

Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections*

Draft review available for public comment from February 10, 2015 to March 10, 2015.

Research Review Citation: McDonagh M, Peterson K, Winthrop K, Cantor A, Holzhammer B, Buckley DI. Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections. Comparative Effectiveness Review No. 163. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 15(16)-EHC033-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
<p>Section 1. Key Themes: There was a set of comments that centered on a few themes in the draft report that were very similar across reviewers. We have grouped them here by theme to address together.</p>				
<p>Theme: Appropriateness</p>				<p>In response to the comments below on the use of ‘appropriate’ prescribing as a key outcome measure, we have made the following changes to the report:</p> <ol style="list-style-type: none"> 1) Improve discussion of concepts and problems with concepts in introduction, as noted by our reviewers, 2) Improve text on studies

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				<p>that <u>did</u> attempt to measure appropriateness – how they did it, and what the flaws with these approaches are (see discussion).</p> <p>3) Increase overall prescribing to same level as appropriate in methods</p> <p>4) Reverse order of presentation of findings (i.e. Overall prescribing results presented first, Appropriate second)</p> <p>5) Re-assess the strength of evidence ratings for overall prescribing. Overall prescribing is now considered a direct measurement of the outcome resulting in several conclusions to change. See Summary of Findings table. We have shifted emphasis to the evidence of a reduction in overall antibiotic use with little or no adverse consequences.</p> <p>6) Re-evaluate conclusions based on new best evidence – abstract,</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				summary table, discussion
1.	Peer Reviewer #2 (TEP Reviewer)	Appropriateness	<p>One of the main issues is that the assumption is made that appropriate antibiotic use is important and implicitly can be measured and there is agreement on its measurement as an outcome. I can see why we included it as an outcome but there is no real discussion of the issue and what text there is refers to US guidelines. If 'appropriate use' is made in reference to guidance this begs the question what is guidance based on - the best guidance is based on evidence of effectiveness but often is not, or guidelines vary widely in what they regard as appropriate. If evidence-based guidance then you are in a circular argument because you are trying to ascertain the evidence of effectiveness and not reply on someone else's view of effectiveness in determining an outcome. The reference to US guidance alone feels a bit parochial to this European reviewer as does the comment about estimates of effectiveness often coming from other settings: worth exploring whether the country setting actually makes a difference? I'm sure it is likely to be relevant but on the other hand we do have evidence from one large international trial to date (the GRACE INTRO trial) that setting (widely different health systems) made very little difference in this context, perhaps surprisingly. Given that determining appropriateness is subject to so much guideline developer bias I would be</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			tempted to under-play the emphasis you put on it and at the very least discuss it more fully and with large health warnings	
2.	Peer Reviewer #3 (TEP Reviewer)	Appropriateness	<p>Although this report acknowledges in many places the difficulties in defining the concept of appropriateness vs inappropriateness, it might be helpful to discuss this early in the report. I found it a little confusing when reading about the outcomes of ‘appropriate’ vs just ‘reduced’ ABX use. The report describes well that there are inconsistencies of definitions, but it might be helpful to give examples of how some of the studies attempt to define ‘appropriate use.’</p> <p>E-17; Line 23; How to define appropriate. Can this report provide some guidance based on the extensive review of studies? Line 48 “There is moderate strength evidence that use of both procalcitonin and CRP point-of-care diagnostic tests reduce overall prescribing and evidence of no impact on mortality with procalcitonin and no increase in return clinic visits or symptom worsening with CRP versus communication training.” Again would be nice to have this referenced or referred to a table of evidence. (again, provided later)</p>	
3.	Peer Reviewer #6 (TEP Reviewer)	Appropriateness	-The biggest challenge is in the definition of appropriate antibiotic use, something that is still lacking a consensus definition. There is little choice but to take the approach taken here, which is to take each author’s definition. However, given that this is the primary outcome of the study, it is an important limitation.	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>-The other primary limitation is the "no clear indication for antimicrobials" criterion, which can be variously defined. For example, studies of acute otitis media differ substantially as to their diagnostic inclusion criteria and thus the degree to which a clear indication for antimicrobials might be considered.</p>	
4.	Peer Reviewer #7 (Peer Reviewer)	Appropriateness	<p>The review includes studies based on the PICOTS framework. The population of interest is defined as "...patients with an acute RTI and no clear indication for antibiotic treatment." Most of the studies included will have included participants with uncertain indication for antibiotic treatment or indeed where it is pretty certain that antibiotics are indicated. Guidelines are contradictory as to which patients should be prescribed antibiotics and there is no agreed definition of a 'clear indication' for antibiotic treatment that applies to these studies. "Clear indication' is a matter of interpretation and influenced by condition, indication, setting (e.g. developed country or less developed country and region), and individual symptom complex. At what 'number needed to treat' to reduce a particular outcome does the indication for antibiotics become clear? There is inadequate data on what sub-groups will benefit for a lot of these RTIs. So the 'clear indication' is a matter of subjective view, often decided by investigators on a study-by-study basis. Thus, by introducing this subjective element, important studies have been excluded. It would have been better to assume that a lot of RTIs in developed</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>countries are treated unnecessarily with antibiotics and that antibiotics could be reduced overall. Specifying that only studies covering participants without a clear indication for antibiotics has resulted in the inclusion of participants in studies who did have a clear indication and the exclusion of studies which included a lot of participants without a clear indication for antibiotics. This then leads onto concerns about the interventions and outcome measures. The review has focussed on studies that consider appropriateness of antibiotics. However, we can never really know in most cases whether an antibiotic is appropriate or not in most of the studies, because the full clinical picture is seldom made clear. Determining appropriateness is a dark art. A positive strep test for sore throat is considered a marker of an appropriate indication for example, but many of those with a positive strep test will not have active streptococcal infections and will not benefit from antibiotics. Without knowing aetiology, it is difficult to determine appropriateness of LRTI. Most of the studies included do not measure this.</p>	
5.	Peer Reviewer #8 (Peer Reviewer)	Appropriateness	<p>There is an inconsistency in the report in the use of resistance as the rationale and appropriate prescribing as the main outcome. All antibiotic prescribing leads to increased resistance, whether it is appropriate or inappropriate. If, as the authors say, “the ultimate goal [is] reduction in antibiotic resistance,” then the principle outcome should be overall antibiotic prescribing, which</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>the authors seem to discount as important. It may be too much to hope that individual studies would find decreased antibiotic resistance associated with an intervention to decrease antibiotic prescribing. Appropriate antibiotic prescribing is a more appropriate outcome when trying to balance risks and benefits for individual patients.</p>	
6.	Peer Reviewer #9 (Peer Reviewer)	Appropriateness	<p>But we are concerned about using ‘appropriate prescribing’ as a main outcome:-</p> <ol style="list-style-type: none"> (1) there is no consensus on how to measure ‘appropriate prescribing’; (2) ‘appropriate prescribing’ is contentious with regard to ARIs as it is well known that the diagnosis in ARIs is highly subjective, and varies considerably among primary care doctors caring for the same case-mix (Howie J. Diagnosis in general practice and its implications for quality of care. J Health Serv Res Policy 2009). It may be that doctors often first decide if they want to prescribe antibiotics, and then select a diagnostic label to justify this. Consequently, the diagnosis may not reflect appropriate prescribing. (3) ‘appropriate prescribing’ is variable: in some countries antibiotics are recommended for some infections while not in other countries (e.g. acute otitis media in the USA and the Netherlands). (4) it is not possible to obtain information about the diagnosis – e.g. in register-based/database-based studies there are solely information about the type of antibiotic prescribed 	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			Overall prescribing of antibiotics would be a more reliable measure/outcome than 'appropriate prescribing'.	
7.	Peer Reviewer #10 (TEP Reviewer)	Appropriateness	Page 1, line 24: would quibble that unnecessary antimicrobial use is not "the chief factor" in the development of antibiotic resistance-- likely all antimicrobial use contributes-- including appropriate and inappropriate use.	
8.	Peer Reviewer #2 (TEP Reviewer)	Appropriateness	Overall I would rate the report as fair. The combined effect of emphasising appropriate use and antibiotic resistance as outcomes (neither of which is sensible in this context as major outcome as I argue above) is that you conclude the evidence is not good; well it might not be but not for those reasons and I think?	
9.	Peer Reviewer #16 (TEP Reviewer)	Appropriateness	If the outcome being measured is reduction in abx use (or appropriateness), why is this downgraded as Indirect (ie this KQ is not assessing effects on patient centered outcomes)? I understand GRADE etc, but this seems odd to me.	
Theme: Resistance				The comments on the issues relating to resistance were handled in the following ways: 1) Re-wrote introduction paragraphs to note that reductions in overall prescribing are bound to reduce resistance. This issue relates to the theme above on overall

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				<p>prescribing as a key outcome.</p> <p>2) Removed resistance from the Summary of Evidence Table (only 1 study had reported it). See revised description of how Summary of Evidence was determined (at least Moderate strength evidence for reducing prescribing <i>and</i> at least Low strength evidence of not causing worsening in other outcomes).</p> <p>3) Noted in results that the only evidence was on patient-level resistance changes after receiving antibiotics or not (watchful waiting).</p> <p>4) Edited future research section to note that studying changes in population-level antibiotic resistance would require long-term monitoring, before-after or comparing two communities over time after an intervention. Measurements of patient-level resistance in the short-term is less useful. This type of research is</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				unlikely to be funded due to being impractical. (see revised Future Research)
10.	Peer Reviewer #2 (TEP Reviewer)	Resistance	Given that we know that antibiotic use is associated with resistance (see below) and that the evidence for symptomatic benefit from antibiotics is modest for all presentation of RTI, for me the key outcome we are looking for is simply evidence for a reduction in antibiotic use for each strategy but matched by evidence of any harm if/when reductions occur (particularly prolonged severe symptoms or complications). i.e. a successful strategy need to be defined by two basic criteria. The other linked point is emphasising the importance of using antibiotic resistance as an outcome. I'm sure some evidence of resistance engendered at an individual level is useful, but we already have good evidence that antibiotic prescribing is related to resistance at both an international level (see Herman Goossens Lancet paper) and at an individual level (The Costello systematic review in the BMJ). If using resistance at an individual level (which I do not think is necessary since the case is made) you need to define what might be clinically important resistance (e.g. low level resistance probably does not matter that much).	
11.	Peer Reviewer #9 (Peer Reviewer)	Resistance	We certainly agree that antibiotic resistance should be included as an outcome in future trials as this is the ultimate outcome of all the efforts for reducing antibiotic prescribing for	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			ARIs.	
12.	Peer Reviewer #10 (TEP Reviewer)	Resistance	-ES-17: the bullet: "Measure resistance as an outcome" should take into account that resistance may take months to reflect prescribing practices, and may be influenced by external factors (use in other facilities which patients also frequent, antimicrobial use in agriculture, etc). Perhaps add: "although detecting changes in resistance from interventions may be difficult"	
13.	Peer Reviewer #15 (TEP Reviewer)	Resistance	The Introduction states antibiotic use is chief cause for bacterial resistance implying that prescription use for infections is the major offender. It is my understanding that the pounds/tons of antibiotics in animal feed far exceeds human prescription use and is probably a big culprit. Discussion/ Conclusion: There is only 1 study assessing bacterial resistance. A recommendation is more studies. Without bacteriology (rarely performed) this will be difficult if not impossible to assess. There are emerging genetic tests to assess for presence of virus (es). Presence of a potentially pathogenic virus does not exclude bacterial infection.	
14.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Resistance	Under " <i>Future Research Needs</i> ," the general recommendation "Measure resistance as an outcome" should be reconsidered as previously mentioned. If this statement is included, this recommendation should include the need for research and guidance on appropriate ways of measuring antibiotic resistance in this patient population. If the	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			patient population is made up of individuals with viral infections, it is unclear how exactly bacterial antibiotic resistance is to be measured.	
15.	Peer Reviewer #17 (TEP Reviewer)	Resistance	Regarding using antibiotic resistance as a primary outcome measure--While in the ideal world, most studies would be larger and conducted over long periods of time which would allow for tracking of antibiotic resistance as an outcome measure, that's not reality. Most studies are small, discrete studies conducted over short periods of time. The primary outcome measure should be changes in antibiotic prescribing/inappropriate prescribing.	
16.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 25 Again, I think it's unrealistic to use the primary outcome measure of antibiotic resistance to compare the different intervention types. I think it would be better to focus on the interventions that reduce/improve antibiotic use.	
Theme: aRTI definition				Comments on some lack of clarity in the diagnoses included and particularly those that were excluded, in our definition of acute RTI were addressed by: 1) Improved text in introduction and methods to note that LRTIs such as pneumonia and acute COPD exacerbations are excluded. 2) Variation across setting prevented us from

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				providing estimates of the % viral vs. % bacterial by diagnosis within Acute RTI. 3) Added some additional text to discussion on results by diagnosis (where possible)
1.	Peer Reviewer #1 (Peer Reviewer)	aRTI definition	Pneumonia could also be considered an acute respiratory tract infection, do you mean upper respiratory tract infection? These infections could be bacterial (e.g. otitis media) so it is misleading to mention “and other viral syndromes”	
2.	Peer Reviewer #6 (TEP Reviewer)	aRTI definition	Introduction: -Might consider explaining that the definition here is meant to exclude pneumonia which could be considered an acute RTI.	
3.	Peer Reviewer #15 (TEP Reviewer)	aRTI definition	Intro: It is stated that the majority of episodes for acute bronchitis are viral. Is there ANY evidence for percent viral vs bacterial? Would be helpful to have some breakdown by condition for bacterial vs viral infection. They included the common cold as a condition- my understanding would be that 100% are viral and all antibiotics inappropriate. Results: Might consider separating the data for each type of RTI. I suspect RTIs may differ in conclusion regarding appropriateness of antibiotics (i.e. otitis media, acute bronchitis, sore throat, etc)	
Theme: Point-of-				Comments regarding the point of care test category

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
Care Tests				<p>were handled in the following ways:</p> <ol style="list-style-type: none"> 1) In results and conclusions we noted the timing issue (hours rather than minutes for PCT and CRP). 2) Clarified the secondary care issue with PCT. We only included studies in primary care/ED's. While some included followup tests to guide discontinuation of antibiotics, we only used initial test results paired with initial prescribing. 3) Clarified the results regarding patient outcomes and how this relates to conclusions. The re-assessment of the strength of evidence using change in overall prescribing modified these conclusions.
4.	Peer Reviewer #1 (Peer Reviewer)	Point of Care Tests	Page 26 Line 12: not only limited by the algorithms, but also the availability of point-of-care procalcitonin testing (with a result within 5 minutes), limiting its usefulness in adults or children where a fast decision is wanted on whether to start antibiotics or refer to hospital.	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
5.	Peer Reviewer #2 (TEP Reviewer)	Point of Care Tests	the procalcitonin studies in secondary care may be useful but in primary care I think they are probably pretty meaningless - a) repeated measurement (as used in the Swiss studies) is not likely to happen and b) we demonstrated in the GRACE observational study that procalcitonin in primary care has no diagnostic value (at least in detecting consolidation among individual presenting with LRTI in primary care) whereas CRP does have some utility (this was published in the BMJ). So trials using procalcitonin in primary care are probably not helpful (measuring PCT may give you a reassuring low PCT value and help you not prescribe but in fact the value does not mean much and you might as well have a random number generator generating low numbers! - cheaper and less bother!)	
6.	Peer Reviewer #8 (Peer Reviewer)	Point of Care Tests	Similar to delayed prescribing, PCT and CRP testing is associated with decreased antibiotic prescribing, but testing does not improve patient outcomes as shown in several studies (Cals, Ann Fam Med 2010. Cals, BMJ 2009. Little, Lancet 2014). PCT and CRP testing is a distraction – you could almost think of it as a random number generator – that the physician can use in helping convince the patient antibiotics are not necessary, but I am not aware of evidence that testing improves patient outcomes. In fact, in the GRACE INTRO study (Little, Lancet 2013), CRP testing was associated with increased hospitalization.	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
7.	Peer Reviewer #16 (TEP Reviewer)	Point of Care Tests	Page 96= description of interventions. Point of care testing lines 40-48, clearly some of these tests were not in fact point of care tests (if the reporting time for results for example includes hours), this is a major limitation of bundling all such tests under POCT. For example CRP is available as a rapid POCT on fingerdrop samples by several manufacturers, while POCT require blood to be centrifuged etc, clearly massive differences.	
8.	Peer Reviewer #17 (TEP Reviewer)	Point of Care Tests	Page 21 I am very concerned about how procalcitonin is portrayed in the abstract and Executive Summary. Procalcitonin may have an application for evaluating patients who are suspected to have pneumonia, but even the data for pneumonia the data are quite limited. Do you really want to make a major conclusion based upon one study?	

