Effective Health Care Program

Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections

Executive Summary

Introduction

Antibiotics transformed the practice of medicine in the last half of the 20th century. With antibiotics, common infections and injuries that would previously have caused death or debility can now be effectively treated and cured. With antibiotic use, however, some bacteria can adapt, which can result in the development of antibiotic resistance, a public health problem that has grown substantially in the last several decades. In the United States, at least 2 million people acquire infections with antibiotic-resistant bacteria each year, causing approximately 23,000 deaths.[1] Although reasons for higher rates of antibiotic resistance at a population level are multifactorial, including the use of antibiotics in livestock and underdevelopment of new antibiotics, a key factor is high outpatient consumption of antibiotics.[1-3] In response to this public health problem, President Obama signed an Executive Order in September 2014 that encourages advancing development of new diagnostics, antibiotics, vaccines, and other therapeutics; strengthening surveillance of resistance; and enhancing antibiotic stewardship strategies.[4]

The problem of inappropriate antibiotic use may be biggest for uncomplicated

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare. ahrq.gov/reports/final.cfm**.

acute respiratory tract infections (RTIs) because they account for approximately 70 percent of primary diagnoses in adults presenting for ambulatory care office visits with a chief symptom of cough.[5] Acute

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RTIs include acute bronchitis, acute otitis media (AOM), pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes, but not community-acquired pneumonia or acute exacerbations of chronic obstructive pulmonary disease, bronchiectasis, or other chronic underlying lung diseases.[6] Despite guidelines recommending no antibiotic treatment for uncomplicated acute RTIs, the majority of outpatient antibiotic prescriptions in the United States are for acute RTIs. The National Ambulatory and National Hospital Ambulatory Medical Care Surveys found that in the period 2007−09, antibiotics were prescribed during 101 million ambulatory visits for patients aged 18 years and above annually.[7] Similarly, although the majority of bronchitis and pharyngitis is viral rather than bacterial, a 2013 report on healthy adults visiting outpatient offices and emergency departments (EDs) for acute bronchitis found that antibiotics were prescribed at 73 percent of visits from 1996 through 2010,[8] and a 2014 analysis of data from the National Ambulatory and National Hospital Ambulatory Medical Care Surveys indicated that 60 percent of children diagnosed with pharyngitis from 1997 through 2010 were prescribed antibiotics.[9]

The reasons for overuse of antibiotics for acute RTIs are numerous, diverse, and complex, with both internal and external factors, including geographic location; environment (e.g., clinic type); patient demographics (e.g., children vs. adults); availability of followup care; patient and clinician preferences, communication, and relationship; clinician specialty, knowledge, and experience; clinical inertia; peer group influence; and oversight or feedback from infectious disease experts.[10-12] Consequently, strategies to reduce antibiotic use for acute RTIs have varied targets. Strategies may target clinicians who care for patients with acute RTIs in outpatient settings, adult and/or pediatric patients with acute RTIs, the parents of pediatric patients with acute RTIs, healthy adults and/or children in the general population without a current RTI, or organizations whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials). Intervention strategies have also varied in the ways they are designed to change antibiotic prescribing behavior, including education, strategies to improve communication between clinicians and patients, clinical strategies such as delayed prescribing or use of point-of-care diagnostic tests, system-level strategies such as clinician reminders or audit and feedback, or multifaceted approaches that incorporate various elements.

Interventions to improve antibiotic use are intended to achieve a variety of outcomes, including diminished antibiotic resistance, fewer adverse drug events, and decreased health care costs. However, long-term studies to evaluate these important impacts are largely yet to be done, and studies of antibiotic resistance would need to be conducted in large populations and over long time periods. In the absence of patient-centered outcomes, it has been suggested that the rate of "inappropriate" prescription of antibiotics would be the best surrogate outcome. But although a number of guidelines define when antibiotic use is warranted, defining and determining "appropriate" use for study purposes is difficult because determination of appropriateness is subjective and requires both access to adequate patient-level data and clinical knowledge. Similarly, while "prescription" and "use" are not synonymous, measuring actual use is much more difficult and resource intensive than counting prescriptions. Therefore, studies have generally evaluated the impact of interventions on overall antibiotic prescriptions, based on the understanding that for certain clinical condition, the majority of antibiotic use is unnecessary and should be reduced. The usefulness of overall prescribing as a proxy for appropriate prescribing may vary because the rate of inappropriate prescribing ranges widely, from 50 to 80 percent, based on patient, provider, and setting factors.[13,14]

A main concern with using a reduction in overall prescribing of antibiotics for RTIs as a measure of success is that it may increase the risk of undertreatment of patients for whom antibiotics would have been indicated and lead to increases in undesirable outcomes, such as hospitalization, medical complications, clinic visits, time off work and/or school, patient dissatisfaction, and longer symptom duration. In addition, the interventions may require substantial time and resources. Therefore, these negative outcomes must be assessed alongside the prescribing outcomes.

A number of existing systematic reviews and guidelines have contributed to our understanding of what works for targeted populations, interventions, or diseases.[15-22] However, because improving antibiotic use has become an increasingly urgent public health priority, there is an important need for an updated comparative effectiveness review that comprehensively addresses a broad range of interventions and populations in one review. The goal of the present systematic evidence review is to assess the comparative effectiveness of possible strategies for reducing antibiotic use in adults and children with acute RTIs. In addition to providing evidence on the benefits and potential harms of strategies, the review identifies gaps in the literature and suggestions to guide future research.

The Key Questions used to guide this report are as follows:

- **Key Question 1.** For adults and children with an acute respiratory tract infection, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

- **Key Question 2.** For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

- **Key Question 3.** For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization, and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

- **Key Question 4.** For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

- **Key Question 5.** For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

- **Key Question 6.** What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

For Key Questions 1 through 4, the following subquestions were also addressed:

a. Does the comparative effectiveness of strategies differ according to how appropriateness is defined? (Key Question 1 only)

b. Does the comparative effectiveness of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, or both)?

c. Does the comparative effectiveness of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?

d. Does the comparative effectiveness of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?

e. Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?

f. Does the comparative effectiveness differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), system-level characteristics, or whether the intervention was locally tailored?

The analytic framework below (Figure A) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis, and their relationship to the Key Questions. Specific details regarding patient population, intervention components, and outcomes are provided in the next section.
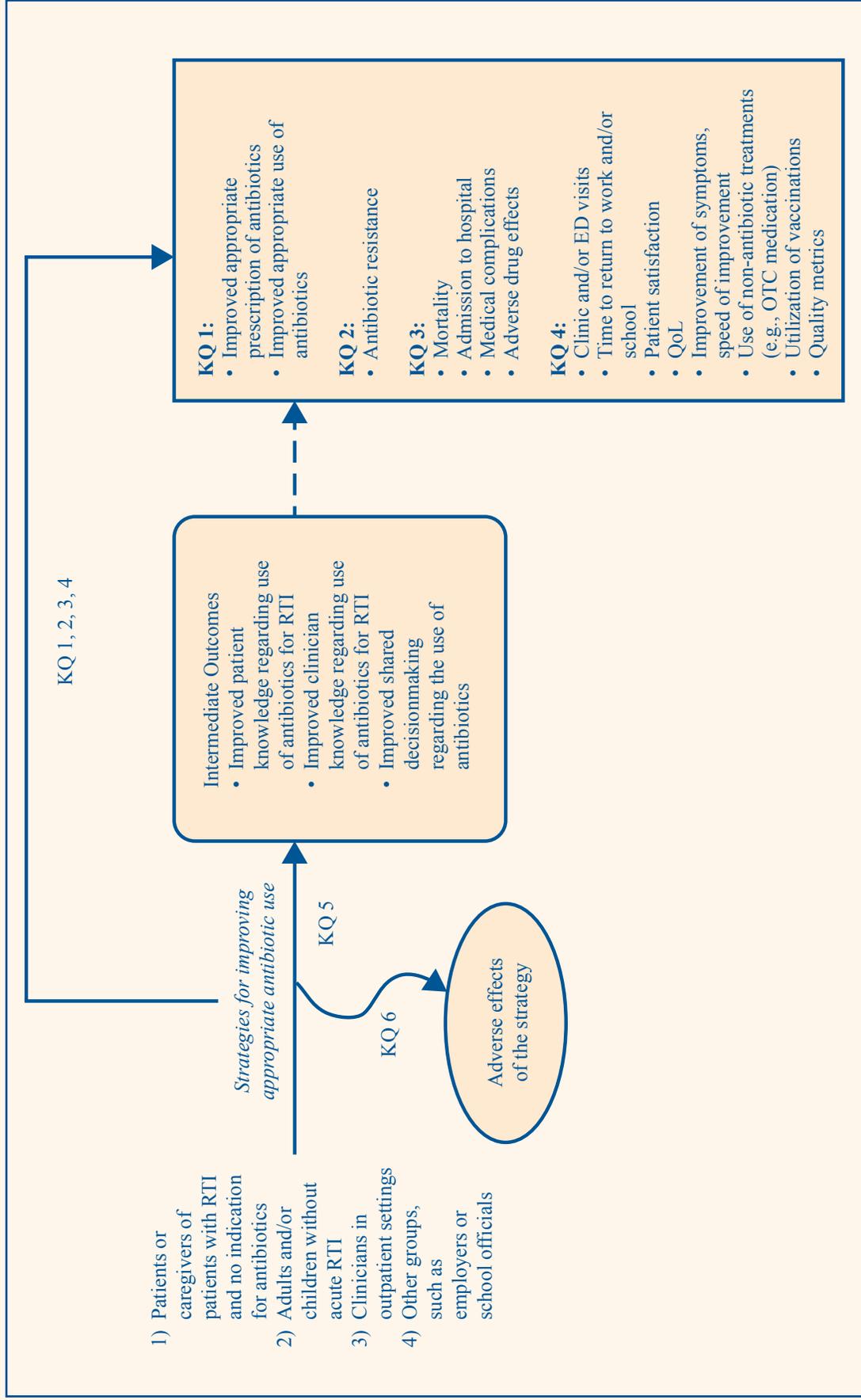
Methods

