Evidence-based Practice Center Systematic Review Protocol

Project Title: Interventions to Improve Appropriate Antibiotic Use for Acute Respiratory Tract Infections

Amendment Date(s): September 17, 2014

(Amendment Details – see Section VII)

I. Background and Objectives for the Systematic Review

Nature and burden of inappropriate antibiotic use for acute respiratory tract infections. Antibiotics transformed medical practice in the last half of the 20th century. Penicillin was even called a miracle drug by many in the 1950s and 1960s. Since that time, however, there has been increasing awareness that treating non-bacterial illnesses or those that are self-limiting with antibiotics contributes to the development of antibiotic-resistant bacteria.[1,2] Reducing inappropriate antibiotic use is critical to slowing the progression of these resistant bacteria. Furthermore, inappropriate antibiotic use exposes patients unnecessarily to potential side effects associated with antibiotics and increases medical costs.

Acute respiratory tract infections (RTIs) account for approximately 70 percent of primary diagnoses in adults presenting for an ambulatory office visit with a chief symptom of cough.[3] Acute RTIs include acute bronchitis, otitis media, pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes[4] Standard management of acute RTIs is to focus on ruling out serious illness in which antibiotics are indicated, such as bacterial pneumonia, and provide education and symptomatic relief for illnesses that do not require antibiotics. Existing clinical guidelines indicate that acute bronchitis and other acute RTIs that can be caused by viral or bacterial infections and are generally self-limiting should generally not be treated with antibiotics unless certain clinical indications are present. [4]Despite guidelines recommending no antibiotic treatment for most acute RTIs, the majority of outpatient antibiotic prescriptions in the US are for acute RTIs. In 1998, an estimated 76 million ambulatory office visits for acute RTIs resulted in 41 million antibiotic prescriptions.[5] A 2013 report of healthy adults visiting outpatient offices and emergency departments for acute bronchitis revealed prescriptions for antibiotics were given at 73 percent of visits between 1996 and 2010,[6] despite the fact that the majority of acute bronchitis cases are caused by viral pathogens for which antibiotics are not helpful. Therefore strategies that can help bring antibiotic use for RTIs in line with current evidence-based guidelines are clearly needed.

Interventions for improving appropriate use of antibiotics for RTI. Strategies to improve appropriate use of antibiotics for RTIs vary by both whose behavior they are trying to influence and how they are seeking to change that behavior. Strategies may target clinicians and others who care for patients with acute RTI in outpatient settings, adult and pediatric patients with acute RTI, the parents of pediatric patients with acute RTI, healthy adults and/or children without a current acute RTI, or groups whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials). Interventions may also fall into one of several

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categories. *Educational strategies* include educating clinicians about current treatment guidelines or providing information to patients or parents of patients about why antibiotic treatment is not recommended. *Strategies to improve communication* between clinicians and patients include interventions designed to improve shared decision making. *Clinical strategies* include delayed prescribing of antibiotics or use of point-of-care diagnostic tests (e.g., rapid strep). *System level strategies* include clinician reminders (paper-based or electronic), clinician audit and feedback, and financial or regulatory incentives for clinicians or patients. Furthermore, multifaceted approaches may include numerous elements of one or more of the strategies.

Relevant outcomes. The increasing prevalence of antibiotic resistant microorganisms is the principal public health concern motivating efforts to improve appropriate antibiotic prescriptions and use. Additionally, improved appropriate antibiotic use is expected to have other benefits, particularly a reduction in adverse drug events related to antibiotics. These are the most important health outcomes of interest in evaluating interventions to improve appropriate antibiotic use. However, because these outcomes can be difficult to measure directly, other outcomes that occur intermediately between the intervention and the health outcome are also important in evaluating the impact of such interventions. For example, antibiotic resistance may be affected by factors other than inappropriate prescribing of antibiotics for acute RTI. The most commonly reported outcome is likely to be the rate of appropriate antibiotic prescription. While this is the most direct outcome of interventions intended to improve appropriate prescription, there is not always consensus on how appropriateness is defined and measured. Therefore it will be important to capture how each study defines and measures appropriateness and consider this heterogeneity in the analysis. Other relevant intermediate outcomes include improved knowledge regarding use of antibiotics for acute RTI and improved shared decision making by patients and clinicians. These outcomes have a weak link to health outcomes, including antibiotic resistance than other intermediate outcomes.

There are also potential negative effects from these interventions. Because individual clinical assessments of the need for antibiotics are not always accurate, a variety of other desirable and undesirable outcomes might be affected by efforts to improve appropriate antibiotic use. For example, if efforts to improve appropriate antibiotic use resulted in under-treatment of patients for whom antibiotics would have been indicated, undesirable outcomes such as medical complications, hospital admissions, and mortality might increase. Similarly, reduced prescription of antibiotics may lead to increased clinic visits, longer duration of symptoms, or longer time to return to school or work. Depending on patients' expectations, patient satisfaction may also be affected. The interventions themselves also may require substantial time and resources. Therefore, a systematic review of interventions to improve appropriate antibiotic use should also include those outcomes.

