

**Reporting the Findings of Updated Systematic  
Reviews of Comparative Effectiveness:  
How Do Users Want To View New Information?**



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# **Reporting the Findings of Updated Systematic Reviews of Comparative Effectiveness: How Do Users Want To View New Information?**

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers; as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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# Reporting the Findings of Updated Systematic Reviews of Comparative Effectiveness: How Do Users Want To View New Information?

## Structured Abstract

**Background.** To remain useful, comparative effectiveness reviews (CERs) and other systematic reviews require periodic updating. Although several studies have been conducted assessing when and how to update, no research has been conducted on optimal formats for presenting the results to users. The aim of the present study was to gather the input of various users of CERs regarding the usability of a range of formatting methods for showing the changes from the original to the update report.

**Methods.** Using the executive summaries of a comparative effectiveness review our Evidence-based Practice Center conducted in 2001 and the update review we conducted in 2008, we initially created five different versions of the update summary. Each succeeding version used a different format to show changes from the original to the update report (e.g., new and retired Key Questions, changes in search strategies and inclusion/exclusion criteria) and changes in the findings. To test the five differently formatted summaries, we identified several categories of users of CERs, convened an informal virtual focus group comprising various users, and asked them to evaluate the summaries on several dimensions, first via an email questionnaire and then in a group conference call where we presented the results of the questionnaire. Based on group feedback, we created two additional versions and tested them in a second focus group and among a third small group. The rationales for the selection of formats were two-fold: to imitate, and thus evaluate, the formats used by several organizations whose role is to conduct systematic reviews and updates and to create and test novel formats in response to users' suggestions.

**Results.** Policymakers who rely on CERs and other systematic reviews as the basis for policy (including health insurance companies, health care organizations, research funders, and guideline makers) expressed the need to see changes in review process as well as outcomes clearly marked, (with changes in outcomes and conclusions preferably shown in graphic form), while at the same time having access to the entire set of data and the analyses on which the conclusions were based. The small group of clinicians preferred to see the skeleton of the report (Key Questions, conceptual framework, inclusion/exclusion criteria) as well as the outcomes and conclusions presented entirely in graphic form for ease of reading.

**Conclusions.** Different users of CERs clearly have different information needs. Yet whereas policymakers need access to the entire data set and analyses that comprise a systematic review (the original and the update), all users benefit from summaries that clearly show what changed in as succinct a format as possible, preferable in graphic form.

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# Introduction

Comparative reviews of the evidence on the effectiveness and safety of medications, medical devices, and care practices are increasingly relied upon to establish policies and guidelines aimed at improving the quality and cost-effectiveness of health care. Yet to remain useful to policymakers, health care providers, and other decisionmakers, comparative effectiveness reviews (CERs) and other systematic reviews of the evidence must be kept up to date. While a growing number of studies have examined how and when to conduct an update, less consideration has been given to the optimal presentation of the results of updated reviews for the various audiences who need to use this information.<sup>1-7</sup> Organizations that traditionally conduct or commission evidence reviews and updates of these reviews rely on a variety of formats to present the results of updates. The formats used to highlight new sources, Key Questions or issues, search and analytic methods, findings, and conclusions—or to contrast the old with the new—vary depending on the organization and the format chosen. For example, one particular organization “highlights” new quantitative findings in gray (without showing the old findings), whereas another provides a table at the end of the report that lists methodological differences between current and prior reviews as well as newly included studies but does not include actual changes in findings.

In 2011, the Agency for Healthcare Research and Quality (AHRQ)’s Evidence-Based Practice Centers (EPC) program, anticipating the need to begin updating the CERs, asked the Southern California Evidence-based Practice Center at RAND to design a format for presenting the results of these update reports. The intent was to create a more or less standard format, recognizing that no one format would necessarily be appropriate for all types of reports or stakeholders. In other words, we hoped to identify a format that would be flexible enough to accommodate differences in the numbers and kinds of Key Questions asked and results obtained (e.g., reports with meta-analyses vs. those with only qualitative findings; reports with only 2 or 3 treatments vs. those with 20 different treatments and/or categories of patients). We also wished to accommodate differences in the information needs of various stakeholders as well as differences in their ways of accessing information.

To shed light on an ideal report format, we decided to assess the needs of users of CERs and their preferences for the formats used for update reports. This report summarizes the process used to identify and query stakeholders and the findings of this effort.

## Methods

To conduct this study, we identified the relevant groups of stakeholders, solicited one or two members of each of these groups with whom we had worked on previous occasions or based on word-of-mouth recommendations, and asked them if they would be willing to participate in small focus groups or one-on-one sessions to evaluate several mechanisms for presenting update reports. We then identified various formats used to present update reports and reformatted the executive summary of a CER we had updated in 2009 to conform to these various formats. Finally, we presented the executive summary in a number of different formats to each of two informal focus groups and three individual providers and asked them to review the summaries and complete a brief questionnaire. We then convened the members of each focus group and asked them for any further input.

### Identification of Stakeholders/Users of Comparative Effectiveness Reviews

Based on our experiences identifying and working with stakeholders on a number of CERs covering a variety of topics (including management of acute otitis media, prevention and treatment of osteoporosis, use of omega-3-fatty acid supplements for the prevention of chronic conditions, and off-label uses of newer antipsychotic medications), as well as our experiences assessing the need to update AHRQ's portfolio of CERs, we initially identified five categories of users: private insurers (payers), health plan administrators, professional practice organizations that establish practice guidelines, academic researchers and physicians, and health communicators. Although we also consider consumers to be potential users of evidence review findings, we did not include consumers in our focus groups, because the Eisenberg Center is responsible for translating the findings of evidence reviews for consumer needs. We then contacted individuals who had served on technical expert panels as well as several former RAND and SCEPC core staff and others recommended by colleagues to ask if they would be willing to participate in an informal virtual focus group to assess various formats for presenting the results of updates of evidence reviews. During our first focus group, we asked the participants for suggestions of additional categories of potential users of the results of evidence reviews; they suggested we convene a group of Federal and municipal policymakers as well as a group of community physicians who were not affiliated with a medical school.

### The Report Formats

In 2009, our EPC conducted an evidence review to update the findings of a review we had conducted in 2001 on management of acute otitis media, similar to a CER.<sup>8,9</sup> We used the executive summaries of the original and update reports to create summaries in five different formats (shown in Appendix C), intending that these summaries should be complete enough to serve as standalone products for users with relatively basic informational needs (to the same extent that we now expect the executive summaries of EPC evidence reviews to stand alone).

Version 1. For this version, we began with the text of the 2001 executive summary (See Appendix C). We made only the minimal number of necessary changes (i.e., revising the search start and end dates, changing effect sizes and confidence intervals for drug comparisons analyzed in both reports, and adding text to report the results of new comparisons and the findings for a new Key Question). We did not highlight these changes in any way. This version replicated a



format used by one of the existing organizations dedicated to conducting systematic reviews of the evidence.

Version 2. For version 2, we highlighted in gray the changes we had made to create version 1 (See Appendix C). This version replicated the format used by another organization that conducts systematic reviews.

