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Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review

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Abstract

Objective: Antibiotic overuse contributes to antibiotic resistance and adverse consequences. Acute respiratory tract infections (RTIs) are the most common reason for antibiotic prescribing in primary care, but such infections often do not require antibiotics. We summarized and updated a previously performed systematic review of interventions to reduce inappropriate use of antibiotics for acute RTIs.

Methods: To update the review, we searched MEDLINE®, the Cochrane Library (until January 2018), and reference lists. Two reviewers selected the studies, extracted the study data, and assessed the quality and strength of evidence.

Results: Twenty-six interventions were evaluated in 95 mostly fair-quality studies. The following four interventions had moderate-strength evidence of improved/reduced antibiotic prescribing and low-strength evidence of no adverse consequences: parent education (21% reduction, no increase return visits), combined patient/clinician education (7% reduction, no change in

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complications/satisfaction), procalcitonin testing for adults with RTIs of the lower respiratory tract (12%–72% reduction, no increased adverse consequences), and electronic decision support systems (24%–47% improvement in appropriate prescribing, 5%–9% reduction, no increased complications).

Conclusions: The best evidence supports use of specific educational interventions, procalcitonin testing in adults, and electronic decision support to reduce inappropriate antibiotic prescribing for acute RTIs without causing adverse consequences.

Keywords

Antibiotics, resistance, overuse, review, acute respiratory tract infections, adverse consequences

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Introduction

Antibiotic resistance is a serious public health problem. In the United States, approximately 23,000 people die of antibiotic-resistant infections every year.[1] Although the reasons for increasing antibiotic resistance are multifactorial, including the use of antibiotics in livestock and underdevelopment of new antibiotics, a key factor is outpatient antibiotic overuse.[1] Research has shown that a multitude of diverse factors may influence overuse of antibiotics for acute respiratory tract infections (RTIs), including location, environment (i.e., clinic type, time, and resources), patient demographics, patient and/or clinician preferences, clinician specialty and experience, and clinician–patient communication and shared decision-making.[2–4] Hence, studies on reducing inappropriate antibiotic use for acute RTIs have employed a variety of approaches and have targeted various factors. In this review, we categorized studies according to their approach and intended target. Interventions to improve antibiotic use are intended to achieve a variety of outcomes, including slower development of antibiotic resistance, decreased use of any antibiotic in situations for which antibiotics are not effective, increased use of a recommended antibiotic when one is indicated, fewer adverse drug events, and decreased healthcare costs. However, these positive effects should not come at the expense of under-treatment of patients who truly need antibiotics, potentially increasing the risk of undesirable outcomes ("adverse consequences") such as hospitalization, medical complications, additional clinic visits, time off of work and/or school, patient dissatisfaction, or a longer symptom duration. Adverse consequences can also occur for patients whose condition is unlikely to require antibiotics for resolution; for example, patients expecting a prescription may be disappointed and even seek care elsewhere. Clinicians may also experience adverse consequences from an intervention (e.g., electronic medical record alert fatigue or increased time required to participate in trainings). Although the weight or value of specific adverse consequences varies according to the perspective, such consequences must be taken into account when assessing the impact of an intervention aimed at reducing antibiotic use.

The best settings for such interventions may be those in which there is a high prevalence of the disease, antibiotics are commonly prescribed, and there is a reasonably

high risk of prescribing an antibiotic when one is not warranted. Acute RTIs, which include a broad group of diagnoses such as bronchitis and acute otitis media, are highly prevalent, frequently do not require an antibiotic (i.e., are self-limiting infections or are caused by viral infections),[5] and are the most common reason for antibiotic prescriptions in the primary care setting. Acute RTIs account for approximately 70% of primary diagnoses in adults presenting for ambulatory care office visits with a chief symptom of cough.[6] A 2013 report regarding healthy adults visiting outpatient offices and emergency departments for acute bronchitis revealed that prescriptions for antibiotics were given at 73% of visits from 1996 to 2010[7] despite the fact that most cases of acute bronchitis are caused by viral pathogens for which antibiotics are not helpful. Similarly, a 2014 analysis of data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey indicated that 60% of children diagnosed with pharyngitis in the United States from 1997 to 2010 were prescribed antibiotics[8] despite the fact that only about 37% of pharyngitis episodes are caused by bacteria. It must be assumed that some antibiotics prescribed in these studies were unnecessary (i.e., inappropriate).

In this report, we summarize and update a large, complex comparative effectiveness review (CER) of the evidence of effectiveness of all potential interventions designed to reduce inappropriate antibiotic use for acute RTIs while not causing adverse consequences. Prior reviews have not covered all possible interventions (including the rapidly developing area of point-of-care diagnostic tests), nor have they considered both benefits and potential adverse consequences of interventions.

