



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Tonsillectomy for Obstructive Sleep-Disordered Breathing or Recurrent Throat Infection in Children*

Draft review available for public comment from June 7, 2016 to July 6, 2016.

Research Review Citation: Francis DO, Chinnadurai S, Sathe NA, Morad A, Jordan AK, Krishnaswami S, Fannesbeck C, McPheeters ML. Tonsillectomy for Obstructive Sleep-Disordered Breathing or Recurrent Throat Infection in Children. Comparative Effectiveness Review No. 183. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2015-00003-I.) AHRQ Publication No. 16(17)-EHC042-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the 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.

| Commentator & Affiliation | Section | Comment | Response |
|---------------------------|---------|---|--|
| Peer reviewer #1 | General | The report contains clinically useful information but is also lacking in defining who the audience/targeted professionals are. Key questions are stated but some key questions are not specifically addressed | We note that the report includes a section (Scope and Uses of the Review) that defines the intended audience. The report addresses each Key Question. If we did not identify relevant literature, we have noted that under each KQ section. |
| Peer reviewer #1 | General | Clarity and Usability: There is a dichotomous outcome in the usability- the report will be useful as a resource for comparisons of surgical techniques or management and outcomes of recurrent tonsillitis but is much less likely to be of use for OSDB in children. | We have revised the section of the report dealing with OSDB to improve clarity and utility. |
| Peer reviewer #2 | General | General Comments: The report is comprehensive and clinically meaningful. The key questions are specific and clinically relevant. There was no attention to health delivery interventions to optimize postoperative care and prevention of complications for non-bleeding complications (e.g. follow-up interventions to optimize pain management or prevention dehydration). | Thank you for your comments. We note that our KQ did not specifically address health delivery interventions to optimize care and prevent complications, though we agree this is an important issue. The review focused on the comparative effectiveness of surgery compared with no surgery; surgical techniques; perioperative NSAIDs, anti-emetics, or steroids; and postoperative pain medications. |
| Peer reviewer #2 | General | Clarity and Usability: Yes. | Thank you for your comments. |
| Peer reviewer #3 | General | f. Clarity and Usability: The report is well structured and organised, clearly presented and lends itself well for policy decision making. The conclusions are not new but may improve understanding as it groups together a number of important aspects regarding the effectiveness of tonsillectomy which is useful for clinicians and other decision makers. | Thank you for your comments. We hope that review will inform decision making for consumers and clinicians. |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer reviewer #3 | General | a. General Comments: This manuscript is well organised and thoughtfully constructed. The target population (policy makers, clinicians and those advising patients/parents) are well defined and the questions posed are relevant to this population. The information given is not particularly new as many of the conclusions draw are widely available in previous review articles. It does, however, bring together many of the relating subjects surrounding tonsillectomy and perhaps makes the conclusions more accessible to a wider population. It also shows that no significant new conclusions can be drawn. | Thank you for your comments. |
| Peer reviewer #3 | General | There is one aspect that has not been discussed however. It is well recognised that the RCTs for tonsillectomy for recurrent sore throats have a number of problems (too small population, too strict inclusion criteria, too few large new studies). There is new evidence from qualitative studies that show the outcome measures used in RCTs for tonsillectomy for sore throats are probably not measuring the most relevant information and this decreases the power of the measured effect. Writing a piece that will have impact on policy decision making may mean that a significant group of children will not receive an operation from which they will benefit. | We have added information about the utility of commonly used outcome measures to the Research Gaps section. |
| Peer reviewer #4 | General | a. General Comments: This review addresses a clinically important topic since tonsillectomy is one of the most common surgical procedures in children. The report is aimed at clinicians who perform tonsillectomies and those who recommend the procedure. The key questions are appropriate and clearly stated. The authors may consider having a sub-question under “recurrent tonsillitis” (KQ2) addressing PFAPA syndrome or addressing this diagnosis in consideration of patients with “recurrent tonsillitis.” | Thank you for your comments. With input from Key Informants and Technical Experts and our content experts, we focused the review on the most common indications for tonsillectomy (throat infections, OSDB). The review does not include studies of children with PFAPA. We have noted the focus on the 2 indications as a potential limitation of the review |
| Peer reviewer #4 | General | The authors frequently address statistical significance but do not address clinical significance. | We have revised the report to improve clarity and highlight implications of the findings. |

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| Peer reviewer #4 | General | f. Clarity and Usability: The report is well-structured and easy to follow. As mentioned above, more discussion of the clinical significance of results would be useful for clinician reader. Particularly in the executive summary, assessments of bias and quality of evidence in the studies make some sections difficult to follow (especially KQ1). | We have revised the Executive Summary to improve clarity and highlight implications of the findings. |
| TEP Reviewer #1 | General | General Comments: The report is clinically meaningful. However, one major omission is that the post-operative complications reviewed were limited to hemorrhage and poor oral intake/dehydration. An important issue that was not evaluated is pulmonary decompensation following tonsillectomy in children with OSDB. | Thank you for your comments. We have added pulmonary decompensation as a harm but identified few studies reporting relevant data (see Other Harms Following Tonsillectomy in Comparative Studies and harms in case series and database analyses—Appendix H). |
| TEP Reviewer #1 | General | Clarity and Usability: Report is well-structured. | Thank you for your comments. |
| TEP Reviewer #2 | General | I congratulate the authors on completing this comprehensive, systematic review, which obviously involved tremendous effort in identifying studies, rating the risk of bias, and extracting data. The numerous evidence tables throughout the report will be very useful to guideline developers and policy makers in rapidly identifying the evidence based for clinical decisions. My comments below relate to the Structure Abstract and Executive Summary, since these are the parts of the document most likely to be read by individuals seeking to grasp the key conclusions and impact of the review. | Thank you for your comments. |

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| TEP Reviewer #2 | General | <p>To summarize some of the key points above, I believe that this document would have more clinical impact if it</p> <ul style="list-style-type: none"> (a) included information on natural history (control group outcomes), (b) discussed tonsillectomy outcomes in absolute terms vs. control outcomes (not just in relative terms), (c) had a more quantitative focus in the abstract and executive summary, including measures of precision (e.g., confidence intervals), (d) dealt with PTH separately for primary hemorrhage, secondary hemorrhage, and hospitalization, (e) clarified if NSAID or steroid use had any impact on PTH, (f) discussed the important outcomes of PTH and dehydration/re-admission for partial vs. total tonsillectomy, and (g) avoid value-laden recommendations in the implication section. | <p>We have revised the Executive Summary and report to address these points. We note, however, that in most cases absolute quantitative statements are not possible given differences in outcome measures and space limitations in the Executive Summary.</p> <p>We have added a table from the main report to the Executive Summary to summarize PTH outcomes by category and note that we address steroids and PTH in the strength of the evidence. We have revised the conclusions.</p> |
| TEP reviewer #3 | General | <p>General Comments: This document achieves its objective of systematically reviewing the evidence from research studies about the effectiveness and safety of tonsillectomy. The key findings are important for clinicians, patients and stakeholders. The methodology is sound and the report is excellent.</p> | <p>Thank you for your comments.</p> |
| TEP reviewer #3 | General | <p>Clarity and Usability: I would recommend a 5-10 key point section with 1-2 lines per point that is easily available to the reader.</p> | <p>We note that each Key Question section in the main report includes a section of Key Points. We have also revised the Executive Summary to present findings more clearly.</p> |