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
9.	Peer Reviewer #17 (TEP Reviewer)	Point of Care Tests	<p>Page 26 It seems that the Executive Summary presents an overly positive spin on the use of CRP and procalcitonin. Please note that the rapid strep test is a guideline-recommended test that has been used for many years and that the recommendation is to not give antibiotics if the test is negative. The main purpose of doing the test is to inform prescribing. It would be difficult to evaluate this as an intervention when it is recognized as the standard of care. I don't think this test should be lumped in with the discussion of CRP and procalcitonin. The data on CRP and procalcitonin are limited and quite mixed, and it's important to note that industry is pushing on this. I have met with the manufacturers of these tests in the hopes that I would learn of convincing evidence that they are helpful in the outpatient setting for upper respiratory infections and bronchitis, but the data are lacking.</p>	
Theme: Delayed Prescribing				<p>Comments regarding the definitions of specific delayed prescribing interventions and terms used to describe them were handled by:</p> <ol style="list-style-type: none"> 1) Improving definitions throughout the text, in particular making descriptions consistent. In particular the term 'Watchful Waiting' was modified to be consistent with other

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				<p>descriptions used in the report.</p> <p>2) Noted the potential problems with logistics of delayed prescribing depending on the method, in the implications section of the discussion.</p>
10.	Peer Reviewer #1 (Peer Reviewer)	Delayed Prescribing	- Line 35: As the conclusion uses the term “delayed prescribing” it might be useful to be consistent and use this term here as heading of point (1) instead of watchful waiting. Be consistent throughout the manuscript.	
11.	Peer Reviewer #8 (Peer Reviewer)	Delayed Prescribing	<p>In the Abstract (page v, line 25), the report conflates, watchful waiting versus delayed prescribing. They are not equivalent and quite different interventions. Watchful waiting entails having the patient either return or stay in contact with the treating clinician. Delayed prescriptions are simpler: clinicians generate and give patients a prescription for antibiotics. Watchful waiting and delayed prescriptions have been evaluated for very different acute respiratory infections (e.g., otitis media in children versus acute bronchitis for adults).</p> <p>Delayed antibiotic prescribing for respiratory infections is not a good solution. While it is true that delayed prescribing results in decreased antibiotic use, it relays a conflicting message about antibiotics to clinicians (“don’t prescribe antibiotics, but you should give patients an antibiotic prescription”) and patients (“you have a viral</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			illness and antibiotics won't work, but you should take antibiotics if you are not better in 2 days") and puts a clinical decision – for example differentiating acute bronchitis from pneumonia – in the hands of patients. Patients with colds, the flu, acute bronchitis, and most cases of sinusitis have a viral illness on the day of the visit and they will still have a viral illness 2 days later	
12.	Peer Reviewer #7 (Peer Reviewer)	Delayed Prescribing	The effectiveness of delayed antibiotic prescribing is likely to depend on the prevailing baseline levels of antibiotic use and threshold for help seeking. These factors are changing rapidly with many consulting less readily for RTIs in the developed world. As the proportion increases of sicker patients among those consulting, so is the appropriateness and indeed effectiveness of delayed prescribing likely to be increasingly limited. So the heavily contextual nature of this approach should be similarly discussed in the strengths and weaknesses.	
13.	Peer Reviewer #10 (TEP Reviewer)	Delayed Prescribing	ES-15: in the discussion of delayed prescribing, some consideration should be given to the logistics of how the delayed prescription is to be delivered to the patient. In some systems, it may be as simple as the patient calling the clinic, and an order is transmitted to a pharmacy near the patient. However, in some areas delayed prescribing may require the patient to return to the clinic, perhaps coming from a considerable distance. This is particularly relevant in the VA system, where patients receive their medications from VA centers, and generally	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			not from local pharmacies. Delayed prescribing then typically entails a return visit, or a delay while prescriptions are mailed. Other systems may have similar logistical hurdles.	
14.	Peer Reviewer #12 (Peer Reviewer)	Delayed Prescribing	In general I'm confused by the summarized findings which say that there are 4 interventions types which stood out. The first intervention is listed as watching waiting in some places, and delayed prescribing in other places (for example, I compared the abstract results versus the conclusions paragraphs).	
Section 2. Remaining Peer Review & Public Comments				
15.	Peer Reviewer #4 (Peer Reviewer)	Abstract	Page V, 11: To assess the comparative effectiveness [of] interventions for reducing antibiotic use when not indicated for acute respiratory tract infections (RTIs) in adults and children.	We have made this revision.
16.	Peer Reviewer #1 (Peer Reviewer)	Abstract	Line 27: "results were mainly qualitatively synthesized": this is a very vague statement. When did you use qualitative methods and when did you use other methods and how were these assessed?	Changed to "Clinical and methodological heterogeneity limited quantitative analysis." As detailed in main report methods, we followed AHRQ guidance in determining the appropriateness of meta-analysis.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
17.	Peer Reviewer #17 (TEP Reviewer)	Abstract	Page 5 Line 33-- I don't understand what the authors mean by "stood out as having the best evidence of benefit over usual care." The criteria for identifying the best interventions should be clearly defined.	We have revised and added a clear description of our criteria for best evidence as: (1) moderate-strength evidence of a reduction in overall prescribing and/or improved appropriate prescribing and (2) at least low-strength evidence of no adverse effects.
18.	Peer Reviewer #1 (Peer Reviewer)	Abstract	Line 36: "it": it is not clear that you are describing the evidence to be low strength	We have completely rewritten the Abstract's Results to identify the revised set of interventions that meet our new best evidence criteria (see comment #32). In doing so, this sentence was eliminated.
19.	Peer Reviewer #1 (Peer Reviewer)	Abstract	Line 53: "note"; drop "e"	We have made this revision.
20.	Peer Reviewer #17 (TEP Reviewer)	Abstract	It is unclear what is meant by the "next tier of best evidence" on Page 5 line 53 means. I am also concerned about the focus on procalcitonin, as there have been many conflicting studies and yet the abstract mentions the specifics of a single study.	We have revised and added a clear description of our criteria for best evidence as: (1) moderate-strength evidence of a reduction in overall prescribing and/or improved appropriate prescribing and (2) at least low-strength evidence of no adverse effects. For procalcitonin, it meets this new criteria in adults

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				because there are multiple RCTs that consistency found reduced overall prescribing.
21.	Peer Reviewer #4 (Peer Reviewer)	Abstract	Page V, 53: should be “not” and not “note”	We have made this revision.
22.	Peer Reviewer #12 (Peer Reviewer)	Abstract	I was puzzled by the third “intervention type”, as it is listed as “two combined clinic-based education interventions that targeted patients, parents, and clinicians...” which doesn’t appear to be an intervention type but a combination of interventions (I also notice it is written in past tense as if to be referring to a specific study). Also, the fourth intervention is described as a “multifaceted intervention that combined a clinical algorithm, clinical tutor training, and provider education...”, again describing interventions which seem to be from a particular study rather than citing an intervention type. This pattern is repeated when the author cites the FeverPain clinical score in the results section of the Abstract, which seemed out of place. I would have expected the authors to summarize intervention types, but they seem to cite specific clinical scoring systems and specific studies instead. Lastly, I thought the phrase “no important consequences” on line 54 page v was unclear. Did the authors mean no evidence of adverse events?	<p>Yes, both are multifaceted interventions which combine various individual interventions. Wherever possible, we have grouped any multifaceted interventions that share similar combinations of components. But, some could not be grouped with others because of the variability of component combinations and had to be discussed separately.</p> <p>Yes, by ‘no important consequences’ we meant no evidence of adverse events and have rephrased this.</p>
23.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 11 Line 20: drop “to beingresistance”	We have made this revision.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
24.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 11 Line 26: does the reference nr 6 correspond with this statement? It is a reference to the effect of antibiotics on childhood obesity.	The Executive Summary has its own reference list and there the corresponding reference is on target: 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 [pdf]. Manchester: National Institute for Health and Clinical Excellence; 2008. http://www.nice.org.uk/guidance/cg69/resources/guidance-respiratory-tract-infectionsantibiotic-prescribing-pdf . Accessed on October 16 2013.
25.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 11 Line 27: for adults or children or both?	Added that this statement refers to both adults and children.
26.	Peer Reviewer #12 (Peer Reviewer)	Executive Summary	1) I would recommend updating the references which are used to estimate ambulatory care visits. The cited study on ES-1 line 28 is over 10 years old - there are more recent numbers published such as those observed in the Daniel Shapiro study from 2014.	Updated with Shapiro 2014 citation and data.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
27.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-1, Line 29: Reference 7 is old. There is more up-to-date data available in the National Health Care Surveys.	Updated with Shapiro 2014 citation and data.
28.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 11 Line 35: use of prescribing?	Changed to “overuse of antibiotics”
29.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-1, Line 35: The reason for inappropriate antibiotic prescribing is well-understood and has been described in many, many qualitative studies of clinicians and patients.	Added list of reasons per May 2014, Hicks 2015, and Barlam 2015
30.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 11 Line 36: “not well understood”: I agree that there are still reasons for inappropriate prescribing of antibiotics” that are not well understood, but the reasons identified are more than well understood.	Added list of reasons per May 2014, Hicks 2015, and Barlam 2015
31.	Peer Reviewer #12 (Peer Reviewer)	Executive Summary	2) On line 36 of ES-1, on line 36 the authors comment that reasons for inappropriate prescribing are not well understood, however, I would disagree. There have been many qualitative studies which have consistently shown the same psychosocial patterns and factors which contribute to inappropriate prescribing. More recently there are several 2014 papers on prescriber behaviors, including those by Guillermo Sanchez and colleagues, another from Jeff Linder and colleagues on bronchitis prescribing, and another from Larissa May and colleagues about ED prescribers.	Added list of reasons per May 2014, Hicks 2015, and Barlam 2015
32.	Peer Reviewer #12 (Peer Reviewer)	Executive Summary	On line 36 of ES-1: In a later sentence in that paragraph, there is a run-on sentence which comments on the usefulness of overall	Clarified that this refers to inappropriate prescribing.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			prescribing as a proxy for appropriate prescribing, which I thought was a good point. However, we don't know whether the 50 to 80 percent cited at the end of this sentence refers to appropriate or inappropriate prescribing.	
33.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 11 Line 37 The statement that the reason for inappropriate antibiotic use is not well understood is not true. Numerous studies have explored the patient and provider-level factors contributing to antibiotic overuse. Most of these studies are qualitative research studies, but they should not be dismissed.	Added list of reasons per May 2014, Hicks 2015, and Barlam 2015
34.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 11 Lines 37-39 This sentence needs to be re-written.	Changed to: "Consequently, strategies to reduce antibiotic use for acute RTIs have varied in their target. Strategies may target clinicians who care for patients with acute RTIs in outpatient settings, adult and pediatric patients with acute RTIs, the parents of pediatric patients with acute RTIs, healthy adults and/or children in the general population without a current RTI, or groups whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials)."

