volume of antimicrobial prescriptions	NA
Finkelstein 2008[28] CRCT	16 communities in Massachusetts	Children 6 years of age or less; residing in study communities and insured by participating health plan; coverage for medications for 90 days or more during study period	NR	Data from 4 large health insurers (including Medicaid); included data from all patients insured by the health plans regardless of whether providers participated in the intervention	Communities
Chazan 2007[29] RCT	Community outpatient clinics in Israel	Adults and children Mean age 32 years, 50% male	NR	Largest clinics in district were selected to participate; antimicrobial use data came from pharmacy database	Clinics
Metlay 2007[30] CRCT	Emergency departments at 8 VA medical centers and 8 non-VA academic medical centers; sites responded to survey indicating willingness to participate; restricted to metropolitan areas with at least 1 eligible VA and 1 eligible non-VA site; stratified by US region (Northeast, South, Midwest, and West)	Adults (age >18 years) with ARIs, unspecified cough illness, or streptococcal pharyngitis (discharge diagnosis)	For follow-up telephone call excluded severely ill or cognitively impaired patients and those who lacked a telephone	Identified potentially eligible patients based on ICI-9-CM codes Follow-up telephone interviews with up to 40 patients from each site to assess need for follow-up care (non-random convenience sample)	Metropolitan areas (2 within each US region) were randomly assigned to intervention or control

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
van Driel 2007[31] CRCT	General practices	Patients with acute rhinosinusitis 75 GPs registered 408 patient encounters Mean age 38 years, 61% female	Quality circles‡ that participated in validation process for guideline on acute rhinosinusitis	Contacted quality circles through representatives listed by national council for accreditation	Quality circles
Varonen 2007[32] RCT	Health centers (primary care)	This article focused on data from patients consulting for the first time during an episode of illness; at least one of the following symptoms: rhinitis, cough or maxillary pain; final clinical diagnosis of acute maxillary sinusitis or URTI	NR	Health centers volunteered to participate in nationwide research initiative assessing management of primary care infections; patients were consecutive patients consulting for any infectious disease during 1 week in November in all study years	Health centers
Little 2005[33] RCT	Primary care clinics	Age 3 years or older with uncomplicated acute illness (≤21 days); cough as main symptom and at least 1 symptom or sign localizing to lower tract (sputum, chest pain, dyspnea, wheeze) 807 randomized 167 lost to follow-up Mean age 38.5 years	History and physical examination suggestive of pneumonia; clinically diagnosed with asthma, other chronic or acute lung diseases including cystic fibrosis, cardiovascular disease, major current psychiatric diagnosis, mental subnormality, dementia, complications from previous episodes of LRTI	Patients who presented in primary care with cough as main symptom	Patients
Pagaiya 2005[34] RCT	Nurse-led health centers (staffed by nurses who had been working at least 6 months prior to study)	Children 0-5 years	NR	Health Centers: Included only center staffed by nurses Patients: Randomly selected patient records for data collection (over 1 month period for ARTI, 3 months for diarrhea due to fewer cases)	Health Centers
Gonzales 2004[35] CCT	Ambulatory office practices in one US metropolitan area (had to have 20 or more patient visits for ARIs present in administrative claims data)	Medicare managed care program patients (adults and elderly) diagnosed with ARI	NR	Recruited practices meeting eligibility criteria	NA
Stewart 2000[36] CBA	Primary care practice in one community (including urgent care clinic and emergency department)	Patients with relevant diagnostic codes for infectious diseases	NR	Obtained prescription claims data from local retail pharmacies, the provincial drug benefit database, and from a private health information company and data on diagnostic visits from medical record system of clinic	NA

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Provider Feedback					
Gjelstad 2013[37] CRCT	General practice clinics (randomized 81 continuing medical education groups)	Adults and children with encounter for ARTI 45% male	NR	Continuing medical education groups were invited to participate in trial; CME credit was given for complete participation by a GP	Continuing medical education groups (general practitioners who are specialists)
Vinnard 2013[21] CBA	University-affiliated clinical practices (included faculty and non-faculty providers)	Visit for URTI (ICD-9-CM for acute bronchitis, bronchitis, cough, acute pharyngitis, and acute URTI not otherwise specified) during baseline or post-intervention periods Included 398 patients pre-intervention and 410 patients post intervention	Diagnosis of chronic bronchitis or emphysema in recorded history; study diagnosis within 60 days prior to index visit; diagnosis of acute or chronic sinusitis or pneumonia within 60 days prior to index visit	*Providers:* Selected faculty providers with highest prevalence of antimicrobial prescribing for acute bronchitis for intensive intervention (n=7) and faculty providers with next highest prevalence for mild intervention (n=7); control group (n=14 providers) selected from affiliated non-faculty providers *Patients:* Study authors selected 15 patients from pre-intervention year and 15 from post-intervention year (individual patients included only once)	NA
Linder 2010[38] CRCT	27 Primary care clinics from a regional healthcare delivery network (1 state)	Intervention: 8,406 ARI visits Control: 10,082 ARI visits Overall: mean age 49 years, 36% male	NR	Identified ARI visits using ICD-9-CM codes a. Antimicrobial-appropriate diagnoses: pneumonia, streptococcal pharyngitis, sinusitis, and otitis media b. Non-antimicrobial-appropriate diagnoses: nonstreptococcal pharyngitis, influenza, acute bronchitis, and non-specific URTI	Clinics
Naughton 2009[39] RCT	98 General practices	All age groups	NA	Invited all general practitioners in the Health Authority with minimum Primary Care Reimbursement Service patient panel size of 500 who had complete prescribing information for 1 year pre-intervention; of 300 eligible, 110 providers from 98 practices volunteered	Practices
Madridejos-Mora 2004[40] CCT	32 Primary care centers from 6 healthcare districts	NR	NR	Included all practitioners (n=282) from group practices equipped with computerized prescribing data	Healthcare districts
Guidelines					
Dowell 2012[41] ITS	Sexually transmitted disease clinics, primary care clinics, emergency departments, urgent care clinics, hospitals	Cases of gonorrhea reported to state and local health departments (n=15,669)	Cases that were missing medication used or recorded as not treated	Data from health department reports (cases and treatment) from 5 areas in the US	NA
Slekovec 2012[42] ITS	General practice clinics	Women ages 15 to 65 years old	NR	Data from regional agency of health insurance	NA

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Venekamp 2012[43] ITS	Family practices	All patients 18 years and older enlisted in family practices that were part of the Research Network (approximately 33,000 patients; 53% female, 71% age 40 years or older)	1) Chronic rhinosinusitis (only included episodes of ARS if they followed a rhinosinusitis-free interval of 28 days or more) 2) Prescription for other indications (*eg*, urinary tract infection)	Data from medical database of a Primary Care Research Network; episodes of ARS determined by ICPC codes	NA
Weiss 2011[44] ITS	NR	NR	NR	Outpatient prescription data from Canadian CompuScript Audit database of Intercontinental Medical Statistics (IMS) Health Canada (prescriptions and costs) and Statistics Canada (population data)	NA
Seager 2006[45] CRCT	General dental practices in 4 health authority areas in Wales	1) Adults (16 years or older) with acute dental pain; included data from 1,497 patients (490 from control practices, 451 from guideline only practices, and 556 from intervention practices); mean age 44.6 years, 43.7% male	Excluded practitioners connected with another practice in the study, connected with development of guidelines, or without antimicrobial prescribing data to allow stratification by prescribing level prior to randomization; for patient satisfaction, excluded patients who could not be contacted within 2 weeks of visit	One general dental practitioner from each dental practice that provided services under the National Health Service	Dental practices (one dental practitioners per practice, n=97 randomized with data from 70)
Martens 2006[46] CCT	General practices	NR	Excluded practitioners with incomplete insurance data or with fewer than 500 patients	Data from insurance databases covering approximately 70% of total population in the region	General practitioners in the intervention group were randomized to more intense role in guideline development or control for one part of the study; data from 2 groups were comparable so intervention group was compared to an external control group

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Delayed Prescribing					
Little 2010[47] RCT	General practices	Non-pregnant women with suspected uncomplicated UTI	Immediate antimicrobial treatment needed; age >75 years; psychosis or dementia or need for terminal care	Patients recruited at presentation	Patients
Worrall 2010[48] RCT	Family practice clinics	18 years and older; ARTIs for whom clinicians thought antimicrobial treatment might be necessary	NR	Family practice physicians and nurse practitioners asked to recruit consecutive adult patients	Patients
Communication Skills Training					
Little 2013[49] CRCT	General practices (eligible to participate if they had not previously used an intervention to reduce rates of antimicrobial prescribing and could include more than 10 patients in the baseline audit)	18 years of age and older; up to the first 30 patients with LRTI and up to the first 5 with URTI who presented at each practice during a 4 month period; first consultation for acute cough of up to 28 days duration, diagnosis of acute LRTI, or diagnosis of acute URTI a. Baseline data for 6771 patients b. Post-intervention data for 4264 patients (36% male, mean age 51 years)	Working diagnosis of a non-infective disorder (*eg*, pulmonary embolism, heart failure, esophageal reflux, allergy), use of antimicrobials in the previous month, inability to provide informed consent (*eg*, dementia, psychosis, severe depression), pregnancy, immunological deficiencies	Contacted all general practices in the localities of the study centers; invited all clinicians (and nurse prescribers in the UK) who prescribed antimicrobials for respiratory tract infections; 446 practices approached, 259 agreed to participate, 246 were randomized	Practices
Légaré 2012[50] CRCT	12 family practice teaching units affiliated with one University	Adults and children with diagnosis of ARTI (bronchitis, otitis media, pharyngitis, rhinosinusitis) and for which the use of antimicrobials was considered either by patient or physician during the visit; patients were recruited in waiting area prior to consultation with physician *Post-intervention:* 72.2% adults (age 18 and older); 33.7% male	Excluded patients who were unable to read, understand, and write French language	Approached all family physicians who provided care in walk-in clinics; included those who had not participated in pilot trial or who did not expect to practice at site during study period	Family practice teaching units
Légaré 2010[51] CRCT	4 family medicine groups	Consulting family practice physician for an ARTI; recruited by research assistant in waiting area; no age restrictions *Post-intervention*: 67% adults; 31% male	Excluded patients who were unable to read, understand, and write French language or who had a condition requiring emergency care	Physicians in charge of family medicine groups contacted by investigators; eligible if had not participated in an implementation trial of shared decision-making and planned to remain in clinical practice for duration of trial	Family medicine groups