Methods

This report is based in part on a systematic review conducted for the Agency for Healthcare Research and Quality (AHRQ);[9] this manuscript updates the evidence and focuses on prescribing and adverse consequences, while the full report also includes other outcomes (e.g., knowledge, attitudes). We followed the current standard methods for AHRQ systematic reviews,[9] including obtaining input from experts and the public, and our protocol is registered with PROSPERO.[10] Detailed methods (search strategies, inclusion criteria, and data abstraction) are available in the AHRQ report.[9]

Search strategy

For the original CER, we searched MEDLINE® and the Cochrane Library from 1990 through June 2016 using a peer-reviewed strategy that included terms for interventions aimed at improving antibiotic prescribing for acute RTIs in the outpatient setting. The electronic search strategy is available in the full report.[11] We updated the search through January 2018 for the present manuscript. We defined acute RTIs as acute bronchitis, acute otitis media (AOM), pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes and excluded community-acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease, bronchiectasis, or other chronic underlying lung diseases.[5] The search had no language limits and no study design limits. For the CER, we also searched reference lists of included studies, reviewed information from point-of-care diagnostic test manufacturers, and consulted a panel of experts that convened for the AHRQ review.[9,10]

Study selection and data extraction

We included randomized controlled trials (RCTs) and comparative observational studies that studied a single or multifaceted intervention compared with usual care

and that reported antibiotic prescribing outcomes. We screened systematic reviews to identify studies. Citations were screened by one reviewer, and any studies deemed ineligible were screened by a second reviewer. Selected studies were then dually reviewed.[12] The outcomes were overall antibiotic prescribing (or use if reported), appropriate versus inappropriate prescribing as defined per study, and measures of adverse consequences (return visits, hospitalization, duration of symptoms, patient satisfaction, etc.). The study characteristics and results were abstracted by one reviewer and checked by a second. All differences in judgment were resolved through consensus.

Critical appraisal and data synthesis

Given that the percentage of acute RTIs for which antibiotics are prescribed commonly exceeds the known prevalence of RTIs for which antibiotics would be effective, we considered a reduction in overall antibiotic prescribing (or use) to be a meaningful measure of an intervention's effectiveness, in addition to measures that more explicitly specified a reduction of "inappropriate" antibiotic prescribing (or use). The quality of trials was assessed based on predefined criteria related to randomization and allocation concealment, outcome assessment and blinding, and amount and handling of missing data, resulting in a rating of good, fair, or poor using dual review and consensus.[13] The observational study criteria included questions on selection bias, attrition bias, specification and ascertainment of outcomes, and statistical analysis, and these studies were required to have controlled for potential confounding or temporal trends to be deemed good or fair quality.[13]

Data from clinically and methodologically similar studies were pooled using a random-effects model.[14] We evaluated statistical heterogeneity using the I^2 statistic. According to AHRQ methodology, we graded the strength of evidence as high, moderate, low, or insufficient for key outcomes based on methodological limitations of the body of evidence, consistency of study findings, directness of outcome measurement, and precision of estimates.[15]

Results

In our original CER, we included 82 (88%) mostly fair-quality studies (88 publications): 57 RCTs and 25 observational studies. For this update, we screened 2486 citations published since the original search (June 2016) and included 13 additional studies (8 RCTs, 5 observational studies) in 14 publications.[16–29] The study characteristics and quality assessment for studies included in the CER can be found in the AHRQ report,[11] and studies added in this update can be found in Table 1. Cumulatively, there were 95 (86%) mostly fair-quality studies: 65 RCTs and 30 observational studies (Figure 1). Most studies were multisite RCTs targeting broad populations of children and adults with any acute RTI (Table 2) and included 101,443 clinics or clinicians and 7,452,357 patients or parents. Educational and clinical strategies were most widely studied. Sore throat, pharyngitis, and tonsillitis were the most common types of RTI; cough was most common in studies of communication interventions. While all studies reported the change in overall prescribing, appropriate or inappropriate prescribing was reported in only 10 studies (10.4%). The proportion of studies conducted in the United States was 35% overall and ranged widely across intervention categories, from 16% for clinical and point-of-care testing strategies to 80% for system-level strategies.

Studies differed substantially in the intervention target (e.g., patient, clinician, both; specific age group; or diagnosis), mode (population-level or individual-level), duration, frequency, and intensity; in outcome

Table 1. Studies of interventions to reduce inappropriate antibiotic prescribing in acute RTIs since 2016

