APPENDIX A. SEARCH STRATEGY

Database: Ovid MEDLINE(R)

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

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

APPENDIX B. RISK OF BIAS CRITERIA*

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

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

Was the allocation sequence adequately generated?

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

Was the allocation adequately concealed?

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

Were baseline outcome measurements similar?[1,2]

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

Were baseline characteristics similar?

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

Were incomplete outcome data adequately addressed?[1]

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

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

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

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

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

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

Was the study adequately protected against contamination?

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

Was the study free from selective outcome reporting?

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

Was the study free from other risks of bias?

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

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

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

Was the intervention independent of other changes?

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

Was the shape of the intervention effect pre-specified?

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

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

Was the intervention unlikely to affect data collection?

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

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

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

Were incomplete outcome data adequately addressed?[3]

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

Was the study free from selective outcome reporting?

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

Was the study free from other risks of bias?

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

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

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

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

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

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

APPENDIX D. EVIDENCE TABLES

Table 1. Study Characteristics

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2. Study Characteristics, Continued

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 3. Prescribing Outcomes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4. Patient Outcomes

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

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

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

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

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

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

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

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

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

Table 5. Cost and Harms Outcomes

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

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

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

†Euros/inhabitant

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

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

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

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

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

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

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

Table 7. Risk of Bias Assessment for ITS Studies

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

ITS = interrupted time series