This Comparative Effectiveness Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[23] All methods were determined a priori. The protocol is registered with the PROSPERO international database of prospectively registered systematic reviews and is available at www.crd.york.ac.uk/PROSPERO/display_record. asp?ID=CRD42014010094.[24]

Literature Search Strategy

Our medical librarian searched Ovid MEDLINE® and CENTRAL from 1990 to May 14, 2014, and the Cochrane Database of Systematic Reviews from 2005 to March 2014. Additional sources included systematic review reference lists, Scientific Information Packets, and consultation with Technical Expert Panel (TEP) members.

Literature searches were updated while the draft report was posted for peer review and public comment in February 2015. Studies identified through the update searches were assessed using the same process of dual review as used for studies identified during the initial searches. Pertinent

Figure A. Analytic framework for improving appropriate antibiotic use for acute respiratory tract infections

KQ 1, 2, 3, 4

1) Patients or caregivers of patients with RTI and no indication for antibiotics
2) Adults and/or children without acute RTI
3) Clinicians in outpatient settings
4) Other groups, such as employers or school officials

Strategies for improving appropriate antibiotic use

KQ 5

KQ 6

Adverse effects of the strategy

Intermediate Outcomes
• Improved patient knowledge regarding use of antibiotics for RTI
• Improved clinician knowledge regarding use of antibiotics for RTI
• Improved shared decisionmaking regarding the use of antibiotics

KQ 1:
• Improved appropriate prescription of antibiotics
• Improved appropriate use of antibiotics

KQ 2:
• Antibiotic resistance

KQ 3:
• Mortality
• Admission to hospital
• Medical complications
• Adverse drug effects

KQ 4:
• Clinic and/or ED visits
• Time to return to work and/or school
• Patient satisfaction
• QoL
• Improvement of symptoms, speed of improvement
• Use of non-antibiotic treatments (e.g., OTC medication)
• Utilization of vaccinations
• Quality metrics

ED = emergency department; KQ = Key Question; OTC = over-the-counter; QoL = quality of life; RTI = respiratory tract infection

new literature meeting inclusion criteria was incorporated before the final submission of the report.

Inclusion and Exclusion Criteria

Studies were included based on the PICOTS (populations, interventions, comparators, outcomes, timing, and settings) detailed in Table A. Based on input from our TEP, and as we recognized that the 1990s marked the decade when many organizations, such as the Centers for Disease Control and Prevention, initiated formal efforts to promote appropriate antibiotic use, we restricted inclusion to studies published since 1990. Because of resource limitations, we included only studies published in English. Studies published in other languages but otherwise appearing to be eligible based on the title or English-language abstract were identified and reviewed in order to evaluate potential language bias.

Study Selection

Study selection followed AHRQ guidance for reducing bias.[25,26] Abstracts for citations identified through searches were screened for eligibility by one reviewer, with any deemed ineligible checked by a second reviewer. Full text of all citations deemed potentially eligible for inclusion by at least one reviewer was obtained for further evaluation by two reviewers, with differences in judgment on eligibility resolved through consensus or inclusion of a third party.

Data Extraction

Study characteristics and results were abstracted from included studies. One reviewer abstracted study data and a second reviewer appraised the abstractions. Intention-to-treat results were recorded if available. We considered

Table A. Criteria for eligibility based on PICOTS framework	
PICOTS	**Criteria for Eligibility**
Populations	Adult and pediatric patients with an acute RTI. RTIs of interest include acute bronchitis, AOM, sore throat/pharyngitis/tonsillitis, rhinitis, sinusitis, cough, and common cold.[6]
	Parents of pediatric patients with an acute RTI.
	Healthy people without a current acute RTI, who may develop an acute RTI in the future.
	Clinicians and others who care for patients with acute RTI in outpatient settings, including ED physicians.
	Groups whose attendance policies may indirectly affect the use of antibiotics, such as employers or school officials.
Interventions	Any strategy for improving appropriate antibiotic prescribing and use for acute RTI. We grouped interventions by their components into the following five categories: • Educational/behavioral interventions for clinicians, patients, or both. • Strategies to improve communication between clinicians and patients. • Clinical strategies, such as delayed prescribing of antibiotics (includes various approaches, including issuing the prescription with instructions to delay, issuing a postdated prescription, and leaving prescriptions for collection), clinical prediction rules, or use of relevant point-of-care diagnostic tests. Any point-of-care tests that are available and used in primary care settings for diagnostic purposes with the ability to provide results within a reasonable period of time were included, such as inflammatory tests (e.g., procalcitonin, CRP, white blood cell); rapid multiplex PCR tests used to rule in/out organisms (e.g., rapid strep test, influenza, RSV); and routine diagnostic tests, such as chest x ray, and blood gases, when used for determining antibiotic use. • System-level strategies, such as clinician reminders (paper based or electronic), clinician audit and feedback, financial or regulatory incentives, outpatient antimicrobial stewardship programs, and pharmacist review. • Multifaceted approaches combining one or more of the above strategies.
Comparators	Different strategies for improving appropriate use of antibiotics.
	Standard care without a strategy for improving appropriate use of antibiotics.

Table A. Criteria for eligibility based on PICOTS framework (continued)

PICOTS	Criteria for Eligibility
Outcomes	**Key Question 1** Increased appropriate prescription or use of antibiotics for acute RTIs. Reduced overall prescribing or use of antibiotics for acute RTIs. **Key Question 2** Antibiotic resistance. **Key Question 3** Admission to hospital. Medical complications. Adverse drug effects, including *Clostridium difficile* infections. Mortality. **Key Question 4** Clinic visits (index, return, and subsequent episodes), ED visits. Time to return to work and/or school. Patient satisfaction. Quality of life. Improvement in patient symptoms, speed of improvement. Use of nonantibiotic treatments, such as over-the-counter medications. **Key Question 5** Intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute RTI (clinician and/or patient) or improved shared decisionmaking. **Key Question 6** Adverse effects of the strategy, such as increased time burden on clinicians, sustainability of intervention, diagnostic resource use, diagnostic coding shifts.
Timing	Any duration of followup.
Setting	Outpatient care settings, including institutional settings, emergency care settings, and other settings, such as school or workplace.
Study Designs	Systematic reviews with similar scope and search dates within past 3 years. RCTs. Prospective and retrospective cohort studies, including database studies. For areas in which such direct comparative evidence is lacking, before-after studies that used methods to control for potential confounding and studies with a time-series design that evaluated temporal trends.

CRP = C-reactive protein; ED = emergency department; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; PCR = polymerase chain reaction; RCT = randomized controlled trial; RSV = respiratory syncytial virus; RTI = respiratory tract infection

potential effect modifiers or sources of heterogeneity, which are listed in Table B.

Quality (Risk-of-Bias) Assessment of Individual Studies

The internal validity (quality) of systematic reviews, randomized controlled trials (RCTs), and observational studies was assessed based on predefined criteria established by the Drug Effectiveness Review Project.[27] All assessments were done at the overall study level and resulted in a rating of good, fair, or poor. We used a dual rating procedure for study quality in which all studies were first rated by one reviewer and then checked by another reviewer. All disagreements were resolved using a consensus process.