Authors, year Country	Patient population	Study design Sample size	Study interventions
Patient or caregiver interventions			
Alexandrino et al., 2017[16] Portugal	Acute uncomplicated RTI Children <3 years old	RCT 177 caregivers	Education caregivers of children <3 years old attending daycare versus no intervention
Alexandrino et al., 2017[17] Portugal	Acute uncomplicated RTI Children <3 years old	RCT 138 caregivers	Education caregivers of children <3 years old attending daycare versus nasal clearing protocol, both, or no intervention
Lee et al., 2017[22] Singapore	Acute uncomplicated RTI	RCT 914 Patients	Patient education versus no intervention
Clinician interventions			
Breakell et al., 2018[18] England	Bronchiolitis	Pre–post 101 patients	Education on National Institute for Clinical Excellence (NICE) guidance
Cioffi et al., 2016[19] Italy	Acute uncomplicated RTI Children	RCT 23 clinicians, 792 patients	Rapid WBC testing plus delayed antibiotic prescribing versus delayed prescribing only
Do et al., 2016[20] Vietnam	Acute uncomplicated RTI Primary care	RCT 2037 patients	CRP point-of-care testing versus no intervention
Hoa et al., 2017[21] Vietnam	Acute uncomplicated RTI Children	RCT 206 clinicians	Education plus posters and quizzes versus no intervention
Link et al., 2016[23]	Acute bronchitis	Pre–post	Education and communication training
Little et al., 2017[24] England	Uncomplicated LRTI	Prospective cohort 28,883 patients	Delayed prescribing versus immediate prescribing versus no antibiotics
Magin et al., 2018[25] Magin et al., 2016[26] Australia	Upper RTI and acute bronchitis	Longitudinal 856 clinicians	Education of trainee GPs

(continued)

Table 1. Continued.

Authors, year Country	Patient population	Study design Sample size	Study interventions
Ouldali et al., 2017[27] France	Acute RTI (pediatric)	Interrupted time-series 7 pediatric EDs	Guideline implementation, education, and feedback
Persell et al., 2016[28] USA	Acute uncomplicated RTI Primary care clinics	RCT 28 clinicians	Education and 1 of 3 behavioral interventions via computer: accountable justifications, alternatives, and peer comparison versus no intervention
Sharp et al., 2017[29] USA	Acute sinusitis Primary care	RCT 126 clinics	Electronic decision support (plus single education al intervention) versus no intervention

CRP, C-reactive protein; ED, emergency department; GP, general practitioner; LRTI, lower respiratory tract infection; RCT, randomized controlled trial; RTI, respiratory tract infection; WBC, white blood cell

selection and assessment; and in the level of detail with respect to the patient characteristics, interventions, and outcomes reported. In addition, while there were several studies involving combinations of multifaceted interventions, they were mostly "one-off" combinations, limiting the strength of the evidence. This level of heterogeneity is often characteristic of complex multicomponent interventions and can be a challenge to constructing a framework for organizing the evidence synthesis. This is because the evidence can be conceptually amalgamated or split by various types of characteristics, and there is no agreed-upon single best approach for doing so.[24]

As a consequence of this variability, the results of the evidence synthesis could not be presented as a simple framework of "winners" and "losers." We grouped the evidence for specific types of interventions into four hierarchical categories based on the direction and strength of evidence of benefits (prescribing outcomes) and adverse consequences (e.g., return clinic visits). In Table 3, we provide an overview of which interventions had low-, moderate-, or high-strength evidence according to these categories, as well as interventions for which evidence was insufficient to draw conclusions. Table 4 presents the findings for interventions with evidence of both a benefit and lack of adverse consequences. Note that the studies varied in how the data were reported; e.g., some reported only the relative change in prescribing (not absolute) or reported on a specific infection (e.g., AOM). For the ease of decision-makers, this approach emphasizes the subset of interventions with the highest combined level of favorable evidence of both benefits and harms and contrasts it with interventions with either mixed evidence or no evidence of harms and/or evidence of either no effect or a negative effect on prescribing. As shown in Table 3, five interventions had evidence that was

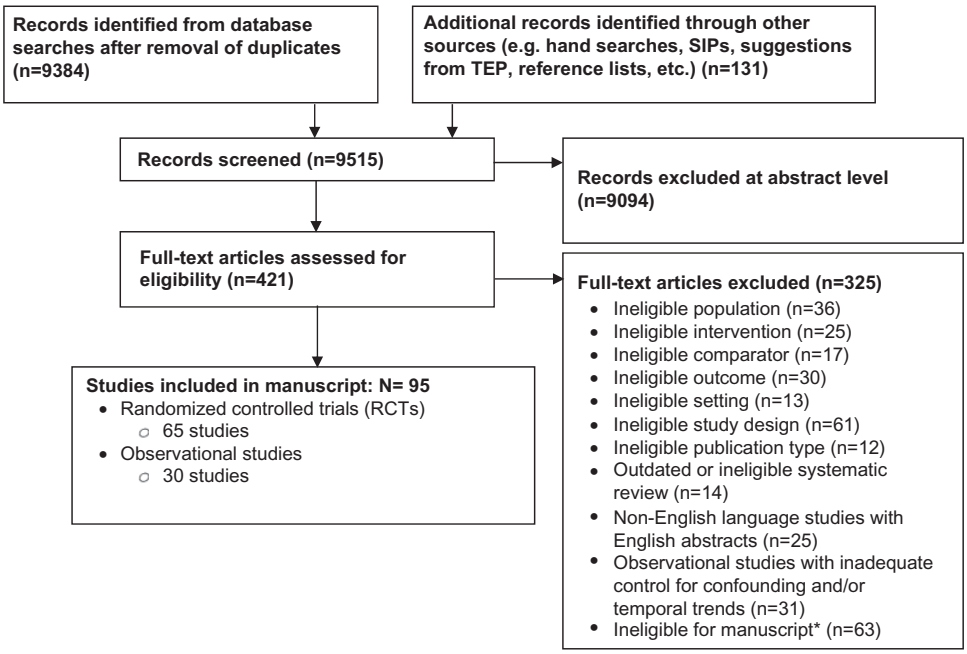

Figure 1. Results of literature search

insufficient to draw conclusions for any included outcome because of methodological limitations, imprecision due to small sample sizes, and inconsistency of findings across studies.