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| TEP reviewer #4 | General | <p>The report considers a topic of considerable clinical importance. Except for tympanostomy tube insertion, tonsillectomy is the most common operation carried out on U.S.children. The target population is explicitly defined, and the key questions are appropriate and explicitly stated. The intended audience is described as "patients and clinicians, health system leaders, and policymakers, among others." (p 2, lines 17-18) I believe that, once finalized, the report, because of its detail and comprehensiveness, could serve as a useful resource for health system leaders and policymakers.</p> <p>On the other hand, I think it likely that most patients and clinicians would find the length and complexity of the report challenging, and for guidance would likely instead consult other, less detailed and more user-friendly sources, such as UpToDate or the American Academy of Otolaryngology–Head and Neck Surgery Clinical Practice Guideline.</p> | Thank you for your comments. We agree that caregivers may find the comprehensive report daunting. The EPC program’s Eisenberg Center creates consumer-friendly synopses of the report that should provide a useful overview of findings for the general public. |
| TEP reviewer #4 | General | f. Clarity and Usability: I found the structure and organization somewhat difficult to navigate. First off, there are 6 sets of references, beginning on pages 39, 136, 177, 646, 678, and 695, respectively, each beginning with #1. I believe it would be helpful to consolidate them into a single set, or at least to alert the reader early in the report that there are 6 separate sets. | The standard for AHRQ reviews is to use separate reference lists for separate sections of the report (Executive Summary, Main Report, Appendices). |
| TEP reviewer #4 | General | As the report is constructed, it is not possible to discern all of the important features and/or critiques of a given study without searching the entire report for recurrences of the study’s reference number. It would be helpful, for each key question, to have an alphabetical listing of all the relevant studies together with their reference numbers. | Each section addressing a Key Question begins with an “overview of the literature” section that introduces all the studies addressing a given question. |

| Commentator & Affiliation | Section | Comment | Response |
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| TEP reviewer #5 | General | a. General Comments: The report is clinically meaningful addressing an important topic in medicine. Populations are clearly defined and the questions asked clinically relevant and important. The key questions are appropriate to the subject matter. | Thank you for your comments. |
| TEP reviewer #5 | General | f. Clarity and Usability: I believe the report is well structured organized in an intuitive manner. It is relevant for both clinical discussions by clinicians as well as policymakers. The information is thoroughly and evenly balanced in his presentation. | Thank you for your comments. |
| TEP Reviewer #2 | Abstract | 1. When stating you "identified 197 unique studies" it would be helpful to state how many of them corresponded to the primary study types (RCT, cohort, case series, database). | We have added this information. |
| TEP Reviewer #2 | Abstract | 2. Stating "...hot" techniques such as cobalation...were generally associated with faster recovery than cold dissection" could be interpreted as an endorsement for this technique, and I am sure the manufacturer will jump on this conclusion. Is our confidence in the evidence, based on the usual factors (precision, directness, consistency, risk of bias, etc) really enough to concluded cobalation is better? If you feel the confidence is sufficient, then add a quantitative estimate of how much "faster" the recovery is to aid interpretation. | We have modified this text to improve clarity. The text now reads "In studies comparing surgical techniques for tonsillectomy, commonly used "hot" techniques were generally associated with faster return to normal diet and activity than was cold dissection." |
| TEP Reviewer #2 | Abstract | 3. Stating the post-tonsillectomy bleeding (PTH) was "low (<4% in meta-analyses)" does not make sense, since up to a 1:25 risk is very significant. The real issue here is PTH that is minor and does not require surgery/re-admission vs. PTH that does require these interventions. I suggest you distinguish the 2 here and include a point estimate and 95% CI to aid interpretation. | We have revised this text to note that bleeding rates were less than 4% in meta-analyses and have added that rates of bleeding-associated reoperation were less than 2%. We calculated bleeding rates and credible intervals for each technique where possible (e.g., cold dissection total tonsillectomy, coblation partial tonsillectomy); we cannot include each percent estimate and credible intervals for each technique in the abstract given word limitations. Thus, we included a broader estimate. |

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| TEP Reviewer #2 | Executive summary | 1. ES-1, line 10: States that tonsillectomy is "the most common surgery performed in the US" and cites a secondary source as the basis (AAO-HNS tonsillectomy guideline). Tonsillectomy is common, but it is definitely not "the most common" surgery in the US, and the AAO-HNS guideline does not state this. I suggest you use a primary source for statements of this type and check the accuracy. | We have added references to the primary sources. |
| TEP Reviewer #2 | Executive summary | 2. ES-1, line 24: The definition of "recurrent or severe tonsillitis" given here is not standard or uniformly accepted so I suggest you remove this. For clinical decision making, the usual definition of recurrent/severe is based more on the Paradise criteria from the 1984 NEJM RCT, as outlined in the AAO-HNS guideline. | We have included the Paradise criteria in our discussion. |
| TEP Reviewer #2 | Executive summary | 3. ES-2, line 6: States that clinicians and parents want to know "the likelihood that surgery will improve clinical outcomes." I disagree with this. What they really want to know is how surgery compares to watchful waiting or supportive care (e.g., natural history). Yes, the comparative outcome is of interest, but more important is knowing what changes to expect from natural history and what absolute increase in outcomes will occur from an intervention. | We have noted watchful waiting as the comparator in interest. |
| TEP Reviewer #2 | Executive summary | I was disappointed, in general, to see nothing mentioned, at least in a quantitative sense, of what happens in the control (non-surgical) groups regarding obstructive/infectious outcomes. In addition to baseline rates of improvement in the control group and absolute changes with surgery, the number needed to treat for benefit would also be useful. | We have added information about control group outcomes to the Executive Summary and have included meta analytic estimates of effect for KQ 1 (children with OSDB). We attempted to complete a meta-analysis for KQ2 (children with throat infection) but were unable to do so given the heterogeneity of the studies and outcomes reported. |
| Peer reviewer #1 | Introduction | Introduction: comparison of OSDB treatment with tonsillectomy vs. CPAP is problematic | We note that in the opinion of our content experts and Technical Expert Panel tonsillar hypertrophy may be treated with either CPAP or surgery, and caregivers and patients want to weigh their options between surgical and non-surgical approaches; thus, this is an important comparison and clinically valid. |

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| Peer reviewer #2 | Introduction | Introduction: Appropriate - no issues. | Thank you for your comments. |
| Peer reviewer #3 | Introduction | b. Introduction: Good overview, to the point. The key questions posed are relevant and easily applicable to the population. They are also important questions to ask. | Thank you for your comments. |
| Peer reviewer #4 | Introduction | b. Introduction: The introduction is appropriate. Additional discussion about variations in how OSDB and “tonsillitis” are defined could be included. These varied definitions likely impact the measured outcomes following tonsillectomy. For example, how effective is defining OSA by clinical history. Also, what AHI value is considered to be OSA by various studies? Similarly for tonsillitis, what areas of discrepancy in the definitions are present – like need for fever, need for physical exam findings, need for sore throat, etc. | We have revised the Introduction and Discussion to include more detail about issues of characterizing study populations. |
| TEP Reviewer #1 | Introduction | Introduction: Appropriate | Thank you for your comments. |
| TEP reviewer #3 | Introduction | Introduction: 1) The term “obstructive sleep-disordered breathing” should be changed to “sleep-disordered breathing” both in the title and throughout the document. Studies on sleep disorders in children are already confusing because of a variety of terminology used such as SDB/ OSA/ OSAS or AHI/ OAH/ RDI that mean different things in different studies. SDB is a clinical definition that includes a spectrum of disorders from snoring to severe OSA. The suggestion that we can distinguish a subset of “obstructive” as compared to “central” SDB is confusing, not practical and not commonly used. | We agree that this concept lacks a consistent definition. In consultation with our Key Informants and Technical Experts, we elected to use the term “obstructive sleep-disordered breathing” in order to avoid narrower terminology that might restrict the review to polysomnography-proven OSA. We defined the term in the report (“breathing difficulties during sleep including OSA and upper airway resistance syndrome”) and have expanded on our discussion of variability in severity of obstruction as a limitation of the review. |
| TEP reviewer #3 | Introduction | I would recommend the authors add a definition of SDB and OSA. | We have added a definition of OSA, but we do not use the term SDB in the report. |