Version 3. For version 3, we revised the text of the original 2001 executive summary to match the 2009 executive summary using “track changes” to highlight the deletions and additions (See Appendix C). However this version lacked a set of summary tables that was included in the actual 2009 version. These tables are described below for version 4.

Version 4. Version 4 was the actual executive summary for the 2009 report (See Appendix C). In addition to providing narrative text, to compare the updated meta-analytic findings on the effectiveness and safety of pharmacological treatments to the 2001 findings, we constructed tables that showed the pooled effect sizes and total numbers of studies for each drug or drug combination from 2001 and 2009, along with our conclusions. For drugs for which no new—or no previous—studies were identified, we simply presented the existing data and noted that no comparison was possible.

Version 5. For version 5, we reformatted the summary tables presented in version 4, so that instead of presenting the actual pooled effect sizes, the tables described the changes from 2001 to 2009 in narrative text (see Appendix C). The reason for including this version was to simulate the way we presented comparative results for an update CER report that included almost no meta-analyses and for which most of the results needed to be described narratively, as was the case for the update of the CER on prevention and treatment of osteoporosis.<sup>10</sup>

Revisions to these versions for subsequent focus groups are described below.

## **The Questionnaire and Focus Groups**

### **Focus Group 1**

Approximately 4 weeks prior to the week we hoped to hold our first virtual focus group (via conference call), we contacted eight potential participants, providing a description of the project and querying them regarding their willingness to participate in exchange for a small honorarium (\$200, although we did not specify the amount). Only one declined to participate, citing a timing conflict; we scheduled the focus group at a time convenient to the seven who agreed to participate. Thus, the first focus group comprised the director of research for a large private insurer; a physician/administrator for a large health maintenance organization; a clinician in an academic medical center with experience conducting and using evidence reviews; two physicians who led and participated in, respectively, the revision of a set of guidelines for a major professional practice organization; a research assistant involved in guidelines setting; and a staff member of RAND’s Office of External Affairs.

One week prior to the first focus group, in April 2011, we sent the five versions of the executive summary to the seven participants with additional background on the project and a brief questionnaire (Appendix A), asking for their feedback on the various differences among the five versions and their assessments of the utility (using a 5-point Likert scale but also allowing for free text comments). We asked that they return the completed questionnaires by the day before the scheduled call. All participants returned their completed questionnaires. We compiled the responses, anonymously in PowerPoint slides. During the call, we shared the results and asked for further feedback and comments, including any suggestions the group had regarding

additional kinds of potential users we should include in a future focus group. The group suggested we conduct a focus group among government policymakers. One member of the group, the HMO physician/administrator, also provided us with a sample of a summary of an updated evidence review his organization had prepared to support a set of treatment guidelines the HMO providers were expected to follow (see description below).

## **Focus Group 2**

In September 2011, based on the suggestions of the first focus group participants, we elicited opinions from a number of Federal and municipal health policymakers with whom we had worked in the past regarding their willingness to participate in a focus group. The resulting group comprised a director of an office at the Food and Drug Administration (FDA) and editor in chief of a major journal, the director of a U.S. Department of Agriculture-funded university research center, an FDA staff scientist whose research group cosponsored a previous evidence review, a researcher involved in policymaking at the Centers for Medicare & Medicaid Services, and a former congressional staffer with experience in health policy. This focus group was conducted identically to the first one (see Appendix B for questionnaire).

## **Focus Group 3**

We then intended to run a third focus group comprising community primary care physicians with no academic appointments. We contacted eight physicians, seven suggested by a member of Focus Group 1, and one suggested by one of the project staff. Only four of eight physicians contacted responded, and of those, only three agreed to participate. Within the timeline for this project, we were unable to identify a time that was mutually agreeable for these three individuals to meet. Therefore, to complete the project on time, we elected to communicate with them individually, sending the materials (the most recent four versions of the executive summary and the questionnaire) and following up to clarify responses to the questionnaire.

## Results

The results for both focus groups and the individual assessments by community physicians are combined and presented according to the unique characteristics of each format.

### The Importance of Seeing What Changed

The questionnaire began by asking respondents to rate the importance of seeing what had changed in an update review. Among the four focus group 1 participants who responded to this question in advance, all said that it was either very important (5 on a scale of 1 to 5) or somewhat important (4 on a scale of 1 to 5) to see what had changed. During the meeting of focus group 1, one participant, an academic research physician with experience in developing evidence-based indications for care, speculated that this desire to see “what’s changed” may be particular to academic physicians and policymakers. He said: The average clinician would actually prefer version 1 of the summary, a version that presents only what is most up to date. This comment was one factor that prompted us to add the third focus group, that of practicing clinicians, to this project.

Among the focus group 2 participants who responded in advance, one said it was somewhat important (4 on a scale of 1 to 5) and one said it was neither important nor unimportant (3 on the scale of 1 to 5) to see what had changed. During the discussion, participants all agreed that they would want to see what had changed.

The two community physicians who responded both rated the importance of seeing what had changed as somewhat important (4 out of 5).

### Using Gray “Highlighting” To Show Changes

Asked about version 2, in which new findings were shaded in gray, four questionnaire respondents in focus group 1 found this highlighting not to be helpful, and three found it to be helpful; however, when asked whether the shading would be more helpful if all the questions remained the same from the earlier to the later version and only the quantitative findings changed, three agreed that the shading would be somewhat helpful. During the discussion, one focus group 1 participant stated:

There are two kinds of readers: people who just want to know what to do, and people who want to know why. For people who just need to know what to do, you could put the changes in bold. For those who want to know why, show the evidence behind the changes, secondarily.

Focus group 2 participants found the gray shading not to be helpful, saying that they would want to see not only the changes but also the context for the changes. The community physicians also found this version not to be helpful.

### Using Track Changes To Show Changes

The original Version 3, which showed all the changes in track change mode, was rated poorly by all respondents in focus group 1; therefore, we dropped this version from subsequent assessments.

## Summarizing Findings in a Quantitative or Narrative Summary Table

When asked to rate the versions of the summary that included one or both of the summary tables, focus group 1 participants rated both versions as somewhat to very helpful. During the discussion, they agreed that for a report with only narrative result, the narrative summary table would be more useful than the quantitative table (and vice versa). They also reiterated the point that many clinicians would want to see only the new conclusions but that anyone involved with setting guidelines would want to see both the old and the new information.

Focus group 2 and the community physicians were asked to comment on a version of the summary that included both the quantitative and the narrative tables (Version 6: See Appendix C). During the discussion, focus group 2 participants found these tables to be helpful and suggested some further steps to increase their utility. These suggestions included showing how the new findings contributed to changing the conclusions; using color coding or different fonts to increase the salience of what changed; and including some wording that would put the changes in context. This group also agreed among themselves that they wanted to see *why* conclusions changed, and that merely providing the tables with version 1 or 2 of the summary would not suffice.

The community physicians rated version 6 as 2 (somewhat unhelpful) and 3 (neither helpful nor unhelpful) on a scale of 1 to 5.