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
35.	Peer Reviewer #12 (Peer Reviewer)	Executive Summary	ES-1 Line 47 typo “in appropriate”	Corrected.
36.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	ES-1, Line 48: The report states that “there is no consensus on how to measure appropriate prescribing,” but there is consensus that antibiotic prescribing and the diagnosis – guideline-concordant versus non-guideline concordant – should be internally consistent.	Changed to: “Although guidelines suggest when antibiotic use is warranted, determining and defining “appropriate” use for study purposes is often difficult because it is subjective and requires both access to adequate patient-level data and clinical knowledge”
37.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 11 Lines 52-56 Please consider rewording this very lengthy and confusing sentence. What do you mean by “background factors”?	Changed to: The usefulness of overall prescribing as a proxy for appropriate prescribing may vary because the ratio of inappropriate to appropriate prescribing can range so widely based on patient, provider and setting factors
38.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 11 Line 55/56: rate of overall prescribing that is inappropriate/appropriate: it is unclear if these percentages refer to appropriate, inappropriate or both, please revise and add references.	Clarified that these rates referred to inappropriate prescribing and added references.
39.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 12 Line 15-Line 22: Add references	References added
40.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 12 Line 16-18 There are multiple reviews on the topic that are well-written and easy to understand. They may be more limited in scope, but they add to our understanding of what works. The reviews	Changed to: There are a number of existing systematic reviews and guidelines that have contributed to our

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			leave gaps, because there are gaps in the science. I think it would be better to state that improving antibiotic prescribing has become an urgent public health priority, so it's important to understand the comparative effectiveness of different strategies...	understanding of what works for targeted populations, interventions, or diseases. However, because improving antibiotic prescribing has become an even more urgent public health priority, there is an important need for an updated comparative effectiveness review that comprehensively addresses a broad range of populations and interventions.
41.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 12 Line 31: specify which patients: adults or children or both (for all key questions)	Changed to, "For adults and children with an acute respiratory infection."
42.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-3, line 36: This sentence is unclear.	Changed to: The analytic framework below (Figure A) provides a visual representation of the relationships between the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest.
43.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	Page 14 Line 44: Why did you limit the search to Medline, CCRCT and CDSR and not use CENTRAL and EMBASE?	We did search CENTRAL and have revised our search strategy to replace the CCRCT abbreviation with CENTRAL to refer to our search of the Cochrane Central Register of Controlled Trials. We did not search EMBASE because

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				we no longer have organizational access.
44.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-4: The report states that they only examined studies published after 1990, but there are several studies that were conducted before 1990. Are the authors potentially missing important studies by starting in 1990? Why does figure B appear to exclude studies published prior to 2000?	Based on input from our Technical Expert Panel (TEP), and as we recognized 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 Pacific Northwest Evidence-based Practice Center (PNW EPC) restricted inclusion to studies published since 1990. Given the existence of good systematic reviews after 2000, and information from our TEP that there are few relevant studies before 2000, we identified studies published from 1990 to 2000 through systematic reviews of the topic, with confirmation by the TEP that nothing important had been missed. Primary literature published from 2000 onward was identified through primary literature searches
45.	Peer Reviewer #8 (Peer	Executive Summary	Page ES-5, line 9: There is a typo in the title of Table A.	We have corrected this typo.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
	Reviewer)			
46.	Peer Reviewer #10 (TEP Reviewer)	Executive Summary	-ES-6, line 12: minor issue, "clostridium" should be capitalized	We have made this revision.
47.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 16 Outcomes Mortality is not an outcome that would be expected with almost any of the respiratory tract infections that this review is targeting. If the review was focused on pneumonia, it may be an appropriate outcome measure, but it's not appropriate for bronchitis, ear infections, etc.	We agree that mortality would be a rare outcome and have not emphasized it in this review.
48.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 17 Line 14: define prescribing and use as these are two different things as mentioned above in my comments.	We agree with your concerns that measurement of prescriptions may be overestimating use because patients may not have actually taken the medication and we have defined them separately in the comprehensive Table A that outlines all eligibility criteria, and noted your concerns in research gaps and future research recommendations. This table B that you are referring to is to complement Table A with a listing of potential sources of heterogeneity.
49.	Peer Reviewer #10 (TEP Reviewer)	Executive Summary	-ES-7, line 25: what is meant by a "fatal flaw" of a study? Can the authors provide examples or a definition within the text to help readers put this in context? I see that	A "fatal flaw" is reflected by failure to meet <i>combinations</i> of items of the quality assessment checklist. All

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			appendix D (page 181) has one example; can	studies that are fatally flawed with a combination of multiple and/or serious limitations are rated poor quality. To increase clarity, we've removed this reference to the "fatal flaw" concept.
50.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 17 line 25 What were the fatal flaws?	failure to meet <i>combinations</i> of items of the quality assessment checklist. All studies that are fatally flawed with a combination of multiple and/or serious limitations are rated poor quality. To increase clarity, we've removed this reference to the "fatal flaw" concept.
51.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 17 Line 34: although correct, the reason for not pooling is clearly a result and should be mentioned in the appropriate section and not in the methods. You can state here: "if meta-analysis was not suitable due to significant heterogeneity, a qualitative approach etc."	Edited as suggested.
52.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 18 Line 17: here you state that a dual review of abstracts was performed: this is inconsistent with the methods section above. If you have performed dual review of abstracts: what was your kappa-value?	Correct. Abstracts were first screened for eligibility by one reviewer, with any deemed ineligible reviewed by a second reviewer. Changed this sentence to: Our review of abstracts led to retrieval and dual assessment of 389 full-text articles

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
53.	Peer Reviewer #9 (Peer Reviewer)	Executive Summary	ES-8, line 19: 37 observational studies – it should say 39.	We have revised this study count.
54.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 18 Line 20: met “our” inclusion criteria?	We have made this revision.
55.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 19 Line 45: Drop “in” before summary	We have made this revision.
56.	Peer Reviewer #9 (Peer Reviewer)	Executive Summary	ES-9, line 48: We included 133 unique studies – shouldn't it be 129?	We have revised this study count.
57.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 19 Line 55: which factors for confounding? This sentence is very vague. As it is now formulated, it seems like you did not examine these factors.	Yes, for appropriate prescribing, we could not assess whether variation in the definition of appropriateness affected outcomes because of potential confounding influences of variation in patient and intervention characteristics. Edited the sentence to clarify this.
58.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-9, Figure B: “Background” is unclear. What are these 30 studies?	“Background” referred to articles we retrieved for contextual information for the Introduction. We’ve removed these from the PRISMA diagram to better focus the content on outcome studies we were evaluating for inclusion in our synthesis.
59.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 20 Comparisons to Usual Care section—where are the citations for all of the references? Again, I still don't understand	Yes, per your previous comment, categories 3 and 4 were both multifaceted

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			categories 3 and 4.	<p>interventions. One combined multiple education interventions and the other combined multiple intervention types (education, clinical algorithm, and clinical tutor training). We have revised their descriptions to better clarify this.</p> <p>Per AHRQ Guidance, we limited citations in Executive Summary to ≤ 50.</p>
60.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 20 Line 5-37: Provide confidence intervals for every percentage as these numbers are not interpretably without their level of confidence.	Studies did not provide confidence intervals for percentages of patients prescribed antibiotics.
61.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 20 Line 5-37: this section should include the study by Cals BMJ 2009 (ref 105) as this study compared both POCT CRP and communication skills with usual care in a factorial design.	This section was previously limited to interventions with evidence of improving <i>appropriate</i> prescribing and/or reducing resistance. CRP and communication were not included here because they don't have that level of evidence. However, how that we're refocusing on interventions with moderate-strength evidence of reducing <i>overall</i> prescribing plus at least low-strength evidence of no adverse effects, CRP has been added here.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
62.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 20 Line 6: the “best evidence” is a bit misleading. These had the most studies performed on, but as mentioned further few have significant results, please rephrase.	We have revised and added a clear description of our criteria for best evidence as: (1) moderate-strength evidence of a reduction in overall prescribing and/or improved appropriate prescribing and (2) at least low-strength evidence of no adverse effects.
63.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 20 Line 12: define antibiotic use	Added this to the Results section: All studies used indirect methods for measuring antibiotic use, ranging from documentation of filling the prescription to patient diary documentation of daily consumption. Because of the variability reliability of these indirect methods in measuring actual use, caution should be taken in interpreting these findings.
64.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	ES-10, line 15: They cite only 2 studies of CDS, but there are others and a recent systematic review concluded that CDS that did not have to be activated by users was potentially effective (Holsteige, J Am Med Inform Assoc 2015).	Yes we included a total of 5 studies. But, as this section had focused on evidence of <i>appropriate</i> prescribing, we cited the only two studies that measured this specific outcome. We excluded the Holsetige 2015 review from our synthesis because of its

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				outdated search (November 2013), but have added it to our Discussion section to note the potential role of variation in level of barrier in provider use.
65.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	ES-10, Line 25: The report says public campaigns targeting adults were not effective, but there was an effective intervention in France (Sabuncu, PLoS Medicine 2009). There is also a summary of the effectiveness of national educational campaigns to improve antibiotic use (Huttner, Lancet Infectious Disease 2010; Goosens, Eur J Pharmacol 2006).	We can appreciate the concern over the lack of high strength evidence regarding the effect of public campaigns. You will see in our revised draft that the combination of public campaigns with clinician education programs does have evidence of both benefit (prescribing) and not causing harm (adverse consequences), but that we still have little evidence of benefit for public campaigns alone, specifically for reducing antibiotic use for acute RTI. The Sanbucu study was about flu-like illnesses, and the other two publications did not meet our criteria for being recent, high quality systematic reviews.
66.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-10, Table C: It is unclear what the parenthetical “L” and “M”s are. Low and medium?	Yes, previously we used L to refer to low and M to medium. Per the Schunemann 2003 publication on how to

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				communicate grades of evidence, we have since changed to symbols and have inserted a key below this table.
67.	Peer Reviewer #10 (TEP Reviewer)	Executive Summary	-ES-10, line 29: the phrase "next tier of best evidence" seems to be contradictory-- best implies top, next tier implies below top. Consider rephrasing.	We have done away with the "tiering" approach and our new criteria for best evidence is: (1) moderate-strength evidence of a reduction in overall prescribing and/or improved appropriate prescribing and (2) at least low-strength evidence of no adverse effects.
68.	Peer Reviewer #10 (TEP Reviewer)	Executive Summary	-ES-10, line 33: "four interventions that have proved to lack benefit"-- difficult to prove a lack of benefit. Perhaps rephrase as "not demonstrated any benefit"	Rephrased as suggested
69.	Peer Reviewer #3 (TEP Reviewer)	Executive Summary	E-11; Line 23; should be S pneumoniae (not pneumonia); Also in Table 20 page 89	We have made these revisions.
70.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 23 Line 12: the study by Cals did multifaceted interventions but was also able to do a head-to-head comparison of CRP and communication skills due to the factorial design. Please revise this section as these results are now omitted.	We have already included the head-to-head comparison of CRP and communication training and its results are consistent with our statement that head-to-head studies found some differences that were of unclear importance.
71.	Peer Reviewer #3 (TEP Reviewer)	Executive Summary	E- 13; Line 5; Any way to provide the "FeverPain" Score? Or reference it.	Added that the FeverPain clinical score is an acronym for the features: <u>F</u> ever during previous 24 hours;

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				<u>P</u> urulence; <u>A</u> ttends rapidly (within three days after onset of symptoms); <u>I</u> nflamed tonsils; <u>N</u> o cough/coryza)
72.	Peer Reviewer #12 (Peer Reviewer)	Executive Summary	4) On ES-13 at the top, the authors write that “For sore throat, ... use of the FeverPain clinical score may be a better choice over delayed prescribing because it both reduced overall prescriptions and led to one fewer day of moderately bad or worse symptoms.” This seemed odd to recommend a specific clinical score that is not commonly used and for what appears to me to be a relatively small benefit.	Changed to: the FeverPain clinical score (acronym for the features: <u>F</u> ever during previous 24 hours; <u>P</u> urulence; <u>A</u> ttends rapidly (within three days after onset of symptoms); <u>I</u> nflamed tonsils; <u>N</u> o cough/coryza) reduced overall prescriptions and led to one fewer day of moderately bad or worse symptoms.
73.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 23 The part about the FeverPain score is really unclear. What exactly is the intervention? The sentences about POC testing are impossible to understand. Please revise.	Added definition of FeverPAIN. Edited sentences about POC testing to improve clarity.
74.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 24: Add Discussion Heading in the middle of this page	We have made this revision.
75.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 24 Line 31 and further: Although no studies were able to compare all interventions using all outcomes, this would probably lead to an almost impossible design with a large problem of confounding and contamination of the possible different intervention groups. It would therefore not be sensible to conduct such research. This should be stated in this section.	This line refers to the scope of previous <i>systematic reviews</i> , which could have been designed to address the same range of outcomes as we have in the present review.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
76.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-14, line 31: The report refers to three prior systematic reviews, but do not provide references for those prior reviews.	Per AHRQ Guidance, we limited citations in Executive Summary to ≤ 50. Citations for previous reviews can be found in the main report.
77.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 24 Line 50: You have not convinced me that, based on the identified research, electronic decision support (low-strength evidence) and procalcitonin (highly selected populations not relevant to most primary care settings) have evidence of benefit. Although you have found some evidence, it might be useful to stat their benefit more carefully.	Electronic decision support: Due to peer review consensus about the challenges of measuring resistance and <i>appropriate</i> prescribing (discussed above), we've shifted our focus to overall prescribing and adverse effects, where electronic decision support has an even stronger level of evidence of moderate-strength. Procalcitonin: The revision of the report, with emphasis on interventions with at least moderate strength evidence for reducing overall prescribing and at least low strength evidence for other outcomes (e.g. Not increasing adverse outcomes) has made the place of procalcitonin more clear. The studies of procaclitonin included in this report are only those that were conducted in primary care settings, including ED's. Additionally, we

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				limited assessment of prescribing outcomes to the initial decision made on whether to prescribe or not prescribe based on the initial procalcitonin test – we did not include any other subsequent testing-based decisions, if reported.
78.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 24 Why try to make it sound like this review is better than others? I am having a lot of trouble understanding this review, because it seems that there is a lack of understanding of the subject matter. That seems to be missing from this review, whereas the other reviews had coauthors with subject matter expertise.	Our point was that although, there are a number of existing systematic reviews and guidelines that have contributed to our understanding of what works for targeted populations, interventions, or diseases, because improving antibiotic prescribing has become an even more urgent public health priority, there is an important need for an updated comparative effectiveness review that comprehensively addresses a broad range of populations and interventions. We have revised as such. Our author team also has coauthors with subject matter expertise that contributed to all phases of this review.
79.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 25 Line 6: Give median ages for children studies and adults since this mean age is not interpretable. In Children the age	Changed to: 45% of studies had a child population, with a mean age of 4 years.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			distribution of those studies are usually skewed to the left, so median age might be a better option to summarize the distribution.	28% studies had a mixed-age population, with a mean age of 33 years. 27% studies had an adult population, with a mean age of 44 years.
80.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 25 Line 8: Define primary care if not general practice.	Changed to: “95% Primary care (14% in emergency departments)”
81.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-15, line 39: The authors state “while it seems clear that patients [who do not get antibiotics] will experience longer symptoms and will have lower satisfaction” is not supported by data and is an assumption. One example is the study by Little (JAMA, 2001) that showed symptoms resolution was exactly the same whether patients were randomly assigned to immediate, delayed, or no antibiotics. In fact, patients who do not receive antibiotics could have fewer adverse effects and have fewer symptoms.	Changed to: “While evidence suggests that patients...”
82.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 25 Line 46: For example, nationwide campaigns are probably more effective in conjunction with waiting room posters.	While we agree that there is a possibility that the combination would increase the effect, we did not find such studies
83.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 25 Line 51: add references to this evidence.	Per AHRQ Guidance, we limited citations in Executive Summary to ≤ 50. Citations can be found in the main report.
84.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 26 Line 13: Did you look at the results from the study by Nijman et al BMJ 2013 describing a clinical prediction model with	Excluded both Nijman 2013 and Van den Bruel because of the population of febrile

