ORIGINAL RESEARCH

Ambulatory Antibiotic Stewardship through a Human Factors Engineering Approach: A Systematic Review

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Introduction: **In the United States, most antibiotics are prescribed in ambulatory settings. Human factors engineering, which explores interactions between people and the place where they work, has successfully improved quality of care. However, human factors engineering models have not been explored to frame what is known about ambulatory antibiotic stewardship (AS) interventions and barriers and facilitators to their implementation.**

Methods: **We conducted a systematic review and searched OVID MEDLINE, Embase, Scopus, Web of Science, and CINAHL to identify controlled interventions and qualitative studies of ambulatory AS and determine whether and how they incorporated principles from a human factors engineering model, the Systems Engineering Initiative for Patient Safety 2.0 model. This model describes how a work system (ambulatory clinic) contributes to a process (antibiotic prescribing) that leads to outcomes. The work system consists of 5 components, tools and technology, organization, person, tasks, and environment, within an external environment.**

Results: **Of 1,288 abstracts initially identified, 42 quantitative studies and 17 qualitative studies met inclusion criteria. Effective interventions focused on tools and technology (eg, clinical decision support and point-of-care testing), the person (eg, clinician education), organization (eg, audit and feedback and academic detailing), tasks (eg, delayed antibiotic prescribing), the environment (eg, commitment posters), and the external environment (media campaigns). Studies have not focused on clinic-wide approaches to AS.**

Conclusions: **A human factors engineering approach suggests that investigating the role of the clinic's processes or physical layout or external pressures' role in antibiotic prescribing may be a promising way to improve ambulatory AS. (J Am Board Fam Med 2018;31:417–430.)**

Keywords: **Antibiotics, Antimicrobial Stewardship, Clinical Decision Support Systems, Patient Safety, Point-of-Care Testing, Quality Improvement**

Antibiotic resistance is increasing worldwide, largely driven by excessive antibiotic use.[1–3] In the United States, antibiotic resistance contributes to 23,000 deaths annually and $20 billion in excess health care costs.[4] Antibiotic stewardship (AS) minimizes the development of resistance as well as the risk of harm from antibiotic-associated adverse events by ensuring that only patients who need antibiotics get them and that each patient who needs antibiotics receives the right antibi-

This article was externally peer reviewed.

Submitted 7 June 2017; revised 28 December 2017; accepted 4 January 2018.

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Funding: This work was supported by the Agency for Healthcare Research and Quality (AHRQ) (HHSP-233201500020I/HHSP23337003T). The findings and con-

otic at the right time at the right dose for the right duration.[5]

Although implementation of hospital-based AS teams have been recommended for a decade[6], the majority of human antibiotic expenditures (62%) and use occurs in the ambulatory setting.[7] At least 30% of these prescriptions are inappropriate.[8] Reducing inappropriate ambulatory antibiotic prescribing is essential to decreasing antibiotic resistance.[9,10]

Human factors engineering is the "scientific discipline concerned with understanding interactions among humans and other elements of a system."[11,12] According to a health care-specific human factors engineering model, the Systems Engineering Initiative in Patient Safety (SEIPS 2.0) model,[13] the characteristics of a workplace (eg, an ambulatory clinic) interact in a work system (comprised of person(s), tools and technologies, the organization, tasks, and the physical environment, within a larger external environment); this work system impacts processes such as antibiotic prescribing, which influence outcomes.[13]

Although human factors engineering approaches have been occasionally used in ambulatory clinics to improve patient safety and quality of care[14–18], human factors engineering approaches and models have not been applied to understanding ambulatory AS. We performed a systematic review because human factors engineering approaches describing the clinic's work system could explain influences on antibiotic prescribing and lead to more effective AS interventions. For example, human factors engineering could explain how clinic characteristics such as the ease with which clinicians adapt the electronic health record (EHR) could enhance the intervention's success. We used the SEIPS 2.0 model[13] to frame what is known about effective ambulatory AS interventions and identify barriers and facilitators to successful implementation of ambulatory AS interventions.

clusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services. SCK received funding from the National Center for Advancing Translational Sciences/Johns Hopkins Institute for Clinical and Translational research, KL2 award KL2TR001077.

Conflict of interest: none declared.

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Methods

Literature Search and Inclusion Criteria

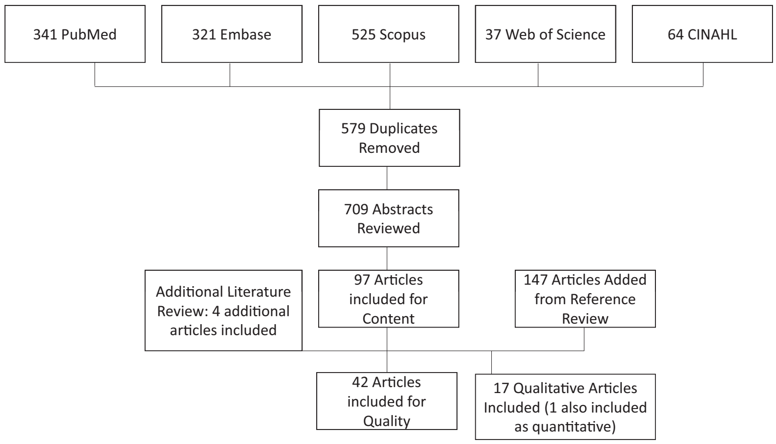
We included quantitative studies to learn whether ambulatory AS interventions were efficacious and qualitative studies to describe barriers and facilitators to AS. We defined ambulatory settings as outpatient practices or offices in which patients came and left on their own (excluding dentistry and emergency medicine practices). We searched the OVID MEDLINE, Embase, Scopus, Web of Science, and CINAHL databases through November 7, 2016, by using a predetermined set of search terms (Appendix A). We identified additional titles from the Cochrane database as well as from the citations in identified articles. Citation titles and abstracts were screened independently by 2 reviewers (SCK and PDT), and full texts were retrieved for all potentially relevant studies. Duplicate studies were removed.

Studies were limited to English-language human studies of antibiotic-prescribing interventions or qualitative studies seeking to understand antibiotic prescribing practices. Quantitative and qualitative studies were assessed by 2 reviewers (SCK and PDT) to determine if they evaluated AS interventions conducted in ambulatory clinics. We considered AS interventions as any intervention that sought to improve the appropriate use of antibiotics in an ambulatory clinic. We included studies that measured the application of an intervention targeting antibiotic prescriptions, described the factors that influence antibiotic prescribing, or explained the process of implementing approaches to improve antibiotic prescribing. For quantitative studies, we a priori only included studies with rigorous designs: randomized controlled trials (RCTs) or quasi-experimental studies using stepped wedge or interrupted time series approaches. Qualitative studies were included if they described the context in which antibiotic prescribing decisions were made or the context, barriers, or facilitators of AS interventions. Any disagreements about study inclusion were discussed until consensus was achieved.

SEIPS 2.0 Model and Data Extraction

Data for studies meeting inclusion criteria were abstracted using components of the SEIPS 2.0 work system model.[13,19] The SEIPS 2.0 work system includes 5 components within a wider external environment: (1) person(s), (2) tools and technolo-

Figure 1. Flow chart demonstrating inclusion of articles in the review. Rigorously designed quantitative studies of ambulatory antibiotic stewardship interventions (randomized controlled trials and quasi-experimental studies with stepped wedge and interrupted time series approaches), as well as qualitative studies describing barriers and facilitators to ambulatory antibiotic stewardship were included. Databases were searched through November 7, 2016, with additional titles added based on knowledge of the literature and relevance to the work.



gies, (3) organization, (4) tasks, and (5) physical environment. The work system centers around the person(s), including health care professionals, the patient and family, their individual characteristics (eg, age and education), and connections between individuals (eg, a patient-clinician relationship).[13] Tools and technologies include objects that people use to do work, such as information technologies, educational materials, medical devices, testing equipment, and physical tools. Organization refers to the structures that organize clinic time, space, resources, and activities, including staff member roles. Tasks are specific actions (eg, placing an electronic order) and have qualities such as difficulty, complexity, ambiguity, variety, and sequence. The physical environment includes the clinic's physical space. The work system lies within a larger external regulatory and cultural environment, including societal, economic, and policy forces that impact a clinic.[13]

We used these work system components to organize aspects of the interventions and the context of AS and to understand which processes and outcomes were addressed by AS interventions. Our aim in using this approach was to identify how aspects of the clinic work system could affect AS intervention successes. We evaluated identified sources and recorded study design and aspects of the studies that could be interpreted in the context of the SEIPS 2.0 model. We also described how measures and outcomes of the studies could be interpreted in the context of the SEIPS 2.0 work system.