## A Skeletal Summary/Report: Tables and Figures With Little Free Text

Focus group 2 was also asked to provide feedback on a version of the summary that included very little text; this version was intended to emulate the mini-evidence review described by the HMO physician manager who participated in focus group 1 (version 7: see Appendix C). This version presented the scope of the report and the context in the form of a table and conceptual framework, respectively; used quantitative tables to present the results for Key Questions for which the findings were reported quantitatively; used bulleted lists to present the results of questions that were answered narratively; and used a modification of the qualitative table to present the conclusions. Limitations to the review and future research recommendations were also presented as bullet points. focus group 2 participants generally liked this version.

We then asked focus group 2, during the discussion, how they would react to this version being substituted for the full evidence review. They liked the idea, but with reservations: The consensus was that more information was needed than the format allowed. They reiterated that it would be important to emphasize what changed and to provide adequate information for the reader to understand the reasons for the changes. One participant thought this version would be preferable for a guidelines creator (in contrast to version 3, which would be preferable for a general reader), whereas another participant emphasized that guidelines creators would need the equivalent of a full evidence report. However, a third participant thought version 4 might serve as a useful pointer to the full report, that is, as a standalone executive summary, rather than as a substitute for the full report.

Both community physicians who assessed the four different summaries overwhelmingly preferred version 4. One attributed her choice to her preference for graphic presentations of the findings over narrative text. The other physician said:

From a nonacademic community doc perspective, just to have a short summary on the conclusion for the Key Question would be most helpful. Hence, I thought the bullet points (version 4) was the easiest to understand... I think community docs usually take for face value that the conclusion is correct, and there is no need to prove that the conclusion is correct with a ton of citations.

## **Additional Issues Raised**

A question raised and discussed at length in focus group 1 was, “Who are the users of EPC evidence reviews?” Although everyone agreed that the needs of users should dictate the format(s) in which the information is presented, no one is quite sure who are the primary users of evidence reviews or updates. Input from several of the participants painted a picture of typical users of full evidence reviews as individuals and groups charged with setting health care policy and/or guidelines, including Centers for Medicare & Medicaid Services, FDA, National Institutes of Health, State and some local health agencies, insurers/health plans, professional practice societies (e.g., American Academy of Pediatrics), and organizations such as the American Heart Association. The participants emphasized that these kinds of users would need a full-length evidence review, with the executive summary serving as little more than a detailed table of contents.

A different group of users of evidence review—namely researchers and funders—was at the center of a discussion by focus group 2. The issue they raised was how evidence reviews identify and present knowledge gaps and future research needs. One participant wanted to see a more complete discussion of the gaps in the research (which version 4 presented as bullet points), stating that her agency uses this information to make decisions about future research needs. Another participant said that such discussion is sometimes helpful but that oftentimes, it would be more helpful if greater attention was paid to the formulation of these recommendations. He added that the evidence reviews are one piece of information used to determine “next steps.” It was mentioned that some groups have begun incorporating modeling and decision analysis in an effort to improve the usefulness of “future research needs” discussions.

## Conclusions, Limitations, and Discussion

We conducted this exercise to gather some information on the needs and preferences of users of evidence review updates (and evidence reviews in general) regarding the format in which results are presented. The process we implemented had a number of limitations:

- We included only the executive summaries.
- We used only one EPC report as the basis for constructing our sample versions.
- The particular report we used presented its main results (efficacy and safety) as meta-analyses, which are relatively simple to summarize and compare, whereas many EPC reports do not identify data that lend themselves to meta-analyses.
- We conducted only a small number of focus groups and their sizes were limited, and
- Our selection of participants may have been biased.

However, we did include what we believe is a fair representation of summary formats and potential users and therefore believe a few conclusions may be drawn.

- Although no one really knows who the principal users of evidence reviews and update reviews are, they clearly range from consumers (in some limited circumstances), to community clinicians, to academic clinicians and researchers, to decisionmakers (including guideline- and policymakers, payers, and research planners).
- With the possible exception of consumers, whom we did not query, the entire spectrum of users of update reviews express interest in knowing, explicitly, what has changed. The depth and breadth of information users wish to have regarding the reasons for change depends, at least in part, on the intended use for the information (e.g., not surprisingly, payers, for whom millions of dollars may ride on a change in the most effective treatment for a condition, want the maximum amount of evidence behind any such changes).
- The optimum presentation of evidence review updates may be a combination of a stand-alone executive summary largely consisting of tables and figures, with the updates made extremely salient (e.g., using boldface and parallel construction) and a full report for those who need further information.

We believe that as the Effective Health Care Program continues to update existing evidence reviews, just as we continue to refine our methods for determining the need for an update and for conducting the update reviews, we should continue to seek feedback from topic-specific groups of stakeholders on the most usable formats for presenting the results of these reviews. In particular, additional work needs to be done on the presentation of updated findings as narrative syntheses.

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# Appendix A. Focus Group Questionnaire 1

## Overview

The updating of evidence reports is becoming more common, and various approaches are being used to present the updates. However, there is little research about which approach(s) would be most useful to policymaking and provider audiences as they use the new report. The goal of this project is to gather qualitative evidence about the usefulness of several different approaches. The purpose of this questionnaire is to get some initial reactions to several approaches, which we will then use as a starting point for our discussion on April 27.

**First let us explain the sample formats that we have developed.** We have provided 5 versions of an executive summary for the update of an evidence review on management of acute otitis media in children. These are representative of actual practices used by various review groups.

1. Version 1 does not call attention in any way to what has changed from the original report to the update report. The implication of this approach is that all of the findings in this document are up-to-date as of the end date of the search.
2. Version 2 uses gray shading to indicate new text (including new questions not addressed in the original report) and new findings.
3. Version 3 is a track-changes version. It shows explicitly what has changed from the original report by underlining new material and scoring through material that was replaced.
4. Version 4 does not follow the structure of the original report; it was drafted expressly for the update report. It explicitly compares the key quantitative findings of the update review with those of the original review in two tables (one for drug effects, one for adverse events).
5. Version 5 is identical to version 4 except that instead of the two quantitative tables, it contains one table that compares all the results of the old and new report in narrative format.

To get started, first tell us on a scale of 1-5 (where 1 is not important and 5 is very important) **how important you think it is to know what has changed from the previous version of the report.** (If knowing what has changed is important, then you will find version 1 to be less useful than versions 2, 3, 4, or 5.) Please circle appropriate response. 1 2 3 4 5

Suppose it has been determined that indicating new material in the update report is important. Please tell us how helpful you would find the following approaches to indicating new material, keeping in mind how you would typically be using the update report.





Approach	Not helpful				Very helpful
<b>Grey shading</b> to indicate new material? (Version 2).					
Would the shading be more useful if only the quantitative findings changed but all the questions remained the same?					
<b>New material underlined; old material crossed out.</b> (Version 3) Is it helpful to see the new findings in the context of the previous ones?					
Versions 4 and 5: In general, it is helpful to have the <b>previous and new findings explicitly compared?</b>					
How helpful are the tables in Version 4, which <b>explicitly compare the quantitative findings</b> of the two reports?					
<ul style="list-style-type: none"> <li>How helpful would it be to have this kind of table in Versions 1, 2, or 3?</li> </ul>					
How helpful is the <b>single narrative table that includes both quantitative and qualitative findings?</b> (Version 5)					
<ul style="list-style-type: none"> <li>Would the narrative table be more useful if the report had only qualitative findings (i.e., no meta-analysis)?</li> </ul>					
<ul style="list-style-type: none"> <li>How helpful would it be to include this kind of narrative table in versions 1, 2, or 3?</li> </ul>					

- Can you suggest other ways to emphasize the information that is important to you in an updated report?
- What guidance can you give us about how to test these, or other approaches, with a broader audience?