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			CRP and the study by Van den Bruel in the BMJ in 2011 concerning diagnostic value of laboratory tests? It would be good to include these results in the manuscript.	children was not limited to RTIs and did not evaluate RTI separately.
85.	Peer Reviewer #3 (TEP Reviewer)	Executive Summary	E-16; Line 16: "For procalcitonin, while there is agreement across algorithms in terms of thresholds for antibiotic use, they were developed for use in adults and use in children led to increased antibiotic use." There are many statements like this that would be nice if citations were provided. (I see there are provided later)	Yes, per AHRQ Guidance, we limited citations in Executive Summary to ≤ 50. Citations for previous reviews can be found in the main report.
86.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 26 Line 19: needed instead of need	We have made this revision.
87.	Peer Reviewer #9 (Peer Reviewer)	Executive Summary	ES-16, line 19: Delete the, and need – should be needed.	We have made this revision.
88.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 26 Line 49-50: setting characteristics are usually given in any study. What exactly do you mean by this?	We had inadequate details on time of year and whether the intervention was implemented during a disease epidemic or outbreak period.
89.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Page 26 A major limitation is that healthcare delivery and cultural expectations related to antibiotics vary greatly from one country to another. Interventions that work well in one setting may not work well in another. There is a very brief mention of this in the Gaps section, but this limitation needs to be more front and center.	We agree with these concerns and have added the following to the discussion, in the Applicability section under Setting: "Fifty-two percent of the studies were conducted in European countries, where some form of nationalized healthcare is common. This is an issue for two reasons;

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				the baseline or background prescribing rate varies by country, sometimes widely, and the healthcare systems, cultural attitudes, and behaviors of clinicians and patients may vary enough in other countries to reduce the generalizability of the findings to a US population."
90.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	Gaps in the Evidence Base—there have been a number of studies that have evaluated other forms of stewardship interventions, like audit and feedback, which are not captured in this review. There are some interventions that have been studied for acute care that would probably translate well to the ambulatory setting. Many large health systems are introducing stewardship interventions in all settings, and it will be important to identify which interventions will be effective across the spectrum of healthcare (ambulatory, acute, longterm care) for different conditions (not only respiratory infections).	Any and all types of interventions implemented in the ambulatory setting were eligible for this review, including audit and feedback and stewardship programs. Many of the interventions included in our review are, in fact, are stewardship programs. But, we have referred to them by their components. Audit and feedback was a component in a number of multifaceted interventional studies we included. But, we did not find any studies of audit and feedback evaluated as a single intervention
91.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary	- Page 27: Future research needs: add comment on difficulties of conducting the proposed future research (see above) Conclusions: Again, the same comment applies concerning the difficulty of such	Added: Although potentially difficult and time and resource-intensive, future studies of interventions to improve antibiotic prescribing in acute RTIs should would

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			research.	add great value to our understanding of how to best address this important public health issue by having the following methodological features
92.	Peer Reviewer #10 (TEP Reviewer)	Executive Summary	-ES-17: in this first bullet: "Most studies in this area can be randomized and in such cases cluster randomization should be used"-- is "can" supposed to be "cannot?"	Correct as stated. Most studies can be randomized.
93.	Peer Reviewer #8 (Peer Reviewer)	Executive Summary	Page ES-17, line 48: The authors state that CRP is not associated with increased complications. However, in the large GRACE INTRO study (Little, Lancet 2013) CRP testing was associated with increased hospitalizations (as noted above).	The difference between CRP and usual care in the GRACE INTRO study was of borderline significance when adjusted for clustering for communication training received by some clinicians and other confounders (adjusted RR 2.91; 95% CI, 0.96 to 8.85; p=0.06
94.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Executive Summary	Page ES17, "Future Research Needs" comments specifically on the paucity of studies examining the impact of interventions on antibiotic resistance (one) and need to measure antibiotic resistance as an outcome, respectively. The document does not discuss the challenges of measuring this outcome in care settings (clinics, EDs) and for conditions in which culture and sensitivity testing is rarely performed.	Added: Because culture and sensitivity testing is rarely routinely performed in outpatient settings, we recognize there are major practical challenges with researching resistance including that it would require years of additional funding and long-term monitoring. However, we still recommend that, under ideal circumstances, measuring an intervention's impact on

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				resistance would be very useful
95.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	<p>Page 27 Future research needs</p> <p>As stated before, I don't think it's realistic for all studies to assess antibiotic resistance as an outcome measure. This would require years of funding and longterm monitoring. Can this recommendation be softened?</p>	<p>Because culture and sensitivity testing is rarely routinely performed in outpatient settings, we recognize there are major practical challenges with researching resistance including that it would require years of additional funding and long-term monitoring. However, we still recommend that, under ideal circumstances, measuring an intervention's impact on resistance would be very useful</p>
96.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary	<p>There are types of interventions that aren't covered in your review, as I mentioned above, and it would be useful to better understand if some of the interventions that have worked in other settings would work in ambulatory care for RTIs.</p>	<p>Any and all types of interventions implemented in the ambulatory setting were eligible for this review, including audit and feedback and stewardship programs you mentioned earlier. Many of the interventions included in our review are, in fact, are stewardship programs. But, we have referred to them by their components. Audit and feedback was a component in a number of multifaceted interventional studies we included. But, we did not find</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				any studies of audit and feedback evaluated as a single intervention.
97.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary; General Comment	No exclusion criteria defined, please add these.	Our exclusion criteria was limited to non-English studies and those published prior to 1990, which are described in the paragraph preceding Table A.
98.	Peer Reviewer #1 (Peer Reviewer)	Executive Summary; General Comment	The study selection states that all citations were screened by one reviewer on abstract. Although according to AHRQ guidance, this introduces bias in study selection as no other reviewer screened these abstracts in order to obtain an kappa value. If this was unavoidable, please ignore this comment.	All abstracts excluded by the first reviewer were checked by a second senior reviewer.
99.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Executive Summary; General Comment	The report does an excellent job succinctly highlighting the challenges of the analysis, specifically that there is no consensus on how to measure appropriate prescribing of antibiotics. It also highlights knowledge gaps and specifically states types of future research that would be helpful to address these gaps.	Thank you for your comment.
100.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Executive Summary; General Comment	It is unclear whether the term “clinicians” includes emergency room physicians as part of “general practice.”	Added ‘including emergency room physicians’ to our inclusion criteria.
101.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Executive Summary; General Comment	In the abstract, the primary message of the results is that the ideal intervention to reduce unnecessary or inappropriate antibiotics for RTI has not been identified. We are concerned that the message to patients and	We understand this concern and by refocusing on the outcomes of reduced overall prescribing with no adverse effects, we are now sending

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
	Reviewer)		clinicians might be that there is no evidence to support limiting antibiotics for RTI.	a stronger message that there are several interventions that have demonstrated overall effectiveness.
102.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Executive Summary; General Comment	This is also related to one of the biggest stated gaps in the literature that except one, no study looked at antibiotic resistance as the outcome. Consider under-stating the importance of this as an outcome for such studies (see specific comment below).	Yes, we have refocused on the outcomes of reduced overall prescribing with o adverse effects and have de-emphasized the lack of evidence on resistance.
103.	Peer Reviewer #17 (TEP Reviewer)	Executive Summary; General Comment	The Executive Summary needs heavy editing to improve readability and clarity of the writing. There are many awkwardly worded sentences.	We have largely rewritten the Executive Summary to reflect our refocusing on the outcomes of reduced overall prescribing without adverse effects and, in doing so, have also made efforts to improve the readability and clarity.
104.	Peer Reviewer #3 (TEP Reviewer)	Introduction	1; Line 43; I cannot link to reference #9	Thank you for this comment. We have tested the link and it appears to be working at this time.
105.	Peer Reviewer #5 (Peer Reviewer)	Introduction; General Comment	This gives a nice synopsis of the work.	Thank you for your comment.
106.	Peer Reviewer #7 (Peer Reviewer)	Introduction; General Comment	Clear	Thank you for your comment.
107.	Peer Reviewer #8 (Peer Reviewer)	Introduction; General Comment	Well written. The argument for addressing the new antibiotic crisis is well put.	Thank you for your comment.
108.	Peer Reviewer #10 (TEP Reviewer)	Introduction; General Comment	Overall the introduction is well written. Similar to the executive summary, it sets up the study well, and provides sufficient	Thank you for your comment.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			background without going into too great a detail.	
109.	Peer Reviewer #13 (Peer Reviewer)	Introduction; General Comment	The introduction was effectively constructed, informative compelling and provided an excellent set-up to the key questions as well as the evidence review. This reviewer was unaware that the key disease category where there is the largest disconnect between guidelines suggesting no antibiotic treatment and the continued use of prescribed antibiotics in the U.S. is for patients with acute RTI's. The section detailing the scope and key questions was well organized and easy to understand. The 'flow' of topic/focus from one key question to the next as well as the inclusion of appropriate subquestions was done effectively	Thank you for your comment.
110.	Peer Reviewer #14 (TEP Reviewer)	Introduction; General Comment	Strong	Thank you for your comment.
111.	Peer Reviewer #16 (TEP Reviewer)	Introduction; General Comment	THis is quite acceptable.	Thank you for your comment.
112.	Peer Reviewer #3 (TEP Reviewer)	Methods; General Comment	I agree with inclusion and exclusion criteria and search strategies. See comment in General Comments regarding definitions of "appropriate use."	Thank you for your comment.
113.	Peer Reviewer #4 (Peer Reviewer)	Methods; General Comment	Yes, the criteria seem justifiable and the search strategies were explicit and logical. As the authors noted, they may have missed some older literature but also relied on TEP members to help in that regard. Definitions and criteria were stated, when applicable, as were outcome measures (though many interim and end point outcomes varied across	Thank you for your comment

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			studies). The statistical methods were straightforward (no meta-analysis was done so the report primarily contained descriptions of published data.	
114.	Peer Reviewer #5 (Peer Reviewer)	Methods; General Comment	The literature search limitations are nicely documented and appear logical (1990s, English only) and although only 45% conducted in US, I think it is good that the studies used were not limited to the USA. Grading was good. Quality of studies were fair and sufficient in number, although mostly qualitative, and only 1 addressed the antibiotic resistance. Most of the studies only addressed antibiotic use or not. The gaps in info are noticeable, but provide room for future study.	Thank you for your comment
115.	Peer Reviewer #6 (TEP Reviewer)	Methods; General Comment	-Criteria seem appropriate for the study.	Thank you for your comment.
116.	Peer Reviewer #7 (Peer Reviewer)	Methods; General Comment	Please see above about excluded studies	We agree about the subjectivity and lack of consensus about a definition of 'clear indication' for antibiotic treatment for RTIs and, accordingly, we found that studies enrolled patients regardless of antibiotic indication. Ultimately we did not use 'clear indication' as a selection criteria and have removed this element.
117.	Peer Reviewer #9 (Peer Reviewer)	Methods; General Comment	The authors state that four intervention types stand out as having the best evidence because they were the only ones that benefit for resistance or appropriate prescribing.	Thank you for your comment. We have clarified how we determined the interventions with the best evidence,

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				organized into categories depending on the direction and strength of evidence for benefit and harm.
118.	Peer Reviewer #10 (TEP Reviewer)	Methods; General Comment	Well described methods. Missing one assessment in this review: categorization of the funding source. Seems particularly relevant for studies of diagnostic tests, such as procalcitonin. I am fairly certain some of these were funded by the makers of the test/hardware. Perhaps I missed it, but a search for "funding" yields no result.	We have reviewed the POC test studies included and found that 3 of 29 had at least partial funding from a test manufacturer (only 1 listed a manufacturer as the sole source). The majority of studies received funding from local or national sources such as the NIH or hospital research foundations. We have added information about these findings to the overview section of the results.
119.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Methods; General Comment	Clearer definitions of which respiratory infections are included and specifically excluded (e.g. community acquired pneumonia, acute exacerbations of chronic bronchitis) in this systematic review should be provided. Better distinction between duration of symptoms used to classify acute vs. chronic infection also should be included.	Added clarification to Table 1a, eligibility criteria,: 'Adult and pediatric patients with an acute RTI, including acute bronchitis, AOM, sore throat, pharyngitis, tonsillitis, rhinitis, sinusitis, cough, and common cold, but not community acquired pneumonia or acute exacerbations of chronic bronchitis. ⁶ We did not use a specific definition of acute as a criterion for inclusion/exclusion, accepting all study

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				definitions'
120.	Peer Reviewer #12 (Peer Reviewer)	Methods; General Comment	<p>c. Methods Please consider the following. Are the inclusion and exclusion criteria justifiable? Are the search strategies explicitly stated and logical? Are the definitions or diagnostic criteria for the outcome measures appropriate? Are the statistical methods used appropriate?</p> <p>The search strategies seemed explicit and logical and the inclusion and exclusion criteria for this review appeared to be clearly laid out. I liked the figures which show the results of the lit review and how many records were screened and assessed for eligibility, etc.</p>	Thank you for your comment
121.	Peer Reviewer #13 (Peer Reviewer)	Methods; General Comment	<p>The inclusion and exclusion criteria as detailed in the PICOTS framework eligibility information are justifiable in the mind of this reviewer. It was a little difficult to find how the criteria, particularly for outcomes, could be very similar or vary slightly from one key question to another. But this reviewer doesn't have any additional thoughts on how this issue could be better addressed. Being familiar with the AHRQ approach to search strategies and conducting a SER from previous efforts, the strategies used were explicitly stated and logical. The definitions or diagnostic criteria for all of the outcome measures also seem appropriate although, as stated elsewhere, this reviewer is neither a clinician, nor microbiologist nor infectious disease expert. This reviewer felt that the</p>	Thank you for your comment

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			table identifying potential sources of heterogeneity in PICOS (Table 1b) was well-done with significant considerations identified. Based on this reviewer's knowledge, application and use of statistical techniques, particularly in CER's or other similar evidence-based reviews, the statistical techniques employed were appropriate.	
122.	Peer Reviewer #14 (TEP Reviewer)	Methods; General Comment	Appropriate	Thank you for your comment.
123.	Peer Reviewer #15 (TEP Reviewer)	Methods; General Comment	The terms usual care and standard care are used but not defined. Are they the same? Although practice probably varies considerably might add a brief comment that usual practice may include maintain hydration, decongestants, cough suppressant, etc.	Added to Table 1a for Comparators: "We use the terms usual care and standard care synonymously. Although practice probably varies considerably between settings, usual and standard practice likely includes maintaining hydration and use of decongestants, cough suppressant, etc."
124.	Peer Reviewer #16 (TEP Reviewer)	Methods; General Comment	THis is quite acceptable.	Thank you for your comment.
125.	Peer Reviewer #10 (TEP Reviewer)	Results	Page 15, line 16: 44% or 45% of studies from the United States? Was 45% in executive summary.	This has been corrected to 45%.
126.	Peer Reviewer #12 (Peer Reviewer)	Results	I thought the Key Points Summaries for each Key Question were helpful. I did notice inconsistency regarding including whether results were statistically significant (see line 45, page 18 as an example). For the third bullet point under Multifaceted Interventions under Key Question 1 on page 19, it was	To be consistent with majority of Key Points, eliminated cases where statistical significance and relative effect measures were mentioned.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			stated that multifaceted interventions involving 4 interventions, but unlike the other bullet points, it failed to list what those interventions were. As a general comment, I noticed the OR or RR were sometimes included and sometimes they were not (one example is in the bullet point for Procalcitonin POC testing on page 54, line 41). I would make this more consistent The detailed syntheses were very helpful, and I appreciated the general organization and the outcomes by subgroups – this makes the document more useful to those who are interested in implementing outpatient interventions in specific settings.	Added description of 4 interventions.
127.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 20 – Under clinic-based, need to check number of studies and their quality –Francis should be good quality based on table but says fair quality in the text.	We have corrected the text to reflect that Francis, 2009 is a good-quality study.
128.	Peer Reviewer #10 (TEP Reviewer)	Results	Please ensure the direction of the association is described in reporting the results. for instance, on page 21 this statement appears (lines 49-51): "Education level. In a study of a brief educational talk by the physician at the time of prescribing a delayed antibiotic approach, the mother's education level was found significantly associated with the decision to give antibiotics (p <0.05)." Were higher-educated mothers more likely to receive antibiotics, or less?	Changed to “, a lower level of mother's education was found to increase the decision to give antibiotics”
129.	Peer Reviewer #4 (Peer Reviewer)	Results	24, line 21-26: The outcomes were confusing. Not sure what the ratio of ORs was referring to? And why would it be higher?	Changed to: Before vs after (change): Clinician education: 43% vs. 33% (-10%); Patient mailings:

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				<p>18.9% vs. 14.2% (-4.7%); Control: 57.8% vs. 58.6% (+0.8%) Compared with control adjusted Ratio of ORs of change for before vs after: Clinician education: 2.80 (95% CI, 1.32 to 5.95) ; Patient mailings: 1.66 (95% CI, 0.73 to 3.80)</p>
130.	Peer Reviewer #13 (Peer Reviewer)	Results	<p>Given this reviewer's areas of expertise, the overall scope of the results (and the size of the full report in general) was overwhelming. The information on POCT clinical interventions, where the evidence suggests that POCT may be a meaningful intervention and where the evidence fails to support this, was of interest. In the opinion of this reviewer, a large percentage of stakeholders, clinicians as well as other caregivers and clinical laboratorians, likely have little knowledge or awareness of these findings, particularly as they relate to affecting the prescription of antibiotics, etc..</p> <p>On p.30 of the main CER (page 61 of 679 overall), it was interesting to read the results of the assessment of studies comparing strategies to improve clinician-patient communication compared with POCT CRP, head to head. This section made this reviewer question why there weren't more studies looking at the benefits of combining both approaches, and potentially replacing PCT with CRP. But this kind of study is apparently not one that has been considered</p>	<p>We appreciate these comments and have added text regarding the type of CRP test used, when reported: "The studies varied in the type and amount of guidance provided to clinicians for interpreting CRP test results and making antibiotic prescription decisions. None of the studies reported using either cardiac CRP (c-CRP) or high sensitivity CRP (hsCRP) assays and are presumed to have used general CRP assays."</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>by the routine clinical investigators in the field.</p> <p>CRP testing is referred to several times throughout the CER. Notably, overall antibiotic prescribing with CRP testing compared with usual care indicates an overall beneficial effect if this reviewer interprets Figure 3 (page 66 of 679) correctly. It is unclear to this reviewer if the category of CRP method being used was consistent throughout all the studies compiled and that made the ‘final cut’ in this review. While there are three CRP method categories in the U.S., the least used and unlikely to have been used in any studies in this CER is marketed as c-CRP where c stands for cardio. It is my expectation that most, if not all, of the studies included in this CER were using a general CRP assay which measures the acute phase response protein known for decades and typically measured by assays in the mg/dl range. In the cardiovascular risk literature and in clinical laboratories, there is now a more widely used hs (high sensitivity) – CRP that measures minimal changes in much lower levels of this same protein on a mg/l basis for assessment of cardiovascular risk and the presence of cardiac disease. This is an important distinction if clinicians read this report in the future and look into the incorporation of a POCT CRP in their practice. To state the issue succinctly, the studies in this CER likely are using tests directed to the older acute phase reactant analyte (mg/dl) where all the current clinical</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			literature largely focuses on the newer hsCRP (mg/L) assays that are used for cardiac and cardiovascular disease and risk assessment. Having previous interest and experience in the procalcitonin literature, it was not surprising to learn the findings outlined in the section on procalcitonin POCT (starting on page 69 of 679). It is important that, while the studies are few, this information was included in this CER. It is also important that there is moderately strong evidence of benefit in using rapid Strep POCT tests. This is somewhat well-known amongst clinicians, but not always embraced by other care givers who, at times, do not value the impact of POCT to the degree the evidence would support.	
131.	Peer Reviewer #4 (Peer Reviewer)	Results	33, line 40-41: the odds ratio is 0 for greatest reduction? Does not sound correct.	PNW EPC verified Cochrane review (Spurling 2013) OR's verified using rates from Dowell 2001 and Little 1997
132.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 33, line 56 – only 5 RCTs are mentioned (and referenced) here – but there are 6 RCTs in figure 3 and table 7 but only 5 mentioned here.	This section has been rewritten, adding a new Cochrane review. There are now 7 total studies, and the text more clearly reflects the included studies and their citations.
133.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 33, line 58 (bottom page) to page 24 line 4 (top page), some text is missing?	No text is missing; therefore, we have made no revision.
134.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 34, line 4-5 says six studies but there are seven in the table 7 (including the observational study).	This section has been rewritten, adding a new Cochrane review. There are

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				now 7 total studies, and the text more clearly reflects the included studies and their citations.
135.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 38, line 33 – remove extra ‘the’ before ‘absolute difference’.	We have made this revision.
136.	Peer Reviewer #3 (TEP Reviewer)	Results	40; Line 40; should be Grp A Strep POC test not ‘S. pneumococcal’	Changed to Group A Beta hemolytic strep
137.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 40 (and page 59, 75, 90 and 106). You write S. pneumococcal Point-of-care testing (Rapid Strep Test). Don’t you mean that you are testing for Group A beta haemolytic streptococcus –and not S. pneumonia?	Changed to Group A Beta hemolytic strep
138.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results	Key Question 1 Page 40 – heading, “S. pneumococcal Point of Care Testing (Rapid Strep Tests).” This would be better as S. pyogenes or Group A Streptococcus (which causes strep throat). Rapid Strep tests refer to Group A strep (S. pyogenes) not S. pneumonia/ Pneumococcus.	Changed to Group A Beta hemolytic strep
139.	Peer Reviewer #16 (TEP Reviewer)	Results	Page 40 (of document pagination, not pdf page) line 40 – confusion of Strep pneumoniae with Group A Beta hemolytic strep, in this case rapid strep tests refers to the latter. (Same in page 59, line 51 – maybe elsewhere too, would be worth checking)	Changed to Group A Beta hemolytic strep
140.	Peer Reviewer #3 (TEP Reviewer)	Results	42 and others; would be nice to describe how the studies defined “appropriate antibiotic use.’	Moved descriptions from overview section down under appropriate prescribing heading.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
141.	Peer Reviewer #3 (TEP Reviewer)	Results	44; Line 55; reference the CDC definition of appropriate ABX (I assume this is from the website of 'CDC principles of appropriate antibiotic use'	Changed to "Appropriate prescribing (as defined by CDC "Get Smart" program, http://www.cdc.gov/getsmart/index.html .)"
142.	Peer Reviewer #12 (Peer Reviewer)	Results	I thought the bullet for system-level interventions from Key Question 3 was not clear (page 54 line 48).	Changed to "There was low-strength evidence of no difference in rates of pneumonia diagnoses or 30-day hospitalizations between electronic decision support compared with usual care or a paper-based support tool in patients with uncomplicated acute bronchitis"
143.	Peer Reviewer #12 (Peer Reviewer)	Results	Page 56 line 56 typo "significant" should be significance.	Corrected.
144.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results	Page 58, Key Points. We suggest including the citation when referencing a particular trial and outcome measure as "best evidence" to facilitate review of study.	For consistency with AHRQ CER style guidance, citations are not included in Key Points.
145.	Peer Reviewer #12 (Peer Reviewer)	Results	I wasn't sure whether some of the non-intuitive results were helpful. For example, the fact that there were communication interventions which resulted in longer length of symptoms (Communication Interventions bullet 1 page 58 line 51) didn't make sense to me, and may be a result which I don't think would be helpful to include.	Changed to "There was low strength evidence that the reduced prescriptions associated with communication interventions resulted in longer duration of symptoms"
146.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 72, line 14-16 – CIs cross 1, consider removing term 'borderline significant'	Changed to "no difference"

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
147.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results	Page 72. Point of care testing seems to be promising for various outcomes assessed and needs to be further investigated. Perhaps these findings indicate that objective measures to inform whether antibiotics are needed improves patient care but also may improve patient satisfaction.	This is definitely a possibility. At this point we had only one study of CRP that directly measured satisfaction when comparing CRP use (alone) to usual care, such that we were unable to draw conclusions.
148.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results	Page 76. Please clarify the “satisfaction score” measure (e.g., mean value out of maximum).	Page 78: The study (McCormick 2005) describes a 13-point questionnaire, but does not describe how the items were scored.
149.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results	Page 76. Please clarify if “small difference” (17% vs. 1%) is a typo.	Yes, it was a typo. It was corrected to (17% vs. 11%; p=0.02)
150.	Peer Reviewer #12 (Peer Reviewer)	Results	Page 79 Line 9 missing a citation here	Citation has been added.
151.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 80, line 40 – remove ‘s’ from ‘believes’.	We have made this revision.
152.	Peer Reviewer #9 (Peer Reviewer)	Results	Page 81, line 20 – remove duplicate ‘was not’.	We have made this revision.
153.	Peer Reviewer #16 (TEP Reviewer)	Results	Page 89 line 47 - risk of reconsultation greater, unclear if this is consistent with evidence.	Confirmed that yes, this is consistent with evidence: Our pooled analysis of three fair quality trials shows a greater risk of reconsultation within four weeks with a CRP

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				testing intervention compared with usual care (RR 1.36; 95% CI 1.05 to 1.76).
154.	Peer Reviewer #16 (TEP Reviewer)	Results	Page 95 - the issue of differing conclusions of the current review compared to the multiple other reviews conducted in this relatively well researched/reviewed area.	The revision in how the outcome of 'overall prescribing' is weighted has changed the key findings such that they are more consistent with other reviews, but there are still some differences due to the broader, more comparative, scope of this review.
155.	Peer Reviewer #3 (TEP Reviewer)	Results; General Comment	The Tables and test explanations of the studies are well presented with good amount of detail. Key messages are clear.	Thank you for your comment.
156.	Peer Reviewer #4 (Peer Reviewer)	Results; General Comment	The details were appropriate for the sections that I reviewed.	Thank you for your comment.
157.	Peer Reviewer #5 (Peer Reviewer)	Results; General Comment	This is a long paper, but it addresses multiple questions with subsets requiring the wordiness and some repetition. I think it is appropriate to have the reviews of the papers answering each of the key questions.	Thank you for your comment.
158.	Peer Reviewer #6 (TEP Reviewer)	Results; General Comment	-The detail presented is more than adequate to justify the recommendations.	Thank you for your comment.
159.	Peer Reviewer #6 (TEP Reviewer)	Results; General Comment	-Figures and tables provide good summary of the available data.	Thank you for your comment.
160.	Peer Reviewer #6 (TEP Reviewer)	Results; General Comment	-The search seems comprehensive. I was not able to identify any articles that I know of that would have fit the inclusion criteria that	Thank you for your comment.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			were not included.	
161.	Peer Reviewer #7 (Peer Reviewer)	Results; General Comment	Fine	Thank you for your comment.
162.	Peer Reviewer #8 (Peer Reviewer)	Results; General Comment	The Abstract Results and the results more generally present the most effective trials or studies and is not a meta-analysis or a true evidence summary. It feels more like advertising for the effective interventions mentioned. This is in contrast to the Abstract Conclusions, which are much more circumspect and do not follow the pro-intervention nature of the Results. It is hard to reconcile the enthusiastic nature of the Results with the muted conclusions.	We revised the abstract and conclusions to highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences).
163.	Peer Reviewer #8 (Peer Reviewer)	Results; General Comment	If only 45% of the studies were conducted in the US, it would be helpful to mention where the other studies were performed. My impression is that most of the remainder have been in Northern European countries with national health systems.	Thank you for this comment; we have added more information on the settings of the non-US studies to the overview of results and the applicability of the evidence sections. Here is a summary: North America: 52%, Europe: 36%, Asia:13%
164.	Peer Reviewer #9 (Peer Reviewer)	Results; General Comment	The search strategy The search is fine, although we agree with the authors that it is a limitation that non-English language publications were excluded. The risk of publication bias has to be taken into account when interpreting the results. It might have been worthwhile to include non-English language literature in the review as	We do not believe that exclusion of non-English language studies has significantly affected the conclusions of this review because our review of English-language abstracts of studies with full text