Existing guidance. Existing guidelines recommend the use of various interventions to improve appropriate antibiotic prescription by physicians and reduce the use of antibiotics by patients. A 2008 guideline by the United Kingdom's National Institute for Health and Clinical Excellence (NICE), entitled "Respiratory tract infections- antibiotic prescribing," recommends delayed antibiotic prescribing and patient education about the expected duration of RTI symptoms.[4] As a strategy to improve appropriate antibiotic use in children, the US Centers for Disease Control and Prevention (CDC) recommends that clinicians educate parents about the ineffectiveness of treating most upper respiratory infections with antibiotics and planning for treatment of

symptoms[7] The Michigan Quality Improvement Consortium suggests similar strategies, and recommends using the term "chest cold" with patients to describe an acute respiratory infection, as this less technical term is thought to sound more commonplace and less likely to require antibiotics.[8] Each of these guidelines is limited – in its scope, in its evidence base, or in its assessment of the comparative effectiveness of different strategies in different patients under different circumstances. For example, the Michigan Quality Improvement Consortium guidelines are based on evidence limited to acute bronchitis. And, the 2008 NICE guideline report recognizes its limited conclusions with recommendations for needed future research into questions of comparative effectiveness of interventions and subgroup differences. Finally, the evidence upon which these guidelines are based is not current.

Availability of scientific data and rationale for an evidence review. Inappropriate prescribing and use of antibiotics for acute RTIs is a common and serious public health problem. Therefore, it is important to understand the comparative effectiveness of strategies for reducing inappropriate antibiotic use. Previous systematic reviews and existing guidelines are lacking in a variety of ways that limit their usefulness for addressing the key questions proposed for the current topic. Notably, these reviews have not assessed the actual *comparative* effectiveness of various strategies. A 2006 technical review by AHRQ, entitled "Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies Volume 4—Antibiotic Prescribing Behavior." included evidence about inappropriate use of antibiotics when none are indicated, as well as use of the incorrect antibiotic when one is indicated. [2] The report concluded that some quality improvement strategies may be moderately effective in reducing inappropriate antibiotic prescription; that no single strategy is clearly superior, but clinician education and delayed prescribing may be more effective in certain settings; and that interventions targeting prescribing for all acute RTIs may be more effective than those that target a single type of RTI. While included was not limited to RTIs, it appears to be designed to adequately address the literature related to RTIs. The most comprehensive review to date, the 2006 AHRQ review, is out of date (published in 2006) and not specific to RTIs. Our literature scan identified three additional systematic reviews of strategies designed specifically to improve appropriate antibiotic use for acute RTI. One of those reviews, from 2004, was limited to a single strategy (delayed prescribing), and was not cited in the 2006 AHRQ technical review.[9] The other two systematic reviews were published in 2012 and 2013.[10,11] Both of these latter two reviews were limited to pediatric patients; one was further limited to interventions targeting parents or caregivers[10] and the other was limited to interventions directly targeting clinicians and/or parents. [11] These reviews leave gaps in knowledge about interventions aimed at adult populations, other types of interventions or outcomes., We find that there are a sufficient number of studies published since these reviews were conducted that conclusions may be altered; in addition to the trials summarized in these reviews, through a preliminary literature search we found 11 randomized controlled trials and 10 nonrandomized studies of strategies to improve appropriate antibiotic use for acute RTI published since the 2006 AHRQ report. For these reasons, the proposed systematic evidence review would be valuable for assessing the comparative effectiveness of a breadth of possible strategies for reducing antibiotic use when not indicated for acute RTIs in adults and children.

II. The Key Questions

The topic was nominated by a diverse group of stakeholders, including patients, clinicians, professional societies, and insurers through an AHRQ-sponsored topic identification exercise. Topic refinement was undertaken by the Pacific Northwest Evidence-based Practice Center (PNW EPC), including consultation with a group of Key Informants and AHRQ representatives. AHRQ posted the revised key questions on the Effective Health Care Website for public comment. The comments received addressed the definition of appropriate use of antibiotics for acute RTI, inclusion of patients in institutional settings, framing of key questions as applying to patients versus a broader population (e.g. the general public, or targeted healthy groups), inclusion of patients with cough as the primary symptom of acute RTI, further delineation of interventions and intervention characteristics to be considered, inclusion of some point-of-care diagnostic tests, further delineation of outcomes and outcome characteristics to be included, consideration of the need to compare settings (e.g. primary care and emergency care), and improvements to the analytic framework. The key questions and inclusion criteria were modified based on these comments, and comments from the key informants and AHRQ representatives. Changes included:

- Stipulating that institutional settings will be included under outpatient settings
- Expanding the interventions list to include point-of-care diagnostic tests and interventions that work through behavioral or psychological mechanisms
- Adding patient-centered communication that is appropriate for culture and level of health literacy to the outcomes for KQ3
- Adding frailty and comorbidity as examples of important factors in the prior medical history to be considered in KQ 1b
- Adding physical signs as part of the patient characteristics considered under KQ1b, to reflect elements of a physical exam relevant to diagnosis of acute RTI
- Definitions and methods for determining appropriate versus inappropriate use of antibiotics in Acute RTI will be recorded as reported in each study, including where one or both are not reported. We will undertake analysis of the results based on variation in these variables to assess their potential impact on outcomes.