Data Synthesis

We used a hierarchy-of-evidence approach that focused on the best evidence for each question, organized into the five intervention categories shown previously (Table A). We synthesized outcome data quantitatively using meta-analysis to pool outcomes where appropriate. When meta-analysis was not suitable because of significant heterogeneity in design, patient population, interventions,

Table B. Potential sources of heterogeneity	
Category	**Sources of Heterogeneity**
Populations	Type of RTI, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained
Interventions	Clinician characteristics: specialty, number of years in practice, type of clinic, geographic region, and population served
	Diagnostic method or definition used
	Clinician's perception of the patient's illness severity
	Clinician's diagnostic certainty
	Local tailoring (e.g., providing intervention in languages used commonly in the local area)
	Accuracy of diagnostic tests
Outcomes	Appropriate prescription/use: definition of appropriateness
	Antibiotic resistance: data source (i.e., population vs. study sample)
Setting	Time of year; whether during a disease epidemic or outbreak period

RTI = respiratory tract infection

and outcomes, we synthesized the evidence qualitatively by grouping studies by similarity of population and/or intervention characteristics, including the sources of variation or heterogeneity listed in Table B.

For this project, one of the primary outcomes that Key Informants were interested in was improved appropriate antibiotic use. As specified in Key Question 1, we looked for studies with outcomes on appropriate antibiotic prescribing and use. However, most studies did not measure outcomes in this way, and the few studies that attempted to assess appropriate prescribing had important limitations in outcome definition and ascertainment methods, and lack of consistency in methods across studies. Similarly, very few studies measured actual use of prescribed antibiotics, and even fewer studies reported antibiotic resistance as an outcome. This left overall prescribing as the most common outcome. In order to address the concern that reductions in overall prescribing might lead to undertreatment, we report adverse events along with overall prescribing. Although no study examined all possible adverse consequences, we considered evidence suggesting no adverse consequences (equal or lower hospitalization, equal or lower return visits, equal or higher patient/parent satisfaction) as reassuring.

To present the evidence in the most useful format for decisionmakers, we grouped the interventions into four categories based on the direction and strength of evidence for benefits (prescribing and/or resistance) and adverse consequences (e.g., reconsultations). These are—

1. **Interventions with evidence of improved or reduced prescribing of antibiotics and evidence of not increasing adverse consequences:** Evidence for improving appropriate antibiotic prescribing, evidence for reducing overall prescribing or antibiotic resistance (Key Questions 1 and 2), and evidence of not causing adverse consequences (Key Questions 3–6). Within this group, interventions with the highest combined level of evidence (benefits and harms) were emphasized.

2. **Interventions with evidence of improved or reduced prescribing of antibiotics and no or insufficient evidence or mixed evidence on adverse consequences:** Evidence for improving appropriate antibiotic prescribing, evidence for reducing overall prescribing or antibiotic resistance (Key Questions 1 and 2), and either (a) no or insufficient evidence about causing adverse consequences (Key Questions 3–6) or (b) mixed evidence on adverse consequences (some showing no impact, some showing adverse impact). In either case, this group represents interventions that require further study to make a determination on their overall effect. The two situations (a) and (b) are discussed separately, as their implications for future research differ.

3. **Interventions with evidence of no effect on prescribing of antibiotics:** Evidence of not improving appropriate antibiotic prescribing, overall prescribing, or antibiotic resistance (Key Questions 1 and 2), with or without evidence on adverse consequences (Key Questions 3–6).

4. **Interventions with evidence of a negative effect on prescribing of antibiotics:** Evidence of having a negative effect on appropriate antibiotic prescribing, overall prescribing, or antibiotic resistance (Key Questions 1 and 2), with or without evidence on adverse consequences (Key Questions 3–6).

Given the large number of interventions to consider, those with insufficient evidence are not discussed in detail in this Executive Summary.

Strength of the Body of Evidence

We used methods outlined in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" to grade strength of evidence.[25,28] After consultation with the TEP members, we prioritized the following outcomes: improved appropriate prescribing (or reduced inappropriate prescribing), overall antibiotic prescribing or use, medical complications, antibiotic resistance, adverse drug effects, admission to hospital, clinic/ED visits, patient symptoms, quality of life, and adverse effects of the intervention. Domains considered in grading the strength of evidence included study limitations, consistency, directness, precision, and reporting bias, with the body of evidence assigned a strength-of-evidence grade of high, moderate, or low. In cases in which evidence did not exist, was sparse, or contained irreconcilable inconsistency, a grade of insufficient evidence was assigned.

Applicability

We assessed applicability by analyzing study eligibility criteria, characteristics of the enrolled population compared with the target population, characteristics of the interventions, comparators compared with care models currently in use, and clinical relevance and timing of the outcome measures.[29]

Peer Review and Public Commentary

The draft report was posted on the AHRQ Web site for 4 weeks to obtain public comments. A disposition of comments with authors' responses to the comments will be posted after publication of the final Comparative Effectiveness Review on the public Web site.

Results

The results of our searches and the selection of articles are summarized in the study flow diagram (Figure B). Our comprehensive searches resulted in 6,245 potentially relevant articles. Our review of abstracts led to retrieval and dual assessment of 389 full-text articles. Of those, a total of 133 studies (88 RCTs, 40 observational studies,

and 5 systematic reviews in 143 publications) met our inclusion criteria and are included in this report.
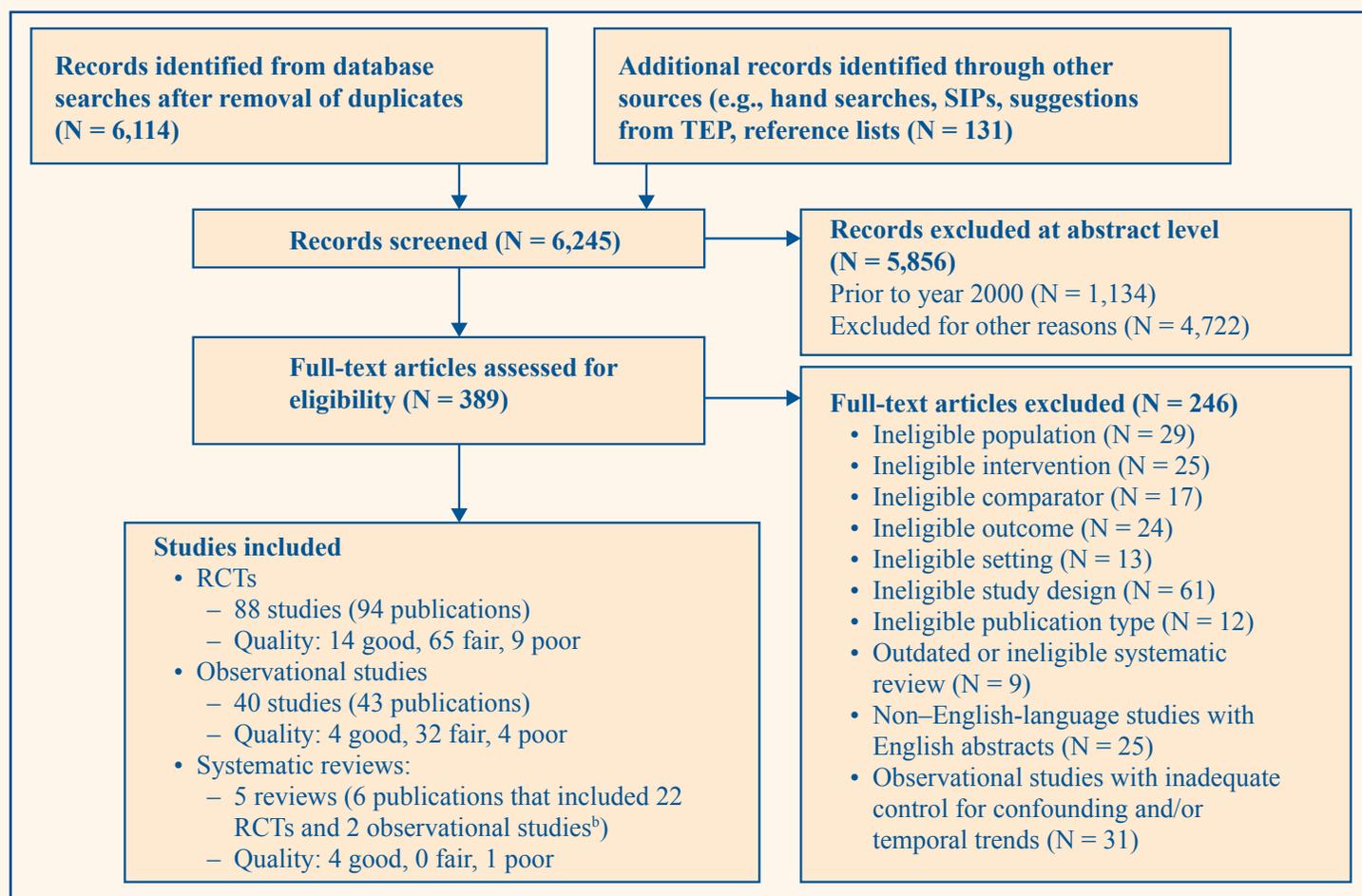
Key Findings and Strength of Evidence