To help us understand your responses better, we would appreciate your answering a few questions about yourself:

- What is your current position?
- In general, how important are evidence reviews to you in making the kinds of decisions for which you are responsible?
- Have you ever worked on an evidence review?

## Appendix B. Focus Group Questionnaire 2

### Overview

The updating of evidence reports is becoming more common, and various approaches are being used to present the updates. However, there is little research about which approach(s) would be most useful to policymaking and provider audiences as they use the new report. The goal of this project is to gather qualitative evidence about the usefulness of several different approaches. The purpose of this questionnaire is to get some initial reactions to several approaches, which we will then use as a starting point for our discussion on October 31.

**First let us explain the sample formats that we have developed.** We have provided 4 versions of an executive summary for the update of an evidence review on management of acute otitis media in children. These are representative of actual practices used by various review groups.

1. Version 1 does not call attention in any way to what has changed from the original report to the update report except for a change in the end-date of the search. The implication of this approach is that all of the findings in this document are up-to-date as of the end date of the search.
2. Version 2 uses gray shading to indicate new text (including new questions not addressed in the original report) and new findings.
3. Version 3\* does not follow the structure of the original report; it was drafted expressly for the update report. It explicitly compares the key quantitative findings of the update review with those of the original review in two tables (one for drug effects, one for adverse events) and compares the key qualitative findings in a table with narrative format.
4. Version 4† dispenses with most of the text and just presents the key findings in bullet points, tables, and figures.

To get started, first tell us on a scale of 1-5 (where 1 is not important and 5 is very important) **how important you think it is to know what has changed from the previous version of the report.** (If knowing what has changed is important, then you will find version 1 to be less useful than versions 2, 3, or 4).

**Please circle your response. 1 2 3 4 5**

Now, suppose it has been determined that indicating new material in the update report is important. Please tell us how helpful you would find the following approaches to indicating new material, keeping in mind how you would typically be using the update report.

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\* This version is referred to as Version 6 throughout the report.

† This version is referred to as Version 7 throughout the report.



Approach	Not helpful				Very helpful
<b>Grey shading</b> to indicate new material? (Version 2).					
Would the shading be more useful if only the quantitative findings changed but all the questions remained the same?					
A <b>narrative description</b> of the results and the <b>previous and new findings explicitly compared in tables</b> (Version 3)?					
How helpful is <b>the table that compares the findings of the two reports narratively</b> compared with <b>the table that compares the quantitative findings</b> of the two reports?					
<ul style="list-style-type: none"> <li>How helpful would it be to have this kind of table in Versions 1 or 2?</li> </ul>					
How useful is a summary that presents the results in bullets, tables, and figures (Version 4)?					

- Can you suggest other ways to emphasize the information that is important to you in an updated report?
- What guidance can you give us about how to test these, or other approaches, with a broader audience?

To help us understand your responses better, we would appreciate your answering a few questions about yourself:

- What is your current position?
- In general, how important are evidence reviews to you in making the kinds of decisions for which you are responsible?
- Have you ever worked on an evidence review?

# **Appendix C. The 7 Versions of the Executive Summary for Which We Elicited Focus Group Feedback**

This appendix presents each version of the executive summary that was provided to the focus groups for their feedback.

Version 1 modified the executive summary included in the original 2001 Acute Otitis Media management report to include the findings in the 2008 update report but did not indicate the changes to the text or the new findings.

Version 2 highlighted the text changes and new findings presented in version 1.

Version 3 tracked the changes from the original to arrive at Version 1 using underlining and strikethrough.

Version 4 is the executive summary included in the update report. It is entirely new text and does not use formatting elements to call attention to the changes (new Key Questions, new findings). However, this version includes tables that compare the numbers of studies and the effect sizes from the original report with the numbers of studies and effect sizes of old and new studies combined, for efficacy and safety.

Version 5 includes the same text as version 4 but instead of the quantitative comparison tables, it includes tables that narratively compare the findings of the old and new reports.

Version 6 combines versions 4 and 5 (both quantitative and narrative tables).

Version 7 contains almost no narrative text. The Key Questions, conceptual framework, search strategy, inclusion and exclusion criteria, and findings are presented graphically.

## **Version 1**

### **Summary**

#### **Overview**

The objective of this report was to analyze the evidence on the initial management of uncomplicated acute otitis media (AOM)<sup>3</sup> in children. AOM represents the most common childhood infection for which antibiotics are prescribed in the United States. Data from the National Ambulatory Medical Care Surveys (NAMCS), which did not differentiate between

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<sup>3</sup>A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

AOM and otitis media with effusion, indicated that the number of office visits for AOM increased more than two-fold from 1975 to 1990. Gates (1996a) believed that the majority of these cases represented AOM. Based on national data from NAMCS and the National Hospital Ambulatory Medical Care Surveys, we estimated that 5.18 million episodes of AOM occurred in 1995 at a cost of approximately \$2.98 billion, including direct and indirect costs and the costs of sequelae such as otitis media with effusion and chronic middle ear infection. These estimates suggest that increased effectiveness in treating AOM could achieve significant national cost savings.

AOM was defined by the Technical Expert Panel as the presence of middle ear effusion in conjunction with the rapid onset of one or more signs or symptoms of inflammation of the middle ear. Uncomplicated AOM was defined as AOM that is limited to the middle ear cleft. An episode of uncomplicated AOM was considered distinct from a previous episode of AOM and was eligible for initial treatment if the most recent course of antibiotics ended 4 weeks prior to the episode of AOM in question, or if there was documentation by an examiner that a prior episode of AOM had been cleared.

Various medical and surgical treatments have been used for AOM. There is controversy about the need for antibiotics, particularly in children older than 6 months of age with uncomplicated AOM. It is routine to use antibiotics for AOM in the United States, whereas in the Netherlands the standard practice is to observe selected children older than 2 years of age for 48 hours and selected children age 6 months to 2 years for 24 hours before initiating antibiotics. Antibiotics are prescribed if clinical resolution does not occur during the observation period. The presence of alternative treatment paradigms of questioned effectiveness suggests that an evidence-based analysis on the management of AOM is needed to determine the efficacy of antibiotic therapy.

### **Reporting the Evidence**

The nominating organization, the American Academy of Pediatrics, and the Technical Expert Panel limited the scope of this evidence report to six key clinical questions:

1. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?<sup>4</sup>
2. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?
3. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?
4. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?
5. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not

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<sup>4</sup>Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

limited to the following: Laterality, i.e., unilateral vs. bilateral; Otorrhea or perforation; AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); Comorbidities, e.g., asthma; Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; Race; Ethnicity; Day care attendance?

6. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ 3 and KQ 4?