Interventions that improved appropriate prescribing or reduced overall prescribing of antibiotics without increasing adverse consequences

Three education interventions, procalcitonin testing, and electronic decision support were the only interventions with evidence of improved prescribing without adverse consequences (Table 4).

Education interventions. Three education-based interventions were found to have a benefit with evidence of not increasing adverse consequences. A clinic-based educational intervention for parents of pediatric patients had the largest reduction in overall antibiotic prescribing among the education interventions (−21.3%) without increasing the number of return office visits. Public education campaigns aimed at parents of young children reduced prescribing (e.g., for AOM: combined odds ratio [OR] = 0.65, 95% confidence interval [CI] = 0.26–0.58, two observational studies, I^2 not estimable), decreased return office visits, and did not increase potential complications. Combining clinician and patient or parent education interventions resulted in smaller reductions in overall prescribing (−7.3%) compared with other education strategies, but this combination also improved appropriate prescribing with no negative impact on medical complications or patient satisfaction.

Procalcitonin point-of-care testing. Procalcitonin was the only point-of-care test with evidence of any benefit and was restricted to adults. Use of procalcitonin

Table 2. Summary of characteristics of studies included in review

Study characteristic	Category	All studies	Educational	Communication	Clinical and POC	System level	Multidimensional[a]
Design	RCTs (% Total, % Cluster RCT)	65 (68%, 47%)	23 (66%, 50%)	5 (100%, 80%)	29 (78%, 25%)	5 (50%, 60%)	15 (54%, 64%)
	Observational studies	31 (33%)	12 (33%)	0	8 (22%)	5 (50%)	13 (46%)
	Total (% of all studies)	*96 (100%)*	*35 (36%)*	*5 (5%)*	*37 (39%)*	*10 (10%)*	*28 (29%)*
Study quality	Good	10 (10%)	7 (20%)	0	4 (11%)	1 (10%)	0
	Fair	86 (90%)	28 (80%)	5 (100%)	33 (89%)	9 (90%)	28 (100%)
	Total (% of all studies)	*96 (100%)*	*35 (36%)*	*5 (6%)*	*37 (39%)*	*10 (10%)*	*28 (29%)*
Sample size	Clinic/Clinicianb	101,443	14,821	450	2,465	2,833	82,236
	Patient/Caregiver[g]	7,452,357	6,708548	12,364	144,145	355,868	595,955
Population	Adult	28 (30%)	9 (26%)	2 (40%)	14 (38%)	3 (30%)	6 (21%)
	Child or both	68 (71%)	26 (74%)	3 (60%)	23 (62%)	7 (70%)	22 (79%)
	Total (% of all studies)	*96 (100%)*	*35 (36%)*	*5 (5%)*	*37 (39%)*	*10 (10%)*	*28 (29%)*
Duration of intervention	Range	3 weeks – 4 years	1 month – 4 years	4 months – 10 months	1 month – 4 years	11 months – 4 years	3 weeks – 4 years
Duration of follow-up	Range	1 day – 4 years	1 day – 4 years	28 days – 3 months	1 day – 2 years	2 weeks – 3 years	1 week – 1 year
Location	United States	34 (35%)	15 (43%)	1 (20%)	6 (16%)	8 (80%)	9 (32%)
	Other	62 (65%)	20 (57%)	4 (80%)	31 (84%)	2 (20%)	19 (68%)
	Total (% of all studies)	*96 (100%)*	*35 (36%)*	*5 (6%)*	*37 (39%)*	*10 (10%)*	*28 (29%)*
Multisite or single sitec	Multisite	81 (84%)	32 (91%)	5 (100%)	27 (73%)	9 (90%)	26 (93%)
	Single site	15 (16%)	3 (9%)	0	10 (27%)	1 (10%)	2 (7%)
	Total (% of all studies)	*96 (100%)*	*35 (36%)*	*5 (5%)*	*37 (39%)*	*10 (10%)*	*28 (29%)*
Type of infection targeted[e]	Acute bronchitis	23 (24%)	11 (31%)	1 (20%)	4 (12%)	4 (40%)	8 (29%)
	Acute otitis media	21 (22%)	13 (37%)	1 (20%)	3 (9%)	3 (30%)	5 (18%)
	Sore throat/pharyngitis/ tonsillitis	32 (33%)	12 (34%)	2 (40%)	9 (26%)	5 (50%)	11 (39%)
	Rhinitis	7 (7%)	3 (9%)	1 (20%)	2 (6%)	2 (20%)	2 (7%)

(continued)

Table 2. Continued.