The key findings of this review are based on 128 unique RCTs and observational studies, as well as 5 reviews; most of the studies and reviews were of fair quality. Key findings are summarized in Tables C, D, and E. The factors used to determine the overall strength-of-evidence grades are summarized in Appendix J of the full report. Changes in overall prescribing were reported in all studies, while attempts to measure changes in appropriate or inappropriate prescribing were reported in nine studies (7%) and antibiotic resistance was reported in one study. In addition to the sparseness of reporting on the outcome of appropriate prescribing, the few studies that attempted to assess appropriate prescribing had important limitations in outcome definition and ascertainment methods, and lack of consistency in methods across studies. Reporting on actual patient use of antibiotics was also rare; only studies of delayed prescribing report patient self-report of filling the prescription, with use assumed.

This executive summary highlights interventions based on the direction and strength of evidence for benefits (prescribing and/or resistance) and adverse consequences (e.g., reconsultations) grouped into four categories, as described in the Methods section: (1) interventions with evidence of improved or reduced prescribing of antibiotics and evidence of not increasing adverse consequences; (2) interventions with evidence of improved or reduced prescribing of antibiotics and no, insufficient, or mixed evidence on adverse consequences; (3) interventions with evidence of no effect on prescribing of antibiotics; (4) interventions with evidence of a negative effect on prescribing of antibiotics. Although we sought to determine whether strategies differed based on various patient, clinical, and contextual factors, this was not possible for any outcome because of the potential confounding influences of a wide variety of other factors. No intervention had high-strength evidence. Given the large number of interventions to consider, those with insufficient evidence are not discussed in the Executive Summary.

Evidence of Improved or Reduced Antibiotic Prescribing and No Increase in Adverse Consequences

Table C summarizes the evidence for these interventions. Four interventions (2 types of education programs, procalcitonin tests, and electronic decision support

Figure B. Results of literature searches[a]

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┌─────────────────────────────────┐    ┌─────────────────────────────────┐
│ Records identified from database│    │ Additional records identified   │
│ searches after removal of       │    │ through other sources (e.g.,    │
│ duplicates (N = 6,114)          │    │ hand searches, SIPs, suggestions│
│                                 │    │ from TEP, reference lists       │
│                                 │    │ (N = 131)                       │
└─────────────────────────────────┘    └─────────────────────────────────┘
                    │                                  │
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        ┌───────────────────────────────────┐      ┌─────────────────────────────────────┐
        │ Records screened (N = 6,245)      │─────▶│ Records excluded at abstract level  │
        │                                   │      │ (N = 5,856)                         │
        └───────────────────────────────────┘      │ Prior to year 2000 (N = 1,134)      │
                        │                           │ Excluded for other reasons          │
                        ▼                           │ (N = 4,722)                         │
        ┌───────────────────────────────────┐      └─────────────────────────────────────┘
        │ Full-text articles assessed for   │
        │ eligibility (N = 389)             │─────▶ [Full-text articles excluded box]
        └───────────────────────────────────┘
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                        ▼
        [Studies included box]
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Records screened (N = 6,245)

Records excluded at abstract level (N = 5,856)
Prior to year 2000 (N = 1,134)
Excluded for other reasons (N = 4,722)

Full-text articles assessed for eligibility (N = 389)

Full-text articles excluded (N = 246)
- Ineligible population (N = 29)
- Ineligible intervention (N = 25)
- Ineligible comparator (N = 17)
- Ineligible outcome (N = 24)
- Ineligible setting (N = 13)
- Ineligible study design (N = 61)
- Ineligible publication type (N = 12)
- Outdated or ineligible systematic review (N = 9)
- Non–English-language studies with English abstracts (N = 25)
- Observational studies with inadequate control for confounding and/or temporal trends (N = 31)

Studies included
- RCTs
  - 88 studies (94 publications)
  - Quality: 14 good, 65 fair, 9 poor
- Observational studies
  - 40 studies (43 publications)
  - Quality: 4 good, 32 fair, 4 poor
- Systematic reviews:
  - 5 reviews (6 publications that included 22 RCTs and 2 observational studies[b])
  - Quality: 4 good, 0 fair, 1 poor

RCT = randomized controlled trial; SIP = Scientific Information Packet; TEP = Technical Expert Panel
[a]Modified version of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart by Liberati et al., 2009.[30]
[b]RCTs and observational studies contained in included reviews are also included in counts of RCTs and observational studies.

systems) had moderate-strength evidence for benefits and low-strength evidence for not causing adverse consequences. These interventions had the highest levels of evidence found in this report. Additionally, public education campaigns for parents had low-strength evidence for both benefits and harms.

Education Interventions

Clinic-based education interventions for parents of pediatric patients (e.g., posters, pamphlets, interactive videos) were found to reduce overall antibiotic prescribing by more than 20 percent and were not found to increase return visits for the same episode of acute RTI (N = 2 RCTs). These interventions not only feature the ability to involve the child's own clinician but also can be customized to local language and cultural needs. Evidence for the use of public education campaigns aimed at parents combined with education interventions for clinicians also

shows some reduction in prescribing, although much smaller reductions of less than 10 percent (N = 5 RCTs). The evidence for this type of intervention shows reduction in inappropriate or increase in appropriate prescribing based on minimal definitions that varied by study (N = 1 RCT) and no negative impact on medical complications (N = 1 observational study) or patient satisfaction (N = 2 RCTs). Data were not available on antibiotic resistance. This evidence was moderate strength for benefits and low for harms.

With public education campaigns aimed at parents of young children (N = 2 observational studies), not combined with other interventions, prescribing for AOM was significantly reduced, while diagnosis of conditions considered potential complications was not increased and subsequent visits were decreased (N = 1 observational study). The strength of this evidence was low for all outcomes.

Table C. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and not causing adverse consequences

Intervention Type	Intervention (vs. Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Improved Appropriate Prescribing, Baseline or Control Group Prescribing Rate, or Resistance: Absolute Change, Relative Effect (Number of Studies), and SOE	Adverse Consequences (Number of Studies) and SOE
Education	Combined patient/parent public education campaign and clinician education	Baseline: 37% to 59% (5 RCTs) Absolute: -7.3% (95% CI, 4.0 to 10.6) (5 RCTs) Relative: OR, 0.56 (95% CI, 0.36−0.87) (2 RCTs) to OR, 0.62 (95% CI, 0.54−0.75) (5 RCTs) SOE: Moderate	Reduced inappropriate prescribing— Children with pharyngitis: Baseline: 37.1% Absolute: −10.4% Relative: OR, 0.62 (95% CI, 0.54 to 0.75) Adults with acute RTIs: Baseline: 43% Absolute: −9.7% Relative: NR (2 RCTs) SOE: Low Resistance: No evidence	No difference in AOM complications (1 observational study) SOE: Low No difference in patient or parent satisfaction (2 RCTs) SOE: Low
	Clinic-based education of parents of children up to age 14 years	Control: 40.8% (1 RCT) Absolute: -21.3% (1 RCT) Relative: pooled OR, 0.39 (95% CI, 0.26 to 0.58) (2 RCTs) SOE: Moderate	No evidence	No difference in return visits (2 RCTs) SOE: Low
	Public education campaigns for parents	Children only— Baseline: 37% to 44% Absolute: NR Relative: URTI: OR, 0.75 (95% CI, 0.69 to 0.81) AOM: OR, 0.65 (95% CI, 0.59 to 0.72) Pharyngitis: OR, 0.93 (95% CI, 0.89 to 0.97) (2 observational studies) SOE: Low	No evidence	No difference in diagnosis of complications and decrease in subsequent visits (1 observational study) SOE: Low

Table C. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and not causing adverse consequences (continued)