The regimens we analyzed were:<sup>5</sup>

- (1) ampicillin or amoxicillin vs. placebo
- (2) amoxicillin tid (7d) vs. prescription –to-hold
- (3) Antibiotic vs. prescription-to-hold
- (4) Amoxicillin vs. wait-and-see
- (5) Phenoxyethylpenicillin vs. wait-and-see
- (6) Ampicillin or amoxicillin vs. Ceftriaxone
- (7) Amoxicillin (50mg/kg/d; bid, 10d) vs. erythromycin (40 mg/kg/d; bid 10d)
- (8) Amoxicillin clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d)
- (9) Amoxicillin clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d)
- (10) Cefaclor vs. Trimethoprim-sulfamethoxazole
- (11) Cefaclor vs. Ampicillin or amoxicillin
- (12) Cefixime vs. Ampicillin or amoxicillin
- (13) Penicillin vs. ampicillin or amoxicillin
- (14) Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d
- (15) High-dose amoxicillin bid vs. lower-dose amoxicillin tid
- (16) Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days
- (17) Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)
- (18) Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)
- (19) Cefaclor (7-10d) vs. Azithromycin (<5d)
- (20) Amoxicillin (7d) vs. Azithromycin (1 dose)
- (21) Amoxicillin-clavulanate (7-10d) vs. Azithromycin

The Technical Expert Panel decided that this systematic review would focus on children ages 4 weeks to 18 years, who had uncomplicated AOM and were seeking initial treatment or treatment for recurring AOM. The major outcomes for studies of efficacy and effectiveness included presence or absence of signs and symptoms within 48 hours, at 3 to 7 days, 7 to14 days, 14 days to 3 months, and after 3 months; presence or absence of adverse effects from antibiotic treatment; and presence or absence of bacteria and/or resistant bacteria. Other outcomes included changes in bacterial colonization in populations that received PCV7 and clinical signs associated with a positive diagnosis.

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<sup>5</sup>A total of 63 different comparisons of treatment options were identified. The 21 listed are key comparisons.

## Methodology

An 11-member Technical Expert Panel consisting of clinical experts, a consumer, and a representative of a managed care organization convened to:

- advise the project in the ranking of proposed Key Questions and influencing factors,
- guide the development of the scope and definition of AOM,
- advise in development of the search strategy, and
- review and comment on the analysis plan.

The Technical Expert Panel and project staff developed a literature search strategy. The initial strategy was developed for MEDLINE and was customized for other databases. Project staff searched MEDLINE (January 1998-July 2010), the Cochrane Library ( January 1998-July 2010),and the Web of Science . Additional articles were identified by review of reference lists in proceedings, published articles, reports, and guidelines.

The initial module of search statements included an explode of "om" (otitis media), which included the headings "om, mastoiditis," "om w/effusion," and "om, suppurative" with the subheading "drug therapy." The next module included the explode of "om," with "om" as a text word. The terms, "recurrent otitis media" and "heptavalent vaccine were also added." The anti-infectives module used an explode of the mesh heading for anti-infective agents, including antibiotics and other drug groups, and the text words antibiotic, antimicrobial, antibacterial, and specific antibiotic names. Combinations of these modules were used for the literature search. The search was limited to human or undesignated studies and to infant, child, preschool, adolescence, or undesignated subjects. . Two physicians independently screened all titles and/or abstracts for potential inclusion, evaluated the quality of the articles, and abstracted data from full-length articles onto predesigned forms. The selection criteria included human studies that addressed a Key Question about AOM in children ages 4 weeks to 18 years. Excluded were case reports, editorials, letters, reviews, practice guidelines, and studies on patients with immunodeficiencies or craniofacial deficiencies, including cleft palate.

Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. Only randomized controlled trials and large observational studies were used to address the Key Questions on the effectiveness of antibiotics. The physician reviewers assessed the quality of controlled trials by using the Jadad criteria. QUADAS criteria were used to evaluate the studies that pertained to diagnosis.

Meta-analyses were performed to determine the effectiveness of antibiotic vs. placebo or observational treatment of uncomplicated AOM and to determine the effectiveness of particular antibiotic regimens. Comparisons were established based on the type of antibiotics and the outcome variable under consideration. The technical experts decided to establish comparison

groups by individual antibiotic, as this best fit the information required for clinical practice. A meta-analysis was performed for each comparison with three or more randomized controlled studies. Heterogeneity was measured for all meta-analyses, and a random effects model was used to estimate the absolute rate differences. Subgroup analyses were performed based on age of the subject, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the  $I^2$  statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the “minimal clinically important difference (MCID)” against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a “small” effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

This evidence report was critiqued by the Technical Expert Panel as well as a peer-review panel consisting of content experts, consumers, representatives of managed care organizations, and methodologists. All comments received from these individuals were reviewed and acted upon as appropriate.

## Findings

### Natural History of AOM

- In children with AOM who were not initially treated with antibiotics, one study showed a clinical failure rate of 7.7 percent at 24 to 48 hours, and another study showed a failure rate of 26 percent at 24 to 72 hours -- that is, clinical resolution was 92.3 percent at 24 to 48 hours and 74 percent at 24 to 72 hours. The pooled estimate of failure at 1 to 7 days was 18.9 percent (95 percent confidence intervals, 9.9 percent and 28.0 percent) and at 4 to 7 days was 22.2 percent (95 percent confidence intervals, 10.1 percent and 34.3 percent).
- A previous information synthesis estimated that 59 percent (95 percent confidence intervals, 53 percent and 65 percent) of children not treated with antibiotics had resolution of pain and fever within 24 hours of diagnosis of AOM, 87 percent (95 percent confidence intervals, 84 percent and 89 percent) of children had resolution of pain and fever within 2 to 3 days, and 88 percent (95 percent confidence intervals, 85 percent and 91 percent) of children had resolution of pain and fever within 4 to 7 days.



- The available evidence on natural history of AOM shows that in studies with close follow-up, few episodes of mastoiditis or other suppurative complications are reported in children with AOM who are not treated initially with antibiotics.

### Diagnosis of AOM

- Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE).
- To address this Key Question, we searched for studies that examined clinicians' accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together.
- A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1]) seemed to predict a clinical diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).<sup>1</sup>
- One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.
- A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had "Type B" tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.
- The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).
- The prior review and three additional studies that we identified for this Key Question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive

tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians' accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **The Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology**

- Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.
- We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that *Haemophilus influenzae* (HF) has become more prevalent as a causative agent of AOM and *Streptococcus pneumoniae* (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.
- We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.
- The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine's effect on these special populations.

### **Effects of Antibiotics on AOM**

- Meta-analysis of the comparison of ampicillin or amoxicillin vs. placebo indicates that in four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95%CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95%CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group. Nine children with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by

day 14 (95%CI: 6, 20). For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

### **Relative Effects of Different Antibiotic Regimens**

- Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95%CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95%CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95%CI: -4, 3) between cefaclor (7-10 days) and azithromycin ( $\leq 5$  days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.
- In pooled analysis, no difference (RD=-0.3%, 95%CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95%CI: 2, 17) and higher success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95%CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate  $>60$ mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid are assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

### **Management of Recurrent, Persistent, or Relapse of Otitis Media**

- The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.
- Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95%CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.
- The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **Treatment Outcomes by Subgroup**

- Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.
- For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity,

characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.