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| TEP reviewer #4 | Introduction | P 12, lines 23-26, and p 40, lines 46-48. (The same paragraph appears at both sites.) The definition is arbitrary and somewhat restrictive, and not used generally. Recurrent is not the same as severe; a child may have recurrent episodes that are not severe or occasional severe episodes that don't meet any criterion for recurrence. I suggest the sentence be revised or deleted. See references 1, 9, and 11 for more fulsome treatment of frequency and severity. | We have revised the definition in both the Executive Summary and main report Introduction to reflect more widely used parameters. |

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| TEP reviewer #4 | Introduction | <p>P 27, lines 16-21 and p 37, lines 35-37. Regarding "modest" and "short-term," it is important to note that the degree of benefit of tonsillectomy varies, depending on the stringency of eligibility criteria for surgery. In the first Paradise et al RCT involving only severely affected children with well documented illness (ref 11), large and highly significant differences in key outcomes favored surgical over control subjects. For example, in the first follow-up year, a 14-fold reduction in throat infection episodes rated as moderate or severe (3 episodes in 38 surgical subjects vs 41 episodes in 35 control subjects), and in the second follow-up year, a 6-fold reduction (5 episodes in 31 surgical subjects vs 30 episodes in 29 control subjects). This seems like more than "modest" reduction. Differences in the 3rd follow-up year were in the same direction but not significant. In the second RCT, involving children meeting slightly less stringent criteria than in the first RCT (ref 9), surgical vs. control differences were smaller than in the first RCT (and not large enough, in the authors' view, to warrant tonsillectomy), but nonetheless statistically significant during each of the 3 years of follow-up.</p> <p>Accordingly, it doesn't seem accurate to refer to the effect of tonsillectomy as limited to "short term (<12 mo)." The data mentioned above in this section are shown in Table 13 (P 72-74), but without mention of the stringency of eligibility criteria for the various trials. Again, the point to be made is that substantial efficacy is demonstrable only in severely affected children. It is important not to group studies of efficacy into a single entity without recognizing key differences between them in methods and results.</p> | <p>We have revised the conclusions to remove subjective terms and have restructured our presentation of results regarding tonsillectomy for throat infection to discuss those studies that required at least 3 prior episodes of throat infection (n=8) together and the one study that required fewer prior infections separately. Most studies did not explicitly rate severity of infection but used counts of prior episodes as a marker of severity.</p> |

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| TEP reviewer #4 | Introduction | P 46, lines 47-55. This section, including Appendix A, seems a restatement, in different format, of material covered previously. | Because we do not include the analytic frameworks in the main report (but in an appendix), we included brief description of their content. We have, however, attempted to reduce potential redundancy throughout the report. |
| TEP reviewer #5 | Introduction | b. Introduction: There are a few grammatical errors, but none detracts from the overall introductory information. In addition, the topics importance to the reader is made clear in the introduction. | Thank you for your comments. We hope we have caught any typos or errors. |
| Peer reviewer #1 | Methods | Methods: there is some ambiguity as to how studies were excluded or whether the efficacy of the searches was corroborated through expert opinions | We note that Technical Experts and content experts on our team informed our search strategies and inclusion and exclusion criteria for studies. A second librarian also peer reviewed the search strategies Table A lists inclusion criteria. |
| Peer reviewer #1 | Methods | Globally, the methodology for extraction and selection of the evidence leading to this report, and the questions posed by the authors are sound. | Thank you for your comments. |
| Peer reviewer #2 | Methods | Methods: Methods are clear and inclusion/exclusion criteria appropriate. No concerns re: statistical methods. | Thank you for your comments. |
| Peer reviewer #3 | Methods | c. Methods: I cannot see any inclusion criteria that are inappropriate. This criteria are well set out and simple to understand. Search strategies are explicit and logical. The multitude of outcome measures are defined. The strength of the body of evidence has been assessed and categorised to provide further meaningful understanding and relevance to the conclusions. The statistical methods do seem appropriate. | Thank you for your comments. |
| Peer reviewer #4 | Methods | c. Methods: Inclusion and exclusion criteria are appropriate. Selection of studies is appropriate and done to minimize bias. | Thank you for your comments. |
| TEP Reviewer #1 | Methods | Methods: Appropriate | Thank you for your comments. |
| TEP reviewer #3 | Methods | Methods: This is a strength. No changes recommended | Thank you for your comments. |

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| TEP reviewer #4 | Methods | P 52, lines 30-35. In any RCT of tonsillectomy, 2 of the 13 elements used in assessing risk of bias as shown in Appendix F (p 647), namely, "allocation treatment concealed" and "outcome assessors blinded" cannot be realized because the presence or absence of tonsils is readily apparent. In grading the risk of bias in such RCTs, might it not be appropriate that the denominator then be 11 rather than 13, with appropriate adjustments downward of the various definitions, so that "low risk" would require 10 of 11, etc? | <p>In line with standards for assessing risk of bias for RCTs, we examined whether studies reported methods for allocation concealment, which attempts to prevent selection bias in assignment of intervention or control by protecting the allocation sequence prior to and until assignment. Adequate allocation concealment prevents foreknowledge of the group to which a patient would be assigned and is possible with any type of trial. Inadequate allocation concealment has been associated with larger treatment effect estimates compared with estimates from studies with adequate concealment (Schulz 1995, Schulz and Grimes, 2002).</p> <p>We also assessed whether studies used blinded outcome assessors. We agree that blinding of assessors is not possible when the throat must be examined. We therefore changed the scoring on the question regarding blinding for studies addressing tonsillectomy for recurrent throat infection; however, we note that the risk of bias ratings did not change for any study.</p> |
| TEP reviewer #4 | Methods | Page 53, lines 6-10. More detail regarding the definitions of the five listed major domains--limitations, consistency, directness, precision, and reporting bias - would be helpful to the reader. Most are described in detail in Owens et al (J Clin Epidem 2010;63:513-523). (I was not able to access ref 39, which contains an updated version of the five domains.) | We have added more information on the domains to Appendix C. |
| TEP reviewer #5 | Methods | c. Methods: The statistical methods used seem appropriate although this is not my area of expertise. The search strategies utilized seem logical and complete. I do not believe any important studies were overlooked. | Thank you for your comments. |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer reviewer #1 | Results | Results: Tables are well constructed but lack available evidence or do not separate properly between clinically relevant issues that are frequently encountered in clinical practice | <p>We included key outcomes (as defined in our protocol) in each summary table included in the report. Appendix H includes more detailed tables of findings.</p> <p>As noted, a Technical Expert Panel and Key Informants provided extensive input on outcomes sought, with an eye toward clinical utility.</p> |