Results

Search Results

The search identified 1,288 abstracts (Figure 1). Four additional studies meeting inclusion criteria identified through knowledge of the literature were added based on their relevance to the work. Ultimately, 42 quantitative and 17 qualitative articles met the eligibility criteria, with 1 study considered both quantitative and qualitative.[19] Fourteen of the quantitative studies were RCTs[20–33], 1 was a randomized crossover trial[34], 2 were pragmatic RCTs[35,36], 14 were cluster randomized trials[37–48], 2 were pragmatic cluster randomized trials[49,50], and 9 were quasi-experimental, interrupted time series studies.[19,51–58]

Of the qualitative studies, 3 were follow-up studies to prior quantitative work[19,59,60] (1 of which had been described in the quantitative review).[19,38] Eight studies used semistructured interviews[61–68] and 1 used focus groups.[69] One combined interviews and focus groups[70] and 2 involved surveys.[71,72] A single study focused on written physician self-reflection, prompting them to review the medical charts of patients.[69] Finally, 1 study used a "think-aloud" approach where physicians commented on their inner thought processes.[73]

AS Interventions and the SEIPS 2.0 Work System

Table 1, Appendix B, and Figure 2 describe how aspects of included studies fit into components of the clinic work system.[13]. Appendix C describes the processes and outcomes used in each included study.

Tools and Technology

Tools and technologies include objects and technologies that people use to do work. AS interventions incorporating tools and technologies included clinical decision support systems (CDSS), interventions based in EHRs, educational tools (eg, newsletters, booklets, and videotapes), AS messaging tools (eg, magnets and lapel pins), and point-of-care (POC) testing.

CDSS tools and other EHR-based interventions were frequent and often effective. Highlighting several CDSS tools, a CDSS incorporated into an EHR encounter template decreased acute respiratory infection (ARI) antibiotic prescriptions from 43% to 38% (versus 40% to 39% in control groups).[41] An RCT of a computerized patient flow manager with evidence-based prompts decreased antibiotic prescriptions for acute otitis media by 34%.[32,74]

EHR-based tools have incorporated behavioral interventions. In a $2 \times 2 \times 2$ randomized factorial study comparing accountable justification (providing a written explanation for prescribing nonindicated antibiotics) and suggested alternatives (pop-up messages with education and nonantibiotic alternatives), the suggested alternatives arm was associated with decreased antibiotic prescriptions for ARIs.[20] In a larger cluster randomized trial, suggested alternatives did not decrease antibiotic prescription, but accountable justification decreased inappropriate antibiotic prescribing (23% to 5%).[43]

However, the context in which electronic tools were deployed impacted their implementation. Factors associated with unsuccessful incorporation of CDSS tools and EHR technologies into clinics included nonintuitive tools, need for additional software,[51] computers not being available in examination rooms, and slow internet connectivity.[19] CDSS tools needed to be used to have an effect; in a cluster randomized trial, EHR-integrated CDSS did not impact antibiotic prescribing, but the CDSS tool was used in only 6% of intervention clinic visits.[75]

The effect of educational tools was mixed. Educational booklets (eg, on self-care for respiratory infections, potential harms of antibiotics, and other topics) were developed with the goals of assisting patients with understanding harms associated with unnecessary antibiotic use and supporting clinicians with antibiotic prescribing.[59,66] As a broader intervention including physician feedback, mailing brochures to parents of children successfully decreased community-wide antibiotic use by 4.6% among those aged 2 to 4 years and by 6.7% among those aged 4 to 5 years.[42] However, in another study involving mailed patient and clinician education, antibiotic use did not decrease.[55] In addition, in a trial of patient educational materials including a letter from the medical director along with pamphlets compared materials mailed to patients and to office practices, pamphlets mailed to offices only, and usual care on antibiotic prescription for acute bronchitis.[56] Only the full intervention sites showed a decline in antibiotic prescriptions for acute bronchitis visits, from 74% to 48%.[56]

Evidence was similarly mixed regarding the impact of multifaceted educational tool bundles. In a cluster randomized trial in 16 Massachusetts communities, clinicians were given tools with AS messages (ie, stickers, lapel pins, and otoscope insufflators), bimonthly newsletters regarding AS, and prescription pads with written recommendations for symptomatic treatment of viral ARIs.[46,53] Parents of young children were also mailed brochures and advertisements were placed in child care centers and pharmacies.[46] Although there was no difference in ARI antibiotic prescribing in children <2 years, a 5% decrease in children 2 to 3 years and a 7% decrease in children 4 to 5 years was observed.[46] In an additional cluster randomized trial, a multifaceted intervention (educational information at pharmacies and clinics, patient mailings, clinic posters, refrigerator magnets, flip charts, patient-initiated chart documentation tools, and CDSS tools) resulted in a decrease in antibiotic prescriptions among children <6 years.[37] Another multifaceted intervention (CDSS, clinician education, audit and feedback, and patient education brochures) also led to decreases in the percentage of adolescents and adults prescribed antibiotics for ARIs at CDSS sites (decreased 12%) versus control sites (increased 1%), with no impact on 30-day return visits.[40]

Table 1. Aspects of Ambulatory Antimicrobial Stewardship Interventions as Applied to Components of the Ambulatory Work System, SEIPS 2.0[13]*

Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
• EHR-based CDSS[20,38,41 to 42,50,54,67,70,72]	• Commitment to use and agreement with CDSS[20]	• CDSS alters practice workflow[20]	• Improves efficiency[20]	• Computer location[20,33]	• External clinician guidelines[20,26,30,37,39–41,54–55,65–67,76]
• Hyperlink to patient education[20,54,66]	• Technically savvy staff[20]	• Role of person initiating task is different in different clinics (ie, triage nurse, medical assistant, and clinician)[20,69]	• Ordering an antibiotic in EHR[21]	• Brochures and posters in exam rooms and waiting rooms[24,31,38,43,46,59–60,66]	• New guidelines written[57]
• Hyperlink to and accessibility of guidelines[39,40,54,66]	• Comfort with prior ARI templates[20]	• Computerized patient flow manager designed by clinics[33]	• Protocols support decision making[73]		• Regional clinician newsletter[61,72]
• EHR-based audit and feedback[20]	• Providers signed letter/poster soliciting support[27,31,56,58,59]	• Patients see physicians with different practices[66,72,73]	• Amoxicillin as placebo if physician did not think they need antibiotics[76]		• Insurance policies regarding cost-sharing[25,66]
• EHR-based antibiotic prescribing agreement[49]	• Prescribing feedback[22,23,37,3–41,44,46,51,54,57,60,62–63,67]	• Previsit triage and education by nurses may prevent visits[72]	• Limited time during patient visits, antibiotics to save time[66,72,73,77]		• Meetings with community leaders[38]
• Template for ARI clinic visits[41]	• Intensive intervention for highest prescribers[58]	• Large health systems enable system-level alerts[66]	• Competing demands[72]		• Mass media campaign[38,56,61,72,74]
• EHR-based accountable justifications and suggested alternatives (pop-up of alternatives and educational material)[21,44]	• Clinician instruction on evidence-based medicine[30,72]	• Need for hospital lab[35,69]	• Restricted susceptibility testing[70]		• Education at pharmacies, health fairs, child care centers, and offices[38,47,48,75]
• Limited printing capabilities[20]	• Clinician instruction on problem solving and communication[30,49,52,53,59]	• Peer comparison[21,23,44,46,51,60,62–63]	• Diagnostic uncertainty[72,76]		• CDC campaigns for judicious antibiotic use[43,54]
• Tool adaptability[20,62,77]	• Older prescribers: prescriptions influenced by habit[70]	• Other clinicians see accountable justification[21,44]	• Checklist completed by clinician and patient[62]		• Disclosed prescribing status monthly to patients, health authorities, and health workers[45]
• Network issues[20]	• Newer prescribers: nervous about making mistakes[73]	• Group follow-up meetings with individual feedback[24,52–54]	• Communicating with patients[59,64,65,77]		• Health ministry-required tasks[70]
• Mailed intervention[22,38,43,47,48,55,58 to 60,75]	• Depend on patient to decide to take antibiotics[36]	• On-site group educational time[24,38–41,43,59,66,67]	• Setting expectations[36,64,66]		• Performance-based incentives[66,70,72]
• Printed patient education[23,36,41–43,47,59–60,65,70,71,73,75]	• Engaged patients: focus groups with elderly volunteers[60]	• Academic detailing[47,75,52–54,58,67]	• Educating patients[59,64,66,70,73]		• Patient can get antibiotics elsewhere[66,68]
• Letters/posters/videos about avoiding inappropriate antibiotic prescribing with clinician photos or signatures[27,31,56,58,59]	• Patient/family pressure and expectations[62,64,72,74]	• Large training sessions[55,59]	• Use physical exam to communicate[64,77]		• Other countries or healthcare settings thought to be responsible for resistance[68]
• Refrigerator magnets[38,59,60]	• Patient physical traits[20,64,65,67,70,77]	• Local clinicians led initiative at local hospital medical staff meetings[38]	• Flexible interventions increase feasibility[67]		• Willing to postpone treatment if told others would do the same[71]