- In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.
- In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

### **Adverse Events**

- In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.
- Meta-analysis demonstrated that children treated with 7 to 10 day amoxicillin-clavulanate had an 18 percent (95 percent confidence intervals, 8 percent and 28 percent) greater rate of gastrointestinal adverse effects than children treated with 5-day azithromycin (although not reported in the studies, the clavulanate concentration was most likely 31.25 mg per 125 mg of amoxicillin, i.e., original formulation.)

### **Limitations of the Literature**

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears
- Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.
- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our

assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.

- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.
- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea .
- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.
- Based on the exclusion factors of the investigations used in this analysis, the study findings are most applicable to children without comorbidities and with AOM of lesser severity.

## **Discussion**

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.<sup>12</sup> Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings.

Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

Overall, children over the age of two years had better outcomes with various antibiotic options than children under age two; laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to monitor response to treatment and outcomes more closely when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.

Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

## **Future Research**

**Diagnosis of AOM** Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

**Influence of the PCV7 Vaccine on Microbiology/Epidemiology** Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

**Treatment Efficacy and Adverse Effects** Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.



## Version 2

### Summary

#### Overview

The objective of this report was to analyze the evidence on the initial management of uncomplicated acute otitis media (AOM)<sup>6</sup> in children. AOM represents the most common childhood infection for which antibiotics are prescribed in the United States. Data from the National Ambulatory Medical Care Surveys (NAMCS), which did not differentiate between AOM and otitis media with effusion, indicated that the number of office visits for AOM increased more than two-fold from 1975 to 1990. Gates (1996a) believed that the majority of these cases represented AOM. Based on national data from NAMCS and the National Hospital Ambulatory Medical Care Surveys, we estimated that 5.18 million episodes of AOM occurred in 1995 at a cost of approximately \$2.98 billion, including direct and indirect costs and the costs of sequelae such as otitis media with effusion and chronic middle ear infection. These estimates suggest that increased effectiveness in treating AOM could achieve significant national cost savings.

AOM was defined by the Technical Expert Panel as the presence of middle ear effusion in conjunction with the rapid onset of one or more signs or symptoms of inflammation of the middle ear. Uncomplicated AOM was defined as AOM that is limited to the middle ear cleft. An episode of uncomplicated AOM was considered distinct from a previous episode of AOM and was eligible for initial treatment if the most recent course of antibiotics ended 4 weeks prior to the episode of AOM in question, or if there was documentation by an examiner that a prior episode of AOM had been cleared.

Various medical and surgical treatments have been used for AOM. There is controversy about the need for antibiotics, particularly in children older than 6 months of age with uncomplicated AOM. It is routine to use antibiotics for AOM in the United States, whereas in the Netherlands the standard practice is to observe selected children older than 2 years of age for 48 hours and selected children age 6 months to 2 years for 24 hours before initiating antibiotics. Antibiotics are prescribed if clinical resolution does not occur during the observation period. The presence of alternative treatment paradigms of questioned effectiveness suggests that an evidence-based analysis on the management of AOM is needed to determine the efficacy of antibiotic therapy.

#### Reporting the Evidence

The nominating organization, the American Academy of Pediatrics, and the Technical Expert Panel limited the scope of this evidence report to six key clinical questions:

1. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic

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<sup>6</sup> A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?<sup>7</sup>

2. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?

3. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?

4. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?

5. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to the following: Laterality, i.e., unilateral vs. bilateral; Otorrhea or perforation; AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); Comorbidities, e.g., asthma; Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; Race; Ethnicity; Day care attendance?

6. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ 3 and KQ 4?

The regimens we analyzed were:<sup>8</sup>

(1) ampicillin or amoxicillin vs. placebo

(2) amoxicillin tid (7d) vs. prescription –to-hold

(3) Antibiotic vs. prescription-to-hold

(4) Amoxicillin vs. wait-and-see

(5) Phenoxymethylpenicillin vs. wait-and-see

(6) Ampicillin or amoxicillin vs. Ceftriaxone

(7) Amoxicillin (50mg/kg/d; bid, 10d) vs. erythromycin (40 mg/kg/d; bid 10d)

(8) Amoxicillin clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d)

(9) Amoxicillin clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d)

(10) Cefaclor vs. Trimethoprim-sulfamethoxazole

(11) Cefaclor vs. Ampicillin or amoxicillin

(12) Cefixime vs. Ampicillin or amoxicillin

(13) Penicillin vs. ampicillin or amoxicillin

(14) Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d

(15) High-dose amoxicillin bid vs. lower-dose amoxicillin tid

(16) Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days

(17) Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)

(18) Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)

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<sup>7</sup>Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

<sup>8</sup>A total of 63 different comparisons of treatment options were identified. The 21 listed are key comparisons.

- (19) Cefaclor (7-10d) vs. Azithromycin (<5d)
- (20) Amoxicillin (7d) vs. Azithromycin (1 dose)
- (21) Amoxicillin-clavulanate (7-10d) vs. Azithromycin

The Technical Expert Panel decided that this systematic review would focus on children ages 4 weeks to 18 years, who had uncomplicated AOM and were seeking initial treatment or treatment for recurring AOM. The major outcomes for studies of efficacy and effectiveness included presence or absence of signs and symptoms within 48 hours, at 3 to 7 days, 7 to 14 days, 14 days to 3 months, and after 3 months; presence or absence of adverse effects from antibiotic treatment; and presence or absence of bacteria and/or resistant bacteria. Other outcomes included changes in bacterial colonization in populations that received PCV7 and clinical signs associated with a positive diagnosis.

## Methodology

An 11-member Technical Expert Panel consisting of clinical experts, a consumer, and a representative of a managed care organization convened to:

- advise the project in the ranking of proposed Key Questions and influencing factors,
- guide the development of the scope and definition of AOM,
- advise in development of the search strategy, and
- review and comment on the analysis plan.

The Technical Expert Panel and project staff developed a literature search strategy. The initial strategy was developed for MEDLINE and was customized for other databases. Project staff searched MEDLINE (January 1998-July 2010), the Cochrane Library (January 1998-July 2010), and the Web of Science. Additional articles were identified by review of reference lists in proceedings, published articles, reports, and guidelines.

The initial module of search statements included an explode of "om" (otitis media), which included the headings "om, mastoiditis," "om w/effusion," and "om, suppurative" with the subheading "drug therapy." The next module included the explode of "om," with "om" as a text word. The terms, "recurrent otitis media" and "heptavalent vaccine were also added." The anti-infectives module used an explode of the mesh heading for anti-infective agents, including antibiotics and other drug groups, and the text words antibiotic, antimicrobial, antibacterial, and specific antibiotic names. Combinations of these modules were used for the literature search. The search was limited to human or undesignated studies and to infant, child, preschool, adolescence, or undesignated subjects. Two physicians independently screened all titles and/or abstracts for potential inclusion, evaluated the quality of the articles, and abstracted data from full-length articles onto predesigned forms. The selection criteria included human studies that addressed a Key Question about AOM in children ages 4 weeks to 18 years. Excluded were case reports, editorials, letters, reviews, practice guidelines, and studies on patients with immunodeficiencies or craniofacial deficiencies, including cleft palate.

Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain

subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. Only randomized controlled trials and large observational studies were used to address the Key Questions on the effectiveness of antibiotics. The physician reviewers assessed the quality of controlled trials by using the Jadad criteria. QUADAS criteria were used to evaluate the studies that pertained to diagnosis.