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Cals 2009[52] Cals 2011[53] Cals 2013[54] CRCT	Netherlands general practitioner clinics	N=431, mean age 49.4-51.4 years, consecutive patients presenting during regular hours with suspected LRTI with cough <4weeks and one focal and one systemic symptom	None	Patients invited by GP to participate	Practices; Clusters of 2 GP non-blindedly randomized to CRP, Communication skills training, CRP and communication skills training, or usual care.
Francis 2009[55] CRCT	83 practices were randomized; 61 of these recruited patients	Children 6 months to 14 years consulting with a RTI (cough, cold, sore throat, earache for 7 days or less) and their parents; mean age 5.2 years, 49.5% male	Children with asthma or serious ongoing medical conditions (*ie*, malignancy, cystic fibrosis)	Participating clinicians asked to recruit sequentially eligible children	Clinicians
Altiner 2007[56] CRCT	General practices in 9 regions (representing varying population densities)	Acute cough (first visit within an episode of acute cough); total of 4,918 patients; mean age approximately 43 years; approximately 42% male	Excluded patients under age 16 years, patients who did not understand German, patients with another episode of cough in past 8 weeks, chronic lung disease (*eg*, asthma, COPD, immune deficiency, malignant disease)	All GPS from 9 regions (n=2036) invited; 239 volunteered to participate; 104 were randomized having completed baseline documentation with at least 18 patients)	General practitioners
Restriction					
Manns 2012[54] ITS	Alberta Health and Wellness (publicly-funded drug coverage for residents of Alberta, Canada age 65 and older)	Physician claims for residents age 65 and older with an outpatient visit to a primary care physician for acute exacerbation of chronic bronchitis, CAP, URTI, or UTI (n=170,247; median age 74, 43% male)	Excluded claims for same infection in the preceding 30 days	NA for antimicrobial prescription (claims data) Invited a convenience sample of physicians for chart review to assess appropriateness of prescribing	NA
Marshall 2006[58] ITS	Ontario Drug Benefit plan (government-funded drug insurance plan); analyzed prescriptions for 20 antimicrobial drug categories	Citizens of Ontario with outpatient prescriptions (filled in a pharmacy); age over 65 years or recipient of social assistance	NR	NA	NA

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Decision Support					
Gonzales 2013[59] CRCT	33 primary care practices 155 providers	Adults and adolescents (13 years of age and older); office visit for uncomplicated acute bronchitis 9,808 visits during baseline periods (3 winters) 6,242 visits during intervention period (1 winter); Note: Table has 3068 visits	Age <13 years or >64 years; chronic lung disease, CHF, HIV, cystic fibrosis, malignant neoplasm, antimicrobial-responsive secondary diagnosis (sinusitis, pharyngitis, otitis media, pneumonia)	Identified patients with incident acute bronchitis visits from medical records (ICD-9 codes) during specified study periods (October 1 to March 31 in study years)	Practices
Jenkins 2013[60] RCT	8 family medicine and internal medicine clinics from 2 networks	Intervention: 52,766 patients Control: 48,881 patients	2 conditions under study diagnosed at the same visit	Identified patients based on ICD-9 codes for upper respiratory infection; acute bronchitis, rhinosinusitis, pharyngitis, otitis media; urinary tract infection, skin and soft tissue infection, pneumonia	Clinics
McGinn 2013[61] RCT	2 large urban ambulatory primary care practices	Intervention providers: 586 patients, median age 43 years, 76% male Control providers: 398 patients, median age 49 years, 77% male All: chief complaint or diagnosis associated with pharyngitis or pneumonia (or a diagnosis and test order combination)	NR	NR	Providers (n=168)
Rattinger 2012[62] CBA	Intervention: VA Maryland Health Care System Control: VA Salt Lake City Health Care System	Intervention: 2,669 patients; 91% male; 67% African-American, 23% white; mean age 56 years Control: 1,162 patients; 94% male, 2% African-American, 60% white; mean age 59 years	Not an outpatient, not an ARTI, not an in-person initial visit for a given ARTI episode, prior ARTI episode in past 3 weeks, prior ARTI during study period (patients only included once); stated diagnosis of COPD, acute pharyngitis as only ARTI diagnosis	Identified patients with ARTI diagnostic code or prescribed a cough suppressant, and if clinical note documented at least 2 ARTI symptoms	NA

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Linder 2009[63] CRCT	27 primary care clinics; 26 were matched on size for randomization	Intervention sites: 116,006 visits by 62,505 patients to 262 clinicians (11,954 ARTI visits) Control sites: 98,894 visits by 49,315 patients to 181 clinicians (10,007 ARTI visits) No differences between intervention and control sites in patient age, gender, race, language, insurance, or income, or clinician age, gender, experience with electronic health record, or visits during intervention period	NR	Identified ARTI visits based on ICD-9 codes for non-specific upper respiratory infections, otitis media, sinusitis, pharyngitis, acute bronchitis, influenza, pneumonia	Practices
Martens 2007[64] CRCT	33 general practices in the Netherlands	NR	NR	Invited 77 general practitioners in 33 practices; all used one specific medical information system including a computerized prescription module; randomized 23 practices with 53 practitioners; usable data from 14 practices with 34 practitioners	Practices
Financial Incentive					
Martens 2007[65] CBA	General practitioners in 2 regions of the Netherlands	Included prescriptions for selected antimicrobials: 1. Chinolones (for UTI) 2. Nitrofurantoin (alternative to #1) 3. Trimethoprim (alternative to #1 4. Amoxicillin plus clavulanic acid 5. Amoxicillin 6. Doxycycline (for sinusitis) 7. Mupirocin (for skin infections)	Excluded practitioners with incomplete records and practices with <500 patients	Chose region for intervention that was known for over-prescription of certain drug categories and new medication; selected control region “as comparable as possible”	NA
Rapid Tests					
Little 2013[66] RCT	21 general practices in England	Age ≥3 years presenting with acute sore throat (duration ≤2 weeks) and abnormal looking throat (erythema and/or pus)	Non-infective causes of sore throat, inability of patient or parent/guardian to consent	Patients recruited by general practitioners and triage practice nurses	Patients

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Brittain-Long 2011[67] RCT	Sweden; 8 primary healthcare centers, 4 outpatient infectious disease clinics	N=447, >18 years, median age 39, diagnosis of ARTI based on at least 2 of: coryza/nasal congestion/sneezing, sore throat/ odynophagia, cough, pleuritic chest pain, shortness of breath or fever for which there was no other explanation with a duration of symptoms <14 days	Confirmed bacterial infection (positive rapid test for Group A *Streptococus* 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) or ongoing antimicrobial treatment	Sunday-Thursday 8am-5pm, patients presenting to clinics with ARTI recruited	Patients
Worrall 2007[68] RCT	Canadian Family Physician Offices	PATIENTS: Successive patients aged 19 or greater presenting to physicians' offices with acute sore throat as primary symptom PHYSICIANS: Randomly selected family physicians in eastern Newfoundland	Not family physicians	Physicians approached in random blocks until 40 recruited; randomized physicians asked to recruit 20 successive, eligible patients	Physicians
C-Reactive Protein					
Diederischsen 2000[69] RCT	Danish General Practice Offices (single practice offices)	N=812, all ages, median age 37, 43% male; presenting during usual business hours with a respiratory infection	Previously seen for this infection, GABHS test performed, chronic inflammatory disease	First 1-2 patients of the day presenting with RI invited to participate	Patients
Takemura 2005[70] RCT	Japanese general medicine clinic	N=305, mean age 35 years; 56% male; presenting with fever (T≥37.5) and "symptoms suspected of infection"	None	NR (recruited from clinic)	Patients
Cals 2009[52] Cals 2011[53] Cals 2013[54] CRCT SEE Communication Skills Training	Netherlands general practice clinics	N=431; mean age 49.8; 39% male; suspected LRTI with cough <4weeks and one focal and one systemic symptom; adults greater than 18 years of age			Practices

Author Year Study Design	Site	Patients	Exclusion Criteria	Recruitment	Randomization (for RCTs and CRCTs)
Cals 2010[71] RCT	Netherlands family practice centers	N=258; mean age 44 years; 11% male; presenting for first consultation for LRTI (cough <4 weeks, regarded by physician as caused by LRTI, with at least one of: shortness of breath, wheezing, chest pain, or auscultation abnormalities AND at least one of: fever, perspiring, headache, myalgia, or feeling generally unwell) or ARS (duration <4 weeks and at least one of: history of rhinorrhea, blocked nose AND at least one of: purulent rhinorrhea, unilateral facial pain, headache, teeth pain, pain when chewing, maxillary/ frontal pain when bending over or worsening symptoms after initial improvement)	Immediate requirement of admission to hospital, no understanding of Dutch language, previous study participation, antimicrobial use or hospitalization in the past 2 weeks, or immunocompromised status.	Patients recruited by family physician among eligible patients	Patients; After initial consultation, patients openly randomized to POC CRP testing or no POC CRP testing by SNOSE
Llor 2012[23,24] CBA SEE Provider and Patient Education	Spanish general practitioner clinics	N=836 patients with ARS, mean age 39.8 years, 35% male N=5,385 LRTIs (patient characteristics not reported)	None	Patients recruited by participating clinicians during 3 week period of winter months of baseline year and intervention year	Physicians; GPs allocated (non-randomly) to full intervention group, partial intervention group, or no intervention group
Little 2013[49] CRCT SEE Communication Skills Training	European general practitioner clinics	18 years of age and older; acute LRTI or URTI			Practices

US = United States; VA = Veterans Affairs; ICD-9 = International Classification of Diseases, 9th Revision; ICPS = International Classification of Primary Care; ED = emergency department; ARI = acute respiratory infection; ARTI = acute respiratory tract infection; ARS = acute rhinosinusitis; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection; UTI = urinary tract infection; CHF = congestive heart failure; HIV = human immunodeficiency virus; RCT = randomized controlled trial; CRCT = cluster randomized controlled trial; NA = not applicable; NR = not reported

*Did not include otitis media – a decision support tool for otitis media was concurrently being implemented in some of the practices

†Included providers with data from at least 1 pre-intervention and 1 post-intervention period if there were not 20 providers who had been in practice during entire study period

‡Quality circles are groups of 8 to 25 general practitioners from a geographical area who meet at least 4 times per year; quality circles are part of the national accreditation program for Belgium