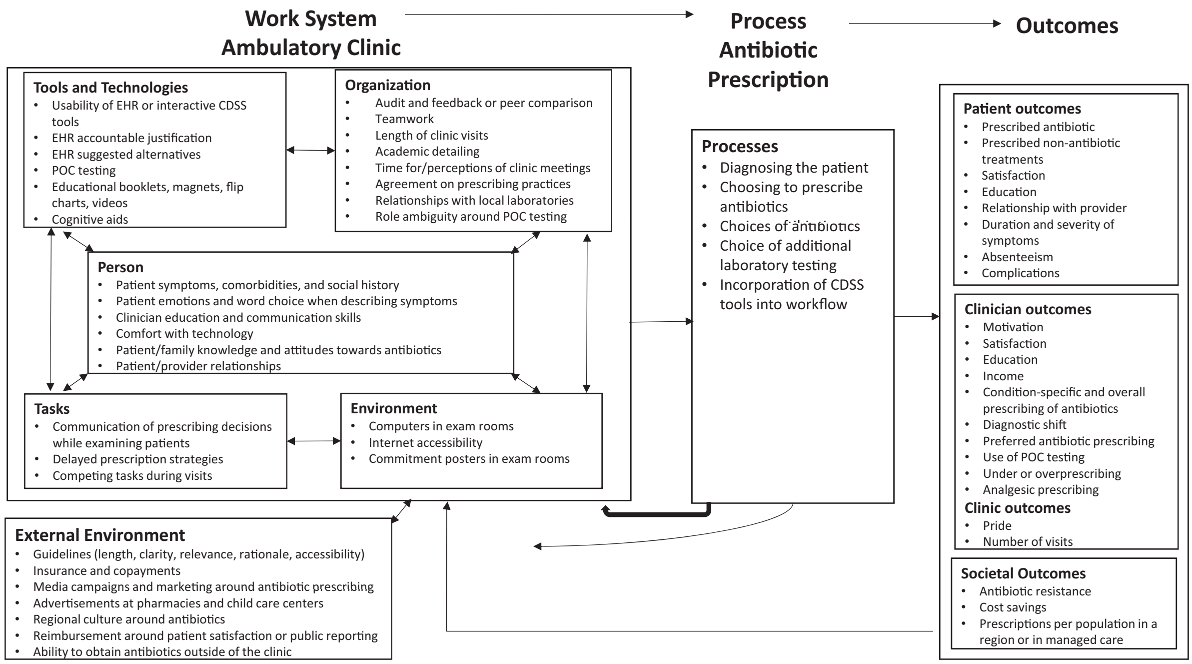
Continued

Table 1. Continued

Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
• Flip chart or reference card for ARI self-management[38,60]	• Patient symptoms[20,62,64,65,73]	• Clinicians compensated for each visit[38]	• Interventions should engage GPs[67]		• Social capital[71]
• Stickers, lapel pins, and otoscope insufflators[47,75]	• Patient background and knowledge[74]	• Practice-specific antibiotic prescribing rates[39,40,43,49,59,70]	• CRP testing has associated tasks (eg, quality assurance)[69]		• Loss of income from POC testing and reimbursement[69]
• All received printed versions of poster and electronic version of guideline[46]	• Avoiding confrontation[64]	• Clinic champions[41–43]			• Legal protections[73]
• Discussion guide at well-child visits[20,47,75]	• Negotiating with patients[64]	• Kick-off dinners[47,75]			• School or day care requires antibiotics[74]
• Prescription pads for treatment of viral infections[47,58,71,75]	• Hedging[64]	• Peer review of colleague transcripts with simulated patients[52,53]			• Adaptability of intervention to regional culture[77]
• Delayed prescription: prescribe antibiotics to take only if symptoms worsen[36,71]	• Patient reward for copays and taking off work[66]	• Clinics set goals[59]			
• Website for feedback required physicians to log in with individual access code[37]	• Most PCPs did not see antibiotic resistance as a problem in their practice[68]	• Clinic pride[64]			
• Dashboard[51]	• Worried about patient illness from not prescribing antibiotics[67,70]	• Relationships with patients[64,71]			
• Want local resistance data[68]		• GPs assume practice already follows guidelines[67]			
• Limit antibiotic availability in outpatient settings[70]		• Antibiotic resistance seen as issue for secondary care rather than primary care[68]			
• CRP POC testing[24,35,52,53,62,65,69,77]		• No accountability for prescribing[72]			
• Procalcitonin testing[26]		• Peer support helpful with demanding patients[73]			
• POC streptococcal testing[65]		• Fewer visits, decreased income[77]			
• Multiplex PCR for respiratory viruses[32]		• Dermatologic consultation[27] • Institutional guidelines[29] • Prior approval of ID physician[70]			

SEIPS, Systems Engineering In Patient Safety; PCP, primary care provider; CDSS, clinical decision support system; POC, point of care; ARI, acute respiratory infection; EHR, electronic health record; CDC, Centers for Disease Control and Prevention; GP, general practitioner; CRP, C-reactive protein; ID, infectious diseases; PCR, polymerase chain reaction.
*Studies described include rigorously designed quantitative and qualitative studies describing antibiotic stewardship interventions and the context around antibiotic prescribing decisions, included through November 7, 2016.

Figure 2. Adaptation of the Systems Engineering Initiative for Patient Safety (SEIPS) 2.0 model of the health care work system to approaches taken in the literature to improve antibiotic stewardship in the ambulatory setting.



Abbreviations: EHR: electronic health record; CDSS: clinical decision support system; POC: point of care.

Interventions involving tools for patient and family education were not always successful. An intervention including mailed information and guideline distribution did not decrease antibiotic use among elderly patients with ARIs.[57] Meanwhile, providing patients with an educational pamphlet and videotape of their pediatricians did not decrease the number of viral ARI visits, antibiotic prescriptions for acute otitis media or sinusitis, or total antibiotic prescriptions.[27] Patient characteristics such as older age and the need to open the pamphlet or view the videotapes may have made these interventions less effective.

Other studies focused on POC testing as a tool. C-reactive protein (CRP) POC testing may perform better than clinical symptoms and signs in predicting the diagnosis of pneumonia[52], but decreases clinician confidence in reducing antibiotic prescribing and decreases patient satisfaction.[59] In a study of POC CRP testing availability, antibiotic prescription improved[49], but on follow-up 2 to 3 years later, POC CRP testing was only performed in 4% of eligible patient visits.[50] POC tests have also been criticized for their short shelf life, need for quality control testing, and difficulties linking the test result to the EHR.[76] These factors may have made the tools more difficult to incorporate into practice and limited their effectiveness.

Person

The person component of the SEIPS 2.0 work system describes individual characteristics and relationships between individuals. However, characteristics and perspectives of other clinic staff members such as medical assistants, nurses, and front desk staff were not described.

Patients and Families

Patient factors such as symptoms and comorbidities influence whether a clinician would prescribe antibiotics.[19,61,66] Patient and family factors such as education, knowledge of antibiotics, or trust in their physician decreased requests for antibiotics.[35,67,71]

Clinicians

Clinician training, particularly focusing on communication training, problem-solving strategies, and peer review, was also studied. In an RCT, French general practitioners were randomized to a day-long seminar focusing on problem-solving strategies after all attended a 2-day seminar on evidence-based ARI management.[29] The intervention group sustained a decrease in the proportion of antibiotics prescribed over 30 months.[29] General practitioners who attended a training session or received in-office instruction along with clinician-specific feedback increased adherence to community-acquired pneumonia guidelines.[45] A workshop including peer reviews of transcripts of interactions with standardized patients reduced antibiotic prescriptions from 54% to 27%,[49] sustained for 2 to 3 years.[50]

Clinician and Patient Relationships

Relationships between individuals are an important part of the ambulatory work system.[13] Some physicians think that patients want antibiotics[61] and prescribe antibiotics to meet perceived patient expectations.[68] Physicians may also believe that patients want something (ie, an antibiotic prescription) in exchange for taking off work and paying copays.[63]

Organization

The organization refers to the structures and roles that organize a clinic. Characteristics of the clinic, roles of clinic members, and the larger organizations in which clinics operate were explored through investigating roles of clinic team members, comparing clinicians to peers, and learning how clinic structures allow clinician education or improve communication.