Study characteristic	Category	All studies	Educational	Communication	Clinical and POC	System level	Multidimensional[a]
	Sinusitis	22 (23%)	6 (17%)	1 (20%)	5 (15%)	4 (40%)	9 (32%)
	Cough and common cold	16 (17%)	3 (9%)	3 (60%)	9 (26%)	2 (20%)	6 (21%)
	Any acute RTI	65 (68%)	23 (66%)	4 (80%)	21 (62%)	6 (60%)	15 (54%)
	Total (% of all studies)[e]	*96*[e]	*35 (36%)*	*5 (5%)*	*37 (39%)*	*10 (10%)*	*28 (29%)*

Note: Study counts include *only* primary studies (*not* companion studies or secondary publications); studies may be counted in more than one intervention category; column percentages reflect percent of studies in a single intervention category.
[a]Multidimensional is defined as more than one intervention category included in a single study arm.
[b]Reflects the sum of clinics and healthcare providers.
[c]Reflects the sum of patients (children and adults), parents of patients, families, patient records, patient visits, and infection episodes.
[d]Multisite or single site status could not be ascertained from two studies of educational interventions.
[e]Does not sum to 100% because of multiple arms and populations across studies.
POC, point of care; RTI, respiratory tract infection; RCT, randomized controlled trial

testing in the emergency department or outpatient setting reduced overall prescribing. The wide range in absolute reductions was related to a wide variation in baseline prescribing, and larger reductions were associated with greater baseline prescribing. There was no negative impact on the days of missed work, days with limited activity, symptom duration, hospitalizations, or a combined outcome of adverse events and efficacy.

Electronic decision support systems. Electronic decision support systems led to modest reductions in overall antibiotic prescribing (−9.2%) and improvements in appropriate prescribing for acute RTI (13%–24% improvement), but only with more frequent use of the system (i.e., used in ≥50% of patient cases). This was accomplished without affecting health care utilization or complications. Evidence of less frequent use of the system was insufficient due to inconsistency.

Interventions that reduced overall prescribing of antibiotics but had a mixed impact on adverse consequences

Some interventions had evidence of reducing antibiotic prescribing but mixed evidence of reducing adverse consequences (i.e., they showed evidence of not affecting some outcomes but worsening others).

Communication training. Interventions to improve clinicians' communication with patients (including shared decision-making interventions) regarding antibiotic prescribing decisions reduced overall prescribing, with the effect ranging from 9% to 26%; however, evidence of symptom improvement was conflicting. There was a slightly longer duration of symptoms but better health ratings at 2 weeks and insufficient evidence for other outcomes.

Table 3. Summary of evidence findings by category of intervention*

Intervention category	Specific intervention	Studies (n, type)	Benefit and no increase in ACs	Benefit but mixed data on ACs	Benefit but no data on ACs	No benefit	Increased prescribing	Insufficient evidence
Education	Clinic or private setting education of parents of children at risk for aRTI	**5 RCTs**	X					
	Public education campaigns for parents	**2 non-RCTs**	X					
	Combined patient/parent education campaign and clinician education	**7 RCTs**	X					
	Clinician education	**5 RCTs** **7 non-RCTs**			X			
	Clinic-based education for parents of children ≤24 months old with acute otitis media	**1 RCT**				X		
Clinical	Delayed versus immediate prescribing	**8 RCTs** **1 non-RCT**		X				
	Electronic decision support (with ≥50% use)	**4 RCTs**	X					
	Electronic behavioral interventions	**1 RCT**				X		
	Decision rules (paper)	**1 RCT**						X
Comm	Communication training for clinicians	**4 RCTs**		X				
Point-of-care testing	Procalcitonin (adults)	**4 RCTs**	X					
	Procalcitonin (children)	**1 RCT**					X	
	Rapid viral testing (adults)	**1 RCT**			X			
	Streptococcal antigen (rapid strep)	**3 RCTs**			X			
	C-reactive protein	**7 RCTs**		X				

(continued)

Table 3. Continued.

Intervention category	Specific intervention	Studies (n, type)	Benefit and no increase in ACs	Benefit but mixed data on ACs	Benefit but no data on ACs	No benefit	Increased prescribing	Insufficient evidence
	Influenza (children)	**4 RCTs**				X		
	Tympanometry (children)	**1 RCT**				X		
Multidimensional	Clinician education + audit/feedback	**2 RCTs** **1 non-RCT**			X			
	Clinician education + clinical algorithm	**1 non-RCT**						X
	Patient/clinician education plus audit & feedback	**3 non-RCTs**			X			
	Patient/clinician education plus communication training plus audit & feedback	**1 RCT** **1 non-RCT**	X					
	Audit & feedback, patient education, or both	**1 RCT**					X	
	Delayed prescribing + patient education	**2 RCTs**						X
	Patient education + electronic decision support + delayed prescribing + audit & feedback	**1 non-RCT**						X
	Peer academic detailing (education, encouraging delayed prescribing) + audit & feedback	**1 non-RCT**						X

(continued)

Table 3. Continued.