The PNW EPC solicited additional input from the Technical Expert Panel (TEP). Refinements of note based on TEP input include:

- Reframed focus from reducing inappropriate use to improving appropriate use
- Further clarified approach to handling variation in appropriateness definitions
- Population: Removed list of indications for antibiotic treatment
- Interventions: Broadened list to include additional point of care tests (e.g. procalcitonin, C-reactive protein (CRP), , rapid multiplex polymerase chain reaction (PCR) tests -influenza, rapid strep, RSV (white blood cell, chest x-ray, pulse oximetry, blood gasses), clinical prediction rules, antimicrobial stewardship programs, risk assessment/prognostic diagnosis, and pharmacist review
- Outcomes: ED visits, all clinic visits (including for index, return and subsequent episodes), *clostridium difficile* infections, sustainability, diagnostic coding according to desired action, improvement in patient symptoms, speed of improvement, utilization of vaccinations, quality of life
- Key sources of variation: When counting began for duration of signs and symptoms, previous RTIs, the diagnostic method or definition used, the clinician's perception of

the patient's illness severity, or the clinician's diagnostic certainty, source of resistance data (population versus study sample)

Final Key Questions

Key Question 1: For patients with an acute respiratory tract infection (RTI) and no clear indication for antibiotic treatment, what is the comparative effectiveness of particular strategies in improving **the appropriate prescription or use of antibiotics** compared with other strategies or standard care?

a) Does the comparative effectiveness of strategies differ according to how appropriateness is defined?
b) Does the comparative effectiveness of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
c) Does the comparative effectiveness of strategies differ according to patient characteristics, such as type of RTI, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, and prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
d) Does the comparative effectiveness of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
e) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
f) Does the comparative effectiveness differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), system-level characteristics, or whether the intervention was locally tailored?

Key Question 2: For patients with an acute respiratory tract infection (RTI) and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on **antibiotic resistance and medical complications** (including mortality and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

a) Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b) Does the comparative effect of strategies differ according to patient characteristics, such as type of RTI, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c) Does the comparative effect of strategies differ according to clinician characteristics,

such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?

d) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e) Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored, system-level characteristics, or the source of the resistance data (i.e., population versus study sample)?

Key Question 3: For patients with an acute respiratory tract infection (RTI) and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on **other clinical outcomes (e.g., hospitalization, health care utilization, patient satisfaction**) compared with other strategies or standard care?

a) Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b) Does the comparative effect of strategies differ according to patient characteristics, such as type of RTI, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c) Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
d) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e) Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored or system-level characteristics?

Key Question 4: For patients with an acute respiratory tract infection (RTI) and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as **improved knowledge regarding use of antibiotics for acute RTIs (clinicians and/or patients), improved shared decision making** regarding the use of antibiotics**, and improved clinician skills** for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

Key Question 5: What are the comparative **non-clinical adverse effects** of strategies for improving the appropriate use of antibiotics for acute RTIs (e.g., increased time burden on clinicians, patients, clinic staff)?

The following inclusion/exclusion criteria reflect input from key informants, public comments, AHRQ and the TEP.

Populations

1) Adult and pediatric patients with an acute respiratory tract infection (RTI) and no clear indication for antibiotic treatment. Respiratory tract infections of interest include: acute bronchitis; otitis media; sore throat/pharyngitis/tonsillitis; rhinitis; sinusitis; cough and common cold.[4]

2) Parents of pediatric patients with acute RTI and no clear indication for antibiotic treatment

3) Healthy adults and/or children without a current acute RTI, who may develop an acute RTI in the future.

4) Clinicians and others who care for patients with acute RTI in outpatient settings

5) Groups whose attendance policies may indirectly affect the use of antibiotics, such as employers or school officials

Interventions

Any strategy for improving appropriate use of antibiotics when not indicated for acute RTI, which may fall into various categories, including:

1) ***Educational, behavioral and psychological interventions*** that target clinicians, patients, or both
2) ***Strategies to improve communication*** between clinicians and patients, such as those designed to improve shared decision making
3) ***Clinical strategies***, such as delayed prescribing of antibiotics, clinical prediction rules, use of risk assessment or diagnostic prediction, use of non-antibiotic alternatives, or use of relevant point-of-care (POC) diagnostic tests.
    a. EPC will include any POC test that is available and used in primary care settings for diagnostic purposes with the ability to provide results within a reasonable period (e.g. during the clinic visit). Examples include inflammatory tests (e.g., procalcitonin, C-reactive protein [CRP], white blood cell, etc.), rapid multiplex polymerase chain reaction (PCR) tests used to rule in/out organisms (e.g. rapid strep test, influenza, RSV), routine diagnostic tests, such as chest x-ray, pulse oximetry, and blood gasses, when they are specifically evaluated as an intervention for improving antibiotic use.
4) ***System level strategies***, such as clinician reminders (paper-based or electronic), clinician audit and feedback, financial or regulatory incentives for clinicians or patients, antimicrobial stewardship programs, pharmacist review
5) ***Multifaceted approaches*** that include numerous elements of one or more of the above strategies

Comparators

1) Different strategies for improving appropriate use of antibiotics when not indicated for

acute RTI
2) Standard care without a strategy for improving appropriate use of antibiotics

Outcomes

Key Question 1

- ***Increased appropriate prescription of antibiotics*** (primary outcome)
- ***Increased appropriate use of antibiotics*** (primary outcome)

Note: studies may vary in how appropriateness is defined or determined. We will accept and record any definition of appropriateness. We will group together studies that use similar definitions of appropriateness and categorize the different groups based on concordance with (e.g., high, medium, low) select clinical practice guidelines (e.g., AAP, ACCP, AAFP). We will then evaluate whether the comparative effectiveness of strategies differ across categories. We may also find that overall reduction in antibiotic prescription or use is reported, without a determination of appropriateness. While this is not a direct measure of the primary outcomes, we will report these as indirect measures of the impact of the intervention.

