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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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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