Intervention category	Specific intervention	Studies (n, type)	Benefit and no increase in ACs	Benefit but mixed data on ACs	Benefit but no data on ACs	No benefit	Increased prescribing	Insufficient evidence
	Nurse telephone care and audit/feedback	**1 RCT**			X			
	Communication training + electronic decision support (prescribing agreements) + audit/feedback	**1 RCT**			X			
	CRP + communication training	**2 RCTs**		X				
	Clinician and patient education plus CRP	**7 non-RCTs**			X			
	Rapid WBC plus delayed prescribing	**1 RCT**			X			
	Guideline implementation, clinician education, audit/feedback	**1 non-RCT**			X			

*Does not reflect direction of findings or strength of evidence. Benefit means reduced antibiotic prescribing, improved appropriateness of prescribing, or both. See subsequent tables for details.

AC, adverse consequence; Comm, communication training; aRTI, acute respiratory tract infection; RCT, randomized controlled trial; CRP, C-reactive protein; WBC, white blood cell

Table 4. Interventions with evidence of benefits in antibiotic prescribing for acute RTI and not causing adverse consequences

	Antibiotic prescribing			Appropriateness of prescribing	Adverse consequences
Intervention	Baseline or control group rate	Absolute change Relative effect	Strength of evidence	Baseline/control Absolute change Relative effect Strength of evidence	Impact on outcomes All low strength of evidence
Combined patient/ parent education and clinician education	37% to 59% (5 RCTs)	−7.3% (95% CI, 4.0–10.6) OR, 0.56 (95% CI, 0.36 – 0.87) to OR, 0.62 (95% CI, 0.54 – 0.75) (5 RCTs)	**Moderate**	Children with pharyngitis: 37.1% −10.4%(1 RCT) OR 0.62 (95% CI 0.54 to 0.75) **Low strength of evidence**	No difference in patient or parent satisfaction (2 RCTs
				Adults with acute RTIs: 43% –9.7% (1 RCT) NR **Low strength of evidence**	No difference in AOM complications (1 observational study).
Clinic-based education of parents of children up to age 14 years	40.8% (1 RCT)	−21.3% (1 RCT) Pooled OR, 0.39 (95% CI, 0.26–0.58) (2 RCTs)	**Moderate**	NR	No difference in return visits (2 RCTs).
Public education campaigns for parents (prescribing for child)	37% to 44%	NR URTI: OR, 0.75 (95% CI, 0.69–0.81) AOM: OR, 0.65 (95% CI, 0.59–0.72) Pharyngitis: OR, 0.93 (95% CI, 0.89–0.97) (2 observational studies)	**Low**	NR	No difference in diagnosis of complications and decrease in subsequent visits (1 observation-al study).

(continued)

Table 4. Continued.

Intervention	Antibiotic prescribing			Appropriateness of prescribing	Adverse consequences
	Baseline or control group rate	Absolute change Relative effect	Strength of evidence	Baseline/control Absolute change Relative effect Strength of evidence	Impact on outcomes All low strength of evidence
Procalcitonin (adults)	37% to 97%	−12% to −72% OR, 0.14 (95% CI, 0.09–0.22) Acute bronchitis: OR, 0.15 (95% CI, 0.10–0.23) (1 SR of 4 RCTs)	**Moderate**	NR	No difference in number of days of limited activity, missing work, or continuing symptoms at 28 days for URTI or LRTI in primary care (1 RCT) No difference in AE/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 (4 RCTs)
Electronic decision support (systems with ≥50% use per patient case)	38% to 47%	−9.2% RR, 0.73 (95% CI, 0.58–0.92) (3 RCTs)	**Moderate**	38% to 47% −13% to 24% (2 RCTs) **Moderate strength of evidence**	No difference in healthcare utilization or complications (1 RCT)

AOM, acute otitis media; CI, confidence interval; NR, not reported; OR, odds ratio; RCT, randomized controlled trial; RTI, respiratory tract infection; SR, systematic review; AE, adverse event; ED, emergency department; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; RR, relative risk

Delayed prescribing. Compared with immediate prescribing, various delayed prescribing methods reduced antibiotic use by 34% to 76% without affecting return visits or the duration of symptoms. However, delayed prescribing decreased patient satisfaction.

C-reactive protein measurement. Measurement of the serum C-reactive protein (CRP) concentration reduced overall prescribing for acute RTIs from 13% to 33% in the trials; the prescribing reductions ranged widely depending in part on the baseline prescribing level. CRP measurement increased return visits within 4 weeks (risk ratio = 1.64, 95% CI = 1.35–2.00, four RCTs, $I^2 = 0\%$).

Multifaceted interventions. Clinician communication training combined with CRP measurement resulted in a large reduction in overall prescribing (combined OR = 0.30, 95% CI = 0.26–0.36, two RCTs, I^2 not estimable). There was no impact on return visits, diagnostic testing use, or days off work; however, there was an increase in hospitalizations at 1 month (combined OR = 4.65, 95% CI = 1.21–17.87, two RCTs, I^2 not estimable) and duration of symptoms. Although 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 increase in the risk of hospitalization were unclear in these two trials involving >4,000 patients.