Few studies involved changing roles of nonclinician staff members to impact AS. Only 1 study included a nonclinician staff member in an educational intervention and the role of this person was not specified.[51] In a qualitative study, clinicians suggested using nurses to perform previsit triage and education.[72] In POC testing interventions, participants found that it was unclear which staff members to train in POC testing, as various organizational roles performed the test in different clinics.[76,77]

Audit and feedback interventions, where clinicians are compared with others, have had success.[20,48] In a Canadian RCT where clinicians were mailed educational information or prescribing feedback, the feedback group was more likely to use first-line antibiotic prescriptions.[21] In a cluster randomized trial, comparing clinicians with top performers (those who seldom prescribe antibiotics inappropriately) decreased inappropriate prescriptions from 20% to 4%.[43] In an RCT, antibiotic use decreased among providers who received a letter from England's chief medical officer saying they were prescribing more antibiotics than 80% of local practices.[22] An RCT found that the combination of clinician education and audit and feedback decreased antibiotic prescribing overall and broad-spectrum prescribing in particular.[38]

However, audit and feedback may not be universally successful. In the above RCT,[38] after the termination of audit and feedback, prescribing of broad-spectrum antibiotics returned to a level above baseline.[39] In a follow-up qualitative study, some clinicians expressed skepticism and discounted the reports.[60] Furthermore, in a recent RCT of high-prescribing physicians across Switzerland, receiving letters and an online log-in code with information about antibiotic prescribing did not impact antibiotic prescribing over 2 years.[36] Only 11% of physicians in the intervention group viewed their prescribing data.[36] Similarly, a cluster randomized trial of an audit and feedback dashboard led to no difference in antibiotic prescribing for ARI visits[78], but only 28% of intervention-group physicians used the dashboard. These clinicians had a lower ARI antibiotic prescribing rate (42% versus 50%).[78]

Organizational structures could pose barriers to AS. Clinic visits were often too brief to discuss guidelines with patients.[63,70] If patients saw multiple clinicians in a practice with different prescribing practices, patients may have expected to receive antibiotics.[63,70] Many clinics did not have protected time for group education.[63] However, in practices where physicians discussed AS guidelines, outcomes improved.[52,46]

If clinics had protected time for group education, academic detailing, where an expert visits a practice to discuss AS,[51,64] was successful.[55] In a study comparing (1) office-based patient education, (2) office- and home-based patient and clinician education (practice profiling, setting clinic goals, and academic detailing), and (3) usual care, full intervention sites had a substantial decline in antibiotic prescriptions for acute bronchitis (74% to 48%), whereas the control and limited intervention sites did not.[56]

Tasks

Tasks describe specific actions and their characteristics. Clinicians pick particular words when describing physical examination findings to patients or perform a thorough physical examination to explain to patients why they were not prescribing antibiotics.[61,66,73]

In delayed prescription strategies, the clinician gives the patient a prescription and leaves it up to the patient whether to fill it after a specified time or with worsened symptoms. Patients with acute uncomplicated ARIs were randomized: (1) deciding to fill the prescription after 2 days, (2) returning to the clinic after 2 days for a prescription, (3) no prescription, or (4) immediate prescription.[35] Patient satisfaction was similar in all groups, and antibiotic use and belief in antibiotic effectiveness was lower in all groups compared with the immediate prescription group.[35]

Physical Environment

The physical environment refers to the clinic's layout. Most physical environment-based interventions used posters.[24,38,46,59,60] By themselves, posters about avoiding antibiotics for "chest colds" did not decrease antibiotic prescription for acute bronchitis.[56] However, visible signed commitments about avoiding unnecessary antibiotics decreased unnecessary antibiotic prescribing by up to 20%.[31] Studies did not discuss optimizing the placement of these posters.[37,45,46,53,56,57]

External Environment

The larger external environment includes guidelines and societal, economic, and policy forces that impact a clinic. External guidelines were not always used because they were sometimes difficult to locate[63,64,69], too long[64], or not seen as relevant.[64] Some physicians did not trust guidelines, wondering whether they were intended to save money instead of improving care.[64]

Media campaigns reinforced what clinicians conveyed.[66] A Colorado-wide campaign of billboards, bus signs, radio advertisements, and newspaper op-eds decreased population-wide antibiotic dispenses.[53,57] Advertisements in child care centers and pharmacies also reduced antibiotic use.[46] In another community-level study, interventions including news releases, community meetings, and presentations at health fairs decreased antibiotic prescriptions.[37] In an Italian study, region-wide campaign materials (posters, brochures, and local media advertisements) and a doctor and pharmacist newsletter decreased antibiotic prescribing by 4%.[58]

Discussion

Human factors engineering approaches have only recently been used in ambulatory clinics to describe defects in testing,[14] apply new EHR technologies[15,18], and improve clinic workflows.[16,17] Our review is the first to incorporate a human factors engineering approach to understanding ambulatory AS.

In the SEIPS 2.0 work system, tools and technologies refer to objects and technologies. Tools and technologies used in ambulatory AS interventions have included CDSS and EHR-based interventions, educational materials, and POC testing. CDSS and EHR-based and educational materials improved AS but only if they were used. POC tools such as CRP testing impacted AS, but many clinicians stopped using the POC tests over time. Human factors engineering would suggest that to make these tools more effective, researchers should make them easier to use.

The person component of the work system includes individual characteristics and relationships between individuals. In particular, clinician communication training had a sustained positive impact on AS, and interventions aimed at educating patients and families also showed a positive impact on AS. However, although clinicians have mentioned the potential impact of other members of the health care team, characteristics of other health care team members have not been studied. Human factors engineering would suggest that the role of other members of the health care team in AS interventions should be studied and these team members should be engaged.

Few studies focused on the organization component of the work system model or the structures and roles that organize a clinic. Audit and feedback and academic detailing had a positive impact on AS. However, we know little about the role of nonclinicians in AS. Engagement of the entire ambulatory team has the potential to send a consistent message about appropriate antibiotic prescribing.[68] Human factors engineering would suggest research exploring the roles of clinic staff and clinic flow in an intervention's effectiveness.

Similarly, few interventions focused on the work system component of tasks or specific actions and their characteristics, although delayed prescription strategies were promising. Few interventions focused on the impact of the physical environment of the clinic on antibiotic prescription. However, clinic posters with signed commitments advocating AS positively impacted AS. Human factors engineering would suggest an investigation into the role of the location of clinic posters and other elements of the physical environment, as well as qualities of tasks related to antibiotic prescription, on AS interventions.

Finally, the work system occurs within the external regulatory and cultural environment. Several interventions incorporated the external environment, showing that media-based interventions could improve AS at a community level and showing that external guidelines needed to be accessible to clinicians and trusted by clinicians. The role of the external environment in the form of external pressures on AS interventions such as patient satisfaction-based reimbursement has not been fully examined and should be a focus of future research.

Our review has several limitations. We only included well-controlled quantitative studies and may have missed other domains if they were targeted only in uncontrolled studies. We did not assess for publication bias. Finally, our findings are more applicable to ARIs, the focus of most studies, as we were unable to identify many high-quality studies that implemented AS for other conditions (eg, urinary tract infections and cellulitis).

Evidence-based AS interventions impact different portions of the ambulatory work system, and using a human factors engineering approach may facilitate the intervention's success. However, interventions did not typically engage all clinic staff in the implementation, a model that has led to successes in patient safety and quality improvement.[79–84] Few interventions have accounted for physical environment or task characteristics in implementing interventions. Future work in ambulatory AS should address the entire work system in which the intervention is implemented. Such work system interventions, if rigorously evaluated, may have greater potential than isolated interventions to improve the effectiveness of ambulatory AS.

We gratefully acknowledge the support of Maria Trusky, MLS, for her assistance in extracting the articles. We also appreciate the assistance of Kathleen Speck, MPH, for assistance in formatting the tables.

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Appendix A: Search Terms

PubMed 341 Results, 11/7/2016

("Anti-Infective Agents"[Mesh] OR "Anti Infective Agents" OR "Anti Infective Agent" OR "Antiinfective Agents" OR "Antiinfective Agent" OR "Anti-infective agents" OR "anti-infective agent" OR "Microbicides" OR "antimicrobial agents" OR "antimicrobial agent" OR "antimicrobials" OR "Anti-Microbial Agents" OR "antimicrobial agent" OR "Anti Microbial Agents" OR "anti microbial agent" OR "antibiotics" OR "antibiotic" OR "antibiotics" OR "antibiotic" OR "Anti Bacterial Agents" OR "Anti Bacterial Agent" OR "Antibacterial Agents" OR "Antibacterial Agent" OR "Bacteriocidal Agents" OR "Bacteriocides" OR "Anti-Mycobacterial Agents" OR "Anti Mycobacterial Agents" OR "Antimycobacterial Agents") AND ("stewardship" OR "stewards" OR "antimicrobial management" OR "antimicrobial prescribing behavior" OR "antibiotic stewardship" OR "antimicrobial stewardship" OR "appropriate use" OR "Drug Utilization"[Mesh] OR "ASP") AND ("Ambulatory Care"[Mesh] OR "ambulatory care" OR "ambulatory health services" OR "outpatient care"

OR “outpatient health services” OR “outpatient health service” OR “urgent care” OR “urgent cares”).

Embase 321 Results, 11/7/2016

(“antiinfective agent”/exp OR “anti infective agent*” OR “antiinfective agent*” OR “anti-infective agent*” OR “microbicide*” OR “antimicrobial*” OR “antimicrobial agent*” OR “anti microbial agent*” OR “antibiotic*” OR “antibiotic*” OR “anti bacterial agent*” OR “antibacterial agent*” OR “bacteriocidal agent*” OR “bacteriocide*” OR “antimycobacterial agent*” OR “anti mycobacterial agent*”) AND (“drug utilization”/exp OR “drug utilization” OR “drug utilization” OR “stewardship” OR “stewards” OR “antimicrobial management” OR “antimicrobial prescribing behavior” OR “antibiotic stewardship” OR “antimicrobial stewardship” OR “appropriate use” OR “asp”) AND (“ambulatory care”/exp OR “ambulatory care” OR “ambulatory health service*” OR “outpatient care*” OR “outpatient health service*” OR “urgent care*” OR “dispensary care” OR “extramural care”).