Meta-analyses were performed to determine the effectiveness of antibiotic vs. placebo or observational treatment of uncomplicated AOM and to determine the effectiveness of particular antibiotic regimens. Comparisons were established based on the type of antibiotics and the outcome variable under consideration. The technical experts decided to establish comparison groups by individual antibiotic, as this best fit the information required for clinical practice. A meta-analysis was performed for each comparison with three or more randomized controlled studies. Heterogeneity was measured for all meta-analyses, and a random effects model was used to estimate the absolute rate differences. Subgroup analyses were performed based on age of the subject, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the  $I^2$  statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the “minimal clinically important difference (MCID)” against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a “small” effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

This evidence report was critiqued by the Technical Expert Panel as well as a peer-review panel consisting of content experts, consumers, representatives of managed care organizations, and methodologists. All comments received from these individuals were reviewed and acted upon as appropriate.

## Findings

### Natural History of AOM

- In children with AOM who were not initially treated with antibiotics, one study showed a clinical failure rate of 7.7 percent at 24 to 48 hours, and another study showed a failure

rate of 26 percent at 24 to 72 hours -- that is, clinical resolution was 92.3 percent at 24 to 48 hours and 74 percent at 24 to 72 hours. The pooled estimate of failure at 1 to 7 days was 18.9 percent (95 percent confidence intervals, 9.9 percent and 28.0 percent) and at 4 to 7 days was 22.2 percent (95 percent confidence intervals, 10.1 percent and 34.3 percent).

- A previous information synthesis estimated that 59 percent (95 percent confidence intervals, 53 percent and 65 percent) of children not treated with antibiotics had resolution of pain and fever within 24 hours of diagnosis of AOM, 87 percent (95 percent confidence intervals, 84 percent and 89 percent) of children had resolution of pain and fever within 2 to 3 days, and 88 percent (95 percent confidence intervals, 85 percent and 91 percent) of children had resolution of pain and fever within 4 to 7 days.
- The available evidence on natural history of AOM shows that in studies with close follow-up, few episodes of mastoiditis or other suppurative complications are reported in children with AOM who are not treated initially with antibiotics.

### **Diagnosis of AOM**

- Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE).
- To address this Key Question, we searched for studies that examined clinicians' accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together.
- A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1]) seemed to predict a clinical diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).<sup>1</sup>
- One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.
- A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had "Type B" tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However,

positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

- The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).
- The prior review and three additional studies that we identified for this Key Question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians' accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **The Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology**

- Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.
- We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that *Haemophilus influenzae* (HF) has become more prevalent as a causative agent of AOM and *Streptococcus pneumoniae* (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.
- We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.
- The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations

(such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine's effect on these special populations.

### Effects of Antibiotics on AOM

- Meta-analysis of the comparison of ampicillin or amoxicillin vs. placebo indicates that in four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95%CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95%CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group. Nine children with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by day 14 (95%CI: 6, 20). For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

### Relative Effects of Different Antibiotic Regimens

- Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95%CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95%CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95%CI: -4, 3) between cefaclor (7-10 days) and azithromycin ( $\leq 5$  days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.
- In pooled analysis, no difference (RD=-0.3%, 95%CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95%CI: 2, 17) and higher

success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95%CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

- Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid are assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

### **Management of Recurrent, Persistent, or Relapse of Otitis Media**

- The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.
- Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95%CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.
- The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered



low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **Treatment Outcomes by Subgroup**

- Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.
- For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.
- In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.
- In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

### **Adverse Events**

- In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.
- Meta-analysis demonstrated that children treated with 7 to 10 day amoxicillin-clavulanate had an 18 percent (95 percent confidence intervals, 8 percent and 28 percent) greater rate of gastrointestinal adverse effects than children treated with 5-day azithromycin (although not reported in the studies, the clavulanate concentration was most likely 31.25 mg per 125 mg of amoxicillin, i.e., original formulation.)

### **Limitations of the Literature**

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its

reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears

- Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.
- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.
- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.
- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea .
- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.
- Based on the exclusion factors of the investigations used in this analysis, the study findings are most applicable to children without comorbidities and with AOM of lesser severity.

## Discussion

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.<sup>12</sup> Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way

to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings.

Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

Overall, children over the age of two years had better outcomes with various antibiotic options than children under age two; laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to monitor response to treatment and outcomes more closely when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.

Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

## Future Research

**Diagnosis of AOM** Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

**Influence of the PCV7 Vaccine on Microbiology/Epidemiology** Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

**Treatment Efficacy and Adverse Effects** Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater

knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.

## Version 3

### Summary

#### Overview

The objective of this report was to analyze the evidence on the initial management of uncomplicated acute otitis media (AOM)<sup>9</sup> in children. AOM represents the most common childhood infection for which antibiotics are prescribed in the United States. . Data from the National Ambulatory Medical Care Surveys (NAMCS), which did not differentiate between AOM and otitis media with effusion, indicated that the number of office visits for AOM increased more than two-fold from 1975 to 1990. Gates (1996a) believed that the majority of these cases represented AOM. Based on national data from NAMCS and the National Hospital Ambulatory Medical Care Surveys, we estimated that 5.18 million episodes of AOM occurred in 1995 at a cost of approximately \$2.98 billion, including direct and indirect costs and the costs of sequelae such as otitis media with effusion and chronic middle ear infection. These estimates suggest that increased effectiveness in treating AOM could achieve significant national cost savings.

AOM was defined by the Technical Expert Panel as the presence of middle ear effusion in conjunction with the rapid onset of one or more signs or symptoms of inflammation of the middle ear. Uncomplicated AOM was defined as AOM that is limited to the middle ear cleft. An episode of uncomplicated AOM was considered distinct from a previous episode of AOM and was eligible for initial treatment if the most recent course of antibiotics ended 4 weeks prior to the episode of AOM in question, or if there was documentation by an examiner that a prior episode of AOM had been cleared.

Various medical and surgical treatments have been used for AOM. There is controversy about the need for antibiotics, particularly in children older than 6 months of age with uncomplicated AOM. It is routine to use antibiotics for AOM in the United States, whereas in the Netherlands the standard practice is to observe selected children older than 2 years of age for 48 hours and selected children age 6 months to 2 years for 24 hours before initiating antibiotics. Antibiotics are prescribed if clinical resolution does not occur during the observation period. The presence of alternative treatment paradigms of questioned effectiveness suggests that an evidence-based analysis on the management of AOM is needed to determine the efficacy of antibiotic therapy.

#### Reporting the Evidence

The nominating organization, the American Academy of Pediatrics, and the Technical Expert Panel limited the scope of this evidence report to six key clinical questions:

1. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish

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<sup>9</sup>A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

- it from otitis media with effusion (OME)?<sup>10</sup>
2. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?
  3. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?
  4. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?
  5. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to the following: Laterality, i.e., unilateral vs. bilateral; Otorrhea or perforation; AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); Comorbidities, e.g., asthma; Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; Race; Ethnicity; Day care attendance?
  6. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ 3 and KQ 4?