Intervention Type	Intervention (vs. Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Adverse Consequences (Number of Studies) and SOE
Point-of-Care Tests	Procalcitonin	Adults only— Baseline: 37% to 97% Absolute: –12% to –72% Relative: Acute RTI: OR, 0.14 (95% CI, 0.09 to 0.22) Acute bronchitis: OR, 0.15 (95% CI, 0.10 to 0.23) (1 SR of 4 RCTs) SOE: Moderate	No evidence	No difference in number of days of limited activity or missing work. or continuing symptoms at 28 days for URTI or LRTI in primary care (1 RCT) No difference in AEs/lack of efficacy (1 RCT) or hospitalizations (1 RCT) No difference in mortality or treatment failure at 30 days in: Acute bronchitis/URTI in primary care or ED; URTI or LRTI in primary care (5 RCTs) SOE: All low
Clinical	Electronic decision support	Systems with ≥50% use— Control group: 38% to 47% Absolute: –5% to –9% Relative: RR, 0.73 (95% CI, 0.58 to 0.92) (2 RCTs) SOE: Moderate	Improved appropriate prescribing for acute bronchitis and AOM— Baseline: 39% to 72% Absolute: –3% to –24% Relative: NR (2 RCTs) SOE: Moderate Resistance—no evidence	No difference in health care use or complications (e.g. diagnosis of pneumonia within 30 days) (1 RCT) SOE: Low

AE = adverse event; AOM = acute otitis media; CI = confidence interval; LRTI = lower respiratory tract infection; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; RTI = respiratory tract infection; SOE = strength of evidence; URTI = upper respiratory tract infection

Note: All populations are adults and children with acute RTI unless otherwise specified.

Point-of-Care Tests

Point-of-care tests are meant to be a rapid way to determine the likelihood that a given patient has a particular type of bacterial or viral infection, or to determine if an infection is more likely to be bacterial rather than viral. Procalcitonin was the only point-of-care test with evidence of benefit, and this benefit was restricted to adults. Use of the test in the ED or outpatient setting as a tool to help determine the need for an antibiotic resulted in reduced overall prescribing, with a fairly wide range in absolute reductions related to a wide variation in baseline prescribing (N = 1 SR of 4 RCTs). There was no negative impact on days missing work or with limited activity, symptom duration, hospitalizations, or a combined outcome of adverse events and efficacy (N = 1 RCT). Data were not available on appropriate antibiotic prescribing or on antibiotic resistance. Currently available procalcitonin tests require a number of hours, so results are not returned rapidly. This evidence was moderate strength for benefits and low for harms.

Electronic Decision Support Systems

Electronic decision support helped to reduce antibiotic prescribing for acute RTI, although the decrease was less than 10 percent and reductions were associated with higher level of use of the system (i.e., used in >50% of cases) (N = 2 RCTs). However, there was also evidence that use of these systems can improve appropriate prescribing (N = 2 RCTs) without affecting health care use or complications (N = 1 RCT). Data were not available on antibiotic resistance. This evidence was moderate strength for benefits and low for harms.

Evidence of Improved or Reduced Antibiotic Prescribing and No, Insufficient, or Mixed Evidence on Adverse Consequences

Some interventions had evidence of improving prescribing but either lacked any evidence on the impact on adverse consequences, had insufficient evidence on such outcomes, or had mixed evidence on adverse consequences (i.e., evidence of not impacting some outcomes but worsening others) (Tables D and E). This leaves important gaps in the evidence base and requires further study. For example, rapid strep testing for sore throat has moderate-strength evidence of large reductions in overall prescribing (N = 3 RCTs) and some evidence of improvement in appropriate prescribing (N = 1 RCT) compared with usual care but no evidence for other outcomes such as return visits or other adverse consequences (Table D). Rapid multiviral point-of-care testing in adults had low-strength

evidence of improving prescribing outcomes compared with usual care but no evidence on adverse consequences. Combining education for patients and providers with practice profiling (audit and feedback) and academic detailing (face-to-face education specific to the provider's profile) (N = 3 observational studies) led to reduced prescribing for bronchitis (low-strength evidence), but evidence on reconsultation visits was insufficient (N = 1 observational study).

Some other interventions had evidence of a benefit in prescribing but also had mixed evidence on adverse consequences associated with their use (Table E). We did not attempt to weigh the various adverse consequences against the benefits of improved antibiotic prescribing because the balance depends on clinical, economic, and patient values. However, by setting the outcomes out clearly, we hope to help decisionmakers form a judgment appropriate to their context.

Communication Training

Interventions to improve clinicians' ability to communicate with patients on decisions regarding antibiotic prescribing resulted in reductions in overall prescribing that ranged from relatively small (<10%) to fairly large (>25%) (N = 5 RCTs). Evidence on reconsultations, patient satisfaction, and hospitalizations was insufficient. Evidence on symptom improvement was conflicting, with slightly longer duration of symptoms (N = 3 RCTs) with the communication training group but better ratings of health at 2 weeks (N = 1 RCT) compared with usual care (low-strength evidence).

Delayed Prescribing

There are multiple methods of implementing delayed prescribing, as well as multiple possible comparison groups. Delayed prescribing (any method) resulted in moderate-strength evidence of large reductions in use of antibiotics compared with immediate prescribing (N = 6 RCTs). The comparison for delayed prescribing is not with usual care, in which some patients get a prescription, some do not, and some may get a delayed prescription. Hence, the reductions seen based on the delayed prescribing comparison cannot be compared with the evidence on other interventions (for which the comparison is usual care). A single study reported on patient-level antibiotic resistance, finding a lower rate with delayed prescribing. Although data were not available on appropriate antibiotic prescribing, delayed prescribing also had the benefit of reducing the incidence of antibiotic-associated diarrhea (N = 2 RCTs). While this evidence showed no impact on reconsultations (N = 4 RCTs), there

Table D. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and no or insufficient evidence on adverse consequences

Intervention (vs. Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Adverse Consequences (Number of Studies) and SOE
Streptococcal antigen testing (rapid strep testing)	Baseline: 58% to 72% Absolute: −20% to −52% Relative: NR (3 RCTs) SOE: Moderate	Inappropriate prescribing— Baseline: 60% Absolute: −33% Relative: NR (1 RCT) SOE: Low	NR
Rapid viral testing (multiviral PCR), adults	Baseline: NR Absolute: -7.8%; p <0.01 Relative: NR (1 RCT) SOE: Low	NR	NR
Provider and patient education + practice profiling + academic detailing	Acute bronchitis— Baseline: 21% to 88% Absolute for acute bronchitis: -24% to -26% Relative: NR (3 observational studies) SOE: Low	NR	Return clinic visits (1 observational study) SOE: Insufficient

NR = not reported; PCR = polymerase chain reaction; RCT= randomized controlled trial; RTI = respiratory tract infection; SOE = strength of evidence

Note: All populations are adults and children with acute RTI unless otherwise specified.

was evidence of a decrease in patient satisfaction (N = 5 RCTs) and an increase in persistence of symptoms (N = 2 RCTs), adverse consequences that need to be balanced against benefits.

C-Reactive Protein (CRP)

Use of the CRP test has been shown to reduce overall prescribing for acute RTIs (N = 7 RCTs), although the absolute reductions range very widely and depend in part on the baseline prescribing rate. The evidence also indicates an increase in reconsultations within 4 weeks (N = 3 RCTs) but no effect on symptom resolution or use of chest x rays (N = 2 to 4 RCTs). Evidence on the impact on hospitalizations is less clear: five studies reported none within 30 days, and two reported higher, but not statistically significant, frequency in the CRP groups. Together, we found this to be low-strength evidence of a potential increase in risk of hospitalization within 1 month. Studies were not combinable; therefore, this evidence was low strength for a small absolute increase in risk.

Combined Interventions

There is moderate-strength evidence that clinician communication training combined with CRP testing (N = 2 RCTs) resulted in a fairly large reduction in overall prescribing (>25%) compared with usual care. There was no impact on reconsultation, diagnostic testing use, or days off work, but increased hospitalizations at 1 month (pooled unadjusted odds ratio [OR], 4.65; 95% confidence interval [CI], 1.21 to 17.87) and duration of symptoms. While these differences were statistically significant, the absolute differences were small (1.1% vs. 0.2% hospitalization at 30 days; 5 vs. 6 days symptom duration). The reasons for even a small increased risk of hospitalization were unclear in these two trials with over 4,000 patients.