Scopus 525 Results, 11/7/2016

(TITLE-ABS-KEY (“antiinfective agent*” OR “anti infective agent*” OR “anti-infective agent*” OR “microbicide*” OR “antimicrobial*” OR “antimicrobial agent*” OR “anti microbial agent*” OR “antibiotic*” OR “antibiotic*” OR “anti bacterial agent*” OR “antibacterial agent*” OR “bacteriocidal agent*” OR “bacteriocide*” OR “antimycobacterial agent*” OR “anti mycobacterial agent*”)) AND (TITLE-ABS-KEY (“stewardship” OR “stewards” OR “antimicrobial management” OR “antimicrobial prescribing behavior” OR “antibiotic stewardship” OR “antimicrobial stewardship” OR “appropriate use” OR “Drug Utilization” OR “drug utilization” OR “ASP”)) AND (TITLE-ABS-KEY (“ambulatory care*” OR “ambulatory health service*” OR “outpatient care*” OR “outpatient health service*” OR “urgent care*” OR “dispensary care” OR “extramural care”)).

Web of Science 37 Results, 11/7/2016

TS = (“antiinfective agent*” OR “anti infective agent*” OR “anti-infective agent*” OR “microbicide*” OR “antimicrobial*” OR “antimicrobial agent*” OR “anti microbial agent*” OR “antibiotic*” OR “antibiotic*” OR “anti bacterial agent*” OR “antibacterial agent*” OR “bacteriocidal agent*” OR “bacteriocide*” OR “antimycobacterial agent*” OR “anti mycobacterial agent*”) AND TS = (“stewardship” OR “stewards” OR “antimicrobial management” OR “antimicrobial prescribing behavior” OR “antibiotic stewardship” OR “antimicrobial stewardship” OR “appropriate use” OR “Drug Utilization” OR “drug utilization” OR “ASP”) AND TS = (“ambulatory care*” OR “ambulatory health service*” OR “outpatient care*” OR “outpatient health service*” OR “urgent care*” OR “dispensary care” OR “extramural care”).

CINAHL 64 Results, 11/7/2016

((MH “Antiinfective Agents+”) OR “antiinfective agent*” OR “anti infective agent*” OR “anti-infective agent*” OR “microbicide*” OR “antimicrobial*” OR “antimicrobial agent*” OR “anti microbial agent*” OR “antibiotic*” OR “antibiotic*” OR “anti bacterial agent*” OR “antibacterial agent*” OR “bacteriocidal agent*” OR “bacteriocide*” OR “antimycobacterial agent*” OR “anti mycobacterial agent*”) AND ((MH “Drug Utilization”) OR “stewardship” OR “stewards” OR “antimicrobial management” OR “antimicrobial prescribing behavior” OR “antibiotic stewardship” OR “antimicrobial stewardship” OR “appropriate use” OR “drug utilization” OR “ASP”) AND ((MH “Ambulatory Care”) OR “ambulatory health service*” OR “outpatient care*” OR “outpatient health service*” OR “urgent care*” OR “dispensary care” OR “extramural care”).

An asterisk indicates that a word stem was used as a search term (for example, antibiotic signified that either “antibiotic” or “antibiotics” was searched for).

Appendix B: Aspects of Ambulatory Antimicrobial Stewardship Interventions as Applied to Components of the Ambulatory Work System (SEIPS 2.0).[13]*

	SEIPS 2.0 Element						
Reference	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Litvin et al[20]	Qualitative analysis of quasi-experimental study	• CDSS through EHR note template • Hyperlink to patient education • EHR audit and feedback • Limited printing capabilities • Not tailored to multiple complaints • Facilitates discussion • Tool adaptability • Network issues	• Patient symptoms • Patient age • Commitment to use CDSS • Agreement with CDSS • Technically savvy staff • Comfort with prior ARI templates	• CDSS alters practice workflow • Role of person initiating CDSS is different in different clinics (ie, triage nurse, medical assistant, and clinician)	• Improves efficiency	• Computer location	• External clinician guidelines
Persell et al[21]	2 × 2 × 2 RCT of patients with ARIs comparing (1) accountable justification, (2) suggested alternatives, and (3) peer comparison with educational module	• EHR used for accountable justifications and suggested alternatives (pop-up of alternatives and educational material)		• Monthly peer comparison emails • Other clinicians see accountable justification	• Ordering an antibiotic in EHR		
Hux et al[22]	RCT of PCPs in Ontario randomized to mailed intervention combining prescribing feedback with educational bulletins	• Mailed intervention	• Prescribing feedback				
Hallsworth et al[23]	Randomized 2 × 2 factorial trial of GPs who prescribed antibiotics in the upper 20th percentile randomized to (1) patient educational leaflet and feedback and (2) patient-focused intervention	• Patient education leaflet • Patient-focused information	• Feedback intervention given letter saying they prescribed ≥80% of local practices				

Continued

Appendix B: Continued

Reference	SEIPS 2.0 Element						
	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Strykowski et al[24]	Spanish RCT of GPs: acute exacerbation of COPD or chronic bronchitis, comparing (1) multifaceted intervention and CRP POC, (2) multifaceted intervention alone, and (3) usual care	• CRP POC testing		• Both groups had follow-up meetings with individual feedback • Both groups had training on ARIs		• Brochures and posters in waiting rooms	
Foxman et al[25]	RCT of nonelderly patients in 6 areas in United States assigned to insurance plans varying by level of cost sharing						• Insurance policies regarding cost sharing
Long et al[26]	Shanghai RCT of patients with suspected CAP, randomized to procalcitonin or guidelines alone	• Procalcitonin testing					• Guidelines for CAP treatment
Arakaki et al[27]	Nonblinded RCT of adults diagnosed with cellulitis by PCP, randomized to outpatient dermatologic consultation			• Dermatologic consultation			
Taylor et al[28]	RCT of educational intervention aimed at parents of children <2 years of age	• Pamphlet, videotape with local pediatrician promoting judicious antibiotic use					
Torres et al[29]	Observer-blinded RCT parallel-group study of clinical prediction rule of which children have bacterial pneumonia	• More chest X-rays in the control group		• Alternative: management based on institutional guidelines			
Le Corvoisier et al[30]	RCT of GPs: interactive seminar presenting evidence-based guidelines for ARIs		• Subgroups: 2-day evidence-based medicine course only or with 1-day problem-solving course				• Specific French guidelines

Continued

Appendix B: Continued

Reference	Study Type	SEIPS 2.0 Element Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Meeker et al[31]	RCT in 5 adult primary care clinics to posted commitment letter or usual care in ARIs	● Letters/posters about avoiding inappropriate antibiotic prescribing included clinician photos and signatures				● Poster-sized commitment letters in exam rooms	
Brittain-Long et al[32]	Swedish randomized open label study to receive a rapid (next day) or delayed (8 to 12 days) result of PCR throat swab	● Multiplex PCR for respiratory viruses					
Christakis et al[33]	RCT of primary care pediatricians for POC evidence delivery on otitis media	● Computerized patient flow manager and online prescription manager	● NPs, physicians, and housestaff	● Computerized patient flow manager designed by clinics		● Computer workstations	
Dahler-Eriksen et al[35]	Danish randomized crossover trial of CRP measured within 3 minutes or with results in 1 to 2 days	● Intervention group: measure CRP within 3 minutes and got results 1 to 2 days later		● Needed hospital lab			
De la Poza Abad et al[36]	Pragmatic open label RCT among 23 Spanish primary care centers and ARIs to (1) delayed patient-led prescription, (2) delayed prescription collection strategy requiring patients to collect prescription from PCP, (3) immediate prescription, or (4) no antibiotics	● All patients given information about antibiotics ● Delayed prescription: prescribe antibiotics to take only if symptoms worsen	● Patients told it was normal to feel worse at first, depend on patient to decide to take antibiotics		● Patients told it was normal to feel worse at first		
Hemkens et al[37]	Swiss pragmatic randomized trial of PCPs with highest antibiotic prescribing randomized to quarterly prescription feedback over 2 years or usual care	● Website required physicians to log in with individual access code	● Personalized feedback by mail and online				● 1 time provision of evidence-based guidelines for ARIs and UTIs