Table 3. Prescribing Outcomes

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Provider and Patient Education				
Gerber 2013[20] CRCT	**Proportion of broad spectrum antimicrobials** *Children prescribed antimicrobials for any indication* Intervention sites: 26.8% baseline, 14.3% end of 12 month intervention Control sites: 28.4% intervention, 22.6% end of 12 month intervention Treatment by time interaction: p=0.01 *Pneumonia* Proportion of broad spectrum antimicrobials Intervention sites: 15.7% baseline, 4.2% end of 12 month intervention Control sites: 17.1% intervention, 16.3% end of 12 month intervention Treatment by time interaction: p<0.001 *Acute sinusitis* Treatment by time interaction: p=0.12 *Streptococcal pharyngitis* Treatment by time interaction: p=0.82 *Viral infections* Treatment by time interaction: p=0.93	NR	NR	NR
Vinnard 2013[21] CBA	*Antimicrobial use* Intervention sites: 23.6% pre; 15.1% 1st year; 15.8% 2nd year, 58.1% 3rd year Pre-post prescribing rate change: 4.7% decrease Control sites: 59.7% pre; 55.8% 1st year, 59.0% 2nd year, 58.1% 3rd year Pre-post prescribing rate change: 1.2% increase (p=0.133 compared to rate change in intervention group)	For visits during which antimicrobials were prescribed there was no change in use of broad versus narrow-spectrum agents associated with the intervention (data not provided)	NR	NR
Butler 2012[22] RCT	*Change in oral antimicrobial dispensing from baseline (all diagnoses)* Intervention sites: -14.1 items/1000 patients Control sites: +12.1 items/1000 patients *% reduction (intervention group relative to control group):* 4.2 [95% CI 0.6, 7.7]; p=0.02	NR	NR	NR
Llor 2012[23,24] CBA SEE Laboratory Tests for CRP testing results	*Baseline* **LRTI** Partial intervention: 510/846 (61.3%) OR 0.57 [95% CI 0.30, 1.10]; p=0.10* **ARS** Partial intervention: 97/111 (87.4%) OR 0.91 [95%I 0.61, 1.37]; p=0.45* *Intervention Period* **LRTI** Partial intervention: 372/662 (56.2%) LRTIs OR 0.42 [95% CI 0.22, 0.82]; p=0.01* **ARS** Partial intervention: 87/105 (82.9%) OR 0.65 [95% CI 0.21, 1.06]; p=0.06 *Control** **LRTI** 399/521 (76.6%) **ARS** 52/60 (86.7%)	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Regev-Yochay 2011[25] CRCT	***Patient Level*** *- antimicrobial prescribing rates (baseline to 1st year of intervention) (prescriptions per 1000 patient-years)* Intervention group: pre 78.4, post 49.9 (40% decrease) Control Group: pre 76.3, post 59.3 (22% decrease) RR 0.76 [95% CI 0.75, 0.78] *Reduction maintained through intervention period and follow-up year* *NOTE: The HMO introduced a campaign for reducing antimicrobial use that coincided with the first year of the study intervention and was determined to be a factor in the reduced use in the control group based on a comparison with non-HMO provider data.* ***Physician Level*** *– antimicrobial prescribing* RR 0.89 [95% CI 0.81, 0.98] (intervention vs control)	***Patient Level*** *-relative risk (RR) for specific antimicrobials (intervention vs control after 1st year of intervention)* Penicillin: RR 0.84 [95% CI 0.82, 0.87] Cephalosporin: RR 0.77 [95% CI 0.73, 0.82] Macrolide: RR 0.58 [95% CI 0.55, 0.62] ***Physician Level*** No difference between groups for penicillin or cephalosporin prescription rates; significant decrease in macrolide prescription rates in intervention group (RR 0.65 [95% CI 0.52, 0.82])	NR	NR
Esmaily 2010[26] CRCT	*Analysis of 13,480 prescriptions from 111 GPs who participated in intervention* 1) Number of antimicrobials per prescription (all drugs at one encounter) Intervention group: Pre-intervention 0.81, Post-intervention 0.83 (p=0.41) Control group: Pre 0.84, Post 0.88 (p=0.33) 2) Percentage of prescriptions with antimicrobial Intervention group: Pre-intervention 61%, Post-intervention 63% (p=ns) Control group: Pre 59%, Post 60% (p=ns)	NR	NR	NR
Smeets 2009[27] CBA	*Number of antimicrobial prescriptions for ARTIs* Baseline (p=0.23) Intervention: 184 per 1000 patients Control: 186 per 1000 patients Post-intervention (p=ns) Intervention: 206 per 1000 patients Control: 202 per 1000 patients 1-year follow-up (p=ns) Intervention: 232 per 1000 patients Control: 227 per 1000 patients	*Second-choice antimicrobials (amoxicillin-clavulanate, macrolides, quinolones) as percentage of total (all p=ns)* Baseline Intervention: 28% Control: 27% Post-intervention Intervention: 27% Control: 27% 1 year follow-up Intervention: 31% Control: 31%	NR	NR
Finkelstein 2008[28] CRCT	*Intervention impact (difference in adjusted percentage change in antimicrobial prescribing between intervention and control communities)* Age 3 to <24 months: -0.5%; p=0.69 Age 24 to <48 months: -4.2%; p<0.01 Age 48 to <72 months: -6.7%; p<0.0001	*Intervention impact on second-line penicillins* Age 3 to <24 months: -2.2%; p=0.48 Age 24 to <48 months: -9.2%; p=0.03 Age 48 to <72 months: -21.3%; p<0.0001 *Intervention impact on broad-spectrum macrolides* Age 3 to <24 months: -6.7%; p=0.02 Age 24 to <48 months: -12.7%; p<0.01 Age 48 to <72 months: -22.5%; p<0.0001	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Chazan 2007[29] RCT	*Total antimicrobial use (last winter under intervention vs baseline) for any diagnosis* Continuous intervention: 28.7 DDD/1000 pt/day baseline, 22.9 post-intervention (20.0% reduction) Seasonal intervention: 27.8 DDD/1000 pt days baseline, 23.2 post-intervention (16.5% reduction) Between groups: p<0.0001	*Narrow-spectrum antimicrobial use* Continuous intervention: 20.2 DDD/1000 pt/day baseline, 15.9 post-intervention (21.2% reduction) Seasonal intervention: 20.3 DDD/1000 pt days baseline, 16.1 post-intervention (20.6% reduction) Between group: p=ns *Broad-spectrum antimicrobial use* Continuous intervention: 8.5 DDD/1000 pt/day baseline, 7 post-intervention (17.6% reduction) Seasonal intervention: 7.4 DDD/1000 pt days baseline, 7.1 post-intervention (4.5% reduction) Between groups: p<0.0001	NR	NR
Metlay 2007[30] CRCT	For upper respiratory tract infections and acute bronchitis visits *Baseline year* Intervention sites: 59% of visits Control sites: 45% of visits *Intervention year* Intervention sites: 49% of visits Control sites: 43% of visits *Adjusted differences* Intervention sites: -10% [95% CI -18%, -2%] Control sites: 0.5% [95% CI -3%, 5%] For antimicrobial-responsive acute respiratory tract infection visits *Adjusted differences* Intervention sites: -2% [95% CI -6%, 3%] Control sites: -4% [95% CI -9%, 2%]	NR	NR	NR
van Driel 2007[31] CRCT	*Antimicrobial prescriptions received* Intervention: 56.9% of patients Control: 58.3% OR_{Adj} 0.63 [95% CI 0.29, 1.37] NOTES: n/N not provided; 29% of GPs in participating quality circles registered patients	*Proportion of first-choice antimicrobials* Intervention: 34.5% Control: 29.4% OR_{Adj} 1.07 [95% CI 0.34, 3.37]	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Varonen 2007[32] RCT	NR	*Use of amoxicillin as 1st line treatment for acute sinusitis (5 year trend)* Problem-based learning: OR 1.10 [95% CI 1.02, 1.20] Academic detailing: OR 1.11 [95% CI 0.99, 1.24] Difference between groups=ns *Use of macrolides as 1st line treatment (5 year trend)* Problem-based learning: OR 0.98 [95% CI 0.90, 1.07] Academic detailing: OR 1.00 [95% CI 0.88, 1.14] Difference between groups=ns	*Use of 7-day courses* Problem-based learning: OR 1.18 [95% CI 1.07, 1.29] Academic detailing: OR 1.17 [95% CI 1.03, 1.34] Difference between groups=ns	NR
Little 2005[33] RCT	*Self-reported use of antimicrobials* Leaflet group: 159/291 (55%) No leaflet group: 160/281 (57%); p=0.58 No antimicrobials: 29/182 (16%) Delayed antimicrobials: 39/197 (20%) Immediate antimicrobials: 185/193 (96%); p<0.001	NR	NR	NR
Pagaiya 2005[34] RCT	*For ARTI (pre- and 6 months post-intervention)* Intervention: pre 41.6%, post 27.0%; mean change -14.6% [95% CI -22.5, -6.7] Control: pre 26.7%, post 29.5%; mean change 2.8 [95% CI -6.0, 11.7]; p=0.022 *For diarrhea (pre- and 6 months post-intervention)* Intervention: pre 84.8%, post 83.0%; mean change -1.8% [95% CI -16.6, 12.9] Control: pre 96.8%, post 94.7%; mean change -2.1 [95% CI -8.4, 4.2]; p=0.308	NR	NR	NR
Gonzales 2004[35] CCT	*Overall prescription rate for ARIs* Intervention: pre 45%, post 40% Control: pre 51%, post 49% Difference was not significant different between groups (p=0.79) after adjusting for patient age, COPD, specific ARI diagnosis, and practice level clustering	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Stewart 2000[36] CBA	*Total antimicrobial claims* Control period: 10,071 Study period: 9,125 Change = 946 (-9.4%) (p=NR) (Analysis of before and after data)	*Likelihood of prescribing 1st line antimicrobials:* No difference post-intervention *Likelihood of study providers prescribing 2nd line antimicrobials after intervention relative to providers in rest of province*: OR^{-1} 0.71 [95% CI 0.62, 0.81] *Likelihood of study providers prescribing 1st line relative to 2nd line antimicrobials after intervention:* OR 1.75 [95% CI 1.55, 1.97]		
Provider Feedback				
Gjelstad 2013[37] CRCT	*ARTI episodes with antimicrobial prescription (based on means from continuing medical education groups)* Intervention: pre 31.7%, post 30.4% Control: pre 32.7%, post 34.2% *Prescribing an antimicrobial for ARTI (intervention vs control)* OR 0.72 [95% CI 0.61, 0.84]	*ARTI episodes with penicillin V prescription (recommended tx)* Intervention: pre 45.0%, post 53.8% Control: pre 45.2%, post 43.2% *Episodes - penicillins (extended spectrum)* Intervention: pre 11.4%, post 10.8% Control: pre 11.8%, post 11.3% *Episodes - macrolides and lincosamides* Intervention: pre 27.1%, post 23.7% Control: pre 26.0%, post 28.9% *Episodes - tetracyclines* Intervention: pre 15.4%, post 10.5% Control: pre 15.7%, post 15.3% *Prescribing a non-penicillin V antimicrobial when antimicrobial was issued (intervention vs control):* OR 0.64 [95% CI 0.49, 0.82]	NR	NR