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| Peer reviewer #1 | Results | <p>There are some major points however that will require some degree of clarification and several glaring omissions that are surprising: The criteria for selection of the studies for inclusion involving T are not well delineated. As such, multiple published studies are not referenced in the bibliography, and it is unclear why these studies were excluded since many of such studies did fulfill the retention criteria in page ES-4. A table in an Appendix delineating the studies that were excluded and the reasons for exclusion when evaluating each of the questions would be very informative.</p> <p>For example, after a quick search the following studies were not included, and there are multiple other studies that address the issue being asked and are also not included:</p> <p>1: Alonso-Álvarez ML, Terán-Santos J, Navazo-Egüia AI, Martínez MG, Jurado-Luque MJ, Corral-Peñafiel J, Duran-Cantolla J, Cordero-Guevara JA, Kheirandish-Gozal L, Gozal D; Spanish Sleep Network. Treatment outcomes of obstructive sleep apnoea in obese community-dwelling children: the NANOS study. <i>Eur Respir J</i>. 2015 Sep;46(3):717-27. doi: 10.1183/09031936.00013815. Epub 2015 Jun 11. PubMed PMID: 26065566.</p> <p>2: Kheirandish-Gozal L, Gileles-Hillel A, Alonso-Álvarez ML, Peris E, Bhattacharjee R, Terán-Santos J, Duran-Cantolla J, Gozal D. Effects of adenotonsillectomy on plasma inflammatory biomarkers in obese children with obstructive sleep apnea: A community-based study. <i>Int J Obes (Lond)</i>. 2015 Jul;39(7):1094-100. doi: 10.1038/ijo.2015.37. Epub 2015 Mar 24. PubMed PMID: 25801692; PubMed Central PMCID: PMC4496251.</p> | <p>Table 3 outlines criteria for inclusion; we note that we included comparative studies (defined for comparative effectiveness reviews as including a treatment and comparison group) for effectiveness outcomes. We note that Appendix D includes a list of all excluded studies with reasons for exclusion. Regarding the specific studies listed, we list reasons for exclusion below.</p> <ol style="list-style-type: none"> 1. Alonso-Álvarez: We do not consider this a true comparative study (including a treatment and comparison group) as assignment to treatment groups was based on severity of OSAS, with children with more severe disease assigned to surgery. We consider this study to be confounded by indication. 2. Kheirandish-Gozal: All children received tonsillectomy; we considered this a case series. |

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| Peer reviewer #1 (continued) | Results (continued) | <p>3: Chan KC, Au CT, Chook P, Lee DL, Lam HS, Wing YK, Li AM. Endothelial function in children with OSA and the effects of adenotonsillectomy. <i>Chest</i>. 2015 Jan;147(1):132-9. doi: 10.1378/chest.14-1307. PubMed PMID: 25275798. 3: Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, Kaditis AG, Splaingard D, Splaingard M, Brooks LJ, Marcus CL, Sin S, Arens R, Verhulst SL, Gozal D. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. <i>Am J Respir Crit Care Med</i>. 2010 Sep 1;182(5):676-83. doi: 10.1164/rccm.200912-1930OC. Epub 2010 May 6. PubMed PMID: 20448096.</p> <p>4: Gozal D, Capdevila OS, Kheirandish-Gozal L. Metabolic alterations and systemic inflammation in obstructive sleep apnea among nonobese and obese prepubertal children. <i>Am J Respir Crit Care Med</i>. 2008 May 15;177(10):1142-9. doi: 10.1164/rccm.200711-1670OC. Epub 2008 Feb 14. PubMed PMID: 18276939; PubMed Central PMCID: PMC2383995.</p> <p>5: Amin R, Anthony L, Somers V, Fenchel M, McConnell K, Jefferies J, Willging P, Kalra M, Daniels S. Growth velocity predicts recurrence of sleep-disordered breathing 1 year after adenotonsillectomy. <i>Am J Respir Crit Care Med</i>. 2008 Mar 15;177(6):654-9. doi: 10.1164/rccm.200710-1610OC. Epub 2008 Jan 3. PubMed PMID: 18174542; PubMed Central PMCID: PMC2267339.</p> <p>6: Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, Gozal D. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. <i>J Pediatr</i>. 2006 Dec;149(6):803-8. PubMed PMID: 17137896.</p> | <p>3. Chan: We considered this a case series as it did not use an appropriate comparison group. In this case, the comparison group was typically developing children without OSDB.</p> <p>4. Gozal: All children received tonsillectomy; we considered this a case series.</p> <p>5. Amin: We considered this a case series as it did not use an appropriate comparison group. In this case, the comparison group was typically developing children without OSDB.</p> <p>6. Tauman: We considered this a case series as it did not use an appropriate comparison group. In this case, the comparison group was typically developing children without OSDB.</p> |

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| Peer reviewer #1 (continued) | Results (continued) | 7: Tal A, Bar A, Leiberman A, Tarasiuk A. Sleep characteristics following adenotonsillectomy in children with obstructive sleep apnea syndrome. Chest. 2003 Sep;124(3):948-53. PubMed PMID: 12970022. | 7. Tal: All children received tonsillectomy; we considered this a case series. |
| Peer reviewer #1 | Results | Comparisons of tonsillectomy alone vs tonsillectomy and adenoidectomy (T&A) vs. adenoidectomy alone (A) are not carried out – this is a critical question for the management of OSDB. There is some literature exploring as to whether the improvements of OSDB after surgery differ between the various surgical approaches (T,A or T&A) | Our KQ specifically addressed tonsillectomy (either partial [tonsillotomy] or total) or adenotonsillectomy. We did not address adenoidectomy alone. We did not include studies comparing adenoidectomy alone to tonsillectomy alone or adenotonsillectomy as those studies would likely be confounded by indication. Nonetheless, we have explicitly noted our focus on tonsillectomy or adenotonsillectomy as a potential limitation. |
| Peer reviewer #1 | Results | The authors also fail to compare between tonsillectomy and tonsillotomy | Key Question 3 addresses total tonsillectomy compared with partial tonsillectomy. |
| Peer reviewer #1 | Results | The authors do not systematically address age of surgery or BMI z score (only 1 study included!!! – page 26) as determinants of outcomes of surgery. | We note that we did not include a Key Question that specifically addressed potential modifiers of outcomes. We attempted to stratify studies based on factors such as age or obesity, but few studies reported data in such a way to allow this. |
| Peer reviewer #1 | Results | <p>There is clearly a misconception when comparing CPAP vs. T, A, or T&A; most of the patients included in CPAP trials have already undergone one of the 3 surgical procedures mentioned above, and have either remained symptomatic or their sleep studies after surgery have revealed residual OSDB of a clinical magnitude that prompted implementation of CPAP.</p> <p>Please note that in the context of adenotonsillar hypertrophy leading to OSDB, application of CPAP would be potentially ineffective in many of the cases since the pressure delivered at the mask would not reach the upper airway due to the obstruction caused by the enlarged lymphadenoid tissues. As such, the authors are comparing apples and oranges.</p> | <p>In the two studies assessing this comparison and meeting our inclusion criteria (Brigance 2009, Sudarsan 2014), children receiving CPAP had not had prior tonsillectomy.</p> <p>We do not agree that CPAP is an ineffective primary treatment in children with OSDB; in the opinion of our team and Technical Expert Panel, comparing CPAP and tonsillectomy is appropriate as caregivers and patients must make choices between surgical and nonsurgical treatment approaches, and CPAP is routinely offered as an option to children with tonsillar hypertrophy.</p> |