Evidence of No Effect on Antibiotic Prescribing

Four interventions had evidence of no impact on overall prescribing: (1) clinic-based education for parents of children 24 months of age or younger with AOM

Table E. Interventions with evidence of improved or reduced prescribing for acute RTI but mixed evidence of adverse consequences

Intervention	Reduced Overall Prescribing: Baseline Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Other Benefits (Number of Studies) and SOE	Adverse Consequences (Number of Studies) and SOE
Delayed vs. immediate prescribing	Baseline: 82% to 100% Absolute: -34% to -76% Relative: OR range, 0.00 to 0.12 (6 RCTs) SOE: Moderate	Appropriate prescribing: no evidence Reduced multidrug resistance for *S. pneumonia* strains in AOM (1 RCT) SOE: Low Reduced diarrhea in AOM (2 RCTs) SOE: Low	No difference in reconsultation (4 RCTs) SOE: Moderate Reduced satisfaction (5 RCTs) SOE: Moderate Increased persistence of moderate to severe symptoms (2 RCTs) SOE: Low
CRP vs. usual care	Baseline: 46% to 91% Absolute: -1.9% to -33.5% Relative: RR, 0.73 (95% CI, 0.60 to 0.90) (7 RCTs) SOE: Moderate	No evidence	Increased reconsultation within 4 weeks (3 RCTs) SOE: Moderate Potentially increased risk of hospitalization at 30 days: 0 events in 5 RCTs but greater in 2 RCTs (not SS) SOE: Low No impact on symptom resolution (4 RCTs) SOE: Low
Provider communication training + CRP testing vs. usual care	Baseline: 59% Absolute: −28% Relative: OR, 0.30 (95% CI, 0.26 to 0.36) (2 RCTs)SOE: Moderate	No evidence	Increased days of moderately bad symptoms (1 RCT) Potential increased risk of hospital admissions (2 RCTs) No difference in reconsultation, diagnostic testing use, or days off work (1 RCT) SOE: Low
Communication training for clinicians vs. usual care	Baseline: 27% to 79% (4 RCTs) Absolute: range, -9.2% to -26.1% Relative: RR range, 0.69 to 0.17 (5 RCTs) SOE: Moderate	No evidence	Conflicting evidence on symptom improvement: slightly longer duration of symptoms (3 RCTs) but better ratings of health at 2 weeks (1 RCT) SOE: Low

AOM = acute otitis media; CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; RTI = respiratory tract infection; SOE = strength of evidence; SS = statistically significant

Note: All populations are adults and children with acute RTI unless otherwise specified.

(N = 1 RCT; moderate-strength evidence); (2) clinician education combined with audit and feedback (N = 2 RCTs; low-strength evidence); (3) point-of-care testing for influenza in children (N = 1 SR of 4 RCTs; moderate-strength evidence); and (4) tympanometry point-of-care testing in children (N = 1 RCT; low-strength evidence). For influenza testing, this finding was not surprising, as clinicians were likely using the test to confirm suspected viral illness. The lack of efficacy of a parent education program for children with AOM or clinician education combined with audit and feedback was more surprising.

Evidence of a Negative Effect on Antibiotic Prescribing

Evidence in children showed that use of the adult algorithm for procalcitonin results in increased prescribing of antibiotics and a related increase in adverse events (N = 1 RCT). This suggests that procalcitonin should not be used to guide antibiotic prescribing in children without further study.

Head-to-Head Comparisons of Interventions

Single Interventions

The evidence from studies that directly compared different interventions with each other was sparse, and few studies reported outcomes other than prescribing of antibiotics. Three comparisons of single interventions found little or no difference between them.

Delayed Prescribing Strategies. Three studies comparing different methods of delaying prescribing found no difference in effect on overall antibiotic prescribing and similar rates of diarrhea or rash, duration of moderately bad symptoms, reconsultations, or satisfaction. However, reports of vomiting and abdominal pain were more frequent for giving prescriptions with instructions to delay versus leaving prescriptions for collection or requesting recontact (moderate-strength evidence).

Delayed Prescribing Versus Clinical Score. For sore throat, a study found a small reduction in overall prescriptions (<10%) and 1 fewer day of moderately bad or worse symptoms with use of a clinical score called FeverPAIN than with delayed prescribing (low-strength evidence).

Education Versus Communication Training for Clinicians. Low-strength evidence (N = 2 RCTs) showed no difference in overall or appropriate (according to guidelines) antibiotic prescribing between a clinician education intervention and a clinician communication training intervention.

Communication Training for Clinicians Versus CRP Testing. In two similar studies using a factorial design to compare communication training for clinicians, CRP testing, and the combination, there were different results for communication training alone than for CRP testing alone. A more intensive communication training program resulted in no difference in prescribing compared with CRP testing alone, while a less intensive program resulted in a lower rate of prescribing than use of CRP testing alone. There were no differences in return clinic visits or rate of improvement of symptoms.

Augmentation of Interventions (Two Versus Single Interventions)

Communication Training for Clinicians. In a trial of communication training combined with clinician education compared with education alone, there was no difference between groups in the proportion of antibiotics that were prescribed according to guidelines for acute RTI.

Point-of-Care Tests. Limited evidence on the addition of a point-of-care test to another intervention found that the combination resulted in less prescribing than the single intervention.

Rapid Streptococcus Antigen Testing. Moderate-strength evidence showed that the rapid strep test combined with a clinical score used as a decision rule (N = 2 RCTs) was superior to the decision rule alone in reducing overall prescribing, but no other outcomes were studied. Low-strength evidence also showed that the combination of a rapid strep test and a decision rule was superior to the decision rule alone (N = 1 RCT) in reducing overall antibiotic prescribing. Also, the combination of rapid strep testing and a clinical score was superior in reducing overall prescribing when compared with delayed prescribing (N = 1 RCT) (low-strength evidence).

C-Reactive Protein Testing. Based on two similar trials, communication training for clinicians combined with CRP testing showed a reduction in prescribing for acute RTIs compared with communication training alone (OR, 0.67; 95% CI, 0.56 to 0.78). The combined OR for hospitalization was 2.17 (95% CI, 0.85 to 5.50), indicating a potential increase with the combined intervention, but was not statistically significant. As noted previously for the comparison of the combination with usual care, the reasons for the small absolute increase in risk of hospitalization were unclear in this study of over 4,000 patients. The combination of communication training and CRP testing was not different from CRP testing alone in overall antibiotic prescribing, hospitalizations, duration of symptoms, reconsultations,

days off work, or diagnostic test use. Low-strength evidence (N = 1 observational study) showed that adding CRP testing to patient and clinician education resulted in lower prescribing for rhinosinusitis, bronchitis, and pharyngitis. Low-strength evidence (N = 1 RCT) showed no difference between CRP testing combined with a clinical algorithm and the algorithm alone in overall antibiotic prescribing.

Differences in Outcomes According to Potential Moderators of Effect

Methods for Assessing Appropriate Prescribing

The methods for assessing appropriate prescribing fell into three categories: (1) ICD-9 (International Classification of Diseases, Ninth Revision) codes or diagnostic category, (2) adherence to a specific guideline's recommendations for antibiotic prescribing, and (3) duration of symptoms for pharyngitis or sinusitis. Although we sought to assess whether the definition of appropriateness affects the apparent effectiveness of interventions, this was not possible because of the potential confounding influences of a wide variety of other factors.

Intended Target of Intervention

The intended target of the interventions varied in the education interventions, in which the reductions in prescribing were greater when the target was the patient or parent and somewhat less when the target was the clinician or combined groups. Direct comparisons were not available, and the ranges in rates of reduction overlapped across the groups such that a clear pattern could not be established. However, it was clear that combining patient and clinician education did not result in clearly greater reductions. Clinical outcomes, including patient or parent satisfaction, were not significantly affected by the identity of the target. With interventions aimed at improving communication, only clinician-targeted interventions were found to have beneficial effects, although the patient-targeted evidence was very limited. Other interventions were either aimed only at clinicians (e.g., point-of-care tests) or always included both clinicians and patients (e.g., delayed prescribing).

Specific Acute Respiratory Tract Infections

The results for studies that either enrolled patients with specific acute RTIs or reported results stratified by type of RTI are presented in Table F. Interventions with mixed results by RTI type were patient education (with evidence of effectiveness for pharyngitis but not for AOM), clinician education (with evidence of effectiveness in AOM and pharyngitis but not sinusitis), combined patient and clinician education (with evidence of effectiveness in bronchitis but mixed evidence for pharyngitis and sinusitis), and the addition of clinician communication training to guideline education (which was found effective for sinusitis but not for bronchitis). Three interventions were found to have a significant effect in improving antibiotic prescribing across three RTI types: electronic decision support and two multifaceted interventions. Both involved clinician and patient education, but one added CRP testing and the other added practice profiling. We had no evidence on the effect of other patient characteristics on any outcome (i.e., nature and duration of signs and symptoms, previous medical history [e.g., frailty, comorbidity], prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained).