Vinnard 2013[21] CBA	*Change in antimicrobial prescribing over time (within group)* Intensive intervention: OR 0.49 [95% CI 0.25, 0.89] Mild intervention: OR 0.76 [95% CI 0.38, 1.51] Control: OR 1.27 [95% CI 0.82, 1.94] *Comparison to control (unadjusted)* Intensive intervention: ROR 2.60 [95% CI 1.23, 5.48] Mild intervention: ROR 1.67 [95% CI 0.74, 3.79] ROR = ratio of odds ratios	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Linder 2010[38] CRCT	*Orally administered antimicrobial agent within 3 days of an ARI visit* Intervention: 3912/8406 (47%) Control: 4761/10082 (47%) OR 0.97 [95% CI 0.7, 1.4]; p=0.87	NR	NR	*Antimicrobial prescribing for antimicrobial-appropriate diagnoses* Intervention: 1718/2624 (65%) Control: 2008/3145 (64%) (p=0.68) *For non-antimicrobial-appropriate diagnoses* Intervention: 2194/5782 (38%) Control: 2753/6937 (40%) (p=0.70)
Naughton 2009[39] RCT	*Immediate post intervention* 2% reduction in rate of antimicrobial prescribing compared with pre-intervention; no difference between groups (p=0.26) *Long-term post intervention (12 Month Trend Analysis)* a. No difference between groups in overall prescribing (p=0.33) b. Both groups returned to pre-intervention prescribing	*Immediate post intervention* a. Increased narrow-spectrum penicillin prescribing: 5% academic detailing practices, 2% postal feedback practices (p=0.04) b. Significant decrease in co-amoxiclav and cephalosporin prescribing; no differences between groups (p=0.58 co-amoxiclav, p=0.70 cephalosporin) *Long-term post intervention (12 Month Trend Analysis)* No differences between groups in narrow-spectrum penicillin (p=0.67), co-amoxiclav (p=0.62), or cephalosporin (p=0.86) prescribing	NR	NR
Madridejos-Mora 2004[40] CCT	*Overprescription of antimicrobials*† Intervention: pre 15.7, post 13.7, p=0.006 Control: pre 16.4, post 16.4, p=0.986 Between groups, post-intervention: p=0.026 (Units are DDD X 1000 inhabitants X day)	*3rd Generation Cephalosporins* Intervention: pre 28.0%, post 22.4%, p=0.017 Control: pre 27.0%, post 25.1%, p=0.583 Between groups, post-intervention: p=0.338 *Broad spectrum quinolones* Intervention: pre 44.4%, post 47.2%, p=0.419 Control: pre 45.5%, post 48.5%, p=0.527 Between groups, post-intervention: p=0.949	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Guidelines				
Dowell 2012[41] ITS	NR	Proportion of gonorrhea cases treated with fluoroquinolones decreased 21.5% [95% CI 15.9%, 27.2%] by 2 weeks post-intervention (range across 5 areas: 7.9% to 48.3%) By clinic type: STD clinics: 28.5% [95% CI 19.0%, 37.9%] Primary care: 8.6% [95% CI 2.6%, 14.6%] Emergency/urgent care/hospital: 2.7% [95% CI 1.7%, 3.7%]	NR	NR
Slekovec 2012[42] ITS	NR	*Slope* a) Stable prior to intervention; significant change (p<0.001) post-intervention for nitrofurantoin (increased), fosfomycin-trometamol (increased), and norfloxacin (decreased) b) No change for single-dose fluoroquinolone or other multi-dose fluoroquinolones (ciprofloxacin, ofloxacin) *Level* a) Significant decrease (p=0.002) for single-dose fluoroquinolones b) No change for nitrofurantoin, fosfomycin-trometamol, norfloxacin or other multi-dose fluoroquinolones (ciprofloxacin, ofloxacin)	NR	NR
Venekamp 2012[43] ITS	*Prescription rate* Increased during pre-intervention period from 56 per 100 ARS episodes in 2000 to 62 per 100 ARS episodes in 2005 (RD 6 [95% CI 1, 10]; p<0.05 for slope) Decreased during intervention period from 62 per 100 ARS episodes in 2005 to 56 per 1000 ARS episodes in 2009; (RD -6 [95% CI -10, -1]; slope significantly different from pre-intervention slope; p<0.05)	Reported no change in type of antimicrobial prescribed over time (doxycycline most frequently prescribed – approximately 70% of episodes in which an antimicrobial was prescribed)	NR	NR
Weiss 2011[44] ITS	*Difference in antimicrobial prescribing between Quebec (intervention) and other provinces (control)* a) Level change of -4.1 prescriptions per 1000 inhabitants monthly [95% CI -6.6, -1.6, p=0.002] immediately following guideline dissemination; maintained during 36 month follow-up b) Significant level changes (all p<0.001) for all classes of antimicrobials studied (cephalosporins, macrolides, penicillins, quinolones, other) also maintained during 36 month follow-up	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Seager 2006[45] CRCT	*Odds of being prescribed an antimicrobial* Control group: reference Guideline group: OR 0.83 [95% CI 0.55, 1.21] Intervention group: OR 0.63 [95% CI 0.41, 0.95]; p<0.05 Patient age significantly associated with prescribing – younger patients significantly more likely to receive antimicrobials (OR 0.82, 95% CI 0.76, 0.89]; p<0.0001‡ *Odds of being prescribed antimicrobials inappropriately*§ Control group: reference Guideline group: OR 0.82 [95% CI 0.53, 1.29] Intervention group: OR 0.33 [95% CI 0.21, 0.54]; p<0.05 No patient or practitioner factors associated with inappropriate prescribing	*Intervention group (all p<0.05)* a) higher percentage of amoxicillin than control group b) lower percentage of penicillin than control group or guideline group c) higher percentage of metronidazole than guideline group	No significant differences between study groups in percentages of patients receiving antimicrobial treatment for less than 3 days, 3 or 4 days, 5 days, or more than 5 days	NR
Martens 2006[46] CCT	*Total antimicrobial prescriptions per general practitioner per year (standardized per 1000 enlisted patients) – median (P_{25}-P_{75} interval), all p=ns* Pre-guideline Intervention (n=53): 639 (551-833) Control (n=54): 491 (388-595) One year post-guideline Intervention (n=53): 667 (532-812) Control (n=54): 489 (386-601) Two years post-guideline Intervention (n=53): 652 (512-767) Control (n=54): 486 (405-602) *Analysis of antimicrobial prescriptions for general practitioners more intensively involved in intervention (n=27) versus matched control group (n=26) showed no differences in prescribing pre-intervention or at one or 2 years follow-up*	NR	NR	NR
Delayed Prescribing				
Cals 2010[71] RCT	*Received delayed prescription* Intervention: 22/129 (17.1%) Control: 29/129 (22.5%); p=0.35 (calculated) *Filled delayed prescription* Intervention: 5/22 (22.7%) Control: 21/29 (72.4%) (p<0.001)	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Little 2010[47] RCT	*Used antimicrobials* Control (immediate): 58/60 (97%) Delayed: 41/53 (77%) OR 0.12 [95% CI 0.03, 0.59] Midstream Urine: 38/47 (81%) OR 0.15 [95% CI 0.03, 0.73] Dipstick: 40/50 (80%) OR 0.13 [95% CI 0.03, 0.63] Symptom Score: 52/58 (90%) OR 0.29 [95% CI 0.06, 1.55] X^2=11.7, p=0.02 *Waited at least 48 hours before taking antimicrobials* Control (immediate): 5/60 (8%) Delayed: 28/53 (53%) Midstream Urine: 20/47 (43%) Dipstick: 15/50 (30%) Symptom Score: 11/58 (19%) X^2=34, p<0.001	NR	NR	NR
Worrall 2010[48] RCT	*Prescriptions filled* Total: 65/149 prescriptions written (43.6%) Usual date: 32/74 (43.2%) Post date: 33/75 (44.0%); p=0.924 *Prescriptions filled within 2 days of being written* Usual date: 16 Post date: 16; p=0.975	NR	NR	NR
Little 2005[33] RCT	Self-reported use of antimicrobials: No antimicrobials: 29/182 (16%) Delayed antimicrobials: 39/197 (20%) Immediate antimicrobials: 185/193 (96%); p<0.001 *See also provider and/or patient education*	NR	NR	NR
Communication Skills Training				
Little 2013[49] CRCT	*Analysis of factorial groups* No CRP training: 984/2040 (48%) CRP training: 734/2224 (33%) RR_{Adj} 0.54 [95% CI 0.42, 0.69]; p<0.0001 No communication training: 876/1932 (45%) Communication training: 842/2332 (36%) RR_{Adj} 0.69 [95% CI 0.53, 0.87]; p<0.0001 *Interaction term (CRP and enhanced-communication training) was not significant (p=0.41)* *Prescribing decreased the most in the combination intervention group (RR 0.38 [95% CI 0.25, 0.55]; p<0.0001*	NR	NR	NR
Légaré 2012[50] CRCT	*Patient decision to use antimicrobials immediately after consulting with physician* Baseline: 41.2% at intervention sites, 39.2% at control sites, p=ns Post-intervention: 27.2% at intervention sites, 52.2% at control sites; absolute difference 25%, RR_{Adj} 0.5 [95% CI 0.3, 0.7] For adults: 26.6% at intervention sites, 50.7% at control sites; absolute difference 24.1%, RR_{Adj} 0.5 [95% CI 0.4, 0.8]	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Légaré 2010[51] CRCT	*Patient decision to use antimicrobials immediately after consulting with physician* Baseline: 56% at intervention sites, 54% at control sites, p=ns Post-intervention: 33% at intervention sites, 49% at control sites; absolute difference 16% [95% CI -31, 1]; p=0.08	NR	NR	NR
Cals 2009[52] Cals 2013[54] CRCT	*Antimicrobials at index consultation (n=431)* a. 55/201 (27.4%) communication training, 123/230 (53.5%) no training; p<0.01 b. 70/227 (30.8%) CRP, 108/204 (52.9%) no CRP; p=0.02 *Percentage of episodes of RTI treated with antimicrobials during follow-up (mean 3.67 years, n=379)* a. 26.3% communication training, 39.1% no training; p=0.02 b. 30.7% CRP, 35.7% no CRP; p=0.36	NR	NR	67% of patients overall received amoxicillin or doxycycline (Dutch first line for LRTI)
Francis 2009[55] CRCT	*Antimicrobial prescribed at index consultation* Intervention: 50/256 (19.5%) Control: 111/272 (40.8%) OR 0.29 [95% CI 0.14, 0.60]	NR	NR	NR
Altiner 2007[56] CRCT	*Baseline* Intervention: 36.4% Control: 54.7% *6-weeks post-intervention* Intervention: 29.4% Control: 59.4% OR_{Adj} 0.38 [95% CI 0.26, 0.56]; p<0.001* *1 year post-intervention* Intervention: 36.7% Control: 64.8% OR_{Adj} 0.55 [95% CI 0.38, 0.80]; p=0.002*	NR	NR	NR
Restriction				
Manns 2012[57] ITS	*Antimicrobial prescription at index visit* Before restriction policy: 53.7% After restriction policy: 54.8%, p<00001 (Analysis of means) *ITS analysis* No significant change in rate of quinolone use (level change -3.5 [95% CI -5.5, 1.4] prescription per 1000 index visits, p=0.74) No significant change in slope of quinolone use (p=0.95)	*Ciprofloxacin* Among antimicrobial users, level change in rate of use for UTIs (-69.1 [95% CI -49.5, -88.7] prescriptions per 1000 unique visits after restriction program, p<0.001) *Levofloxacin* Among antimicrobial users, significant level changes in rate of use for acute exacerbations of chronic bronchitis, URTI, and pneumonia No significant change in slope	NR	*Quinolone prescriptions consistent with formulary guidelines* Before restriction: 42.5% After restriction: 58.5% (p=0.002)