Key Question 2

- Mortality
- Antibiotic resistance
- Medical complications
- Adverse drug effects, including *clostridium difficile* infections

Key Question 3

- Admission to hospital,
- Clinic visits (Index, return and subsequent episodes), ED visits
- Time to return to work and/or school
- Patient satisfaction
- Quality of life
- Improvement in patient symptoms, speed of improvement
- Use of non-antibiotic treatments, such as over-the-counter medications
- Utilization of vaccinations
- Quality metrics

Key Question 4

Intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute RTI (clinician and/or patient), or improved shared decision making

Key Question 5

Adverse effects of the strategy, such as increased time burden on clinicians, sustainability of intervention (e.g. measures of continued effectiveness over time), diagnostic resource use associated with POC testing, diagnostic coding (e.g. ICD billing codes) according to desired action (prescribe/not prescribe)

Timing

Any duration of follow-up

Setting

1) Outpatient care settings including institutional settings
2) Emergency care settings
3) Other settings, such as school or workplace

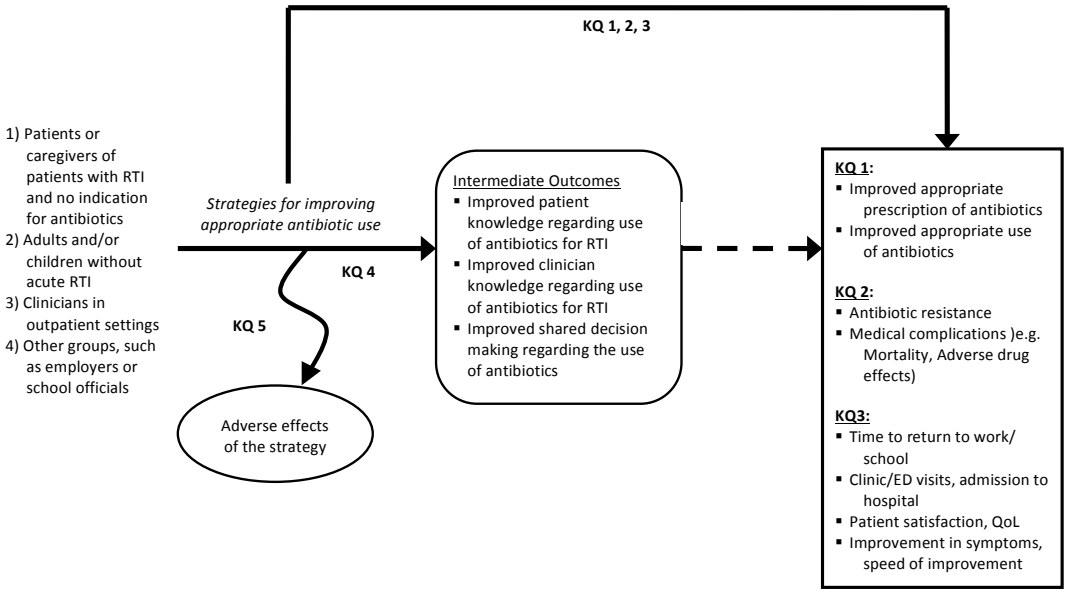
Study design

We will prioritize comparative studies with concurrent control groups (e.g. randomized controlled trial, prospective and retrospective cohort studies including database studies). For areas in which direct comparative evidence is lacking, we will include before-after studies, with or without a control group and with or without repeated measures.

III. Analytic Framework

The analytic framework below illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.

Figure 1. Analytic framework for Improving Appropriate Antibiotic Use for Acute RTIs.



Abbreviations: RTI, Respiratory Tract Infection; ED, Emergency Department; QoL, Quality of Life. *Including adults, children, or the parents of children with acute RTI.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included based on the population, intervention, comparator, outcomes, timing settings and study designs set out above. No sample size limits will be applied. Based on input from our TEP, and as we recognize that the 1990s mark the decade when many organizations, such as the Centers for Disease Control and Prevention, initiated formal efforts to promote appropriate antibiotic use, the PNW EPC will restrict inclusion to studies published since 1990.[12] Given the existence of good quality systematic reviews after 2000, and information from our TEP that there are few relevant studies before 2000 we will identify studies published from 1990 to 2000 though systematic reviews of the topic (with confirmation by the TEP that nothing important has been missed). Primary literature published from 2000 onward will be identified through primary literature searches. Due to resource limitations, we will include only studies published in English; studies published in other languages but appearing to be eligible based on the title or English-language abstract will be identified to evaluate potential language bias.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

To identify articles relevant to each KQ, the librarian will search the MEDLINE®, Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts of Reviews of Effects (DARE), and National Health Service Economic Evaluation Database (NHS EES). Multiple strategies were developed, a sample MEDLINE search strategy appears in the Appendix. Grey literature will be identified by searching clinical trial registries (ClinicalTrials.gov, WHO Trial Registries) and Scientific Information Packets will be solicited from relevant stakeholders (e.g., manufacturers of point of care tests, advocacy groups, professional societies, large healthcare organizations, etc.) through the Scientific Resource Center. The search strategy was reviewed by a second medical librarian who provided comments to improve the strategy.

All above-described electronic searches will be updated when the draft report is posted for public comment and sent to peer reviewers.

Regardless of publication status, any additional studies identified during public and peer review—found from the updated literature search or found in the grey literature or Scientific Information Packets will be reviewed for inclusion using the same study selection process described above. The PNW EPC will include supplemental unpublished data (e.g., additional outcomes and analyses) relating to a published study only if the following details of the analysis are provided: type of statistical test used, numbers analyzed, and whether an intention-to-treat analysis was conducted. Study authors will be contacted for additional data only related to key outcomes and only when we are missing data necessary for a meta-analysis.