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			the authors already did an additional search and evaluated the English abstracts of these studies, or at least undertaking an analysis to estimate language-publication-bias.	published in other languages primarily found a small amount of low-strength observational evidence of interventions for which we already have RCT evidence.
165.	Peer Reviewer #10 (TEP Reviewer)	Results; General Comment	The authors do a good job in plowing through a large body of evidence. By nature, results sections like this are full of detail, and require considerable concentration to get through. Clarity of language is particularly appreciated here-- thanks.	Thank you for your comment.
166.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results; General Comment	<p>Key Question 2</p> <ul style="list-style-type: none"> The lack of studies that use antibiotic resistance as a key outcome is cited as a major limitation of research to date, and this outcome is given equal “weighting” alongside inappropriate prescribing. This should be reconsidered. There is likely a good reason why this has not been studied as an outcome. While resistance is an important undesirable consequence, emergence of resistance is a complex issue, and is difficult to assess on an individual level, especially in the population of individuals with respiratory viral, and not bacterial, infections. Further, the association between antibiotic use and resistance is well established, and forms the basis of antimicrobial stewardship 	Agreed. Restructured conceptual framework to highlight interventions with the best evidence of improving benefits (prescribing outcomes) and not causing harm (adverse consequences). Also de-emphasized lack of resistance data as a limitation.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>interventions, so there should not be a perceived need for proving this principle.</p>	
167.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results; General Comment	<p>Key Question 3 The panel's conclusions of the study results could be written and interpreted in a somewhat different manner. Under "<i>Strategies to Improve Communication between Clinicians and Patients</i>", "...It found that slightly more patients treated by clinicians who received the communication intervention only were hospitalized within 4 weeks after the clinic visit (0.5%; 6/1101) compared with the usual care group (0.2%; 2/861), but the difference was not statistically significant (RR 2.35; 95% CI, 0.48 to 11.60). 67 When compared with patients in clinics using point-of-care CRP testing, fewer patients in the communication intervention group were hospitalized (0.5% [6/1101] vs. 1.0% [10/1018]; RR 0.56; 95% CI, 0.20 to 1.52), which was also not statistically significant..."</p> <p>Instead of stating that there was a difference but not statistically significant, the authors should consider stating that there was NO DIFFERENCE. Stating this in such a manner would lead to less likelihood of misinterpretation.</p> <p>Further, it is stated that, "<i>The small size and relatively low</i></p>	<p>Thank you for these comments. The sample size of this study was less than 2000 patients, and as noted hospitalization is somewhat uncommon (although not rare). The needed sample size would be about double. Even allowing for hospitalization being an uncommon event, the confidence interval is very wide such that we cannot conclude that there is no difference, but must conclude that a statistically significant difference was not found. Further studies – adding more statistical power – would resolve this issue.</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p><i>quality of the single study prevents firm conclusions.”</i></p> <p>The study size does not seem small, but the outcome of hospitalization is rare, which in of itself is an important point of emphasis. Does the panel really believe that intervention studies of reducing antibiotics for RTI could be designed to be powered to adequately assess hospitalization as an outcome?</p>	
168.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results; General Comment	There is a dearth of studies that assess C. difficile infection as an outcome. This fact should be included as a comment on this section	We have added this to the gaps in the evidence and future research sections.
169.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Results; General Comment	<p><u>Key Question 4</u></p> <p>The authors performed a thorough review of the literature and consistently highlight the strength of the evidence when they are reporting results. Although it is challenging to report results for both children and adults when examining RTIs, the authors adequately distinguish when they are reporting findings that were distinct for children or adults and acknowledge when data was not pooled due to the variation of the symptoms or population.</p> <p>Some of the studies reported are from outside the US which may limit the generalizability to practitioners in the US; however the authors mention throughout the document that this is a limitation.</p>	Thank you for these comments.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			The fact that the authors tried to examine outcomes by subgroups adds strength to the report.	
170.	Peer Reviewer #12 (Peer Reviewer)	Results; General Comment	I particularly appreciated the inclusion of CRP and procalcitonin in this review as I have not yet seen something so thorough and up-to-date on this literature. I thought the evidence supporting these tests was interesting, particularly the higher rates of secondary outcomes such as hospital admissions and reconsultations which you don't hear as much about. Additionally, I appreciated the summary of evidence showing the additional time commitment which may be needed for such interventions (page 83).	Thank you for these comments.
171.	Peer Reviewer #12 (Peer Reviewer)	Results; General Comment	I didn't see anything mentioned about PCV7 or PCV13 release in the limitations section and how this might confound study results from the early 2010s when assessing frequency of antibiotic prescribing (PCV likely reduced incidence of pneumococcal-caused infections such as cases of AOM or bacterial sinusitis, and therefore reduced antibiotic prescribing as a whole).	While we agree with the concept, we feel that few studies would potentially be affected. RCTs, for example, would not be affected, and only pre-post studies without a control group, that happen to span the period before and after their introduction would be affected.
172.	Peer Reviewer #12 (Peer Reviewer)	Results; General Comment	I found the review for Key Question 5 to be a particularly helpful summary of education/communication interventions.	Thank you for your comment.
173.	Peer Reviewer #14 (TEP Reviewer)	Results; General Comment	Clear and accurate. The classification of 'rapid strep' testing as testing for Streptococcus pneumoniae is incorrect. Rapid strep testing identifies Streptococcus pyogenes otherwise known as Group A beta-hemolytic Streptococcus, the	Changed to Group A Beta hemolytic strep

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			cause of strep throat. This needs to be corrected throughout the document.	
174.	Peer Reviewer #16 (TEP Reviewer)	Results; General Comment	<p>KQ1 Note that all the CRP studies limited to adults, none include children - this limitation should be added to overall conclusions.</p> <p>Systematic review of effectiveness of CRP point of care test not cited (Huang, Br J Gen Pract 2013 which notes 13 studies of POCT for CRP - unclear why this review not included, and which of its included papers were included/excluded and why).</p>	<p>Added statement to Limitations section on lack of evidence in children.</p> <p>The Huang review was identified, but was not useable due to an error in the meta-analysis. We have added notation of the study in the text on CRP.</p>
175.	Peer Reviewer #16 (TEP Reviewer)	Results; General Comment	Need to separate out the ED studies from primary care based studies, this currently unclear. As well as by diagnosis and baseline rate of use of abx.	We agree that noting these variations is important. We have separated these out where possible, and address them in the Subgroup sections. The baseline prescribing rates have been added to the Summary Table in the discussion and executive summary.
176.	Peer Reviewer #16 (TEP Reviewer)	Results; General Comment	Procalcitonin (PCT) studies showed greater effect on reducing abx use overall, but opposite effect in children - suggests inconsistency, unless mechanism is differing in age groups. And only 2 PCT trials included.	Because the procalcitonin results vary by age group (adults vs children) we took the method proposed by EPC and GRADE and considered these as separate bodies of evidence
177.	Peer Reviewer #16 (TEP Reviewer)	Results; General Comment	Effects of viral testing in adults, was significant, why labeled insufficient not low?	As we have revised the rating for the outcome of overall prescribing of antibiotics, this evidence is

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				now rated low strength.
178.	Peer Reviewer #16 (TEP Reviewer)	Results; General Comment	KQ3 treatment failure I thought that the above mentioned SR of CRP testing did include evidence for effects on reconsultation/treatment failure?	The Huang review was rated poor quality as noted due to an error in the meta-analysis, but our own analysis includes these outcomes.
179.	Peer Reviewer #3 (TEP Reviewer)	Discussion/ Conclusion	88; line 6; extra 'in'	Deleted the extra 'in'
180.	Peer Reviewer #9 (Peer Reviewer)	Discussion/ Conclusion	Page 90, line 6 – empty box in 'knowledge, SDM...' column for 'procalcitonin' intervention.	Added 'No evidence'
181.	Peer Reviewer #9 (Peer Reviewer)	Discussion/ Conclusion	Page 90 – tympanometry is not included in Table 20 but is included in the associated appendix.	Added a line for tympanometry.
182.	Peer Reviewer #9 (Peer Reviewer)	Discussion/ Conclusion	Page 94, line 17 – empty box under 'pharyngitis' for multifaceted interventions, should it be greyed out?	Added '-' and footnote that combination of patient and provider education plus audit and feedback ineffective in children with pharyngitis.
183.	Peer Reviewer #3 (TEP Reviewer)	Discussion/ Conclusion	97; Line 31 (also page 98, line 40); agree that the short time period of most studies does not allow the duration of effect (e.g. the benefit may wane if the intervention is not continued)	Thank you for the comment.
184.	Peer Reviewer #4 (Peer Reviewer)	Discussion/ Conclusion	Page 98, line 23: Not sure why is is clear that patients will have longer symptoms when viral infections would not be influenced by antibiotics? Can you clarify? "While it seems clear that patients will experience symptoms longer and will have lower satisfaction compared with receiving a prescription	Changed to, "While there is low-strength evidence that patients will...."

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			immediately..."	
185.	Peer Reviewer #10 (TEP Reviewer)	Discussion/ Conclusion	Page 98, line 28-- again the contradictory phrase "The next tier of best evidence"	Based on reviewer feedback, we have eliminated the 'tiers of evidence' approach and highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences). We have organized the evidence into categories based on the direction and strength of evidence for benefit and harm.
186.	Peer Reviewer #10 (TEP Reviewer)	Discussion/ Conclusion	Page 102, future research needs: is this supposed to read "cannot be randomized"?	No, it is correct as stated that most studies can be randomized.
187.	Peer Reviewer #9 (Peer Reviewer)	Discussion/ Conclusion	Page 102-103 – we encourage the authors to note the need to use reporting guidelines to ensure better reporting, particularly for interventions (the TIDIER extension of CONSORT) plus STROBE of nonrandomised studies.	Noted.
188.	Peer Reviewer #3 (TEP Reviewer)	Discussion/ Conclusion	103; consider also studying the time effect of an intervention if that intervention is stopped?	We included sustainability as an outcome of interest, but found very little evidence and none that was comparative. Added this to the Future Research section.
189.	Peer Reviewer #3 (TEP Reviewer)	Discussion/ Conclusion;	Major findings are clearly stated, but see comments above regarding some confusion	Thank you for your comment here and above. We have

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
	Reviewer)	General Comment	of "appropriate use" vs "reduced use"	addressed these comments by revising the discussion of how studies attempted to measure appropriateness.
190.	Peer Reviewer #4 (Peer Reviewer)	Discussion/ Conclusion; General Comment	Implications were well stated; limitations were also pointed out clearly. Future research sections were explicit.	Thank you for your comment.
191.	Peer Reviewer #5 (Peer Reviewer)	Discussion/ Conclusion; General Comment	The results are as clear as can be based upon the research. The bold print in Comparisons to Usual Care on p119 helps the reader focus on the important points. Table 22 also helps to put it into perspective. The limitations are again addressed along with the gaps in information, and need for further research.	Thank you for your comment.
192.	Peer Reviewer #6 (TEP Reviewer)	Discussion/ Conclusion; General Comment	-It is quite disheartening that so few studies used resistance as an outcome given that reducing contributing to resistance is essentially the primary reason for most of these interventions, and that so few examined the resources used for the interventions.	We agree. Thank you for the comment.
193.	Peer Reviewer #6 (TEP Reviewer)	Discussion/ Conclusion; General Comment	-Overall the discussion is an excellent summary of what was learned from the study as well as the (large) gaps in knowledge. -The conclusion is a succinct summary of the report.	Thank you for your comment.
194.	Peer Reviewer #7 (Peer Reviewer)	Discussion/ Conclusion; General Comment	The strengths and weaknesses of the work are not fully covered.	Please see revised discussion.
195.	Peer Reviewer #9 (Peer Reviewer)	Discussion/ Conclusion; General	Are there ways this review could be made more reader-friendly? Currently the text is crushingly huge, at 115 pages with	We thank the reviewer for the suggestions on how to improve the accessibility of

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
		Comment	Appendices bringing it up to 650 pages. More sign-posting headings would help (some are confusing right now). It is easy to become lost. Perhaps it could be published as a journal article, with the extra material available off-line?	this huge body of evidence. We have improved the clarity of the subheadings and intend to publish a more condensed version as a journal article.
196.	Peer Reviewer #9 (Peer Reviewer)	Discussion/ Conclusion; General Comment	Presumably there are no plans to update the review. Perhaps this should be discussed, with a set of options.	AHRQ has a surveillance process for determining need to update.
197.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Discussion/ Conclusion; General Comment	The opening paragraph (Key Findings and Strength of Evidence) acknowledges a lot of the weaknesses of the report. Although the reader is aware of these weaknesses when reading the document it appears that in some cases it was not possible to assess some of the goals of the study given the limitations in the data or other factors.	Yes, several gaps and serious limitations of the evidence base prevented us from reaching conclusions on several aspects of this review. The 'Gaps in the Evidence Base' section provides a detailed description of the data limitations.
198.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Discussion/ Conclusion; General Comment	One of the strengths of the report is a section discussing how the findings fit into what is already known and the variations in existing guidelines.	Thank you for your comment.
199.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Discussion/ Conclusion; General Comment	The "Implications for Clinical and Policy Decision Making" section rightly acknowledges that most studies did not look at the sustainability of the various interventions, and that this should be a future area for research.	Thank you for your comment.
200.	The Society for Healthcare Epidemiology	Discussion/ Conclusion; General	As similarly stated in the Executive Summary, it is excellent that the authors highlight several specific areas of future research that	Thank you for your comment.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
	for America (Public Reviewer)	Comment	are needed to help address the problem of over prescribing antibiotics for acute RTIs.	
201.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Discussion/ Conclusion; General Comment	The authors should consider incorporating <i>C. difficile</i> infection as an outcome, given its rise as a pathogen even outside the hospital setting, and strong association with antibiotic use.	Agree, we included <i>C. difficile</i> infection as an outcome, but found no evidence. We've added more clear statements to this effect.
202.	Peer Reviewer #12 (Peer Reviewer)	Discussion/ Conclusion; General Comment	<p>I think in general the discussion points which are presented can be better grouped in a way more comprehensible by the reader. While I do not doubt the cited studies are high quality, it seems almost whimsical the way the 4 interventions were chosen given the rigorous criteria which were used in the lit review.</p> <p>For example, I appreciate the quality of the RCT upon which the first intervention recommendation is based, however, I am concerned that only 1 study is cited for this recommendation, and the subjects and condition for which it may be most applicable (children with AOM) may not be generalizable to other settings, populations, and conditions. I agree CDSS (Intervention #2) appears to have strong evidence supporting its use to reduce inappropriate prescribing, it remains less clear to me why only 2 RCTs were cited for this part of the discussion. As mentioned above, I don't consider "two combined clinic based education interventions" to be an intervention type, this seemed inconsistent and confusing to me.</p>	Previously our criteria for best evidence of overall effectiveness were presence of any evidence of reduced resistance or improved <i>appropriate</i> prescribing. Based on reviewer feedback, we have organized the evidence into categories based on the direction and strength of evidence for benefit and harm and highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences).