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| Peer reviewer #1 | Results | Watchful waiting for T, A or T&A has been pooled as a large bag that includes supportive measures vs. non-surgical therapeutic interventions. I am surprised that such interventions have not been separated since at least several RCT have now been published on the use of intranasal corticosteroids or leukotriene modifiers. | No studies addressing watchful waiting with supportive care reported results by specific agent or approach that may have been included in “watchful waiting.” We did not identify studies comparing tonsillectomy with specific pharmacologic agents and no concomitant tonsillectomy. While a number of studies have addressed agents such as leukotriene inhibitors to ameliorate residual obstructive symptoms <i>post</i> -tonsillectomy, such studies did not meet eligibility criteria for this review. |
| Peer reviewer #1 | Results | No mention of opioids for pain management and concerns regarding potentially adverse outcomes after T. | We did not identify studies comparing opioids with other agents given in the postoperative period that met our inclusion criteria and had low or moderate risk of bias. Many studies address perioperative use of opioids; however, our KQ did not address perioperative opioid use given US Food and Drug Administration warnings about use of opioids such as codeine in children (http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm). |

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| Peer reviewer #1 | Results | <p>Regarding behavioral or cognitive outcomes, several omissions are noteworthy. For example:</p> <p>1: Friedman BC, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M, Tarasiuk A, Tal A. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. <i>Sleep</i>. 2003 Dec 15;26(8):999-1005. PubMed PMID: 14746381.</p> <p>2: Amiri S, AbdollahiFakhim S, Lotfi A, Bayazian G, Sohrabpour M, Hemmatjoo T. Effect of adenotonsillectomy on ADHD symptoms of children with adenotonsillar hypertrophy and sleep disordered breathing. <i>Int J Pediatr Otorhinolaryngol</i>. 2015 Aug;79(8):1213-7. doi: 10.1016/j.ijporl.2015.05.015. Epub 2015 May 27. PubMed PMID: 26066853.</p> <p>3: Giordani B, Hodges EK, Guire KE, Ruzicka DL, Dillon JE, Weatherly RA, Garetz SL, Chervin RD. Changes in neuropsychological and behavioral functioning in children with and without obstructive sleep apnea following Tonsillectomy. <i>J Int Neuropsychol Soc</i>. 2012 Mar;18(2):212-22. doi: 10.1017/S1355617711001743. Epub 2012 Jan 25. PubMed PMID: 22272653.</p> <p>4: Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. <i>Eur Respir J</i>. 2005 Feb;25(2):336-42. PubMed PMID: 15684300.</p> | <p>As noted above, we required that studies addressing these outcomes include a treatment and comparison group (no surgery, other treatment approach). We excluded the studies noted here because of the following reasons:</p> <ol style="list-style-type: none"> 1. Friedman: We considered this a case series as it did not use an appropriate comparison group. In this case, the comparison group was typically developing children without OSDB. 2. Amiri: All children received tonsillectomy; we considered this a case series. 3. Giordani: We considered this a case series as it did not use an appropriate comparison group. In this case, the comparison groups were typically developing children without OSDB or children with negative PSGs who received tonsillectomy. 4. Montgomery-Downs: We considered this a case series as it did not use an appropriate comparison group. In this case, the comparison group was typically developing children without OSDB. |

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| Peer reviewer #1 | Results | Another point that is not well discussed is whether T, A or T+A lead to normalization of the f/u sleep study vs. only leading to improvements in AHI or other important sleep measures; of note, there is no effort to include other measures derived from the sleep study such as the degree of hypoxemia or the severity of sleep fragmentation. | <p>Our key outcomes of interest included AHI, desaturation nadir, and measures of sleep quality including the OSA-18. The AHI is a surrogate for sleep fragmentation. We recognize that changes in AHI do not necessarily reflect resolution of obstruction, but it is widely used to reflect objective improvement.</p> <p>We did not address “resolution” as defined by an AHI cutoff as ages of children varied across studies and few reported outcomes by age range. AHI cutoffs for resolution of obstructive breathing would vary by age.</p> |
| Peer reviewer #1 | Results | Other important outcomes such as enuresis are not included in this assessment (multiple papers have been published over the years on the relationship between OSDB and enuresis and some interventional studies have reported improvements) | We extracted data on enuresis outcomes where reported. No studies comparing tonsillectomy vs. watchful waiting for OSDB reported enuresis as an outcome. |
| Peer reviewer #1 | Results | <p>T in OSDB and sickle cell is not addressed</p> <p>T in OSDB and infants is not addressed</p> <p>T in other pediatric conditions</p> | <p>Our Key Questions did not target sickle cell disease as an indication for tonsillectomy; rather, we focused on the most common indications for the surgery. We note that KQ 1b does address children <3 years of age and that questions 1a, 1c, and 1d address children with specific conditions (Down Syndrome, craniofacial or neuromuscular abnormalities, and obesity).</p> <p>We did not address tonsillectomy for children with PFAPA or other indications as, in the opinion of our team and Technical Experts, most tonsillectomies are performed for the indications of OSDB and throat infections; thus, the report should be broadly useful for informing decisions for children with these common indications.</p> |

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| Peer reviewer #1 | Results | Using symptoms of OSDB as an outcome variable is flawed (Table 18 – page 42) | In our opinion and in the opinion of our Technical Experts, resolution or non-resolution of OSDB post-surgery, which may include persistent snoring or obstructive symptoms, is a valid gauge of the effectiveness of the surgery. The AHI is an objective measurement of sleep-related changes, but it does not necessarily reflect patient-reported effects; thus, we included more subjective measures to capture the full range of effects. |
| Peer reviewer #1 | Results | Improved analyses for re-admission and mortality would have been of great importance – if such data are unavailable then the absence of such important evidence should be emphasized. | We report readmissions related to bleeding, pain, nausea and vomiting, and dehydration as reported in each study in the Harms section of the report. We also report mortality in this section. We agree that additional data are needed to inform analyses and have added a statement to the research gaps section of the report. |
| Peer reviewer #2 | Results | Results: Detailed results appropriate. Key points help to provide a nice summary prior to details. | Thank you for your comments. |
| Peer reviewer #3 | Results | d. Results: Study attrition has been accounted for. Details of the included studies have been provided. The strength of the studies (low, moderate, high degree of bias) has also been provided for each of the key questions. The balance of detail has been maintained so that readers can draw meaningful conclusions from each of the results summaries. The tables of included and excluded studies are comprehensive and descriptive enough. I do not know of any studies that ought to have been included or any that were included that should not have. | Thank you for your comments. |
| Peer reviewer #4 | Results | Did any studies address children with “recurrent tonsillitis” under 3 years old undergoing tonsillectomy? | We did not identify studies or analyses explicitly focused on this population, though some studies may have included children younger than age 3. |
| Peer reviewer #4 | Results | d. Results: The amount of detail is appropriate and tables clearly show important study characteristics. A few tables are missing P values. | Thank you for your comments. We extracted and reported p values where reported, but we generally did not calculate them if not reported. We have added “NR” (not reported) as needed in tables to clarify. |