Study Selection

Study selection will follow AHRQ guidance for reducing bias.[13,14] Citations identified through searches will be screened for eligibility by one reviewer, with any deemed ineligible reviewed by a second reviewer. Full-text of all citations deemed potentially eligible for inclusion by at least one reviewer will be obtained for further evaluation. Full-text articles will be reviewed by two reviewers, with differences in judgment on eligibility resolved through consensus or inclusion of a third party. The review team will hold discussions after <10% of papers have been screened to refine understanding of the criteria for study inclusion. Any refinements to the criteria will be noted in protocol amendments.

Data Abstraction and Data Management

The following data will be abstracted from included studies: design; setting (community/private/public clinic, hospital); population characteristics (race, age, socioeconomic status, population prevalence); eligibility and exclusion criteria; characteristics of acute RTI diagnosis; intervention characteristics; numbers of participants screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. One reviewer will abstract study data, and a second reviewer will review abstractions. Intention-to-treat results will be recorded if available. Potential effect modifiers that will be considered are listed in Table 1, below.

Assessment of Methodological Risk of Bias of Individual Studies

The internal validity (quality) of systematic reviews, randomized trials, and cohort and case control studies will be assessed based on predefined criteria established by the Drug Effectiveness Review Project.[15] For trials, these criteria were based initially on the criteria used by the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom).[16,17] In rating the internal validity of trials, we evaluate methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; adequate reporting of dropouts, attrition, loss to follow-up; and the use of intention-to-treat analysis.

The internal validity of observational studies will be rated based on the adequacy of the patient selection process; whether there was important differential loss to follow-up or overall high loss to follow-up; the adequacy of event ascertainment; whether acceptable statistical techniques were used to minimize potential confounding factors; and whether the duration of follow-up was reasonable to capture investigated events.

All assessments will be done at the overall study level and will result in a rating of good, fair, or poor. Studies that have a fatal flaw will be rated poor in quality; studies that meet all criteria will be rated good in quality; the remainder will be rated fair in quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality study is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared interventions. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist, for example unclear randomization and allocation concealment methods combined with differences between randomized groups at baseline in potentially prognostic characteristics and either high attrition or lack of an intention to treat analysis.

All studies will first be rated by one reviewer and then checked by another reviewer. All disagreements will be resolved using a consensus process.

Data Synthesis

Evidence tables will be constructed to show the study characteristics, quality ratings, and results for all included studies.

To determine the appropriateness of pooling outcomes (e.g. percent reduction in antibiotic prescribing or use) using meta-analysis, the quality of the studies and the heterogeneity among studies in design, population, interventions, and outcomes will be considered. In consultation with our statistician, we will consider a network analysis to make comparisons across interventions if direct comparisons of interventions are incomplete.

Sources of heterogeneity, those that may contribute to variation in outcomes as effect modifiers, of particular interest include:

Table 1. Potential sources of heterogeneity

Category	Sources of heterogeneity
Population	Type of RTI, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, and prior use of antibiotics, age, ethnicity,

	socioeconomic status, and educational level attained
Interventions	Clinician characteristics: Specialty, number of years in practice, type of clinic organization, geographic region, and population served Diagnostic method or definition used Clinician's perception of the patient's illness severity Clinician's diagnostic certainty Local tailoring Accuracy of diagnostic tests
Outcomes	Appropriate prescription/use: Definition of appropriateness Antibiotic resistance: Data source (i.e., population versus study sample)
Setting	Time of year; during a disease epidemic or outbreak period

Appropriate measures will be chosen based on the type of data for meta-analysis (e.g. relative risk, odds ratio). The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) will be calculated to assess heterogeneity in effects between studies.[18,19] Random-effects models will be used to estimate pooled effects.[20] Statistical heterogeneity will be explored by using subgroup analysis or meta-regression. Forest plots will be used when applicable to graphically summarize the results of individual studies and of the pooled analysis.[21]

Good and fair quality trials will be given more weight than poor quality trials. If quantitative syntheses are conducted, sensitivity analyses with and without poor quality studies will be undertaken. If both trial and observational studies are found for a given intervention-outcome pair, trial evidence will be given more weight except in situations where the observational evidence meets criteria for upgrading as outlined in the EPC guidance on grading the strength of the evidence. [13] Sensitivity analyses are also planned to evaluate differing definitions for inappropriate antibiotic use.

When meta-analysis cannot be performed, the data will be summarized qualitatively, grouping studies by similarity of population and/or intervention characteristics, including the sources of variation or heterogeneity listed above.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will use the methods outlined in chapter 10 of the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews13 to grade strength of evidence. Outcomes selected for grading will be those that are likely to be of considerable importance to most users of the report. After consultation with the TEP members, we will prioritize the following outcomes: appropriate antibiotic prescription, antibiotic resistance, medical complications, adverse drug effects, admission to hospital, clinic visits (index, return and subsequent episodes), ED visits, improvement in patient symptoms, speed of improvement, patient satisfaction, quality of life, and adverse effects of intervention.

Domains considered in grading the strength of evidence include study limitations, consistency, directness, precision and reporting bias. Reporting bias will be assessed following EPC guidance (Appendix A), [13] using tests for funnel plot asymmetry when $\geq$ 10 studies are pooled to assess publication bias. Selective outcome and analysis reporting bias will be assessed during individual study quality assessment, using trial registry protocols where available, and study publication Methods where protocols are not available. Based on assessment of these domains, the body of evidence will be assigned a strength-of-evidence grade of high, moderate,

or low. In cases where evidence does not exist, is sparse, or contains irreconcilable inconsistency, a grade of insufficient evidence will be assigned.