Seasonal Influences

Most of the studies were timed for the season with highest prevalence of disease, mainly winter months, and no clear pattern could be discerned in the results based on this factor. Local tailoring was typically done for educational interventions (e.g., using ethnically sensitive materials). Comparisons of no tailoring versus tailoring or between degrees or methods of tailoring were not possible because of the wide variation in the combinations of specific intervention details, population, and outcome measurement across studies.

Baseline Prescribing Rates

A key background factor may be baseline prescribing rates. Baseline prescribing rates varied extremely widely across studies (from a low of <10% to >90%). In some situations, the background prescribing rate was declining during the study period. While it is likely true that baseline prescribing rates influence the impact of interventions to reduce antibiotic prescribing, the poor reporting of this information severely limits the ability to analyze the potential impacts. Other background contextual factors—known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak) or system-level characteristics—were not studied explicitly and were reported inadequately to allow analysis.

We did not find evidence on other factors as potential effect modifiers (i.e., clinician characteristics such as specialty or number of years in practice, type of clinic organization, geographic region, population served, diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty).

Table F. Effectiveness of interventions in improving antibiotic prescribing by type of respiratory tract infection				
Intervention Category	Acute Otitis Media	Bronchitis	Pharyngitis	Sinusitis
Patient and education clinician		+	Mixed	Mixed
Patient education	-		+	
Clinician education	+		+	-
Electronic decision support	+	+	+	
Delayed prescribing	+			
CRP testing				+
Procalcitonin testing		+		
Rapid strep testing			+	
Combination of patient and provider education plus audit and feedback			a	
Combination of physician education, patient education, and audit and feedback		+	+	+
Combination of physician and patient education plus CRP test		+	+	+
Adding clinician communication training to clinician education		-		+
Adding an educational leaflet for patients to a suggestion to delay prescription filling		+		

CRP = C-reactive protein

a Ineffective in children with pharyngitis.

+ means at least low-strength evidence of effectiveness; - means at least low-strength evidence of ineffectiveness; blank cells mean evidence not reported by diagnosis.

Discussion

Findings in Relationship to What Is Already Known

A number of existing systematic reviews and guidelines have contributed to our understanding of what works for targeted populations, interventions, or diseases. The reviews are generally narrowly focused on specific types of interventions, but broadly they have concluded that multifaceted education interventions, clinician education, delayed prescribing, CRP, and procalcitonin testing may be effective in certain settings.[15-18,21,31-35] Our conclusions overlap with these findings but are not identical in that our results add evidence on more point-of-care tests and electronic decision support, as well as concluding that clinician education alone does not currently show benefit. Reasons for these differences include the addition of a large volume of newer evidence, the use of a formal system to grade the strength of the evidence, and the scope of interventions considered (e.g., point-of-care tests). However, a very recent systematic review of outpatient antimicrobial stewardship programs that had a broader scope than this review (including cost outcomes, antibiotic selection outcomes, and a broader range of diagnoses) had similar findings for several interventions: education, delayed prescribing, communication training, electronic

decision support, audit and feedback, and point-of-care testing.[36]

Specific interventions that have been recommended by professional organizations and societies include delayed prescribing for children with nonsevere symptoms and persistent sinusitis (American Academy of Pediatrics), patient and family education for uncomplicated acute bronchitis (Michigan Quality Improvement Consortium [MQIC] and the American College of Chest Physicians), and rapid strep testing for pharyngitis (MQIC and the Infectious Disease Society of America). Our findings expand on the evidence used to create these recommendations.

Applicability

Table G summarizes the applicability of the evidence within the elements of the PICOTS framework.

Implications for Clinical and Policy Decisionmaking

In an effort to appropriately reduce prescribing of antibiotics for acute RTIs, clinicians and policymakers need to make choices among the relevant interventions based on the best evidence, taking into account the characteristics of the setting in which the intervention

Table G. Summary of applicability

Element		Details
Population	Patients	Almost half of studies were conducted in pediatric populations (45%; mean age, 4 years), with the remainder split between adult populations (27%; mean age, 44 years) and mixed-age populations (28%; mean age, 33 years).
		In 62% of studies, patients had any acute RTI; in 41%, patients had pharyngitis or sore throat; in 30%, they had otitis media; and in 20−23%, they had cough or the common cold, sinusitis, or acute bronchitis.
	Clinicians	Of clinicians, 95% were in primary care (14% in emergency departments).
Intervention	Education	Education varied widely in method, duration, intensity, and local tailoring.
	Communication	Communication varied from in-person to online methods and varied in intensity and duration.
	Delayed prescribing	Methods varied widely—leaving the decision to the patient, requiring the patient to return to the clinic, or other methods.
	Point-of-care testing	CRP algorithms varied across studies. Procalcitonin algorithms were consistent across studies. Rapid viral tests included one that was multiviral, and the rest were specific for influenza. When reported, diagnostic accuracy was consistent for rapid viral and strep tests.
	System level	Computer decision support tools were somewhat variable, with some requiring active clinician access, while others used a pop-up screen.
	Multifaceted	Multifaceted interventions most often included some form of education and/or communication training combined with other interventions.
Comparators		Most often, the comparison was with usual care, but most studies of delayed prescribing compared it with immediate or no prescribing. There were few head-to-head trials of competing interventions.
Outcomes		Most studies focused on overall prescribing, with few studies reporting on appropriate prescribing and resistance or on the clinical consequences of reduced prescribing. Those that did used inconsistent definitions and methods.
Timeframes and settings		Of the studies, 52% were conducted in European countries, where some form of nationalized health care is common. This is an issue because the baseline or background prescribing rate varies by country, and the health care systems, cultural attitudes, and behaviors of clinicians and patients may vary enough to reduce the generalizability of the findings to a U.S. population.
		Most studies evaluated outcomes only over a single season. Public education campaigns are the only intervention type that evaluated outcomes over multiple seasons.

CRP = C-reactive protein, RTI = respiratory tract infection

is to be applied. Although the ultimate goal is reducing antibiotic resistance while not adversely affecting clinical outcomes, antibiotic resistance was rarely studied. Although the most logical primary outcome would be changes in appropriate antibiotic use, appropriateness too was understudied. Therefore, it was necessary to consider the most widely studied, but proxy, outcome of overall prescribing to evaluate effectiveness. However, the reliability and validity of overall prescribing as a proxy for appropriate prescribing may vary because the ratio of inappropriate to appropriate prescribing can range widely based on patient, provider, and setting. Although the best

evidence to date supports the use of four interventions from all categories outlined in this report (2 types of education interventions, electronic decision support, and procalcitonin), the benefit is likely to vary from situation to situation. Furthermore, these interventions have varying resource use in both implementation and maintenance, and evidence on sustainability is not available. Unfortunately, the evidence was inadequate to guide selection of the best intervention for a given setting or patient population.

Elements that could be considered in making decisions about implementation include the ability to tailor the intervention to local situations. With combined patient

and clinician education programs, patient education can be simple and tailored—for example, waiting room posters featuring a letter from a local clinician. Clinician education interventions should be locally tailored and balance intensity with clinician ability and willingness to participate.

Electronic decision support systems have been shown to improve prescribing for bronchitis and AOM, and may be easily implementable in electronic medical record systems. The resources required to initiate a program and for clinicians to use such systems have not been studied, but ease of use (i.e., pop-up systems that do not require clinicians to seek out the information) may be key to ensuring adequate levels of use to result in benefit.

While rapid strep testing is the standard of care in assessing the need for antibiotics for sore throat, evidence did not support the regular use of viral testing as a way to improve prescribing of antibiotics at this time. For procalcitonin, there was agreement across algorithms in terms of thresholds for antibiotic prescribing, but the thresholds were developed for use in adults and their use in children led to increased antibiotic prescribing.

Limitations of the Review Process

Potential limitations include the exclusion of non–English-language publications, aspects of literature search strategies, and exclusion of observational studies that did not control for either potential confounding or temporal trends. However, examination of the non-English studies that had English abstracts did not identify inconsistencies in findings, suggesting that this is not a significant concern. Since no standard search terms uniformly cover all interventions and outcomes of interest, it is possible we were unable to identify all potentially relevant studies; however, our TEP members and reference lists of previously published systematic reviews were particularly useful in identifying additional citations for consideration. There was limited ability to assess potential publication and reporting bias because of the few opportunities to pool studies and the lack of availability of study protocols.