Continued

Appendix B: Continued

		SEIPS 2.0 Element					
Reference	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Samore et al[38]	Cluster RCT in rural communities in Utah and Idaho comparing community intervention with CDSS on paper and CDSS with handheld computer	● Mailings to parents ● Refrigerator magnets ● Spiral bound flip chart for ARI self-management ● 3 CDSS tools made for ARIs ● Patient-initiated documentation tool ● CDSS generated diagnostic and therapeutic recommendations		● Local clinicians led initiative at local hospital medical staff meetings ● Continuing medical education ● Clinicians compensated for each visit and could keep handheld computers		● Exam room posters and brochures	● Meetings with community leaders ● News releases on self-management of ARIs ● Self-care materials distributed at health fairs ● Education at pharmacies and offices
Gerber et al[39] and Gerber et al[40]	Cluster randomized trial of pediatric practices focusing on ARIs,[39] and follow-up for 18 months after intervention terminated[40]	● ARI guidelines available as links in EHR	● Quarterly personalized feedback and audit	● 1 hour on-site clinician education ● Practice-specific antibiotic prescribing rates			● Used prescribing guidelines
Gonzales et al[41]	3-arm cluster randomized trial, with 11 practices in each group: (1) printed CDSS, (2) computerized CDSS, and (3) control.	● Arm 1: printed CDSS for acute cough ● Arm 2: EHR CDSS ● Arm 3: no decision support ● Arm 1 and 2: printed patient education material ● Arm 1 and 2: template for ARI clinic visits	● Provider education and feedback in both intervention groups	● Half-day training session	● Provider education ● Practice guidelines ● Clinical champions ● Audit and feedback		
Jenkins et al[42]	Cluster randomized study of 8 primary care clinics randomized to CDSS pathways and patient education or usual care	● 1 page CDSS pathway incorporated into EHR encounter template ● Patient education		● Peer champion provider at each clinic			

Continued

Appendix B: Continued

		SEIPS 2.0 Element					
Reference	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Finkelstein et al[43]	Cluster randomized trial: 12 pediatric practices in 2 MCOs in eastern Massachusetts and Washington State	• Parents mailed CDC brochure on antibiotic use		• Physician peer leaders reviewed prescribing guidelines in practice meetings • Given feedback on practice prescribing		• Education displayed in waiting rooms	• CDC campaigns for judicious antibiotic use
Meeker[44]	Cluster randomized study of 47 primary care practices randomized to receive 0, 1, 2, or 3 behavioral interventions: (1) suggested alternatives, (2) accountable justification, and (3) peer comparison	• Suggested alternatives: electronic order sets suggesting nonantibiotic treatments • Accountable justification: prompts to enter justifications for prescribing antibiotics for nonindicated diagnoses • All groups received online ARI diagnosis and treatment education	• Peer comparison: emails comparing antibiotic prescribing rates with those of top performers	• Accountable justification: written justification would be seen in EHR as a note			
Yang et al[45]	Matched-pair cluster randomized trial in China						• Disclosed prescribing status monthly to patients, health authorities, and health workers
Schnoor et al[46]	Cluster randomized trial of 8 German clinical centers and 4 computer-based interventions	• All received printed versions of poster and electronic version of guideline	• Every other month, GPs given peer comparison			• All received poster	

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Appendix B: Continued

Reference	SEIPS 2.0 Element: Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Finkelstein et al[47] and Ackerman et al[75]	Controlled, community-level cluster randomized trials in 16 Massachusetts communities: physician behavior change strategy[47] with follow-up[75]	• Discussion guide at well-child visits • Prescription pads for treatment of viral infections • Stickers, lapel pins, and otoscope insufflators • Bimonthly educational briefs • Patient brochure	• Introductory letter to pediatricians and family practitioners	• Educational coordinator visited practices • Kick-off dinners			• Advertisements at child care centers and pharmacies
Huang et al[48]	Cluster randomized trial of 3-year community-wide intervention for parents of children in 16 communities[11]	• Educational newsletters					• Educational materials in pediatrician offices, pharmacies, and child care settings
Vervloet et al[49]	Matched randomized study of meeting with PCPs and pharmacists, 4 groups with intervention, and 4 matched controls	• PCP communication skills training • Antibiotic prescribing agreements in EHR		• Feedback session about group's prescribing • More variation between physicians than within practices			
Linder et al[50]	Cluster randomized trial of 27 primary care practices to receive an EHR-integrated ARI CDSS	• CDSS tool integrated into EHR					
Linder et al[51]	Cluster RCT of 27 primary care practices, by using an ARI quality dashboard	• ARI quality dashboard	• Audit and feedback				
Cals et al[52] and Cals et al[53]	Pragmatic cluster randomized trial of Dutch PCPs of the impact of POC CRP testing and communication skills on antibiotic use in LRTIs,[52] with follow-up of 3.5 years[53]	• POC CRP testing	• Communication training for physicians	• Peer review of colleague transcripts with simulated patients			

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Appendix B: Continued

Reference	Study Type	SEIPS 2.0 Element: Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Mainous et al[54]	Quasi-experimental design with 3-month baseline data collection period and 15-month follow-up in 9 intervention and 61 control practices	• EHR CDSS tool is populated when ARI diagnosis entered • CDSS installed on each practice's EHR progress note template • Hyperlinks to patient and provider education	• Performance review • Audit and feedback	• Quarterly meetings with audit and feedback • Academic detailing • Monthly phone calls with staff			• NIH and CDC guidelines to improve antibiotic prescribing for ARIs • CDC Get Smart program
Slekovec et al[55]	Quasi-experimental study of French GPs on quinolone prescription for UTIs	• Guidelines mailed to GPs and available on website		• 200 GPs attended training sessions			• Regional guidelines
Gonzales et al[56]	Quasi-experimental community-level study of mass media campaign in Colorado with comparison communities		• Providers signed postcard soliciting support				• Mass media campaign including outdoor and radio advertisements, billboards, bus tails, bus stop posters, interior bus signs, health fairs, and opinion pieces
Hurlimann et al[57]	Swiss quasi-experimental study of sustained feedback of antibiotic prescription for ARIs and UTIs		• Sustained individual feedback				• New guidelines written
Vinnard et al[58]	Quasi-experimental study with concurrent control groups of academic detailing and educational mailings	• Educational mailings to providers and patients • Prescription pads for symptomatic treatments • Providers signed letters to patients	• Intensive intervention for highest prescribers	• Academic detailing of providers (visits from pharmacist and antimicrobial stewardship expert)			

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Appendix B: Continued

Reference	Study Type	SEIPS 2.0 Element: Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Gonzales et al[59]	Nonrandomized controlled trial, with (1) full intervention, (2) limited intervention, or (3) usual care	• Full intervention: household and office-based patient education materials • Limited intervention: office-based educational materials • Full intervention: educational refrigerator magnets • Full intervention: patients mailed pamphlet and letter from medical director		• Full intervention: clinician education • Full intervention: clinic-specific antibiotic prescription rate for acute bronchitis • Full intervention: 30 minutes of staff meeting • Full intervention: setting clinic goals	• Full intervention: education on acute bronchitis management • Full intervention: clinicians taught how to refuse antibiotic prescriptions	• Both intervention groups: educational posters in exam rooms	
Gonzales et. al[60]	Nonrandomized controlled trial of elderly patients with ARIs: 4 intervention practices and 51 control practices in Denver	• Mailed campaign to patients • Office-based materials • Introductory letter from Department of Public Health • Patient reference card on ARIs • Patient refrigerator magnet • Patient brochures on antibiotic resistance	• Focus groups with elderly volunteers for feedback	• Individual prescribing profiles	• Colorado-wide initiative to provide PCPs with performance feedback	• Office-based materials: CDC posters, patient reference cards, and exam room posters	
Formoso et al[61]	Community-level, controlled, nonrandomized trial in northern Italy of educational campaign						• Region-wide posters, brochures, and local media advertisements • Region-wide physician and pharmacist newsletter

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Appendix B: Continued

Reference	Study Type	SEIPS 2.0 Element: Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Yardley et al[62]	Process analysis of RCT of GPs in study of LRTI antibiotic prescribing, including web-based training in use of CRP	● Training software modifiable ● Patient booklet with checklist ● CRP intervention helpful	● Symptoms important to patients		● Completing patient booklet checklist		
Szymczak et al[63]	Semistructured interviews with pediatricians, following an intervention[39]		● Parental pressure as a barrier to stewardship	● Skepticism of audit and feedback reports ● One respondent admitted to gaming behavior			
Mustafa et al[64]	Semistructured interviews of family doctors on ARIs		● Avoiding confrontation ● Negotiating with patients ● Hedging ● Physical traits ● Exaggerated symptoms ● Patient expectations	● Clinicians ask patients about antibiotic expectations ● Pride ● Rapport	● Use physical exam findings to minimize signs ● Careful word choice ● Thorough exam ● Education ● Setting expectations		
Grondal et al[65]	Semistructured interviews of GPs regarding pharyngitis	● GPs believed rapid Streptococcus test to be unreliable, as it only detects one bacterium ● CRP used to diagnose bacterial pharyngitis as way to screen for all bacterial infections	● Clinical presentation outweighs test results ● Streptococcal pharyngitis should be diagnosed based on appearance		● All bacteria must be treated		● Clinical presentation outweighs guidelines for management of Streptococcal pharyngitis