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
203.	Peer Reviewer #13 (Peer Reviewer)	Discussion/ Conclusion; General Comment	<p>The discussion section and the conclusions were comprehensive and extensively detailed. This reviewer is unaware of any additional important literature that was omitted from consideration by those who did the literature search, data abstraction and drafting of this CER report. While the scope was very large with a strong degree of comprehensiveness, the general thrust of evidence findings that support the various key questions was clear and well-articulated. While this is not a criticism of the CER, this reviewer generally felt some degree of disappointment that so many of the key questions and subquestions generally, in the final assessment as nicely described in the Discussion section, were simply not supported or inconclusive by the level and quality of available evidence. However, the overall quality of effort in conducting, organizing and drafting this CER was excellent.</p> <p>Again, it was encouraging to note that there is moderate strength evidence that both procalcitonin and CRP POCT can reduce overall prescribing without increasing symptoms of disease, mortality or additional clinic visits. In the U.S., the FDA has approved a couple of isolated procalcitonin assays although, as of mid-March, 2015, there are no major IVD analytical platforms for which procalcitonin is FDA-approved in the U.S. despite some of these same platforms and assays being used and available in countries outside the U.S..</p>	Thank you for your comments.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
204.	Peer Reviewer #14 (TEP Reviewer)	Discussion/ Conclusion; General Comment	Clear	Thank you for your comment.
205.	Peer Reviewer #16 (TEP Reviewer)	Discussion/ Conclusion; General Comment	See some of the above points. The main issue is to be consistent in summarizing the effects of different interventions. As noted above. I understand this is difficult given the multiple types of interventions/effect sizes/differences in PICOTS etc etc, but need to be a bit more consistent and fair to the multiple types of interventions and summarize slightly more fairly.	Previously our criteria for best evidence of overall effectiveness were presence of any evidence of (1) reduced resistance or (2) improved <i>appropriate</i> prescribing. Based on reviewer feedback, we have organized the evidence into categories based on the direction and strength of evidence for benefit and harm and highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences). This modified our conclusions and we also improved our explanation of our revised methods for selecting the interventions with the best evidence of overall effectiveness.
206.	Peer Reviewer #16 (TEP Reviewer)	Discussion/ Conclusion; General Comment	I would strongly urge a far greater list of research gaps, and exactly what evidence is needed to address these. the Future research needs pages 102-3 gets a mere 1/2	Please see revised future research section with more detail on what is needed for primary studies in terms of

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>page. Given the massive work that the authors have put into this considerable synthesis, it would be extremely helpful for AHRQ and research funders, researchers etc, to have even more details here about WHAT is missing in the evidence. For example there have been many systematic reviews in this area (I have published several myself), but the authors were only able I think to use only 1 Cochrane review. Clearly the systematic review community is missing something here, and the Cochrane ARI group (and others) needs to know which reviews to prioritize. And in terms of primary studies, I would like to see far more detail on what is needed in terms of PICOTS for the different interventions, based on the findings of this synthesis. So for example , are studies needed of CRP or procalcitonin POC tests in children, or primary care, or strep A testing...?</p> <p>I realise there is a whole separate future research needs program but a small expansion of this would vastly help the field move ahead, and generate evidence that is needed.</p>	<p>PICOTS for the different interventions. There are multiple reasons that only a few of the existing reviews were useful to us in this review. They include 1) Population – we were limited to acute RTI, 2) interventions – we had a broad perspective from the point of view of making implementation decisions while the reviews include a small range or even only one type of interventions, 3) the age of the review – in cases where new studies would need to be synthesized with the older body of evidence it made more sense to use the older reviews to identify studies rather than use them as a primary source of synthesis.</p>
207.	Peer Reviewer #10 (TEP Reviewer)	Tables	Table C: Presumably "L" and "M" refer to low and moderate strength evidence? Would add footnotes to define.	Yes, those abbreviations refer to low and moderate strength of evidence. We've since changed to symbols per the GRADE Working Group recommendations on how to communicate grades of evidence (Schunemann

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				2003) and added a footnote to define.
208.	Peer Reviewer #1 (Peer Reviewer)	Tables	Table C and D: add references where appropriate	We can really appreciate this suggestion. It is hard to balance the need to provide more details to summary tables without overcrowding. We already expanded the tables with additional symbols to differentiate findings of no difference from those showing a difference, as well as added data on magnitude of effect to assist with interpretation.
209.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Tables	Table E which summarizes the “population,” we recommend more specificity for age since children and adults are included. The report only provides a mean age of 26 years; the authors may want to include a range of age or standard deviation since a large proportion of the studies included involve children; the mean age alone is a little misleading.	Added: 45% of studies had a child population, with a mean age of 4 years. 28 % studies had a mixed-age population, with a mean age of 33 years. 27 % studies had an adult population, with a mean age of 44 years
210.	The Society for Healthcare Epidemiology for America (Public Reviewer)	Tables	Table 2 is effective in that it clearly outlines the type of research that has been done in relation to the key questions addressed and highlights areas where more research may be needed.	Thank you for this comment.
211.	The Society for Healthcare Epidemiology for America	Tables	Tables 15, 16. We suggest including study population (adult/children), clinics, provider information as done in Table 14.	Study population is already available in Tables 15 and 16. Practice N and provider N Information presented

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
	(Public Reviewer)			where available throughout the report.
212.	Peer Reviewer #3 (TEP Reviewer)	Tables	Tables 20 and 21: nice summary	Thank you for your comment.
213.	Peer Reviewer #10 (TEP Reviewer)	Tables	Summary tables 20 and 21 are particularly helpful in terms of getting the big picture. Consider bolding significant results to help them stand out even more.	We added symbols to differentiate findings of no difference from those showing a difference, as well as added data on magnitude of effect to assist with interpretation.
214.	Peer Reviewer #10 (TEP Reviewer)	Tables	Summary table 22 also very good, like the clean way of presenting the data. But-- need a legend to ensure readers interpreting the + and - signs correctly	Added: + some evidence of effectiveness; -evidence of ineffectiveness
215.	Peer Reviewer #9 (Peer Reviewer)	Figures	Figure 3 - overall effect (RR 0.73) is not the same as in the text page 34 line 22 (RR 0.69)	The error has been fixed with the inclusion of a revised forest plot and text
216.	Peer Reviewer #10 (TEP Reviewer)	Figures	Figure 3: suggest a legend indicating which direction favors CRP vs. usual care. Presumably left favors CRP.	Added
217.	Peer Reviewer #10 (TEP Reviewer)	Figures	Figure 4: similar comment as for figure 3.	Added
218.	The Society for Healthcare Epidemiology for America (Public Reviewer)	References/ Appendices	As the authors acknowledge in the limitations, a proportion of studies are from outside the US which may limit the generalizability to clinicians/clinics in the US. However, we support the inclusion of some of these studies as results can be used to inform gaps in knowledge and future areas of research.	Thank you for your comment.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
219.	The Society for Healthcare Epidemiology for America (Public Reviewer)	References/ Appendices	A recent study published in <i>Infection Control and Hospital Epidemiology</i> related to antibiotic prescribing for RTIs potentially could be included in the introduction/background section of the report. The study examines factors associated with inappropriate antibiotic prescribing for acute RTIs (Barlam, et al. ICHE, Feb 2015).	Thank you. We added this reference to the Introduction.
220.	Peer Reviewer #1 (Peer Reviewer)	General	Thank you for the opportunity to assess this clinically meaningful report. The authors have produced an impressive report. However a few issues need to be addressed first. Although the target population is clearly defined, it should be noted that adults and children are two very different populations when it comes to antibiotic prescribing. Not only does age probably influence the antibiotic prescribing rate, physicians are more likely to prescribe antibiotics in children to reassure anxious parents or due to previous experiences with serious infections in children. The possible rapid deterioration of an acute infection with serious complications and death triggers the clinician to prescribe antibiotics at an early stage, often inappropriately. This difference in population should be clear from the start of this review. I believe the key questions to be appropriate and clearly stated.	We agree very much that the issues in adults and children are different, and have added this to our introduction, hand have attempted to address this as much as possible with the studies available. We have expanded the future research section as well, including this issue.
221.	Peer Reviewer #1 (Peer Reviewer)	General	I would advise the authors to clearly separate antibiotic use and antibiotic prescribing. It is very difficult to measure whether a patient has actually taken his medication, so assuming he used his medication based on the prescription or even collecting the	Our scope included both prescription and use outcomes, but data on use was limited to the some of the delayed prescribing studies, where the

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			medication from pharmacy might be overestimating the use and it is known that inappropriate intake of antibiotics (missing a dose or shortening the course) influences resistance etc.	comparison groups were typically 'immediate prescribing'. We've added to the Future Research section the need for studies evaluating use.
222.	Peer Reviewer #2 (TEP Reviewer)	General	The large DESCARTE cohort published in Lancet ID is within your search dates and addresses the issue of the protective effect of antibiotics or delayed antibiotics - worth discussing a little more? (DOI: http://dx.doi.org/10.1016/S1473-3099(13)70294-9)	The comparison groups of interest for this review were usual care and direct comparisons among interventions. Because the DESCARTES study used 'no antibiotics' as the comparison group, rather than usual care that would include both immediate and no prescribing, and possibly even delayed prescribing, we were not able to use the study in our review.
223.	Peer Reviewer #3 (TEP Reviewer)	General	<p>GENERAL COMMENTS</p> <p>The report is very comprehensive and from my perspective is an excellent systematic review of this topic. Somewhat disappointing with the conclusions as to unable to definitively identify strategies that are effective based on strong evidence and easy to apply in general practice.</p> <p>Other messages from my perspective: A primary message is the lack of consistency of studies to be able to make definitive recommendations. Use of Procalcitonin seems promising. Reductions in prescribing was greater when</p>	Thank you for your comments.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			the target was the patient or parent rather than prescriber.	
224.	Peer Reviewer #4 (Peer Reviewer)	General	The report focuses on inappropriate antibiotic use for acute respiratory tract infections and on what evidence based strategies are available to combat that problem. While there is a paucity of well established evidence, not surprisingly the more robust evidence surfaces for watchful waiting or delayed prescribing. Also, education programs (patient or combined patient/provider); electronic decision support systems appear to have a role. Point of care tests such as procalcitonin, CRP and rapid strep tests hold promise in terms of reducing overall prescribing but there are limits in knowledge about how to best apply these, and to whom. Of note, most studies honed in on prescribing (e.g., overall antibiotic use) and not outcomes. Studies were often limited by singular ("one off") assessments and a majority were conducted outside the US. The report is clinically meaningful and key questions appear to be appropriate and well stated. Please note that I was not able to complete the review of the entire document but was able to review the Executive Summary and selected portions of the main text of the report.	Thank you for your comments.
225.	Peer Reviewer #5 (Peer Reviewer)	General	Well written, addressing all the key questions. Very relevant to primary care, a major cause of doctor visits and antibiotic prescriptions for usually viral infections. The target population and key question objectives are well defined	Thank you for your comment.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			and explicitly stated. The gaps in prior studies were noted as reason to reassess at this time. Future research needs were addressed.	
226.	Peer Reviewer #6 (TEP Reviewer)	General	-Overall I think this is a well-organized approach to a complex question with a huge amount of data, with clear definitions and recognition of limitations. -The key questions are clearly defined and stated.	Thank you for your comments.
227.	Peer Reviewer #7 (Peer Reviewer)	General	This is a very rigorous, thorough review and the 'internal validity' is undoubtedly high. The reproducibility will be excellent, given the fulsome description of the methods and search strategies. A lot of consultation has gone into the methods development (for example around the eligibility period for studies). The study questions and sub questions are focussed. The findings are well supported and have face value in so far as they go. However, the review has a narrow focus that undermines its potential usefulness in guiding strategic responses and research focus on the crucial topic of intervening to limit unnecessary prescribing in order to help contain antibiotic resistance. There are key conceptual problems that could be addressed to enhance the impact of this substantial piece of work Almost paradoxically, the narrow focus on RTIs has also led to the exclusion of a large number of studies, which are of fundamental importance to the enterprise of reducing	Skin and soft tissue and urinary tract infections are outside the scope defined by the key informants, the TEP and also the original nomination. We did include studies of mixed populations where the aRTIs were separated out.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>unnecessary antibiotics for RTIs. Most antibiotics are prescribed in primary care for RTIs (>80%). However, some unnecessary prescribing also occurs for skin and soft tissue, and urinary tract infections etc. Many interventions, especially in primary care, have been aimed at more appropriate prescribing overall, but will have been focussed mostly on RTIs and the effects seen (or not seen) with have been felt mostly on RTIs. These broader-based intentions and evaluations are directly relevant to the RTI question and are central to the mission of achieving more appropriate antibiotic prescribing for RTIs. This broader approach may be more meaningful for policy makers in declining which approach to follow that smaller often poorer quality single focus studies on specific RTIs or RTIs only. It is inconceivable that this document will carry the gravitas it deserves if the key studies are left out, which are often pragmatic and thus speak more directly about what may happen in the real world. At minimum, this issue should be prominently recognised in the limitations. Right now, the reader would get a very skewed impression of the field and about what should be done, because of this narrow interpretation of eligibility. After all, while RTIs account for most antibiotic prescribing, it is more appropriate antibiotic prescribing generally that is the purpose of the interventions covered in this report and what policy makers, purchasers of care, clinicians, and patients seek to achieve. Pragmatic studies</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>with a broad approach that are primarily (but not exclusively) focussed on RTIs should have a voice in this review.</p> <p>In fact, the more measurements that are made to inform judgements such as appropriateness, the more the study's applicability becomes open to question. Efficacy studies generally give higher effect sizes in this and other fields when compared to implementation and effectiveness studies. By focussing on appropriateness of antibiotic prescribing at an individual level rather than overall levels of prescribing at a facility level, the review becomes biased against pragmatic evidence. However, it is pragmatic studies that will give the best indication of possible effect sizes should the studies be rolled out in the real world. Efficacy studies usually consider the effect of an intervention in a single consultation. It is easy to change prescribing behaviour in a single consultation. Studies that measure overall antibiotic prescribing outside the artificial constraints of a consultation during which a patient has been enrolled in a study and randomised and which consider prescribing over a long period are a much more powerful reflection of what an intervention is likely to achieve practically.</p> <p>Studies in this field are particularly prone to section bias in that those who are trained in interventions often also recruit the participant and deliver the intervention and indeed sometimes assess outcomes. Often 'friendly'</p>	