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Marshall 2006[58] ITS	*Total antimicrobial prescriptions before and after restriction policy* Level: p=ns Trend: decreasing	*Fluoroquinolone group (6 antimicrobials, 3 restricted)* Level: 1905 fewer prescriptions/wk, p<0.0001 Trend: p=ns *Ciprofloxacin (restricted)* Level: 2084 fewer prescriptions/wk, p<0.0001 Trend: p=ns *Levofloxacin (restricted)* Level: p=ns Trend: increasing *Ofloxacin (restricted)* Level and trend data not reported (included in fluoroquinolone group) *TMP/SMX* Level: 532 more prescriptions/wk, p<0.0001 Trend: decreasing *Nitrofurantoin* Level: 200 more prescriptions/wk, p<0.0001 Trend: increasing	NR	NR
Decision Support				
Gonzales 2013[59] CRCT	PDS: 80.0% baseline, 68.3% intervention CDS: 74.0% baseline, 60.7% intervention UC: 72.5% baseline, 74.3% intervention PDS difference vs UC difference (p=0.003) CDS difference vs UC difference (p=0.01) PDS difference vs CDS difference (p=0.67) OR_{Adj} (tx during intervention vs baseline): PDS: 0.57 (95% CI 0.40, 0.82) CDS: 0.64 (95% CI 0.45, 0.91) UC: 1.10 (95% CI 0.85, 1.43)	NR	NR	NR
Jenkins 2013[60] RCT	*For acute respiratory infection* Intervention sites: 42.7% baseline, 37.9% post-intervention (relative reduction 11.2%, p<0.0001) Control sites: 39.8% baseline, 38.7% post-intervention (relative reduction 2.8%, p=0.25) Trend analysis: significant time trend (p<0.0001) and significant difference in trend between intervention and control (p<0.0001) with greater decline in use in the intervention group	*Proportion of all clinical pathway conditions for which a broad-spectrum antimicrobial was prescribed* Intervention sites: 26.4% baseline, 22.6% post-intervention (p<0.0001) Control sites: 20.0% baseline, 19.4% post-intervention (p=0.35) Trend analysis: greater decline in broad-spectrum antimicrobial use in study group (p=0.001)	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
McGinn 2013[61] RCT	*Overall* Intervention: 171/586 (29.2%) Control: 153/398 (38.4%) ARD 9.2; RR_{Adj} 0.74 [95% CI 0.60, 0.92]; p=0.008 *For pharyngitis* Intervention: 56/374 (15.0%) Control: 44/224 (19.6%) ARD 4.6; RR_{Adj} 0.76 [95% CI 0.53, 1.10]; p=0.15 *For pneumonia* Intervention: 115/212 (54.2%) Control: 109/174 (62.6%) ARD 8.3; RR_{Adj} 0.79 [95% CI 0.64, 0.98]; p=0.03	*Quinolones* Intervention: 9.9% Control: 19.6% ARD 9.7; RR for intervention orders 0.50 [95% CI 0.29, 0.88]; p=0.02 *Penicillins, Cephalosporins, and Macrolides* No significant differences between intervention and control (RRs 0.81 to 1.11, p>0.05)	NR	NR
Rattinger 2012[62] CBA	*Proportion of unwarranted prescriptions* Intervention site: *Targeted antimicrobials:* 22% baseline, 3.3% post-intervention (p<0.0001) *Other antimicrobials:* 30.1% baseline, 30.5% baseline (p=ns) Control site: *Targeted antimicrobial:* 16% baseline, 20% post-intervention (p=ns) *Other antimicrobials:* 22% baseline, 27% post-intervention (p=ns)	NR	NR	*Proportion of visits where antimicrobial use was congruent with guidelines* Intervention site: 0.63 baseline, 0.72 post-intervention (p=0.0001) Control site 0.74 baseline, 0.69 post-intervention (p=0.69) RR (of congruent prescription) 1.24 [95% CI 1.11, 1.39]
Linder 2009[63] CRCT	Antimicrobials inappropriate for non-specific upper respiratory tract infections, non-streptococcal pharyngitis, acute bronchitis, and influenza NOTE: *ARI Smart Form* used at least once by 33% of intervention clinicians (6% of ARI visits (742/11,954)) *Prescriptions to patients with ARI diagnoses* Intervention: 39% of patients Control: 43% (OR 0.8 [95% CI 0.6, 1.2]; p=0.30) *Antimicrobial prescribing for antimicrobial appropriate ARIs* Intervention: 54% Control: 59% (OR 0.8 (95% CI 0.5, 1.3); p=ns) *Antimicrobial prescribing for non-antimicrobial appropriate ARIs* Intervention: 32% Control: 34% (OR 0.9 (95% CI 0.6, 1.4); p=ns)	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Martens 2007[64] CRCT	*No prescribing of a particular drug advised* a. No statistically significant differences between intervention and control in percent of prescriptions according to recommendations b. For volume per practitioner per 1000 enlisted patients -Sum score for all antimicrobials which were expected to decline with intervention did not differ significantly: intervention 28.2 [95% CI 20.8, 44.5]; control 39.7 [95% CI 29.7, 64.1]; p=ns -Of 8 prescribing recommendations, 2 were significant (p<0.05) 1) feneticilline, azithromycin, fenoxymethylpenicillin (first choice drugs) for acute sore throat: intervention 0.2 [95% CI 0.0-0.4], control 0.8 [95% CI 0.3, 2,4] 2) quinolones for cystitis among women >12 years: intervention 1.5 [95% CI 0.8, 2.2], control 4.6 [95% CI 2.8, 8.1] *Prescribing of a particular drug advised* a. Of 8 prescribing recommendations, 1 was significant (p<0.05) - appropriate prescription for cystitis in women >12 years: intervention 73% [95% CI 69, 80], control 57% [95% CI 52, 63] b. No statistically significant differences between volume prescribed between intervention and control	NR	NR	NR
Financial Incentive				
Martens 2007[65] CBA	*Baseline Period* No statistically significant differences between intervention and control regions *Short Term (post-intervention)* ‖ Quinolones (mean): intervention 0.0, control 0.1, p=ns Nitrofurantoin (median): intervention 0.0, control 0.0, p=ns Trimethoprim (median): intervention 0.3, control 0.0, 7% improvement in intervention group compared with control, p=0.006 Amoxicillin+clavulanic acid (median): intervention -0.6, control 0.0, 17% improvement in intervention group compared with control, p=0.008 Amoxicillin (mean): intervention -1.1, control -0.7, p=ns Doxycycline (median): intervention -0.1, control -0.6, 2% improvement in intervention group compared with 14% in control, p=0.01 favoring control group Mupirocin (median): intervention 0.0, control -0.5, p=ns *Long Term (one year post-intervention)* No statistically significant changes from baseline for intervention or control regions (range of changes‖ = -0.5 to 0.8)	NR	NR	NR
Rapid Tests				
Little 2013[66] RCT	Clinical score + RADT: 52/164 (35%); RR 0.73 [95% CI 0.52, 0.98]; p=0.03) Clinical score: 60/161 (37%); RR 0.71 [95% CI 0.50, 0.95]; p=0.02) Delayed prescribing (control): 75/164 (46%) Results controlled for fever in past 24 hrs and baseline severity of sore throat/ difficulty swallowing	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Brittain-Long 2011[67] RCT	Initial prescription: 9/303 (4.5%) (early result) vs 25/204 (12.3%) (late result); p=0.005 At 8-12 day follow-up: 13.9% (early result) vs 17.2% (late result); p=0.359	NR	NR	NR
Worrall 2007[68] RCT	94/170 (55.3%) (STDR) vs 32/120 (26.7%) (RADT) vs 39/102 (38.2%) (STDR and RADT) vs 82/131 (58.2%) (usual care) p<0.001 for RADT vs usual care p<0.001 for STDR and RADT vs usual care p=ns for STDR vs usual care)	NR	NR	NR
C-Reactive Protein				
Diederischsen 2000[69] RCT	179/414 (43%) (CRP) vs184/398 (46%) (usual care) OR 0.9 [95% CI 0.7-1.2]; p=ns	NR	NR	NR
Takemura 2005[70] RCT	76/147 (51.7%) (CRP+WBC) vs 135/154 (87.6%) (usual care); p<0.001	*Patients with non-pneumonic ARTIs*: absolute number receiving newer agents (cefcapene pivoxil or clarithromycin) reduced in advance testing group (41 vs 55) but rate of prescription (new antimicrobials/total antimicrobials) increased (41/61 [67%] vs55/122 [45%]; p=0.0031) *All advance testing patients:* a. cefcapene pivoxil started in 51% (WBC ≥9x10^9/l) vs 26% (WBC ≤9x10^9/l) (p=0.025) b. macrolides prescribed in 50% (WBC ≤9x10^9/l) vs 7.7% (WBC ≥9x10^9/l) (p<0.001)	NR	NR
Cals 2009[23] CRCT SEE Communication Skills Training	70/227 (30.8%) (CRP) vs 108/204 (52.9%) (no CRP); p=0.02	NR	NR	NR
Cals 2010[71] RCT	56/129 (43.4%) (CRP) vs 73/129 (56.6%) (usual care); RR 0.77 [95% CI 0.56-0.98] *Received delayed prescription* Intervention: 22/129 (17.1%) Control: 29/129 (22.5%) *Filled delayed prescription* Intervention: 5/22 (22.7%) Control: 21/29 (72.4%)	NR	NR	NR