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| Peer reviewer #4 | Results | <p>Regarding KQ1, more discussion of (1) clinical significance of the changes in outcomes like AHI and (2) the longer-term durability of improvements would be helpful to clinicians.</p> <p>Also, were the behavioral outcomes measured objectively by blinded observers – this information on causes of bias in particular studies may be helpful to the reader.</p> | <p>We have revised KQ1 and included more quantitative information. Few studies reported longer term data, but we have reported it where available.</p> <p>Appendix F reports the risk of bias ratings for each study in the review and includes information on blinding of outcome assessors. We have also integrated brief information on sources of bias in the report text.</p> |
| Peer reviewer #4 | Results | Table 10 is missing some p values. | We extracted and reported p values where reported, but we generally did not calculate them if not reported. We have added “NR” (not reported) as needed in tables to clarify. |
| Peer reviewer #4 | Results | Also in KQ1, did studies of tonsillectomy vs. CPAP assess the feasibility of and compliance with CPAP use in children? | Studies generally did not comment on compliance with CPAP. We have noted this as an issue for future research. |
| Peer reviewer #4 | Results | Regarding KQ2, were any additional stratifications of outcome measured like the number of episodes/year, having positive group A strep testing for episodes, age of child? | Table 13 outlines outcomes including strep infections. |
| Peer reviewer #4 | Results | Some p values are missing from Table 13. | We extracted and reported p values where reported, but we generally did not calculate them if not reported. We have added “NR” (not reported) as needed in tables to clarify. |
| Peer reviewer #4 | Results | Brief mention of PFAPA as a diagnosis that could be considered as “recurrent tonsillitis” may be useful to clinicians to remember. | We have added discussion of PFAPA to the future research section. |
| Peer reviewer #4 | Results | KQ3: In the evaluation of data on tonsillar regrowth with partial tonsillectomy, are there data on rates of regrowth with complete tonsillectomy for comparison purposes? | Few studies reported regrowth of tonsils after total tonsillectomy. We note that one case series described in the Harms section of the report does provide some data (see harms reported in case series and database studies). |
| Peer reviewer #4 | Results | KQ4: Were there differences in the risk tonsillectomy by age of the patient? | If this comment is referring to the risk of bleeding post-tonsillectomy, we reported details on postoperative bleeding in the Harms section of the Results. |

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| Peer reviewer #4 | Results | KQ5: Did studies of steroids address delayed pain desaturations/hospitalizations (i.e. were there rebound symptoms)? What was the longest duration of follow-up in these studies (appears to be about 24 hrs)? | Few studies addressing steroids had longer term followup (<10 days postoperatively). Few studies reported revisits for non-bleeding indications (reported in Table 41 of the main report). |
| Peer reviewer #4 | Results | In all questions, some brief mention of what kind of bias was present in studies would be useful to put the results into context. | We note that Appendix F includes risk of bias ratings for each study. We have added brief information on bias in the report text as well. |
| Peer reviewer #4 | Results | There are a few typos. | We have revised the report and hope that we have corrected any typos or errors. |
| Peer reviewer #4 | Results | On page ES-18, line 45, is the number presented correct? | This number is correct and includes data reported in large (>1000 children) case series, database studies, and registry studies. |
| TEP Reviewer #1 | Results | Results: Good amount of detail in text, tables and figures. | Thank you for your comments. |
| TEP Reviewer #2 | Results | ES-6, line 54: You mention you retain "high risk of bias studies" because only a small number of overall studies were identified. This same assumption carries through to other Key Questions. If you wish to do this then you need to justify the basis for including highly biased, potentially unreliable information with a presumably low confidence in the accuracy of the results. If you do include these high risk of bias studies then at the very least come sensitivity analysis should be done to see if the bias impacts outcomes, but in reality the statistical power to do this will be low to non-existent. | While we noted in the full report that we included studies with high risk of bias only to address key questions 1 and 2 (tonsillectomy vs. watchful waiting with supportive care) given the relatively few studies addressing this comparison, we reviewed the findings and determined that including high risk of bias studies did not contribute meaningful information; thus, we have eliminated discussion of these studies from the report but note that we did include them in meta analyses after sensitivity analyses showed no significant effects. |
| TEP Reviewer #2 | Results | 2. ES-6, line 57: State the quantitative improvement in AHI, and how it differed from controls. Vague statements about "improvement" are not helpful for decision making or critical analysis. | We have included more quantitative data and a meta analysis of AHI outcomes, but we could only combine 3 studies given differences in outcome measurement and populations. |

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| TEP Reviewer #2 | Results | 3. ES-8, line 35, partial vs. total tonsillectomy. The proponents of partial tonsillectomy (and there are many) often substantiate their position with statements about lower rates of PTH and dehydration/re-admission. You do not mention either of these here and they should be mentioned, given the frequency that proponents invoke them as better outcomes to justify their technique. My understanding of the literature is that when high quality RCTs are analyzed there is no significant difference in PTH or dehydration/re-admission. | We have added data on non-PTH related readmissions to the Executive Summary. We note that few studies of partial tonsillectomy reported data on non-bleeding revisits. |
| TEP Reviewer #2 | Results | 4. ES-8, line 52: Again, instead of stating a simplistic outcome like "significantly faster return to normal diet" make this a quantitative outcome so readers can judge the clinical importance. | Differences in the way outcomes were reported (e.g., mean days, range of days, number of children consuming normal diet) precluded quantitative analyses for most outcomes. We have, however, added the general range of days in this section where possible. |
| TEP Reviewer #2 | Results | 5. ES-9, line 18: Make the outcomes here, and in the remainder of the paragraph, quantitative. | Differences in the way outcomes were reported (e.g., mean days, range of days, number of children consuming normal diet) preclude quantitative analyses for most outcomes. We have, however, added the general ranges where possible. |
| TEP Reviewer #2 | Results | 6. ES-10, line 13: The section on "Harms of Tonsillectomy" would be more meaningful if instead of lumping all bleeds together under the single heading of PTH there were separate data for (a) primary hemorrhage, (b) secondary hemorrhage, and (c) hemorrhage requiring hospitalization (surgery or admission for observation). | We have added a table of results from the bleeding meta-analysis to the Executive Summary so that data are presented by type and technique. |
| TEP Reviewer #2 | Results | 7. ES-11, line 7: You state here the hemorrhage rates for partial tonsillectomy but do not state how it compared to total tonsillectomy. As stated above, proponents of partial techniques claim superiority. What did you find? | This section notes rates for total tonsillectomy (<2%) in the text preceding this line. |

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| TEP Reviewer #2 | Results | <p>8. ES-11, line 55: In discussing NSAIDs for pain relief the key question that arises is can they safely be used without an increased risk of PTH? The Cochrane review suggests "yes" (with the exception of ketorolac), but you say nothing about this in the CER. Instead of just stating the NSAID PTH rates it would be much more useful to offer some comment as to whether or not they increase PTH risk.</p> | <p>We note that 9 of the 15 studies included in the 2013 Cochrane review were published before 2000 and thus not eligible for inclusion in the current review, in which we addressed drug studies published from 2000-2016. We included 4 of the remaining 6 studies and discuss them in KQ5 (Antila 2006, Keidan 2004, Kokki 2002, Oztekin 2002). We excluded one study addressing rofecoxib because it is not used in the US and one that addressed codeine because of changes in its use in the US.</p> <p>While we included 16 studies (including the 4 noted above) of perioperative NSAID administration in the review, few studies addressed the same agent or outcomes. Those that did rarely reported bleeding: one of 5 diclofenac studies reported bleeding; one of 2 studies of ibuprofen reported bleeding; one of 2 studies of ketorolac reported bleeding. Two of 2 studies of ketoprofen and 2 of 2 studies of lornoxicam reported bleeding, but we did not attempt to combine these few studies.</p> |
| TEP Reviewer #2 | Results | <p>9. ES-12, line 38: In discussing steroids it would again help to state whether or not they had any impact on PTH rates, since a least 1 study published a few years ago in JAMA suggested they did, despite methodological flaws that question this conclusion.</p> | <p>We note in the section discussing strength of evidence that "PTH and related utilization was low across [steroid vs. placebo] studies (moderate strength of evidence for minimal bleeding)." We have amended the text to specify that PTH or associated revisits or reoperations occurred in less than 5% of children. We also conducted a meta-analysis of studies comparing dexamethasone and placebo and reporting bleeding and found no significant effects, with wide confidence bounds.</p> |