Interventions that reduced overall prescribing of antibiotics but had no evidence or insufficient evidence of adverse consequences

Rapid strep testing for sore throat, rapid viral testing (multi-viral polymerase chain reaction) in adults, clinician education combined with audit and feedback, nurse telephone care combined with audit and feedback, rapid white blood cell count testing combined with delayed prescribing, and clinician communication training combined with electronic decision support and audit and feedback had low- to moderate-strength evidence of improved prescribing outcomes but no evidence on potential harms. Clinician education alone and combined clinician and patient education, audit and feedback, CRP measurement, and academic detailing had low-strength evidence of reducing overall prescribing, but evidence regarding other outcomes was insufficient to draw conclusions. The evidence on adverse consequences was insufficient because of combinations of methodological limitations, imprecision due to few studies reporting a given outcome, and inconsistency in findings across studies.

Interventions with no effect or increased prescribing of antibiotics

Clinic-based education for parents of children aged ≤24 months with AOM, public education campaigns aimed at adults, clinician education combined with audit and feedback, point-of-care testing for influenza in children, and tympanometry in children with suspected AOM had no impact on overall prescribing.[25–31]

Audit and feedback, patient education (a pamphlet), or the combination resulted in *increased* prescribing, although patient education alone and audit and feedback combined with patient education increased prescribing at a lower rate than in the control group.[32] Using the adult algorithm for procalcitonin test results in children *increased* prescribing of antibiotics with a related increase in adverse events.[33]

Other considerations

In our CER, we examined several factors identified *a priori* that could potentially have an effect on the results of studies of

interventions to improve antibiotic prescribing for acute RTIs.

Methods for assessing appropriate prescribing

Significant improvement in appropriate prescribing of antibiotics was found in 7 of the 10 studies that measured appropriateness.[28,30–38] Improvement was seen for each of the three methods used to assess appropriate prescribing: ICD-9 codes or diagnostic category (reduction of 13%–24%), guideline adherence (reduction of <1%–22%), and symptom duration in patients with pharyngitis or sinusitis (reduction of 10%–24%).

Intended target of intervention. Absolute reductions in prescribing were greater when the target was the patient or parent in educational interventions, and combining patient and clinician education did not result in clearly greater reductions. The intended target population did not affect other outcomes. Communication training for clinicians had evidence of a benefit while similar training for patients did not, although this evidence was sparse.

Baseline prescribing rates. Baseline prescribing rates varied extremely widely across studies (from <10% to >90%), and several studies noted temporal trends of declining prescribing during the study period. In general, the magnitude of the reduction in overall antibiotic prescribing correlated with the prescribing rate at baseline, such that locations with higher prescribing at baseline showed greater reductions.

Discussion

This summary and update of a CER of interventions to improve antibiotic prescribing for acute RTIs included a heterogeneous group of interventions that varied in their number (i.e., single or multiple), targets, mode, duration, frequency, and intensity of interventions as well as in the outcomes studied and variation in reporting of important factors such as the characteristics of patients, interventions, and outcomes. The outcomes were grouped into categories regarding the prescribing of antibiotics and other related outcomes, such as adverse consequences of the interventions (e.g., increased return visits). With this complex network of interventions and possible outcomes, we organized the findings into groups according to evidence of a benefit plus or minus evidence of adverse consequences. Notably, the adverse consequences reported may have differing value or weights to individual patients or clinicians; however, evaluating this issue was beyond the scope of our work.

While all 96 mostly fair-quality studies reported the change in overall prescribing, only 10% reported the changes in appropriate prescribing. The studies used a variety of definitions and methods of ascertainment for appropriate prescribing. Three types of education interventions, procalcitonin testing, and electronic decision support were the only interventions with evidence of improved prescribing and no adverse consequences (details on these interventions can be found in the AHRQ report and in Table 1 for newer studies). Several other interventions improved prescribing, but lacked adequate evidence of adverse consequences. Tympanometry or parent education (alone) for suspected AOM, clinician education plus audit/feedback, and influenza testing in children had at least low-strength evidence that they were each ineffective, and adult procalcitonin test algorithms used for children *increased* antibiotic prescribing.

Because the evidence base represents heterogeneous study methods and settings, there may be variability in the real-world results. Even with moderate-strength evidence, further study is needed to present a

more complete picture of the relevant outcomes.