Author Year Study Design	% Prescribed Antimicrobials	Selection	Duration	Guideline Concordant Use
Llor 2012[23,24] CBA SEE Provider and Patient Education for Education results	*Baseline* **LRTI** Full intervention: 1288/1868 (69.0%) OR 0.81 [95% CI 0.46, 1.43]; p=0.47* **ARS** Full intervention: 252/285 (88.4%) OR 1.01 [95% CI 0.66, 1.58]; p=0.44* *Intervention Period* **LRTI** Full intervention: 653/1488 (43.9%) LRTIs OR 0.22 [95% CI 0.12, 0.38]; p=0.00* **ARS** Full intervention: 156/275 (56.7%) OR 0.12 [95% CI 0.01, 0.32]; p=0.01* *Control** **LRTI** 399/521 (76.6%) **ARS** 52/60 (86.7%) *Antimicrobial prescriptions in full intervention group* **LRTI** If used CRP test: 239/545 (43.9%) If did not use CPR test: 2992/4840 (61.8%) (p<0.001) **ARS** If used CRP test*:* 46.7% If did not use CRP test: 82.9% (p<0.001)	NR	NR	NR
Little 2013[49] CRCT SEE Communication Skills Training	*Analysis of factorial groups* No CRP training: 984/2040 (48%) CRP training: 734/2224 (33%) RR_{Adj} 0.54 [95% CI 0.42, 0.69]; p<0.0001 *Interaction term (CRP and enhanced-communication training) was not significant (p=0.41)* *Prescribing decreased the most in the combination intervention group* RR 0.38 [95% CI 0.25, 0.55]; p<0.0001	NR	NR	NR

CBA = controlled before and after; CRCT = cluster randomized trial; NR = not reported; ns = not statistically significant; RR = risk ratio; ARI = acute respiratory infection; ARS = acute rhinosinusitis; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection; RTI = respiratory tract infection; UTI = urinary tract infection; CRP = C-reactive protein; PDS = paper decision support; CDS = computer-assisted decision support; TMP/SMX = trimethoprim-sulphamethoxazole; UC = usual care; DDD = defined daily dose; WBC = white blood cell; FIG = full intervention group (CRP testing plus supplemental activities); PIG = partial intervention group (no CRP testing or CRP education)

*Compared with control group; data from control group collected during intervention period

†Higher than average number of DDDs per 1000 inhabitants per day

‡Noted in Discussion that older patients were less likely to present with a symptom of spreading infection than younger patients

§Prescriptions were inappropriate if patient did not have facial swelling, lymphadenopathy, limited mouth opening, raised temperature, difficulty swallowing, or acute necrotizing ulcerative gingivitis (ANUG)

‖Changes in mean or median (as indicated) total number of prescriptions per 1000 patients per general practitioner during a 3 month period; means were reported for normally distributed variables, medians were reported for skewed variables

Table 4. Patient Outcomes

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Provider and Patient Education					
Butler 2012[22] RCT	*Re-consultation rates for respiratory tract infections (median number of individuals per 1000 registered patients)* Within 7 days: Intervention: 2.66 Control: 3.35 Median difference -0.65 [95% CI -1.69, 0.55]; p=0.45 Within 31 days: Intervention: 9.06 Control: 11.38 Median difference -2.32 [95% CI -4.76, 1.95]; p=0.50	*Annual number of episodes for possible respiratory tract infection and complications of common infections* Intervention sites: baseline period = 7.7/1000 registered patients; intervention period = 7.5/1000 registered patients Control sites: baseline period = 8.7/1000 registered patients; intervention period = 8.0/1000 registered patients *% reduction (intervention relative to control)*: -1.9 [95% CI -13.2, 8.2]; p=0.72	NR	NR	NR
Metlay 2007[30] CRCT	*Return Emergency Department visits during 2-week follow-up period** Intervention sites: baseline period = 8.1 events/100 persons, intervention period = 9.5 events/100 persons Control sites: baseline period = 5.5 events/100 persons, intervention period = 10.1 events/100 persons Site by time interaction p=0.48 (adjusted)	*During 2-week follow-up period** Intervention sites: baseline period = 6.3 events/100 persons, intervention period = 4.8 events/100 persons Control sites: baseline period = 6.0 events/100 persons, intervention period = 4.2 events/100 persons Site by time interaction p=0.51 (adjusted)	NR	*NR*	*Self-reported satisfaction with visit (1=very unsatisfied, 5=very satisfied)* Intervention sites: baseline period =2.5, intervention period = 2.7 Control sites: baseline period = 2.7, intervention period = 2.9 Site by time interaction p=0.71 (adjusted)

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Little 2005,[33] Moore 2009[72] RCT	*During 1 month after physician visit (mean attendances)* Leaflet group: 0.17 No leaflet group: 0.11 IRR 1.63 [95% CI 1.07, 2.49]; p=0.02 No antimicrobials: 0.19 Delayed antimicrobials: 0.12 IRR 0.65 [95% CI 0.40, 1.04]; p=0.08 vs no antimicrobials Immediate antimicrobials: 0.11, IRR 0.55 [95% CI 0.33, 0.91]; p=0.02 vs no antimicrobials Overall p=0.04 *With cough between 1 month and 1 year after physician visit*† Leaflet vs no leaflet: IRR_{Adj} 1.27 [95% CI 0.86, 1.87]; p=0.23 Delayed prescription (vs immediate prescription): IRR_{Adj} 0.81 [95% CI 0.51, 1.28] No prescription (vs immediate prescription): IRR_{Adj} 1.05 [95% CI 0.68, 1.63] Delayed prescribing in patients with antimicrobial use prior to index visit associated with decreased reconsultation 1 month to 1 year after index visit	NR	No antimicrobial group: 1 patient developed pneumonia, was admitted, administered antimicrobials, and recovered fully Diarrhea slightly more common in delayed antimicrobial (OR 1.17 [95% CI 0.67, 2.03]; p=0.58) and immediate antimicrobial (OR 1.22 [95% CI 0.70, 2.23]; p=0.48)	NR	NR
Guidelines					
Seager 2006[45] CRCT	NR	NR	NR	NR	*NOTE: Data from 89 control, 67 guideline, and 0 intervention group patients* "No evidence that patients who had not received a prescription for an antimicrobial were less likely to feel that the treatment they had received had been effective" (compared with those receiving antimicrobial p>0.05)
Delayed Prescribing					
Little 2010[47] RCT	*Return clinic visit within 1 month* Control (immediate): 22/58 (55%) Delayed: OR 0.44 [95% CI 0.21, 0.95] Midstream Urine: OR 0.65 [95% CI 0.30, 1.40) Dipstick: OR 0.87 [95% CI 0.40, 1.90] Symptom Score: OR 0.57 [95% CI 0.27, 1.18]	NR	No major adverse events (major illness, admission to hospital, death) were reported for any group	NR	NR

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Communication Skills Training					
Little 2013[49] CRCT	NR	30 patients admitted (all cause hospitalization): Usual care group: 2 CRP group: 10 Enhanced communication group: 6 Combined group: 12 Overall (controlling for clustering) higher hospitalization in CRP group (22 vs 8; OR 2.61 [95% CI 1.07, 6.35]; p=0.034 Controlling for all potential confounders OR 2.92, 95% CI 0.96, 8.85]; p=0.060	*Mortality: 0%* ***Factorial groups*** *Resolution of symptoms (moder-ately bad or worse); median (IQR):* No CRP training: 5 (3-9) days CRP training: 5 (3-9) days HR_{Adj} 0.93 [95% CI 0.83, 1.04]; p=0.21 No communication training: 5 (3-7) days Communication training: 6 (3-10) days HR_{Adj} 0.83 [95% CI 0.74, 0.93]; p<0.01 *New/worse symptoms AND severity score 2-4 days after index visit:* No significant difference (CRP vs no CRP, communi-cation vs no communication)	NR	NR
Légaré 2012[50] CRCT	*Repeat consultation for same reason*‡ Baseline: 21.6% at intervention sites, 13.4% at control sites Post-intervention: 22.7% at intervention sites, 15.2% at control sites; absolute difference 7.5%, RR_{Adj} 1.3 [95% CI 0.7, 2.3]	NR	NR	NR	*Intention to engage in shared decision-making in the future regarding ARIs*‡§ Post-intervention: 2.1 intervention site patients, 1.9 control site patients, mean difference 0.2 [95% CI -0.1, 0.4] *Regret over decision*‡‖ Post-intervention: 12.4 Intervention site patients, 7.6 control site patients, mean difference 4.8 [95% CI 0.9, 8.7]