Assessing Applicability

Applicability will be assessed by paying special attention to study eligibility criteria, characteristics of the enrolled population in comparison to the target population, characteristics of the intervention and comparator used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. Technical experts assisted the PNW EPC in identifying key features that may impact applicability. In general, these will include subgroups specified in Key Questions 1-3 (sub-questions a-e) that are based on the intended target of the strategy (i.e., clinicians, patients, both), patient characteristics (type of RTI, nature and duration of signs and symptoms, previous medical history, prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level), clinician characteristics (specialty, number of years in practice, type of clinic organization, geographic region, and population served), intervention characteristics (local tailoring, diagnostic method or definition used), comparisons, and setting characteristics (time of year; during a disease epidemic or outbreak period). We will summarize issues of applicability qualitatively.

V. References

1. Hueston WJ, Mainous AG, 3rd. Acute bronchitis. Am Fam Physician. 1998 1998 Mar 15;57(6):1270-6. PMID: 9531910.
2. Ranji S, Steinman M, Shojania K. Antibiotic Prescribing Behavior. In: Shojania KG MK, Wachter RM, Owens DK, ed Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies. Technical Review 9 (Prepared by the Stanford University-UCSF Evidence-based Practice Center under Contract No. 290-02-0017). AHRQ Publication No. 04(06)-0051-4. Vol. 4. Rockville, MD: Agency for Healthcare Research and Quality. ; 2006.
3. Metlay JP, Stafford RS, Singer DE. National trends in the use of antibiotics by primary care physicians for adult patients with cough. Arch Intern Med. 1998 Sep 14;158(16):1813-8. PMID: 9738612.
4. National Institute for Health and Clinical Excellence. Respiratory tract Infections-Antibiotic Prescribing: Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. http://www.nice.org.uk/nicemedia/pdf/cg69fullguideline.pdf. Accessed on October 16 2013.
5. Gonzales R, Malone DC, Maselli JH, et al. Excessive antibiotic use for acute respiratory infections in the United States. Clin Infect Dis. 2001 Sep 15;33(6):757-62. PMID: 11512079.
6. Barnett ML, Linder JL. Antibiotic Prescribing for Adults with Sore Throat in the United States, 1997-2010. JAMA Intern Med. 2013;Published online October 03, 2013. doi:10.1001/jamainternmed.2013.11673 PMID: 24091806.
7. CDC. Careful antibiotic use: Make promoting appropriate antibiotic use part of your routine clinical practice. . http://www.cdc.gov/getsmart/campaign-materials/info-sheets/child-practice-tips.pdf.

8. Michigan Quality Improvement Consortium. Management of uncomplicated acute bronchitis in adults. : Michigan Quality Improvement Consortium; Southfield (MI). 2010
9. Spurling GKP, Del Mar CB, Dooley L, et al. Delayed antibiotics for symptoms and complications of respiratory infections. Cochrane Database Syst Rev. 2004(4):CD004417. PMID: 15495108.
10. Andrews T, Thompson M, Buckley DI, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PLoS ONE 2012;7(1):e30334. PMID: 22299036.
11. Vodicka TA, Thompson M, Lucas P, et al. Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. Br J Gen Pract. 2013 Jul;63(612):e445-54. doi: 10.3399/bjgp13X669167. PMID: 23834881.
12. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. Jama. 2002 Jun 19;287(23):3096-102. PMID: 12069672.
13. Berkman ND, Lohr KN, Ansari M MM, Balk E, Whitlock E,, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Comparative Effectiveness Reviews (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13(14)-EHC130-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
14. McDonagh M, Peterson K, Raina P, et al. Avoiding Bias in Selecting Studies. Methods Guide for Comparative Effectiveness Reviews. (Prepared by the Oregon Health & Science University, McMaster University, and Southern California Evidence-based Practice Centers under Contract No. 290-2007-10057-I.) AHRQ Publication No. 13-EHC045-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
15. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the Drug Effectiveness Review Project. BMC Med Res Methodol. 2012;12(140).
16. Center for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). 2001.
17. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med. 2001;20(3Suppl):21-35. PMID: 11306229
18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. PMID: 12958120.
19. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539--58.
20. Sutton AJ, Abrams KR, Jones DR, et al. Methods for Meta-Analysis in Medical Research: John Wiley & Sons, Inc.; 2000.
21. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. BMJ. 2001; 322(7300):1479-80. PMID: 11408310

VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
9/17/2014	Introduction	**Interventions for improving appropriate use of antibiotics for RTI.** Strategies to improve appropriate use of antibiotics for RTIs vary by both whose behavior they are trying to influence and how they are seeking to change that behavior. Strategies may target clinicians and others who care for patients with acute RTI in outpatient settings, adult and pediatric patients with acute RTI, the parents of pediatric patients with acute RTI, healthy adults and/or children without a current acute RTI, or groups whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials). Interventions may also fall into one of several categories. *Educational strategies* include educating clinicians about current treatment guidelines or providing information to patients or parents of	**Strategies to improve appropriate use of antibiotics for RTIs.** Strategies to improve appropriate use of antibiotics for RTIs vary by both whose behavior they are trying to influence and how they are seeking to change that behavior. Strategies may target clinicians and others who care for patients with acute RTI in outpatient settings, adult and pediatric patients with acute RTI, the parents of pediatric patients with acute RTI, healthy adults and/or children without a current acute RTI, or groups whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials). Interventions can vary in degree of active participation required on the part of the clinician or patient, and can vary in scope (i.e., the intervention can address all acute RTIs or focus on a single or a few RTIs considered most likely to be problematic for appropriate antibiotic use). Because interventions vary based on these factors, and we believe that these sources of variation may be important in terms of their effectiveness, cost and potential for any type of adverse consequence, we have categorized them as follows: *Educational strategies* include educating clinicians about current treatment guidelines or providing information to patients or parents of patients about why antibiotic treatment is not recommended. There is wide variation in the types of education programs that may be used. In addition to	Edited to give more explanation of the types of interventions, including more details on point of care diagnostic tests and multi-component strategies.

		patients about why antibiotic treatment is not recommended. *Strategies to improve communication* between clinicians and patients include interventions designed to improve shared decision making. *Clinical strategies* include delayed prescribing of antibiotics or use of point-of-care diagnostic tests (e.g., rapid strep). *System level strategies* include clinician reminders (paper-based or electronic), clinician audit and feedback, and financial or regulatory incentives for clinicians or patients. Furthermore, multifaceted approaches may include numerous elements of one or more of the strategies.	content, some require active participation while others are more passive. For example, regional or national mass media education campaigns are aimed broadly at potential patients and do not require active participation. On the other hand, education programs for clinicians may involve small group discussion with a local thought leader, programs that require active participation. Education programs may also be implemented on a seasonal basis, a regular basis regardless of season, or only once. *Strategies to improve communication* between clinicians and patients include interventions designed to improve shared decision-making. Communication skills, particularly around topics where patient and clinician may have differing views about the appropriate action, may be at the core of resolving potential over-use of antibiotics for acute RTI. Surveys have shown that clinicians are concerned about patient satisfaction with their care, and that these concerns may inhibit consistent appropriate prescribing of antibiotics for acute RTI. Measuring improvement in such skills, however, may be difficult. *Clinical strategies* include delayed prescribing of antibiotics or use of point-of-care diagnostic tests (e.g., rapid strep). The use of delayed prescribing can take multiple forms, but generally invokes the 'watchful waiting' theme. One factor that may be limiting improvements in the appropriate use of antibiotics in acute RTI is the lack of	

			diagnostic certainty in some cases. The advent and rapid development of point of care tests that improve the clinician's ability to make an accurate diagnosis, for example, definitively differentiating bacterial and viral upper RTIs during the clinic or emergency department visit, may be able to increase the magnitude of effect of strategies to improve appropriate use of antibiotics in acute RTI, and may provide consistency and sustainability to the results. However there is controversy whether these tests are accurate enough to be useful and whether the benefits are worth the added cost and resources required for testing. *System level strategies* include clinician reminders (paper-based or electronic), clinician audit and feedback, and financial or regulatory incentives for clinicians or patients. Clinical strategies, such as a clinical prediction rule, that are implemented at the system-level such as an electronic medical record prompt are considered here as well. System-level strategies may be implemented continuously or intermittently, are aimed primarily at clinicians, and are mostly passive interventions. They may be easier to implement compared to some other strategies. *Combinations of strategies,* within or across different strategy types, could potentially improve the effectiveness by addressing different aspects of patient or clinician behavior that impede appropriate use of antibiotics for acute RTI. For example, it may be that education interventions	

			aimed at patients or parents need to be combined with training in improved communication skills for both patient and clinician for optimal effect. It is also possible that combining strategies within the categories of strategies above improve the effect, such as education programs aimed at clinicians combined with education of patients, is superior to either approach alone. It is likely, however, that specific combinations of interventions are more effective than others.	
9/17/2014	Key Questions	KQ1: Appropriate antibiotic use / overall antibiotic use KQ2: Antibiotic resistance and Medical complications (mortality, antibiotic adverse events) KQ3: Other clinical outcomes (health care utilization, hospitalization, patient satisfaction) KQ4: Intermediate outcomes (improved knowledge, communication or shared decision making skills) KQ 5: Non-clinical adverse effects of the intervention (increased time burden)	The abbreviated version of the new KQ's is: KQ1: Appropriate antibiotic use / overall antibiotic use KQ2: Antibiotic resistance KQ3: Medical complications (mortality, hospitalizations, antibiotic adverse events) KQ4: Other clinical outcomes (health care utilization, patient satisfaction) KQ 5: Intermediate outcomes (improved knowledge, communication or shared decision making skills) KQ 6: Non-clinical adverse effects of the intervention (increased time burden)	To separate out antibiotic resistance to highlight its importance as an outcome. KQ 3 will now focus on medical complications only and will include hospitalizations, because they most likely reflect medical complications of acute RTI. Because of these changes, the remaining KQ's were renumbered.
9/17/2014	Analyses	List of factors to be considered listed in Table.	The diagnostic accuracy of the point of care tests will be considered as a source of heterogeneity, and considered for sensitivity analyses.	Variation in accuracy may affect the ability of the intervention to improve prescribing.
9/17/2014	Literature searches	Original searches included Medline and	In order insure a comprehensive search was conducted, we will	Embase was considered

		the Cochrane Library databases.	additionally search the SCOPUS database, which includes citations from databases outside those searched previously (e.g. Embase).	highly relevant to this topic..
9/17/2014	Peer Review	Two peer reviewers selected have some expertise in this area, none were explicitly experts.	To insure adequate commentary on the review of evidence on point of care tests, we will identify an expert in such tests to participate in reviewing the draft report.	Expert review of the point of care tests evidence review will improve the final report.