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| TEP reviewer #3 | Results | Results: 1) Key decisional dilemmas (ES-2)- Clinicians and parents need to know three key things: 1) what is the likelihood that the surgery will improve clinical outcomes around recurrent throat infections and sleep disorders; Should read: “that the surgery will improve clinical outcomes versus a period of observation/ watchful waiting around recurrent throat infections and sleep disorders | Changed, thank you. |
| TEP reviewer #3 | Results | KQ2 (ES-8) change Tw to Two | Corrected, thank you. |
| TEP reviewer #3 | Results | Harms of tonsillectomy (ES-10)- there are 2 important clinical questions that could be better addressed in this section (literature is available): a. Does a cold versus hot technique lead to less PTH? b. Does partial versus total tonsillectomy lead to less PTH? | We have revised the Executive Summary to include more detailed results of our findings regarding bleeding associated with different techniques (see Table B). |
| TEP reviewer #3 | Results | KQ6 (ES-12-13): this section is short and does not address the clinical issues. KQ5 is more detailed but less controversial. KQ6 needs to be expanded to address: a. Role of post T&A narcotics versus non-narcotics b. Association of post T&A NSAIDS (specifically Motrin) and PTH | We note that few studies addressed this question. We did not identify comparative studies addressing postoperative narcotics that met our inclusion criteria. We have expanded our discussion of postoperative NSAIDs and PTH. |
| TEP reviewer #4 | Results | P P 45, lines 10-13. I'm not aware that decongestants, antihistamines, leukotriene inhibitors, or steroids have ever been considered appropriate treatments for throat infection, whether or not recurrent. | In the opinion of our technical and content experts, these medications may be used if a provider felt symptoms were due to a viral cause or allergies. |

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| TEP reviewer #4 | Results | 38, lines 19-24. Regarding long-term data concerning tonsillectomy for recurrent throat infection, such data would of course be of interest, but the recommendation doesn't appear to take into account the considerable difficulty and high cost of screening a large population of children and documenting their illnesses in order to identify a suitable number of appropriate subjects for study, and then recruiting, maintaining, and closely monitoring that cohort over long periods. In the first trial discussed above (ref 11), 2,043 children were screened to identify 187 eligible subjects, of whom consent to randomize was obtained in 91. In the second trial it was 2174 screened, 373 eligible, and 328 randomized (ref 9). It seems questionable that, in the present climate, comparable but longer-term studies could gain adequate funding, and also questionable whether longer-term studies would actually provide substantial additional relevant information. Rather, it seems likely that most of the important effects of tonsillectomy are realized in the first few post-surgical years. | We have noted difficulties associated with longer term studies in the Research Gaps section. |
| TEP reviewer #4 | Results | d. Results: There is more than sufficient detail. Studies are clearly described, key messages are explicit and applicable, and figures, tables and appendices are adequate and descriptive. Studies were included or excluded appropriately. | Thank you for your comments. |
| TEP reviewer #4 | Results | P 47, lines 3-33. Is it necessary to describe the organization in such detail? Isn't it more concisely conveyed by the Contents (pp 7-10)? | We have reduced the Organization section. |

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| TEP reviewer #4 | Results | Pp 54-56. The detailed description seems tedious and not very informative. Why list the individual subject characteristics--risk of bias, locale, age--in isolation from the various study goals and findings? Better to list the individual studies in relation to the particular key questions. There is much overlap, redundancy, and minute detail. For example, Turkey is mentioned twice, with lists of some of the same references (p 55, lines 20 and 22). (One wonders whether many readers would be interested in knowing which of the many studies on tonsillectomy were carried out in which countries.) | We include an overview of included studies to orient readers to the body of literature. We have, however, attempted to reduce redundancy while providing an overview of the literature. |
| TEP reviewer #4 | Results | P 55, lines 36-37. None of the 22 references listed concern recurrent throat infection; probable mix-up. | The studies referenced included children with recurrent throat infection as an indication for tonsillectomy. Not all of these studies were included under the KQ that addressed tonsillectomy vs. no surgery for throat infection (KQ2) as many were comparing surgical techniques or perioperative medications. |
| TEP reviewer #4 | Results | P 58, line 4. Enlarged adenoids are an integral, major contributor to OSDB, and are usually removed along with removal of tonsils. Thus most of the operations for OSDB considered in this review were probably adenotonsillectomies, not merely tonsillectomies. The authors do state (p 40, lines 24-26) that they use the word "tonsillectomy" to include adenotonsillectomy, but the role of adenoids specifically is not discussed and deserves more attention. | We agree but note that the current review was focused solely on tonsillectomy or adenotonsillectomy. We have noted this as a limitation of the review process. |
| TEP reviewer #4 | Results | P 59, line 18. I think the word "bias" is missing. | Corrected, thanks. |
| TEP reviewer #4 | Results | P 65, lines 54,55 and p 66, line 3. See detailed comments above in Introduction re degree of benefit and long- vs short-term. Lumping together the results of various studies of tonsillectomy for recurrent infection oversimplifies the issue, and obscures the key fact that tonsillectomy is highly effective for severely affected children, but not very effective for moderately or mildly affected children. The only place in the review that I was able to find that fact articulated was Appendix I, p 751, lines 23-32. | As noted, we have restructured our presentation of KQ2 results to focus on those studies including children with a greater number of infections and those requiring few infections. |

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| TEP reviewer #4 | Results | P 67, lines 23,24. Reference 10 seems not to concern tonsillectomy; was 11 intended? | We have corrected the reference list. |
| TEP reviewer #4 | Results | P 68, lines 9-10. As discussed in the published report (ref 11), to the extent that bias existed, the result would probably have been an understatement rather than an overstatement of actual efficacy. | Thank you for your comment. |
| TEP reviewer #4 | Results | P 84, line 44. As written, might be interpreted as activity limitations greater. Suggest insert "in" before "activity." | Corrected, thank you. |
| TEP reviewer #4 | Results | Table 41, P 109 constitutes an example of minutiae that I believe could be summarized more briefly without loss of key information. | We used a table to attempt to summarize lengthy information, most of which we present in more detail in an appendix. |
| TEP reviewer #4 | Results | P 109, lines 53-54. States four categories but mentions only three. | Corrected, thank you. |
| TEP reviewer #4 | Results | P 112, line 28. I don't understand "G2: 19 (48)." | That text should have been deleted. We have corrected the error. |
| TEP reviewer #5 | Results | d. Results: The results were comprehensively presented. Some of the findings were novel and provided fresh insights. Separating the data according to the strength of the study was one of the strong points. The rationale utilized seem logical. | Thank you for your comments. |
| TEP reviewer #4 | Discussion | The conclusions are certainly relevant to policy or practice decisions, although, as noted above, I don't agree with some of them. To the extent that the report probably makes reference in one way or another to every word published on tonsillectomy in the specified period, it contributes new information. I'm not aware of an equally comprehensive review. I don't believe the report contributes, nor was it intended to contribute, new knowledge or understanding. Rather its intent, as I understand it was to aggregate and comment on work that has been done. | Thank you for your comments. We believe that the report will inform clinical and caregiver decision making and future research in the area. |
| Peer reviewer #1 | Discussion | Discussion/ Conclusion: There is a very disproportionate level of comfort dealing with recurrent infections and surgical approaches than with the reason for the majority of tonsillectomies being performed nowadays - i.e., OSDB It would seem that expertise in pediatric sleep medicine was lacking during the processes leading to the document | We note that pediatric sleep experts were on both our review team and Technical Expert Panel. We have revised the section of the report dealing with OSDB to improve clarity and utility. |