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Légaré 2010[51] CRCT	NR	NR	*Patients who felt they had stable, a little better, or much better health 2 weeks after consultation* Post-intervention: 94% of intervention site patients, 85% of control site patients; mean difference 9 [95% CI -2, 18]; p=0.08	NR	*Intention to engage in shared decision-making in the future regarding ARTIs*‡§ Post-intervention: 0.7 intervention site patients, 0.8 control site patients, mean difference -0.1 [95% CI -0.6, 0.4]; p=0.16 *Regret over decision*‡‖ Post-intervention: 7% Intervention site patients, 9% control site patients, mean difference -2 [95% CI -12, 5]; p=0.91
Cals 2009[52] Cals 2013[54] CRCT	*Return visit within 28 days* 27.9% (communication training) vs 38% (no training) (p=ns)	*During study period:* None reported *During follow-up (mean 3.67 yrs, n=379)* Usual care: 5 episodes in 2 patients CRP group: 1 episode CRP + communication skills training group: 2 episodes	None reported	*Total prescribing (index visit plus 28 day follow-up)* 37.8% (communication training) vs 63% (no training) (p<0.001)	*Patients at least "very satisfied"* 78.7% (communication training) vs 74.4% (no training) (p=ns)
Francis 2009[55] CRCT	*Primary care return clinic visit within 2 weeks of index visit* Intervention: 33/256 (12.9%) Control: 44/272 (16.2%) OR 0.75 [95% CI 0.41, 1.38] Outcome similar if telephone consultations were included (OR 0.81 [95% CI 0.47, 1.42]) or if accident and emergency department consultations were included (OR 0.85 [95% CI 0.48, 1.51])	*Admitted to hospital or observed in a pediatric assessment unit* Intervention: 3 patients Control: 4 patients	NR	NR	*"Very satisfied" or "satisfied" with the consultation* Intervention: 222/256 (90.2%) Control: 246/272 (93.5%) OR 0.64 [95% CI 0.33, 1.22] *Information received "very useful" or "useful"* Intervention: 210/256 (85.4%) Control: 224/272 (85.2%) OR 1.01 [95% CI 0.60, 1.68]
Restriction					
Manns 2012[57] ITS	*Outpatient claim in 30 days after index visit* Before restriction: 55.6% After restriction: 56.5% (p<0.001)	*All-cause* Before restriction: 4.9% After restriction: 5.2% (p=0.0001) *Related to infections of interest* Before restriction: 1.4% After restriction: 1.4% (p=0.20)	*Mortality* Before restriction: 0.3% After restriction: 0.3% (p=0.54)	NR	NA

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Decision Support					
Gonzales 2013[59] CRCT	*For bronchitis, pneumonia, COPD* PDS: 0.5% baseline, 0.9% intervention (p=0.16) CDS: 0.6% baseline, 0.5% intervention (p=0.81) UC: 0.3% baseline, 1.4% intervention (p<0.001) No significant difference between sites	*For bronchitis, pneumonia, COPD* PDS: 0.05% baseline, 0.0% intervention (p>0.99) CDS: 0.1% baseline, 0.0% intervention (p=0.57) UC: 0.1% baseline, 0.1% intervention (p>0.99)	*Diagnosis of pneumonia at return visit* Reported range 0.5 to 1.5%	NR	NR
Jenkins 2013[60]* RCT	*8 to 30 days after initial visit* Intervention sites: 3.7% baseline, 3.0% post-intervention (p=0.13) Control sites: 3.3% baseline, 4.2% post-intervention (p=0.02)	Intervention sites: 0.02% baseline, 0.0% post-intervention (p=1.0) Control sites: 0.05% baseline, 0.07% post-intervention (p=1.0)	NR	*8 to 30 days after initial visit* Intervention sites: 4.9% baseline, 3.9% post-intervention (p=0.06) Control sites: 6.1% baseline, 7.1% post-intervention (p=0.06)	NR
McGinn 2013[61] RCT	*2 weeks after initial visit* Intervention: 45/586 (7.7%) Control: 45/398 (11.3%) p=0.10	NR	NR	*2 weeks after initial visit* Intervention: 16/586 (2.7%) Control: 15/398 (3.8%) p=0.45	NR
Linder 2009[63] CRCT	*30-day revisit rate* Intervention 23% Control 26% (p=0.32) *30-day revisit rate attributable to ARIs* Intervention: 8% Control 9% (p=0.29)	NR	NR	NR	NR

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Rapid Tests					
Little 2013[66] RCT	*Within 1 month with sore throat* Clinical score + RADT: 13/212 (6%); RR 0.74 [95% CI 0.36, 1.47]; p=0.40) Clinical score: 167/210 (8%); RR 0.91 [95% CI 0.47, 1.72]; p=0.78) Delayed prescribing (control): 17/207 (8%) *After 1 month with sore throat (mean follow-up 0.73 years)* Clinical score + RADT: 34/211 (16%); RR 1.06 [95% CI 0.66, 1.63]; p=0.81) Clinical score: 26/210 (12%); RR 0.79 [95% CI 0.47, 1.29]; p=0.35) Delayed prescribing (control): 31/207 (15%)	NR	*Skin rash or diarrhea within 1 month of visit* Clinical score +RADT: 1/211 (0.5%) Clinical score: 2/210 (1%) Delayed prescribing (control): 0/207 *Mean severity of sore throat/difficulty swallowing on days 2-4 (0=no problem, 6=as bad as it could be)* Clinical score + RADT: 2.83 (1.62); mean diff. -0.30 [95% CI -0.61, 0.004]; p=0.05 Clinical score: 2.88 (1.52); mean diff. -0.33 [95% CI -0.64, -0.02]; p=0.04 Delayed prescribing (control): 3.11 (1.49)	NR	*Belief in need to see doctor in future episodes* (slightly likely or less) Clinical score + RADT: 64/161 (40%); RR 1.03 [95% CI 0.76, 1.32]; p=0.86) Clinical score: 54/155 (35%); RR 0.97 [95% CI 0.71, 1.27]; p=0.85) Delayed prescribing (control): 62/163 (38%)

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Brittain-Long 2011[67] RCT	NR	NR	NR	Total antimicrobial prescriptions at 10+/-2 days follow-up: 28/166 (13.9%) (early result) vs 35/204 (17.2%) (late result); p=0.36 (NOTE: 71 patients lost to follow-up; during follow-up, 19 patients [early result] and 10 patients [late result] received antimicrobial prescriptions)	NR
C-Reactive Protein					
Diederischsen 2000[69] RCT	NR	NR	Increased or unchanged patient-reported morbidity: a) 50/407 (12%) (CRP) vs 31/384 (8%) (usual care) (OR=1.6 [95% CI 1.0, 2.6]; p=0.05) b) 56/436 (13%) (not receiving antimicrobials) vs 25/355 (7%) (receiving antimicrobials), (OR 2.0 [95% CI 1.2, 3.1]; p=0.006)	NR	NR
Takemura 2005[70] RCT	44/147 (29.9%) (CRP+WBC) vs 36/154 (23.4%) (usual care) (p=0.20)	3/147 (2.0%) (CRP+WBC) vs 2/154 (1.3%) (usual care) (p=0.68) (calculated)	Fever >3 days after starting treatment 27/59 (45.7%) (CRP+WBC) vs 19/45 (42.2%) (usual care); p=0.72	Antimicrobials prescribed at return clinic visit: 5/147 (3.4%) (CRP+WBC) vs 9/154 (5.8%) (usual care); p=0.11	NR

Author Year Study Design	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescription	Patient Satisfaction with Care
Cals 2009[52] Cals 2013[54] CRCT SEE Communica-tion Skills Training	*Return visit within 28 days* 79/227 (34.8%) (CRP) vs 62/204 (30.4%) (no CRP) (p=ns)	*During study period:* None reported *During follow-up (mean 3.67 yrs, n=379)* Usual care: 5 episodes in 2 patients CRP group: 1 episode CRP + communication skills training group: 2 episodes	None reported	*Total prescribing (index visit plus 28 day follow-up)* 102/227 (44.9%) (CRP) vs 119/204 (58.3%) (no CRP); p<0.01	*Patients at least "very satisfied"* 159/227 (76.8%) (CRP) vs 136/204 (76%) (no CRP); p=ns
Cals 2010[71] RCT	Return clinic visit: 33/129 (25.6%) (CRP) vs 23/129 (17.8%) (usual care) (p=ns)	None reported	None reported	68/129 (52.7%) (CRP) vs 84/129 (65.1%) (usual care); RR 0.81 [95% CI 0.62, 0.99]	Patients at least "very satisfied": 90/118 (76.3%) (CRP) vs 79/125 (63.2%) (usual care); p=0.03
Little 2013[49] CRCT SEE Communica-tion Skills Training	NR	30 patients admitted (all cause hospitalization): Usual care group: 2 CRP group: 10 Enhanced communication group: 6 Combined group: 12 Overall (controlling for clustering) higher hospitalization in CRP group (22 vs 8); OR 2.61 [95% CI 1.07, 6.35]; p=0.034 Controlling for all potential confounders OR 2.92, [95% CI 0.96, 8.85]; p=0.060	*Mortality: 0%* ***Analysis of factorial groups*** *Resolution of symptoms rated moderately bad or worse; median(IQR):* No CRP training: 5 (3 to 9) days CRP training: 5 (3 to 9) days HR_{Adj} 0.93 [95% CI 0.83, 1.04]; p=0.21 *New or worse symptoms AND symptom severity score 2-4 days after index consultation:* No significant difference - CRP vs no CRP	NR	NR

ARTI = acute respiratory tract infection; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; IQR = interquartile range; HR = hazard ratio; RR = risk ratio
*Data from 776 patients enrolled for follow-up assessment across all sites during baseline and intervention years
†Data from 658 patients with notes available for extraction
‡Data obtained from telephone interview 2 weeks after initial consultation
§Mean from 3-item scale with -3=strongly disagree, 3=strongly agree
‖0 = very low regret, 100 = very high regret

Table 5. Cost and Harms Outcomes

Author Year Study Design	Dispensing Cost/Practice	Program Costs	Harms
Provider and Patient Education			
Butler 2012[22] RCT	Intervention sites: baseline period = £2199.7, intervention period = £2078.9 Control sites: baseline period = £2254.6, intervention period = £2252.3 *% reduction (intervention group relative to control group):* 5.5 [95% CI -0.4, 11.4]; p=0.07	For 33 intervention practices: Administration Costs: £4,754 Seminar Preparation: £2,536 Seminar Delivery: £17,510 Total cost of trainee time: £71,659 Total cost of STAR training: £96.460 Mean cost per practice: £2,923	NR
Chazan 2008[29] RCT	*Savings (in total antimicrobial cost) - last winter season (Nov-Feb) compared to baseline* Continuous intervention group: $330 per 1000 patients/season Seasonal group: $186 per 1000 patients/season	NR	NR
Pagaiya 2005[34] RCT	*For ARTI (pre- to 6 months post-intervention)* Intervention: pre 16.7 Baht, post 15.1 Baht Control: pre 16.2 Baht, post 17.1 Baht (p=0.002)		
Provider Feedback			
Naughton 2009[39] RCT	NR	*Cost of Postal Prescribing Feedback (first year)* Staff (Senior pharmacists, secretary, computer programmer) €155,000 Equipment €12,000 Administrative €43,000 Total €210,000 (Per practice €175)	NR
Madridejos-Mora 2004[40] CCT	*Pharmaceutical Expenditure*† Intervention: pre 2.94, post 2.49, p=0.004 Control: pre 3.18, post 3.25, p=0.766 Between groups, post-intervention: p=0.013	NR	NR
Guidelines			
Weiss 2011[44] ITS	*Difference in antimicrobial prescription costs between Quebec (intervention) and other provinces (control)* a) Level change of -134.5 $Can per 1000 inhabitants monthly [95% CI -270.5, 1.6, p=0.054] immediately post-intervention; maintained during 36 month follow-up b) Significant level changes for cephalosporins (-44.3 $Can/1000; p<0.001), quinolones (-53.5 $Can/1000; p<0.001), and other antimicrobials (-13.7 $Can/1000; p=0.003); maintained during 36 month follow-up c) Significant level change for penicillins (-20.7 $Can/1000 p=0.006); not maintained during follow-up	NR	NR