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>patients consulting at quiet times are preferentially included. The review rightly supports cluster-randomised trials, but bias can be associated with opportunistic individual recruitment when the interventionists are also the recruiters and select which patients to approach. This source of potential bias a generic problem of this class of stud could be motioned in the discussion under limitations.</p> <p>Although scrupulously rigorous and with high interval validity, sadly, by strictly focussing the inclusion to studies of RTIs only (and not including major studies that focus on RTIs mostly), this review has left outs some of the most important pragmatic evidence and will therefore give a misleading, less useful impression.</p>	
228.	Peer Reviewer #8 (Peer Reviewer)	General	<p>This report is clinically meaningful. The authors strive to summarize quite a lot of information for investigators and health system leaders interested in decreasing inappropriate and overall antibiotic prescribing. I've been able to spend about a day with the report, but have not been able to really get into the minutiae of each individual intervention and comparison.</p> <p>The report asks 6 key questions regarding a host of outcomes regarding the comparative effectiveness of interventions to improve the appropriateness of antibiotic prescribing for respiratory infections. The authors consider a wide range of potential effect modifiers on</p>	<p>Based on advice from the Key Informants and TEP, we originally were emphasizing resistance and <i>appropriate</i> prescribing and had concluded that there was a general lack of evidence on this topic due to limited data on those specific outcomes.</p> <p>In response to peer review, now that we've changed the emphasis to interventions with the best evidence of improving benefits (prescribing/resistance</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>page ES-3.</p> <p>Thinking beyond the data, there are a few big concepts and social factors that limit the reports' interpretation and conclusions.</p> <p>There is an inconsistency in the report between the recommendation that future investigators, particularly when "interventions that involve changing behavior" – all interventions that seek to decrease antibiotic prescribing "involve changing behavior" – should be based on the best evidence to date and the fact that the authors conclude there is a general lack of evidence on this topic.</p>	<p>outcomes) and not causing harm (adverse consequences), the inconsistency the reviewer points out has been eliminated because the associated evidence is more robust and can provide more of a basis for guiding future research.</p> <p>We have revised the recommendation to be more clear.</p>
229.	Peer Reviewer #9 (Peer Reviewer)	General	<p>We are delighted to critique this enormous systematic review. It contains 129 studies and systematic reviews (conducted between 1990 and 2014) of interventions to improve appropriate prescribing of antibiotics in primary care for acute respiratory infections.</p> <p>It is not quite clear what the purpose of the review is. One can infer that it is to set a research agenda, and possibly to re-direct policy towards addressing the antibiotic resistance crisis.</p> <p>The review concludes that: (1) watchful waiting for acute otitis media reduces resistance; (2) decision support and a multi-faceted intervention of clinical algorithm and education improved appropriate prescribing; and,</p>	<p>AHRQ intends that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole.</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>(3) procalcitonin use offers the strongest evidence for reduction in overall prescribing.</p> <p>Importantly, the review also highlighted four interventions which have been demonstrated to be effective based on the current evidence:</p> <ol style="list-style-type: none"> (1) procalcitonin in children, (2) public campaigns targeting adults, (3) a sore throat decision rule; and (4) rapid viral testing in children. <p>This is a worthwhile review. It makes a valuable contribution to the literature in this important area. It highlights the gaps for further research, and make some recommendations for policy.</p>	
230.	Peer Reviewer #10 (TEP Reviewer)	General	Well-written introduction to the executive summary. Frames the issue nicely and provides sufficient background. The entire executive summary is informative. Comments below refer to the executive summary.	Thank you for your comment.
231.	Aurelian Udristioiu (Public Reviewer)	General	“Rapid diagnosis of acute respiratory infections by multiplex endpoint PCR technology”	Thank you for bringing this manuscript to our attention. Unfortunately it does not meet our inclusion criteria.
232.	Peer Reviewer #12 (Peer Reviewer)	General	In general I found this review to be thoroughly done and worth the effort. The indepth and focused Key Questions lay out this review in a cogent manner and provides value to those who are interested in implementing evidence based outpatient stewardship interventions in different settings. I do think there are opportunities for improvement, however, such as the overall length of the document, superfluous tables throughout, and fine	The Abstract and Executive Summary have both been rewritten to revise and fine-tune the main messages.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			<p>tuning the main messages which the authors promote in the results and discussion sections. In general I found the main body of this review to be well-written, however, I think the Abstract and Executive Summary may need some refinements. I am very glad to see this report is being written, because an updated systematic review of this literature is greatly needed.</p>	
233.	Peer Reviewer #13 (Peer Reviewer)	General	<p>There is a very large body of evidence in the literature on these topics. This report is exceptionally clinically meaningful. It is very significant for AHRQ to have conducted and published this draft comparative effectiveness review (CER) on ‘Interventions to Improve Appropriate Antibiotic Use for Acute RTI’s.’ The need for robust evidence on this topic has never been greater and with the advent of antibiotic stewardship programs, the ongoing problems associated with sepsis and the growing difficulties if general antibiotic resistance, this was a very important comparative effectiveness review (CER) topic to undertake.</p> <p>The target population and audience were explicitly defined. This review has worked as a pathology faculty member and laboratory director in an academic medical center associated with a large national hospital health care network. While the general scope of key questions are outside of my immediate areas of expertise (with the exception of studies comparing point-of-care testing strategies to other interventions with selected key questions), I felt the key</p>	Thank you for your comments.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			questions were appropriate, explicitly stated and clear to this reviewer including the respective subquestions. I cannot suggest any changes, deletions or additions. The scope of the key questions and the nature of the analytic framework seem completely appropriate to this reviewer.	
234.	Peer Reviewer #14 (TEP Reviewer)	General	The report is meaningful. It is very detailed and portions will be used by investigators interested in interventions to reduce antimicrobial prescribing in ARTI. The length of the article precludes use by clinicians. An executive summary for practitioners should be considered.	We can really appreciate these comments. It is hard to balance the length needed to provide adequate details to respond to concerns as noted by other reviewers and with simplifying the message. We hope the executive summary serves this purpose for some, and the abstract for others. Also, the Eisenberg Center will be developing some additional translational products that will hopefully be of more use to practitioners and others.
235.	Peer Reviewer #15 (TEP Reviewer)	General	The report does a reasonable job of posing key questions. The approaches in the studies are most heterogenous making it difficult to compare and summarize. I would have separated by children vs adults and types of infection (otitis, sore throat, acute bronchitis). The manuscript reviews studies of comparative effectiveness strategies. Some comment is needed about risks and benefits of this type of research in the RTI literature reviewed (Risks (and Benefits) in Comparative Effectiveness Research	We took advice from the TEP to organize the report by intervention and outcome to better facilitate implementation, but we did separate out by age and infect types within that structure.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			Trials, Chris Feudtner, M.D., Ph.D., M.P.H., Mark Schreiner, M.D., and John D. Lantos, M.D. <i>N Engl J Med</i> 2013; 369:892-894. September 5, 2013. DOI: 10.1056/NEJMp130932.	
236.	Peer Reviewer #16 (TEP Reviewer)	General	<p>This is a very large and comprehensive review, the authors should be congratulated on such a detailed and broad scope evidence synthesis. I had few criticisms of the methods used and the data extracted, my comments mostly refer to some nuances of interpretation and consistency of interpretation.</p> <p>In the summary/executive summaries and Structured abstract, there are various comments on fidelity of interventions, populations to which these results apply (age group, setting), sustainability, resources needed are somewhat variably applied in summarizing the overall effects of different interventions— need to be consistent. For example, why does Watchful waiting with a single RCT of 223 people ‘stand out’, whereas other interventions with far more numbers of studies and quality of results not ‘stand out’?</p>	<p>Previously our criteria for best evidence of overall effectiveness were presence of any evidence of reduced resistance or improved <i>appropriate</i> prescribing. Based on those criteria, watchful waiting stood out because it was the only intervention with any evidence on resistance. Based on reviewer feedback, we have organized the evidence into categories based on the direction and strength of evidence for benefit and harm and highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences). This modified our conclusions and we also improved our explanation of our revised methods for selecting the interventions with the best evidence of overall</p>

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				effectiveness.
237.	Peer Reviewer #17 (TEP Reviewer)	General	I only reviewed the abstract and the Executive Summary, but I highly recommend that the manuscript be revised to improve readability. I found the Executive Summary very difficult to read, because of awkward phrasing and wording. Some of the content made it feel like the authors were unfamiliar with the subject matter. Is it possible for the next stage of revisions to involve a subject matter expert?	We appreciate the comments and have revised the Executive Summary, which unfortunately included a few important editing errors. All authors, including the two with subject matter expertise, contributed to the draft and the revision.
238.	Peer Reviewer #17 (TEP Reviewer)	General	Healthcare delivery, access to antibiotics, antibiotic prescribing practices, and cultural expectations related to antibiotic use vary tremendously from one country to another. Interventions that work in one country may not work nearly as well or at all in another. Is this review intended for a U.S.-based audience? It's not clear. If so, I think it is very important that the authors/review process take that into account.	This review is generally intended for a U.S.-based audience and we agree that the fact that only 45% of studies are U.S.-based potentially limits their applicability and we've noted this in the Applicability section in the Discussion.
239.	Peer Reviewer #17 (TEP Reviewer)	General	The categorization of different interventions is confusing, particularly categories 3 and 4 in the abstract. Category 3 is a multifaceted intervention and so is category 4. It appears that the recommendation for category 4 is based upon a single study and I found it odd that the abstract included details of that single study. Isn't this supposed to be a review? Rather than include details about a single study in the abstract, it would be useful to mention which interventions didn't appear to change prescribing practices. There are	Previously our criteria for best evidence of overall effectiveness were presence of any evidence of reduced resistance or improved <i>appropriate</i> prescribing. Based on reviewer feedback, we have organized the evidence into categories based on the direction and strength of evidence for benefit and harm and

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			other types of appropriate use interventions that aren't mentioned at all in the abstract (e.g. audit and feedback), and it would be useful to know where the gaps are in the evidence base.	highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences). This modified our conclusions and we also improved our explanation of our revised methods for selecting the interventions with the best evidence of overall effectiveness.
240.	Peer Reviewer #1 (Peer Reviewer)	Clarity and Usability	Apart from the missing heading discussion, this report is well structured and organized. Apart from some missing references and some concerns regarding the order of importance, the main points are clearly presented. The conclusions need to be revised to inform policy and/or practice decisions with the information from the suggested studies above.	Please see revised conclusions.
241.	Peer Reviewer #3 (TEP Reviewer)	Clarity and Usability	Well organized. I did find some redundancy of the presentations of the main points repeated in each section, but reasonable to include in each section.	Thank you for your comment.
242.	Peer Reviewer #4 (Peer Reviewer)	Clarity and Usability	The report (to the extent reviewed) appears to be well structured and organized. The conclusions are informative.	Thank you for your comment.
243.	Peer Reviewer #5 (Peer Reviewer)	Clarity and Usability	Well outlined report. I would suggest providing a risk assessment tool (or recommending use of an EMR along with education materials) which could make a	Thank you for your comment.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			difference in decreasing antibiotic usage.	
244.	Peer Reviewer #6 (TEP Reviewer)	Clarity and Usability	The report has a nice "layered" structure allowing for easy viewing of the summaries followed by more detailed information as the reader desires.	Thank you for your comment.
245.	Peer Reviewer #6 (TEP Reviewer)	Clarity and Usability	-I think the main limitation of the conclusions comes from the data that is provided from the studies. It seems to be presented clearly enough.	Thank you for your comment.
246.	Peer Reviewer #7 (Peer Reviewer)	Clarity and Usability	The focus is too narrow Please see above/	Skin and soft tissue and urinary tract infections are outside the scope defined by the key informants, the TEP and also the original nomination. We did include studies of mixed populations where the aRTIs were separated out.
247.	Peer Reviewer #8 (Peer Reviewer)	Clarity and Usability	Please see above regarding the inconsistency between the enthusiastic results and the muted conclusions. It will be difficult for policy-makers and health system leaders to make concrete changes based on the conclusions of this report. The report concludes that the evidence is weak, varied, and mentions many seemingly disparate interventions. I don't feel the Executive Summary captures the nuance between many interventions. Within categories (e.g., "CDS" or "Communication") there can be big differences between	Based on reviewer feedback, we have organized the evidence into categories based on the direction and strength of evidence for benefit and harm and highlight interventions with the best evidence of improving benefits (prescribing/resistance outcomes) and not causing harm (adverse consequences). We revised our Abstract and Executive

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			interventions.	Summary to reflect these changes to our conclusions and also refined our descriptions of the interventions to better capture their nuances.
248.	Peer Reviewer #10 (TEP Reviewer)	Clarity and Usability	Well written, with consistent reporting between the many key questions and interventions. The consistent reporting is especially helpful when going through such a long document, and can be difficult, especially with multiple authors working on individual sections. The authors should be commended for keeping all sections consistently structured and presented.	Thank you for your comments.
249.	Peer Reviewer #12 (Peer Reviewer)	Clarity and Usability	I thought the structure was appropriate and the organization was good. I think the presentation of key questions and related points were quite helpful, though I think in order to maximize the impact of this report, I would recommend reducing the number of tables built into the main text body and, where possible, reducing the number of pages. I think what made previous reviews so helpful (e.g. Arnold et al Cochrane Review 2005) was that they were concise and made easily digestible recommendations about outpatient stewardship. I agree with the authors that a lot of new evidence has come out since previous reviews, but I also think it would be helpful if some of the superfluous information is either left out or relegated to an appendix. I think the overall conclusions and discussion points could be refined to clarify the authors message to readers, and I feel	We can really appreciate these comments. It is hard to balance the length needed to provide adequate details on this huge body of evidence to respond to concerns as noted by other reviewers and with simplifying the message. However, we have edited the abstract, executive summary, discussion and conclusions to revise and improve the clarity of our key messages.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			the executive summary could use some revisions for clarity.	
250.	Peer Reviewer #13 (Peer Reviewer)	Clarity and Usability	The focus on the appropriate use of antibiotics and their prescription has never been stronger. Like many institutions around the world, certainly here in the U.S., my institution has an active antibiotic stewardship program and the clinical laboratory plays a key role in the recently adopted rapid bacterial identification program. It is always important to focus on reduction of mortality due to all causes and, yet, in our institution, like many, sepsis is the leading cause of unexpected mortality. Our physicians and other stakeholders continue to prioritize appropriate use and prescribing of antibiotics as well as activities to reduce or limit the inappropriate use or prescribing of antibiotics. Again, there is a very large body of evidence in the literature on these topics. It is meaningful and significant for AHRQ to have conducted and published this draft comparative effectiveness review CER on ‘Interventions to Improve Appropriate Antibiotic Use for Acute RTI’s.’ The section on implications for clinical and policy decision making starting on page 128 of 679 is well articulated, but less than a page long. For the conclusions of this CER to be used to inform policy and/or practice decisions with any significant degree of impact, it will take other stakeholders, most notably, clinical societies and organizations to distill out the key areas where evidence on various	Our scope included both all-cause and cause-specific mortality, but we only found data on all-cause mortality. For the section on clinical and policy implications, since this review is intended to be broadly useful for multiple health plans, providers, purchasers, government programs, and the health care system as a whole, all with varying values and needs, it is difficult to balance the need for more specific and detailed implications against the need focus on the key messages that are most broadly applicable.

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
			interventions are shown to have at least a low, if not moderate effect.	
251.	Peer Reviewer #14 (TEP Reviewer)	Clarity and Usability	As above, the document is not usable by clinicians given the extreme length and detail.	We can really appreciate these comments. It is hard to balance the length needed to provide adequate details to respond to concerns as noted by other reviewers and with simplifying the message. We hope the executive summary serves this purpose for some, and the abstract for others. Also, the Eisenberg Center will be developing some additional translational products that will hopefully be of more use to practitioners and others.
252.	Peer Reviewer #15 (TEP Reviewer)	Clarity and Usability	There is no level of evidence in any of the strategies high enough to guide practice.	We appreciate that the threshold for action varies based on user perspective. But, it is encouraging that several strategies do have moderate-strength evidence of reducing overall prescribing, which may be an acceptable threshold for action in some situations.
253.	Peer Reviewer #16 (TEP Reviewer)	Clarity and Usability	The report is very long, see my comments above about perhaps slight edits needed to abstract/conclusions to summarize results more balanced way.	We revised the abstract and conclusions to highlight interventions with the best evidence of improving benefits (prescribing/resistance

Source: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2112>

Published Online: January 27, 2016

Comment Number	Commentator & Affiliation	Theme or Section	Comment	Response
				outcomes) and not causing harm (adverse consequences).