The multiple layers of findings in this study exemplify a gray area that has inhibited implementation of specific interventions more broadly across the United States, as outlined by Gonzales et al.[35] Challenges to employing interventions to reduce inappropriate antibiotic use include the potential for unintentionally causing adverse consequences and the logistics of implementing interventions. The concern regarding adverse consequences can be addressed by selecting interventions from the short list of interventions with evidence of some benefit and at least some evidence of not increasing adverse consequences. While implementation of several of the interventions is likely to be most achievable by organized or integrated health systems or public health organizations, determining which interventions might best be implemented in a given setting or by a particular clinician requires close evaluation of the evidence and characteristics of the intervention, population, and setting that can be found in the AHRQ evidence report.[9] The combination of procalcitonin measurement and clinical evaluation has shown promise for use as a decision aid for excluding clinically relevant lower respiratory bacterial infections (e.g., pneumonia) and determining when to safely withhold antibiotics in adults with low serum procalcitonin concentrations (<0.1–$0.25\,\mu g/L$) and likely viral lower respiratory infections; however, its limited availability in the United States is a primary barrier to its use.

It is possible that interventions with evidence of improved antibiotic prescribing but without evidence related to adverse consequences (e.g., communication strategies, including shared decision-making) may not cause adverse clinical consequences. Given the importance of balancing considerations of the benefit and potential harm in the use of these potentially valuable interventions, further research into possible adverse consequences is clearly needed. Similarly, further research is needed to elucidate potential adverse consequences for interventions with evidence of a benefit but with mixed evidence of adverse consequences (e.g., delayed prescribing, CRP measurement, communication training, and communication training with CRP measurement). Such research should include evaluations of patients' and clinicians' values related to specific adverse consequences, particularly because some of these interventions have already been recommended.[38] Arguably, some interventions are unlikely to cause serious adverse consequences (e.g., patient education) and may not require conclusive evidence to establish that fact.

This work adds to a fairly robust body of reviews on this general topic.[39–42] The reviews are generally more narrowly focused on specific types of interventions, but they have broadly concluded that multifaceted educational interventions, clinician education, delayed prescribing, CRP measurement, and procalcitonin measurement may be effective in certain settings without assessing adverse outcomes. Our review adds significant depth by providing an updated search, evaluating adverse consequences, and including strength-of-evidence assessments. While our findings overlap with some others, they are not identical because of differences in intervention types (e.g., inclusion of point-of-care tests), intervention goals (e.g., quality improvement), indication/disease, and outcomes (e.g., inclusion of adverse consequences).

Even with a large body of evidence, there are important limitations and gaps in the body of evidence that should be considered when designing future studies. Most of the studies described herein only reported on overall prescribing, neglecting the important outcomes of appropriate prescribing, antibiotic resistance, or the potential consequences of reduced prescribing. Only electronic decision support and the combined

parent–clinician educational intervention had evidence of improving appropriate prescribing. However, the definition of appropriateness in these studies was simplistic and the methods of measurement were less than robust. The inability to accurately measure appropriate prescribing is a major gap in the evidence. For overall prescribing, our ability to judge the meaningfulness of the magnitude of reductions was limited by the general lack of established parameters regarding minimally important differences. While many studies used a difference of 15% (versus usual care) in sample size calculations, there is no agreement on what percent reduction is meaningful in terms of improving resistance to antibiotics. Similarly, the change in prescribing is closely tied to the baseline prescribing rates, such that the measurement of change should take this level into account. Another drawback of the body of evidence is variation in geographic study locations, with 35% and 64% inside and outside the United States, respectively (52% in European countries). This is an issue for two reasons: the baseline or background prescribing rate varies by country, sometimes widely, and the healthcare systems, cultural attitudes, and behaviors of clinicians and patients may vary enough in other countries to reduce the generalizability of the findings. Reporting issues and small numbers of studies assessing similar interventions limited analysis of the evidence according to these factors.

Although there were numerous studies, many were flawed, and this area of research seems to be more immature than the volume of publications suggests. Better agreement on several issues is needed before this field of study can fully mature. For example, among the many ill-defined outcomes, the highest priority is the need for agreement on defining and measuring the appropriateness of antibiotic use in acute RTI. Similarly, we need evidence on the possible correlation between improvements in improved overall or appropriate prescribing and reduced antibiotic resistance, including what degree of reduction in overall prescribing is clinically important. Future studies must also regularly measure adverse outcomes. We suggest that the use of complex intervention concepts in both the design and reporting of studies will improve the consistency of key elements across studies such that cumulative results can lead to stronger conclusions, particularly in evaluating which combinations of interventions result in greater improvements than single interventions without increasing adverse consequences.[24]

Potential limitations in our review methods and procedures include the lack of standard search terms that uniformly cover all interventions and the limitation of the studies to non-English language papers that had an abstract in English. However, we do not believe that we excluded important information using these methods. We had limited ability to assess potential publication and reporting bias because of few opportunities to pool studies and the lack of availability of study protocols.

Conclusions

There is evidence that several interventions can effectively reduce inappropriate use of antibiotics in acute RTI without adverse consequences; the best evidence supports clinic-based education for parents, public campaigns for parents combined with clinician education, procalcitonin testing in adults, and electronic decision support. The magnitude of the benefit varied, and evidence on modifying factors was inadequate. Evidence for numerous other interventions was inadequate to draw conclusions in favor of their implementation. Future research must better define and measure key outcomes (e.g., appropriate prescribing); assess adverse consequences; compare interventions, sustainability, and resource use; and evaluate effect-modifiers.

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