Author Year Study Design	Dispensing Cost/Practice	Program Costs	Harms
Communication Skills Training			
Cals 2009[52] Cals 2011[53] CRCT SEE Communication Skills Training	*Medication cost per patient (GP prescribed)* €10.47 (communication training) €12.54 (CRP and communication training) €18.18 (usual care) *Total health care costs per patient (mean (SD) (includes intervention costs)* €25.61(44.49) (communication training) €37.78 (42.08)(CRP and communication training) €35.96 (58.12) (usual care)	*Intervention costs (per patient)* Communication skills training intervention: €5.34 CRP plus communication skills training: €10.06 Usual care: €0.00	NR
Restriction			
Marshall 2006[58] ITS	*Total antimicrobials* Level and trend: p=ns *Fluoroquinolone group (6 antimicrobials, 3 restricted)* Level: Can$105,707 less/wk, p<0.0001 Trend: p=ns *Ciprofloxacin (restricted)* Level: Can$129,429 less/wk, p<0.0001 Trend: p=ns *Levofloxacin (restricted)* Level: p=ns Trend: increasing *Ofloxacin (restricted)* Level and trend data not reported (included in fluoroquinolone group) *TMP/SMX* Level: Can$1,473 more/wk, p<0.0001 Trend: decreasing *Nitrofurantoin* Level: Can$2,082 more/wk, p<0.0001 Trend: increasing		
C-Reactive Protein			
Cals 2009[52] Cals 2011[54] CRCT SEE Communication Skills Training	*Medication cost per patient (GP prescribed)* €16.89 (CRP) €18.18 (usual care) *Total health care costs per patient (mean (SD) (includes intervention costs*) €37.58 (45.24) (CRP) €35.96 (58.12) (usual care)	*Intervention costs (per patient)* CRP: €4.72 Usual care: €0.00	NR

$Can = Canadian Dollars; Baht = currency of Thailand (40 Baht = 1 US$)

†Euros/inhabitant

Table 6. Risk of Bias Assessment for RCT, CCT, and CBA Studies

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Provider and Patient Education								
Gerber 2013[20] CRCT Medium	Unclear	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Vinnard 2013[21] CBA High	Not applicable	Not applicable	High risk	Unclear (not reported)	High risk	Unclear (not reported)	Unclear	Low risk
Butler 2012[22] RCT Medium	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk (database)	Unclear	Low risk
Llor 2012[23,24] CBA Medium	High risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Regev-Yochay 2011[25] CRCT High	Unclear	Low risk	Low risk	Low risk	High risk	Low risk (pharmacy database)	High risk	Low risk
Esmaily 2010[26] CRCT High	Unclear	Low risk	Unclear	Low risk	High risk	Unclear	Low risk	Low risk
Smeets 2009[27] CBA High	Unclear	Unclear (GPs in control groups not informed about role in study)	High risk	Low risk	Unclear	Low risk (claims data)	Unclear	Low risk
Finkelstein 2008[28] CRCT Medium	Low risk	Low risk	Unclear	Unclear	Low risk (claims data)	Low risk (claims data)	Unclear	Low risk
Chazan 2007[29] RCT High	Unclear	Unclear	High risk	Low risk	Low risk (database)	Low risk (database)	Unclear	Low risk
Metlay 2007[30] CRCT Medium	Unclear	High risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Van Driel 2007[31] CRCT High	Unclear	Low risk	Unclear	Low risk	High risk	Low risk	Unclear	Low risk
Varonen 2007[32] RCT High	Unclear	Unclear	Unclear	Low risk	High risk	High risk	Unclear	High risk

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Little 2005[33] RCT Medium	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
Pagaiya 2005[34] RCT Medium	Low risk	Low risk	Unclear	Low risk	Low risk (randomly selected)	Low risk	Unclear	Low risk
Gonzales 2004[35] CCT High	Not applicable	Not applicable	Unclear	Low risk	Unclear	Low risk (claims data)	High risk	Low risk
Stewart 2000[36] CBA High	Unclear	Unclear	Low risk	Unclear	Low risk (database)	Low risk (database)	Low risk	Low risk
Provider Feedback								
Gjelstad 2013[37] CRCT High	Unclear	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Low risk
Vinnard 2013[21] CBA High	See Provider and/or Patient Education							
Linder 2010[38] CRCT High	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk (electronic records)	Unclear	Low risk
Naughton 2009[39] RCT High	Unclear	Unclear	High risk	Low risk	Unclear	Low risk (database)	Unclear	Low risk
Madridejos-Mora 2004[40] CCT Medium	Not applicable	Not applicable	Low risk	Low risk	Unclear	Low risk (pharmacy files)	Low risk	Low risk
Guidelines								
Seager 2006[45] CRCT Medium	Low risk	Low risk	Low risk (stratified by prescribing)	Low risk	Unclear	Unclear	Low risk	Low risk
Martens 2006[46] CCT High	Not applicable	Not applicable	Unclear	High risk	Unclear	Low risk (insurance data)	Low risk	Low risk

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Communication Skills Training								
Little 2013[49] CRCT see CRP Medium	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Légaré 2012[50] CRCT Medium	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Low risk
Légaré 2010[51] CRCT Medium	Low risk	Low risk	Unclear	Low risk	Unclear	High risk	Unclear	Low risk
Francis 2009[55] CRCT Medium	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Altiner 2007[56] CRCT High	Unclear	Low risk	High risk	Low risk	Low risk	High risk	Unclear	Low risk
Decision Support								
Gonzales 2013[59] CRCT High	Unclear	Unclear	Unclear	High risk	Low risk	Low risk	Unclear	Low risk
Jenkins 2013[60] RCT Medium	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Low risk
McGinn 2013[61] RCT High	Low risk	Low risk	Unclear	Low risk	Low risk	High risk	Unclear	Low risk
Rattinger 2012[62] CBA High	Not applicable	Not applicable	High risk	Low risk	Low risk	High risk	Unclear	Low risk
Linder 2009[63] CRCT High	Unclear	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Low risk
Martens 2007[64] CRCT High	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Low risk	Low risk

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Financial Incentive								
Martens 2007[65] CBA High	High risk	Unclear ("GPs" in control group not informed of intervention beforehand")	High risk	Low risk	Low risk	Low risk (insurance database)	High risk (seasonal differences)	Low risk
Delayed Prescribing								
Little 2010[47] RCT Medium	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk
Worrall 2010[48] RCT High	Unclear	Low risk	Unclear	Low risk	Unclear	High risk	Unclear	Low risk
Rapid Tests								
Little 2013[66] RCT High	Low risk	Low risk	Unclear	High risk	High risk	Low risk	Low risk	High risk
Brittain-Long 2011[67] RCT Medium	Low risk	Low risk	Low risk	Low risk	Unclear risk (similar rate of followup - study [82%] and control group [83%])	Low risk	Low risk	Low risk
Worrall 2007[68] RCT Medium	Low risk	Low risk	Low risk	Low risk (providers) Unclear risk (patients)	Unclear risk (3/40 providers entered no patients)	Low risk	Low risk	Low risk
C-Reactive Protein								
Diederischsen 2000[69] RCT Medium	High risk (first patients of the day)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Takemura 2005[70] RCT High	Low risk	Unclear risk (not stated)	Low risk	Unclear risk ("almost similar" between groups)	High risk (follow-up questionnaire returned by 40.1% advance testing, 28.7% control; not clear how hospitalized patient data were treated	Low risk	Unclear risk (control group still had access to CRP testing)	Low risk

Author year Study design Risk of bias	Adequate allocation sequencing	Adequate allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data addressed	Any blinding reported	Study protected against contamination	Study free from selective outcome reporting
Cals 2009[52] CRCT High	Low risk	Low risk	Low risk	Unclear risk (3 providers in the enhanced communication skills training group were on maternity leave during the study but were randomized)	Unclear risk (diary return rates: 89% [CRP],. 88% [communica-tion skills training], 94% [combined group], 87% [usual care])	Low risk	Low risk	Unclear risk (data planned to be collected from >28 days to 10 weeks not reported)
Cals 2010[71] RCT Medium	Low risk	Low risk	Low risk	Low risk	Unclear risk (patient reported outcomes available in 94% of patients)	Low risk	Low risk	Low risk
Llor 201223,24 CBA Medium	High risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Little 2013[49] CRCT Medium	Low risk	Low risk	Low risk	Low risk	Unclear risk (practices recruiting no patients: 8/61 [usual care], 4/62 [CRP training], 6/61 [communica-tion training], 0/62 [com-bined group]	Low risk	Low risk	Low risk

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

Table 7. Risk of Bias Assessment for ITS Studies

Author year Risk of Bias	Did study address trend changes	Intervention independent of other changes	Shape of intervention pre-specified	Intervention unlikely to affect data collection	Knowledge of the allocated interventions adequately prevented during study	Incomplete outcome data adequately addressed	Study free from selective outcome reporting
Guidelines							
Dowell 2012[41] Medium	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Slekovec 2012[42] Medium	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Venekamp 2012[43] Medium	Low risk	Low risk	Unclear	Low risk	Low risk (database)	Low risk	Low risk
Weiss 2011[44] Medium	Low risk	Unclear	Unclear	Low risk	Low risk (database)	Low risk	Low risk
Restriction							
Manns 2012[57] ITS Medium	Low risk	Unclear	Unclear	Low risk	Low risk (claims data)	Low risk	Low risk
Marshall 2006[58] ITS Low	Low risk	Low risk	Low risk	Low risk	Low risk (claims data)	Low risk	Low risk

ITS = interrupted time series