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Appendix B: Continued

Reference	SEIPS 2.0 Element						
	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Munoz-Plaza et al[66]	In-depth interviews of 6 PCPs and 3 urgent care providers about acute sinusitis	• Need to find guideline when needed • Visual cards and graphs to show patients when they will improve • EHR with web-based patient education	• Help patients understand symptoms • Patients want reward for copays and taking off work	• Patients see physicians with different practices • No protected group education time • Large health systems enable system-level alerts • Limited time during patient visits		• Large educational posters in exam rooms	• External pressures for patient satisfaction • Patient can get antibiotics elsewhere • Information overload with updated guidelines • Copays for visits
Tonkin-Crine et al[67]	Semistructured interviews of experts involved in GP ARI guideline development across 5 countries	• Complementary patient education • Computer reminders to reinforce guidelines	• Address GP concerns and explain the need for guidelines • GPs worry about patients becoming ill without prescription • Prescribing feedback helpful	• Academic detailing • GPs assume practice already follows guidelines • GPs may not engage with mandatory meetings	• Flexible interventions increase feasibility • Interventions should engage GPs		• Develop guidelines based on research, not to save money • Guidelines should be consistent • Guidelines difficult to locate and lengthy • Local versions of national guidelines • Governmental funding and national campaigns

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Appendix B: Continued

	SEIPS 2.0 Element						
Reference	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Wood et al[68]	Qualitative interviews with PCPs in 9 European countries	• Request access to local resistance data	• Most PCPs did not see antibiotic resistance as a problem in their practice	• Antibiotic resistance seen as issue for secondary care rather than primary care			• Other countries thought to be responsible for resistance • Self-prescribing of antibiotics • Prescribing by dentists and hospital physicians leads to resistance
Mauffrey et al[70]	Qualitative study of French PCPs about preferences for interventions	• Dedicated prescription for antibiotics considered excessive • Limit antibiotic availability in outpatient settings • Computerized prescription aids • Educational resources for patients in office	• Physician training • Patient characteristics • Avoiding prescribing antibiotics is dangerous • Older prescribers: prescriptions influenced by habit	• Practice evaluation is difficult due to competing demands • Prior approval of ID physician would make practice harder	• Restricted susceptibility testing • Explain and repeat key messages • Role of PCPs in educating patients • Too many other health ministry-required tasks		• Performance-based incentives • Public campaigns reinforce what they tell patients • Physician awareness campaigns
Ronnerstrand et al[71]	Qualitative semistructured interviews: patients asked to imagine seeing a physician for ARI, and how long they would delay filling prescription	• Given prescription to fill later	• More trust means patients would delay prescription				• Willing to postpone treatment if told others would do the same • Social capital
Dempsey et al[72]	Semistructured interviews of 13 PCPs	• Prefer of CDSS • Prefer over-the-counter prescription pad • Prefer patient educational materials	• Meet patient expectations	• No accountability for prescribing • Other clinicians' misconceptions about acute bronchitis • Previsit triage and education by nurses may prevent visits	• Prescribe antibiotics to save time and money • Diagnostic uncertainty		• Reporting of quality measures may help

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Appendix B: Continued

Reference	SEIPS 2.0 Element						
	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Huddy et al[69]	Qualitative focus group study of barriers and facilitators to use of CRP for diagnosing CAP among European GPs	● Want not just POC CRP but other lab testing in the same system ● Need to test equipment and stay aware of shelf life of cartridges	● CRP as aid to communication	● Centralized labs ● Different people perform test in different clinics (GP, nurse, and in-house lab)	● Quality control tasks ● Responsibility of GP		● Although CRP is cost-effective, individual practices may be liable for the cost of the test ● Loss of income to central labs
Rowbotham et al[73]	Semistructured interviews and focus groups of UK NPs about experience with ARIs	● Used drawings or information leaflets to teach patients	● New NPs worried about making mistakes ● Patients exaggerated symptoms	● Peer support helpful with demanding patients ● Previous experiences with getting antibiotics from other providers		● Protocols support decision making ● Visits are time consuming and complex ● Provide self-management education ● Educate patients to prevent return visits	● Legal protection of NPs versus GPs
Kuzujanakis et al[74]	Parenteral surveys		● Parents demand antibiotics ● Privately insured and with more or older children had more knowledge		● Alternatives to antibiotics		● Media information about antibiotics ● School or day care requires antibiotics
Murphy et al[76]	Qualitative interview of GPs reviewing own charts of ARI encounters		● Children less likely to receive antibiotics		● Amoxicillin as placebo if physician did not think they need antibiotics ● Uncertainty in prescribing antibiotic		● External guidelines

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Appendix B: Continued

Reference	SEIPS 2.0 Element						
	Study Type	Tools / Technology Components	Person(s) Components	Organizational Components	Task Components	Physical Environment Components	External Environment Components
Anthierens et al[77]	Qualitative study using think-aloud approach with European GPs about using online tool for CRP ordering	• Online intervention • CRP used as evidence for patients on condition's seriousness • Tailoring for individual countries and languages	• Considering needs of patients • Level of attention and time taken needs to be brief	• Managing patient demands, fewer visits, decreased income •	• GPs use communication skills • Clarity of intervention • Physical exam used to communicate to patients		• Countries differ in how involved patients expect to be in the decision • Study in one country may not help in other countries

PCP, primary care provider; CDSS, clinical decision support system; RCT, randomized controlled trial; POC, point of care; ARI, acute respiratory infection; EHR, electronic health record; NIH, National Institutes of Health; CDC, Centers for Disease Control and Prevention; GP, general practitioner; LRTI, lower respiratory tract infection; CRP, C-reactive protein; ID, infectious diseases; MCO, managed care organization; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; NP, nurse practitioner; UTI, urinary tract infection; PCR, polymerase chain reaction; GAS, Group A Streptococcus; CAP, community-acquired pneumonia; UTI, urinary tract infection.

*Studies described include rigorously designed quantitative and qualitative studies describing antibiotic stewardship interventions and the context around antibiotic prescribing decisions, included through November 7, 2016.

Appendix C. Summary of the Impact of Ambulatory Antimicrobial Stewardship Interventions*

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Litvin et al[20]		• Choice of prescribing antibiotics			
Persell et al[21]	• Prescribing antibiotics		• Prescribed antibiotics in 24.7% of inappropriate ARI diagnoses prior to and only 5.2% after the study • Suggested alternative intervention decreased antibiotic prescribing • Suggested alternatives and peer comparisons decreased antibiotic prescribing for all ARI diagnoses combined		
Hux et al[22]			• Most providers were satisfied with intervention • More first line antibiotics used	• Median prescription cost rose in control group	
Hallsworth et al[23]			• Antibiotic prescription/1,000 people decreased		
Strykowski et al[24]					• GPs in full intervention reduced antibiotic overprescribing (OR, 0.35; 95% CI, 0.18 to 0.68) • Underprescribing was not significantly increased (OR, 0.25; 95%CI, 0.06 to 1.0; P = .075)
Foxman et al[25]					• 85% more antibiotics prescribed among those without copays than among those with copays
Long et al[26]		• Median duration of antibiotic: 5 days in intervention versus 7 days in control group • Prescription of antibiotics 84.4% in intervention versus 97.5% in control group			
Arakaki et al[27]	• Diagnosis of cellulitis made in 2/20 in intervention group and 3/9 in control group	• Antibiotic use in 2/20 patients in intervention versus all in control group • All improved 1 week later			

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Taylor et al[28]		• Number of ARI visits did not change • Number of diagnoses and antibiotic prescriptions for otitis media and sinusitis did not change • Antibiotic prescriptions per patient did not change			
Torres et al[29]		• Five patients in each group had unfavorable outcomes		• Antibiotic use decreased in clinical prediction group (48.6% versus 86.6%, $P < .001$)	
Le Corvoisier et al[30]			• Proportion of prescriptions containing an antibiotic decreased in intervention (15.2% to 12.3%; $P < .001$) but not control (15.3% to 16.4%; between group difference 3.93%) • Maintained improvement for 30 months after intervention terminated • More symptomatic treatment prescribed in treatment than control (7.8% versus 3.9%)		
Meeker et al[31]		• Antibiotic prescribing for nonindicated ARIs decreased in intervention (42.8% to 33.7%) but not control (43.5% to 52.7%) • Posted commitment letter decreased antibiotic prescribing for nonindicated diagnoses by 19.7% • No change in appropriate antibiotic prescriptions	• No diagnostic coding shift		
Brittain-Long et al[32]		• Rapid test result group prescribed fewer antibiotics within 48 hours of visit (4.5% versus 12.3%) • No difference in symptoms at follow-up • No significant adverse events			