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| Commentator & Affiliation | Section | Comment | Response |
|---------------------------|------------|--|--|
| Peer reviewer #2 | Discussion | Discussion/ Conclusion: Discussion hits on important issues but is also nuanced. No omitted literature that I have identified. | Thank you for your comments. |
| Peer reviewer #3 | Discussion | Th research gaps section does appear a little short and non-specific. | We have revised the Research Gaps section to comment more directly on issues we identified in the review process. |
| Peer reviewer #3 | Discussion | e. Discussion/ Conclusion: The implications of the study are well described in the discussion section. The are set out well so that each key question is discussed in turn. The limitations of the studies are discussed especially as the lack of strong evidence for many of the key questions is lacking. | Thank you for your comments. |
| Peer reviewer #4 | Discussion | e. Discussion/ Conclusion: In the executive summary, the results section could be clearer for KQ1 – the different areas of outcomes could be more clearly delineated. | We have revised the Executive Summary to improve clarity and highlight implications of the findings. |
| Peer reviewer #4 | Discussion | An important research gap that was presented in the introduction and results is the importance of having clear definitions of the major disorders. | Thank you for your comments. We have expanded our discussion of characterizing populations appropriately. |
| Peer reviewer #4 | Discussion | How do these findings relate to existing guidelines for tonsillectomy in children? Are they in concordance? | The review aligns with several recommendations in the 2011 American Academy of Otolaryngology-Head and Neck Surgeons guidelines (i.e., tonsillectomy as an option for children with sleep-disordered breathing or frequent recurrent throat infections, potential recurrence of symptoms, use of perioperative steroids), but the review did not address all areas touched on in the guidelines (e.g., use of antibiotics). 2012 guidelines from the Infectious Diseases Society of America do not recommend tonsillectomy solely to reduce the frequency of streptococcal infections. |
| TEP Reviewer #1 | Discussion | Discussion/ Conclusion: Implications are clearly stated. As noted in the general comments, the omission of post-operative respiratory decompensation as a complication needs to be addressed. | Thank you for your comments. |

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|---------------------------|------------|--|--|
| TEP Reviewer #2 | Discussion | 1. ES-13, line 23: Stating that tonsillectomy offers "modest" improvement for OSDB is value-laden and not very helpful; this should be quantified. | We have revised the conclusions to eliminate qualitative language. |
| TEP Reviewer #2 | Discussion | 2. ES-16, line 27: On this Table, and the ones that follow, I did not see any endnotes/citations to the source articles. | AHRQ guidelines for Executive Summaries limit the number of references. We have noted that all references to studies are in the main report. |
| TEP Reviewer #2 | Discussion | 3. ES-26, line 28: Your statement "Despite the large body of literature, evidence is inadequate to provide clear evidence for consistent, and long term benefits either for OSDB or throat infection" could readily be used by providers/payers to deny surgery. We could say with equal conviction that the "large body of literature...is insufficient to exclude consistent and long-term" benefits as well. Given the extreme difficulties in conducting and funding large scale randomized trials of tonsillectomy in children it is quite likely we will never have the evidence needed to confidently show consistent, long-term effects. Consider rewording or eliminating this statement. | We have reworded clinical implications section. |
| TEP Reviewer #2 | Discussion | 4. ES-26, lines 30-43. This section moves from summarizing the evidence (which is the purpose of this CER) to providing advice on when to do surgery (which is absolutely not the subject of a CER). The information here is value-laden and is what should be relegated to guideline/policy makers. Please removed recommendations for clinical action and stick to summarizing the literature for others. | We have revised this section to remove information that can be perceived as prescriptive. |
| TEP reviewer #3 | Discussion | Discussion/ Conclusion: The discussion sounds like a repetition of the results with little true discussion. For example, under KQ1 I would like to read something about whether the AHI versus symptom relief is a better measure of outcomes. This is an often-debated point that gets very little mention in this section. This applies to the remainder of the discussion | Thank you for this comment. We have expanded our discussion of outcome measures in the Research Gaps section of the Discussion. |

| Commentator & Affiliation | Section | Comment | Response |
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| TEP reviewer #3 | Discussion | I would also recommend a 5-10 key point section that summarizes research gaps. | Thank you for your comment. We have not revised the presentation of this section as we feel that the information presented is succinct and necessary to understand the context and implications of gaps in the research. We have, however, attempted to streamline the presentation to the extent possible. |
| TEP reviewer #4 | Discussion | e. Discussion/ Conclusion: P 133, lines 21-22 and 28-30. I disagree that "evidence is inadequate to provide clear evidence for consistent and long-term benefit either for OSDB or throat infection. Evidence may not always be conclusive in individual studies considered in isolation, but I believe that taken together the studies strongly support adenotonsillectomy for children with OSDB, and tonsillectomy as a reasonable option for children severely affected with recurrent throat infection. Again, see comments above re "long-term" and "modest." | Thank you for your comment. We have revised this language somewhat but note that few studies provided long term data. |
| TEP reviewer #4 | Discussion | P 134, lines 33-35. In a parallel trial in which children were assigned nonrandomly, ie according to parental preference, results were similar to results in the randomized trial (ref 11). | Thank you for this information. |
| TEP reviewer #4 | Discussion | P 135, lines 13-19. See comments above re same statement in Introduction P 38, lines 19-24. | We have expanded this text (Research Gaps) to note that characterization of populations should include characterizing the severity of throat infections. |
| TEP reviewer #4 | Discussion | P 135, lines 35-36. Evidence contradicts "failure of tonsillectomy for primary management of . . . throat infections." | This text is commenting on the fact that few studies addressed factors that may contribute to recurrence of the symptoms of OSDB or throat infection that prompted tonsillectomy. We have clarified the wording to note recurrence of symptoms. |
| TEP reviewer #4 | Discussion | P 135, line 43. "modest" and "short term" are discussed above. | We have removed subjective language from the Conclusions. |

| Commentator & Affiliation | Section | Comment | Response |
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| TEP reviewer #4 | Discussion | P 664, lines 36-37. As noted above, in an RTC of tonsillectomy it is not possible to conceal allocation or to have outcome assessors blinded | <p>In line with standards for assessing risk of bias for RCTs, we examined whether studies reported methods for allocation concealment, which attempts to prevent selection bias in assignment of intervention or control by protecting the allocation sequence prior to and until assignment. Adequate allocation concealment prevents foreknowledge of the group to which a patient would be assigned and is possible with any type of trial. Inadequate allocation concealment has been associated with larger treatment effect estimates compared with estimates from studies with adequate concealment (Schulz 1995, Schulz and Grimes, 2002).</p> <p>We also assessed whether studies used blinded outcome assessors. We agree that blinding of assessors is not possible when the throat must be examined. We therefore changed the scoring on the question regarding blinding for studies addressing tonsillectomy for recurrent throat infection; however, we note that the risk of bias ratings did not change for any study.</p> |
| TEP reviewer #4 | Discussion | P 692, lines 44-45. Patients were also selected from primary care offices and clinics. | We have corrected the applicability table to note that patients came from primary care clinics as well. |
| TEP reviewer #5 | Discussion | e. Discussion/ Conclusion: Limitations of the study are clearly described. Future directions for research can easily be translated into funding priorities. The literature is well summarized and the conclusions appropriately drawn. | Thank you for your comments. |

Note: AHRQ received no public comments for this report.

KQ=Key Question

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