VIII. Review of Key Questions

For all EPC reviews, Key Questions were reviewed and refined as needed by the EPC with input from the TEP to assure that the questions are specific and explicit about what information is being reviewed.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and in identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and

recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the evidence report.

Potential reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XI. EPC Team Disclosures

No team member disclosed potential financial conflicts of interest.

XII. Role of the Funder

This project was funded under Contract No. HHSA 290-2012-00014-I, Task Order Number 8, from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix. Sample Literature Search Strategy

Box1. Sample Ovid MEDLINE® search strategy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to February Week 2 2014>

Search Strategy:

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1 (((cold or colds or flu or influenza or acute$ or rti or (respiratory tract$ adj3 infect$)) adj5 (cough$ or bronchitis)) or (otitis media or (middle ear$ adj3 infect$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (27771)

2 exp acute disease/ (180380)

3 exp cough/ (11865)

4 2 and 3 (369)

5 respiratory tract infections/ (30472)

6 exp common cold/ (3395)

7 exp influenza/ (34320)

8 exp Respiratory Syncytial Virus Infections/ (4550)

9 exp otitis media/ (21363)

10 4 or 5 or 6 or 7 or 8 or 9 (90588)

11 1 or 10 (96398)

12 (antibiotic$ or antimicrobial$ or anti-infective$ or anti-bacterial or antibacterial).ti,ab. (299639)

13 exp Anti-Infective Agents/ (1235464)

14 12 or 13 (1335464)

15 (point of care adj5 (diagnos$ or test$ or assay$ or kit or kits)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3001)

16 (immediat$ adj5 (test$ or diagnos$)).mp. (9277)

17 ((rapid$ or quick$ or swift$ or office$) adj3 (test or diagnos$)).mp. (23070)

18 (strep$ adj5 test$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4525)

19 exp Streptococcal Infections/ (65351)

20 exp Streptococcus/ (63745)

21 19 or 20 (104236)

22 ((lab or labs or laborator$) adj5 (test$ or kit or kits or assay$ or swab$)).mp. (46652)

23 21 and 22 (461)

24 procalcitonin.mp. (2271)

25 (calcitonin adj5 (precursor$ or biomarker$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (205)

26 exp calcitonin/ and exp biomarkers/ (1973)

27 24 or 25 or 26 (3247)

28 exp C-Reactive Protein/ (29107)
29 c-reactive protein$.mp. (42921)
30 monospot$.mp. (75)
31 mononucleo$.mp. (14111)
32 (direct$ adj5 antibod$ adj5 stain$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (752)
33 exp Fluorescent Antibody Technique/ (110079)
34 exp Reverse Transcriptase Polymerase Chain Reaction/ (131459)
35 (reverse transcriptas$ adj5 (polymerase chain reaction$ or pcr)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (146727)
36 ((singleplex$ or multiplex$) adj5 (polymerase chain reaction$ or pcr)).mp. (9501)
37 34 or 35 or 36 (155071)
38 15 or 16 or 17 or 18 or 23 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 37 (351480)
39 11 and 14 and 38 (854)
40 (education or communication or strategy or strategies).ti,ab. (825514)
41 exp Health Education/ (133075)
42 exp Persuasive Communication/ (2874)
43 exp Physician-Patient Relations/ (58999)
44 exp attitude to health/ (284418)
45 exp physician practice patterns/ (39962)
46 exp clinical competence/ (63269)
47 exp guideline adherence/ (19720)
48 exp drug utilization/ (19338)
49 exp sick leave/ (3753)
50 exp workplace/ (13005)
51 ((inappropriat$ or imprudent$ or unreasonab$ or unwis$ or improper$ or unnecessar$ or useless$ or incorrect$ or worthless$ or useless$ or unneeded or gratuitous$ or ineffect$ or overus$ or over-us$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (2609)
52 ((appropriat$ or judicious$ or judge$ or judging or wise$ or prudent$ or sensible or reasonabl$ or proper$ or necessar$ or useful$ or correct$ or worthwhile$ or needed or effectiv$ or delay$ or postpon$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (10961)
53 ((critical$ or clinical$) adj3 (path or paths or pathway$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (11052)
54 ((antibiotic$ or anti-biotic$) adj3 steward$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (261)
55 ((worker$ or job or jobs or workplace$ or employe$ or student$ or school$ or daycare or day care or pupil$ or child$ or infant$ or baby or babies or toddler$) adj5 ((keep$ or stay$ or remain$) adj3 (home or away))).mp. [mp=title, abstract, original title, name of substance word,

subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (227)

56 ((return$ or (com$ adj back)) adj5 (work$ or job or jobs or school$ or class or daycare or day-care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9428)

57 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 (1288787)

58 11 and 38 and 57 (226)

59 exp Decision Making/ (116996)

60 11 and 38 and 59 (10)

61 39 or 58 or 60 (958)

62 11 and 14 and 57 (2715)

63 46 or 47 or 51 or 52 or 53 or 54 (105565)

64 62 and 63 (591)

65 61 or 64 (1508)

66 limit 65 to english language (1293)

67 limit 65 to abstracts (1373)

68 66 or 67 (1471)

69 limit 68 to yr="2008 -Current" (687)

70 limit 68 to yr="1902 - 2007" (784)