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Christakis et al[33]			● Proportion of prescriptions for otitis media <10 days decreased 34% in intervention group ● Less likely to prescribe antibiotics in intervention		
Dahler-Eriksen et al[35]		● Antibiotics started earlier in patients with lower CRP concentrations ● No reduction in antibiotics		● Use of ESRs decreased by 8% in intervention ● Blood samples sent to hospital lab decreased by 6% ● Proportion of study patients needing a follow-up telephone call reduced from 63% to 53%	
De la Poza Abad et al[36]		● Symptom duration increased only for the no-prescription group ● No difference in symptom severity ● Antibiotic use less in no-prescription and delayed strategies ● Patient satisfaction similar across all groups ● Patient belief in antibiotic effectiveness decreased in no-prescription and delayed strategies			
Hemkens et al[37]	● Only 11% of physicians in the intervention group logged onto the online audit and feedback tool		● Overall antibiotic prescription in defined daily doses/100 clinic visits did not decrease in the first or second year (0.81%, $P = .64$; −1.73%, $P = .32$; respectively) ● Antibiotic prescribing decreased 8.61% among 6 to 18-year-old children in first year only ($P = .01$) ● Antibiotic prescribing declined 4.59% among adults aged 19 to 65 in second year only ($P < .01$)		

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Samore et al[38]					● Macrolides decreased in CDSS but not in community intervention alone ● Greater decrease in antibiotic prescribing in CDSS than in community intervention alone
Gerber et al[39]			● Combination of 2 practices decreased overall and broad-spectrum antibiotic prescribing		
Gerber et al[40]				● Antibiotic prescribing increased after intervention ended (intervention, 16.7% to 27.9%; controls, 25.4% to 30.2%; $P = .02$)	
Gonzales et al[41]				● Educational intervention did not further decrease ARI antibiotic prescription	
Jenkins et al[42]				● Antibiotic prescriptions decreased 42.7% to 37.9% versus 39.8% to 38.7% ● Decreased broad-spectrum antibiotic use	
Finkelstein et al[43]				● Ages 3 months to 3 years: intervention decreased 18.6% versus 11.5% in controls (16% adjusted effect) ● Age 3 to 5 years: intervention decreased 15% versus 9.8% in controls (12% adjusted effect)	
Meeker[44]			● Control practices: antibiotic prescription decreased from 24.1% to 13.1% ● Suggested alternatives: prescriptions decreased from 22.1% to 6.1% (insignificant) ● Accountable justification: prescriptions decreased from 23.2% to 5.2% ● Peer comparison: prescriptions decreased from 19.9% to 3.7% ● No interactions seen		

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Yang et al[45]			• Reporting at individual and institutional level		• Public reporting resulted in 9% decline in antibiotics
Schnoor et al[46]		• Decrease in CAP-related mortality higher in intervention (2.9% versus 0.5%) • No change in patient adherence to duration of treatment	• Increased proportion of visits adhering to antibiotic guidelines (5.6%)		
Finkelstein et al[47]					• Downward trend in prescribing even without intervention • Change in antibiotics dispensed per person-year: no decrease in those <2 years, but 4.6% decrease in 2 to 3 years and 6.7% decrease in 4 to 5 years
Huang et al[48]					• More parents in intervention communities correctly answered survey questions
Vervloet et al[49]		• Number of ARI antibiotic prescriptions decreased overall, but intervention group improved more			
Linder et al[50]	• 6% of ARI visits in the CDS group used the CDS		• Antibiotic prescribing rate for ARIs 39% in intervention versus 43% in control clinics (OR, 0.8; 95% CI, 0.6 to 1.2) • For antibiotic-appropriate ARIs, no difference antibiotic prescribing in intervention and control clinics (54% versus 59%) • For nonantibiotic appropriate diagnoses, no difference intervention and control clinics (32% versus 34%) • When CDSS used, associated with a lower antibiotic prescribing rate for acute bronchitis (OR, 0.5; 95% CI, 0.3 to 0.8)		

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Linder et al[51]	• Only 28% of intervention clinicians logged into the quality dashboard		• No difference in antibiotic prescribing for ARI visits overall (47% versus 47%, $P = .87$), antibiotic-appropriate ARI visits (65% versus 64%, $P = .68$), or nonantibiotic-appropriate ARI visits (38% versus 40%, $P = .70$) • Those who used the dashboard had a lower ARI prescribing rate (42% versus 50%, $P = .02$)		
Cals et al[52]		• Antibiotic prescribing at index visit: 31% in CRP and 53% without CRP; 27% in education and 54% in no training • Antibiotic prescribing during 28-day follow-up: no difference • Total antibiotic prescribing: 45% versus 58% with and without CRP and 38% versus 63% in communication skills training			
Cals et al[53]		• Long-term follow-up over next 2 to 3 years: no difference number of LRTI visits	• CRP not used over time: only in 3.7% of visits 2 to 3 years later	• Communication training led to a long-term decrease of 10.4% in visits resulting in antibiotic prescription	
Mainous et al[54]	• Use of CDSS tool • Help with diagnosis • Decide about antibiotics • How often CDSS template used	• Decreased overall prescribing of broad-spectrum antibiotics in adults and children (16.6% to 1.1% and 19.7% to 0.9%, respectively) and antibiotics overall among adults	• How often CDSS template used • Inappropriate prescribing • Diagnostic shift		

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Slekovec et al[55]					• Quinolone prescriptions decreased by 9%, but nitrofurantoin and fosfomycin increased by 36.8% and 28.5% respectively
Gonzales et al[56]		• No adverse impact on emergency department visits or ARI complications		• Fewer pediatric clinic visits	• Cost savings • 3.8% decrease in antibiotic prescriptions/1000 persons • 8.8% decrease in antibiotic dispenses/1000 managed care members
Hurlimann et al[57]				• Increased percentage of prescriptions of penicillins for ARIs treated with antibiotics (49% to 57%) • Did not decrease the percentage of COPD exacerbations treated with fluoroquinolones • Did not decrease the proportion of sinusitis and other upper ARIs treated with antibiotics	
Vinnard et al[58]			• Nonindicated antibiotic prescriptions decreased from 43% to 33% in academic detailing group		
Gonzales et al[59]		• Full intervention decreased antibiotic prescription for acute bronchitis (74% to 48%) but not control (78% to 76%) or limited intervention (82% to 77%)		• Diagnoses of acute bronchitis did not change	
Gonzales et al[60]		• Antibiotic prescribed to 64% of respondents at intervention and control clinics • Patient satisfaction did not differ: 69% very good or excellent satisfaction in intervention clinic, 63% in control clinic			

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Formoso et al[61]					• Defined daily doses of antibiotics/1,000 person-days decreased 4.3% in intervention area • Broad-spectrum antibiotics decreased more • Intervention did not affect knowledge and attitudes about antibiotic resistance
Yardley et al[62]	• Communication patient and clinician • Decision to provide antibiotic	• Belief in harm or need for antibiotics • Attitudes towards antibiotics • CRP: patient feels less enabled and less satisfied	• Importance of reducing antibiotic use • Perceptions of damage to patient/clinician relationship • Those who did CRP testing showed trend of lost confidence in ability to reduce antibiotic prescribing		• CRP testing means less antibiotics
Szymczak et al[63]	• Gaming of audit and feedback		• Belief in audit and feedback reports		
Mustafa et al[64]	• Learn patient expectations• Decide on antibiotic	• Patient/provider relationship • Education • Set expectations with next ARI	• Avoid confrontation • Patient/provider relationship • Dissatisfaction • Be a good physician	• Pride in practice	• Antibiotic resistance
Grondal et al[65]	• Choice to do rapid Streptococcus test • Choice to do CRP	• Antibiotics prescribed			
Munoz-Plaza et al[66]		• Poor satisfaction	• Unwarranted prescribing practices for sinusitis • Poor patient satisfaction score		
Tonkin-Crine et al[67]	• Use of guidelines among GPs		• Engage GPs in interventions		
Wood et al[68]					• GPs perceive antibiotic resistance as due to secondary care, pharmacists, dentists, and even other countries
Mauffrey et al[70]				• Interventions should not impact clinic flow	
Ronnerstrand et al[71]					• Patient trust in others

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Appendix C. Continued

Reference	Process Outcome	Patient Outcome	Provider Outcome	Clinic Outcome	System Outcome
Dempsey et al[72]		• Perception of patient requests			
Huddy et al[69]	• Quality checks of POC CRP testing	• Patients like the test	• Increase job satisfaction	• Too many visits	
Rowbotham et al[73]			• Clinician confidence		
Kuzujanakis et al[74]		• Prescribed antibiotic • Education on antibiotics			
Ackerman et al[75]	• Preferred an exam room poster with diagnostic algorithm	• Patient expectations seen as impacting prescribing	• Compared with prior surveys, clinicians demonstrated greater awareness of antibiotic resistance and impact of their prescribing decisions		
Murphy et al[76]			• Reminder of danger of antibiotic resistance		
Anthierens et al[77]	• Communication with patients	• Patient satisfaction	• Education about antibiotic resistance	• Fewer visits, decreased income	

ARI, acute respiratory infection; CDSS, clinical decision support system; OR, odds ratio; CI, confidence interval; CAP, community-acquired pneumonia; CRP, C-reactive protein; LRTI, lower respiratory tract infection; COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; POC, point of care; GP, general practitioner.

*As studied in rigorously designed quantitative and qualitative studies describing the context around antibiotic prescribing decisions and antibiotic stewardship interventions, through November 7, 2016 on outcomes, including process outcomes and outcomes to the patient, provider, clinic, and health system.