Gaps in the Evidence Base

The biggest gaps in evidence were reporting on resistance to antibiotics and use of a consistent definition of appropriate prescribing, the two most relevant outcomes for this topic. The few studies that reported appropriate prescribing had important limitations in outcome definition and ascertainment methods, and lack of consistency in methods across studies. The methods fall into three categories: ICD-9 codes or diagnostic category, adherence

to a specific guideline's recommendations for antibiotic prescribing, and duration of symptoms for pharyngitis or sinusitis. None of the studies provided detailed information on how the information was obtained or assessed. Dependence on ICD-9 codes alone is a limited approach in that patient-level characteristics that may indicate the need for antibiotic therapy are not assessed. Use of a guideline to determine appropriateness of prescribing is also limited in that the determination of whether a decision adhered to the guideline is subjective and requires both access to adequate patient-level data and clinical knowledge. While the duration of symptoms beyond a suggested cutoff may be an indicator for when antibiotics are needed, this information alone is inadequate to make a precise determination.

For overall prescribing outcomes, our ability to judge the meaningfulness of the reductions was limited because of a general lack of established parameters for minimally important difference. There was also limited and inconsistent reporting on adverse clinical outcomes, hampering assessment of benefit and adverse consequences. We also could not assess how to optimize use of effective interventions because of the lack of sufficient detail on potential effect modifiers (e.g., patient, clinician, setting characteristics). Since individual interventions have been previously shown to have some benefit in reducing unnecessary antibiotic prescribing for acute RTI, the concept of multifaceted interventions holds promise for improved outcomes with greater magnitude of effect. However, the consistency of multifaceted interventions is largely unknown, and collectively they do not provide a cohesive picture of effectiveness because most studies represent a "one-off" intervention that could not be combined. In studies that measured adverse consequences, there was rarely adequate statistical power to identify statistically significant differences and no consensus about what constitutes an important difference (clinically, economically, or from the patient's perspective).

The potential for increased risk of hospitalization within 1 month of the index visit found with CRP testing, communication training, and their combination is concerning and deserves further scrutiny (Table H). The evidence of potential increased risk comes largely from three trials: a single, large (N = 4,264), fair-quality factorial-design trial of CRP testing, communication training, or their combination conducted in clinics; a smaller (N = 431) study with similar design; and a small study of CRP testing only, conducted in EDs (N = 139). The larger multifactorial study presented an analysis

Table H. Risk of hospitalization at 1 month after index visit

Intervention Versus Usual Care	Study	Incidence	Relative Risk (95% Confidence Interval)
CRP testing	Little, 2013[37]	1% vs. 0.2%	Adjusted 2.91 (0.96 to 8.85)
	Gonzales, 2011[38]	6% vs. 3%	1.77 (0.34 to 9.30)
	Aabenhus, 2014[22]	5 studies = 0 events	Not estimable
Communication training	Little, 2013[37]	0.5% vs. 0.2%	2.35 (0.48 to 11.60)
Combination of CRP testing and communication training	Little, 2013[37] Cals, 2011[39]	1.1% vs. 0.2%	Pooled (unadjusted) 4.65 (1.21 to 17.87)

CRP = C-reactive protein, EPC = Evidence-based Practice Center

considering CRP test use with or without communication training compared with usual care or communication training alone. After adjusting for potential confounders, this study found a non–statistically significant increased risk with use of CRP testing (22 vs. 8 events). An analysis of only CRP use versus only usual care was not done. The small study of only CRP testing found a similar non–statistically significant increased risk; however, in five other studies there were no hospitalizations in either group. These studies were not pooled because of clinical and methodological differences between studies.

Based on events reported in the larger study, communication training also resulted in a non–statistically significant increase in risk of hospitalization within a month. For the combination of CRP testing and communication training, reported in two similar multifactorial trials, we found a statistically significant increased risk, although this pooled estimate was unadjusted for potential confounders.

The reasons for a potential increased risk of hospitalization are unclear because the studies were not designed to examine this outcome in depth. Since the absolute numbers of events were low, the estimates are likely to be unstable and could change with additional data.

Finally, with only 45 percent of studies conducted in the United States, there may be concern about whether evidence generated in other cultures and health care systems is applicable to U.S. settings. Differences in effect were not seen where similar studies were conducted in U.S. and non-U.S. settings.

Future Research Needs

Based on the gaps and weaknesses identified through the systematic review of the literature, the following areas present an opportunity for new research to support health care decisions. All studies of interventions to improve appropriate antibiotic prescribing in acute RTIs should have the study design and reporting features identified in Table I.

Conclusions

The best evidence supports the use of specific education interventions for patients/parents and clinicians, procalcitonin testing in adults, and electronic decision support to reduce overall antibiotic prescribing (and in some cases, improve appropriate prescribing) without causing adverse consequences, although the reduction in prescribing varied widely. Additionally, public parent education campaigns had low-strength evidence of reducing overall prescribing, not increasing diagnosis of complications, and decreasing subsequent visits. Other interventions had evidence of improved prescribing, but evidence on adverse consequences was lacking (streptococcal antigen testing, rapid multiviral testing in adults), insufficient (clinician and patient education plus audit and feedback plus academic detailing), or mixed (delayed prescribing, CRP testing, clinician communication training, communication training plus CRP testing). Interventions with no impact on antibiotic prescribing were clinic-based education for parents of children 24 months of age or younger with AOM, point-of-care testing for influenza or tympanometry in children, and clinician education combined with audit and feedback. Furthermore, limited evidence suggested that using adult procalcitonin algorithms in children is not effective and results in increased antibiotic prescribing. Future studies should use a complex intervention framework and better evaluate measures of appropriate prescribing, adverse consequences such as hospitalization, sustainability, resource use, and the impact of potential effect modifiers.

Table I. Future research recommendations based on evidence gaps

Evidence Gap	Recommendation
Study design and reporting	Most studies in this area can be randomized, and in such cases, cluster randomization should be used.
	Nonrandomized studies must adhere to the best methods, particularly using methods to control for potential confounding.
	Future systematic reviews should be comparative. Several interventions are now known to improve overall antibiotic prescribing, specifically for acute RTIs, such that the questions now include how competing interventions compare with each other. All relevant and reasonable interventions that might be considered should be included.
	To ensure better reporting of important details about methods and PICOTS characteristics, we encourage increased adherence to standardized reporting guidelines, such as the TIDieR extension of CONSORT and STROBE for nonrandomized studies
Interventions and comparators	Interventions and comparators should include competing interventions from the best ones identified in this report rather than designing a new intervention each time a study is undertaken. When developing new interventions, consider evidence on what has and has not worked to date.
	Studies of procalcitonin point-of-care tests in children with acute RTIs in primary care are needed after an algorithm specific to this population has been developed.
	Studies comparing combined patient and clinician education, communication training, delayed prescribing, point-of-care tests, electronic decision support, and combined communication training and CRP testing should be undertaken. Delayed prescribing should also be compared with usual care.
	Studies of multifaceted interventions, using components of the interventions noted in this report to be effective and having adequate design and sample size, should be undertaken.
Outcome measures	The lack of consensus on how to define and measure appropriate antibiotic prescribing and use needs to be resolved. The definition needs to be clinically defensible; the ascertainment of this outcome needs to include some level of chart review. Measuring change in actual antibiotic use, rather than antibiotic prescribing only, is preferable.
	Clinical outcomes and adverse consequences of the competing interventions in addition to benefits should be measured.
	Resistance should be measured as an outcome. Because culture and sensitivity testing is rarely routinely performed in outpatient settings, we recognize that there are major practical challenges with researching resistance, including that it would require years of additional funding and long-term monitoring. However, we still recommend that, under ideal circumstances, measuring an intervention's impact on resistance would be very useful.
	Sustainability of interventions shown to be effective needs to be studied, including what happens if and when the intervention is withdrawn and effects of time and changing baseline prescribing rates.
Analysis	Background contextual factors must be reported and considered, particularly baseline prescribing rates for particular acute RTIs.
	Patient and provider characteristics should be reported more clearly and analyzed as effect modifiers.
	Methods for studying complex interventions should be applied to future research to address issues such as intervention setting characteristics; variability of interventions across studies and time, particularly multifaceted interventions; and generalizability of interventions and results.[40]
	Multifaceted interventions should be studied as systems, and issues of generalizability of the intervention system should be considered.

CONSORT = Consolidated Standards of Reporting Trials; CRP = C-reactive protein; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RTI = respiratory tract infection; STROBE = STrengthening the Reporting of OBservational studies in Epidemiology; TIDieR = Template for Intervention Description and Replication

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Full Report

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