The regimens we analyzed were:<sup>11</sup>

- (1) ampicillin or amoxicillin vs. placebo
- (2) amoxicillin tid (7d) vs. prescription –to-hold
- (3) Antibiotic vs. prescription-to-hold
- (4) Amoxicillin vs. wait-and-see
- (5) Phenoxyethylpenicillin vs. wait-and-see
- (6) Ampicillin or amoxicillin vs. Ceftriaxone
- (7) Amoxicillin (50mg/kg/d; bid, 10d) vs. erythromycin (40 mg/kg/d; bid 10d)
- (8) Amoxicillin clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d)
- (9) Amoxicillin clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d)
- (10) Cefaclor vs. Trimethoprim-sulfamethoxazole
- (11) Cefaclor vs. Ampicillin or amoxicillin
- (12) Cefixime vs. Ampicillin or amoxicillin
- (13) Penicillin vs. ampicillin or amoxicillin
- (14) Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d
- (15) High-dose amoxicillin bid vs. lower-dose amoxicillin tid
- (16) Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days
- (17) Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)
- (18) Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)

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<sup>10</sup>Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

<sup>11</sup>A total of 63 different comparisons of treatment options were identified. The 21 listed are key comparisons.

- (19) Cefaclor (7-10d) vs. Azithromycin (<5d)
- (20) Amoxicillin (7d) vs. Azithromycin (1 dose)
- (21) Amoxicillin-clavulanate (7-10d) vs. Azithromycin

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The Technical Expert Panel decided that this systematic review would focus on children ages 4 weeks to 18 years, who had uncomplicated AOM and were seeking initial treatment or treatment for recurring AOM. The major outcomes for studies of efficacy and effectiveness included presence or absence of signs and symptoms within 48 hours, at 3 to 7 days, 7 to 14 days, 14 days to 3 months, and after 3 months; presence or absence of adverse effects from antibiotic treatment; and presence or absence of bacteria and/or resistant bacteria. Other outcomes included changes in bacterial colonization in populations that received PCV7 and clinical signs associated with a positive diagnosis.

## **Methodology**

An 11-member Technical Expert Panel consisting of clinical experts, a consumer, and a representative of a managed care organization convened to:

- advise the project in the ranking of proposed Key Questions and influencing factors,
- guide the development of the scope and definition of AOM,
- advise in development of the search strategy, and
- review and comment on the analysis plan.

The Technical Expert Panel and project staff developed a literature search strategy. The initial strategy was developed for MEDLINE and was customized for other databases. Project staff searched MEDLINE (January 1998-July 2010), the Cochrane Library (January 1998-July 2010), and the Web of Science. Additional articles were identified by review of reference lists in proceedings, published articles, reports, and guidelines.

The initial module of search statements included an explode of "om" (otitis media), which included the headings "om, mastoiditis," "om w/effusion," and "om, suppurative" with the subheading "drug therapy." The next module included the explode of "om," with "om" as a text word. The terms, "recurrent otitis media" and "heptavalent vaccine" were also added. The anti-infectives module used an explode of the mesh heading for anti-infective agents, including antibiotics and other drug groups, and the text words antibiotic, antimicrobial, antibacterial, and specific antibiotic names. Combinations of these modules were used for the literature search. The search was limited to human or undesignated studies and to infant, child, preschool, adolescence, or undesignated subjects. Two physicians independently screened all titles and/or abstracts for potential inclusion, evaluated the quality of the articles, and abstracted data from full-length articles onto predesigned forms. The selection criteria included human studies that addressed a Key Question about AOM in children ages 4 weeks to 18 years. Excluded were case reports, editorials, letters, reviews, practice guidelines, and studies on patients with immunodeficiencies or craniofacial deficiencies, including cleft palate.

Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies



that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. Only randomized controlled trials and large observational studies were used to address the Key Questions on the effectiveness of antibiotics. The physician reviewers assessed the quality of controlled trials by using the Jadad criteria. QUADAS criteria were used to evaluate the studies that pertained to diagnosis.

Meta-analyses were performed to determine the effectiveness of antibiotic vs. placebo or observational treatment of uncomplicated AOM and to determine the effectiveness of particular antibiotic regimens. Comparisons were established based on the type of antibiotics and the outcome variable under consideration. The technical experts decided to establish comparison groups by individual antibiotic, as this best fit the information required for clinical practice. A meta-analysis was performed for each comparison with three or more randomized controlled studies. Heterogeneity was measured for all meta-analyses, and a random effects model was used to estimate the absolute rate differences. Subgroup analyses were performed based on age of the subject, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the  $I^2$  statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the “minimal clinically important difference (MCID)” against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a “small” effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

This evidence report was critiqued by the Technical Expert Panel as well as a peer-review panel consisting of content experts, consumers, representatives of managed care organizations, and methodologists. All comments received from these individuals were reviewed and acted upon as appropriate.

## Findings

### Natural History of AOM

- In children with AOM who were not initially treated with antibiotics, one study showed a clinical failure rate of 7.7 percent at 24 to 48 hours, and another study showed a failure rate of 26 percent at 24 to 72 hours -- that is, clinical resolution was 92.3 percent at 24 to 48 hours and 74 percent at 24 to 72 hours. The pooled estimate of failure at 1 to 7 days was 18.9 percent (95 percent confidence intervals, 9.9 percent and 28.0 percent) and at 4 to 7 days was 22.2 percent (95 percent confidence intervals, 10.1 percent and 34.3 percent).
- A previous information synthesis estimated that 59 percent (95 percent confidence intervals, 53 percent and 65 percent) of children not treated with antibiotics had resolution of pain and fever within 24 hours of diagnosis of AOM, 87 percent (95 percent confidence intervals, 84 percent and 89 percent) of children had resolution of pain and fever within 2 to 3 days, and 88 percent (95 percent confidence intervals, 85 percent and 91 percent) of children had resolution of pain and fever within 4 to 7 days.
- The available evidence on natural history of AOM shows that in studies with close followup, few episodes of mastoiditis or other suppurative complications are reported in children with AOM who are not treated initially with antibiotics.

### Diagnosis of AOM

- Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE).
- To address this Key Question, we searched for studies that examined clinicians' accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together.
- A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1]) seemed to predict a clinical diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).<sup>1</sup>
- One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.
- A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the

criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had “Type B” tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

- The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).
- The prior review and three additional studies that we identified for this Key Question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians’ accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **The Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology**

- Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.
- We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that *Haemophilus influenzae* (HF) has become more prevalent as a causative agent of AOM and *Streptococcus pneumoniae* (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.
- We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.

- The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine's effect on these special populations.

### **Effects of Antibiotics on AOM**

- Meta-analysis of the comparison of ampicillin or amoxicillin vs. placebo indicates that in four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95%CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95%CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group. Nine children with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by day 14 (95%CI: 6, 20). For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

### **Relative Effects of Different Antibiotic Regimens**

- Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95%CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95%CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95%CI: -4, 3) between cefaclor (7-10 days) and azithromycin ( $\leq$  5 days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.

- In pooled analysis, no difference (RD=-0.3%, 95% CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95% CI: 2, 17) and higher success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95% CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid are inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.
- Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid are assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

### **Management of Recurrent, Persistent, or Relapse of Otitis Media**

- The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.
- Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95% CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing

regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.

- The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **Treatment Outcomes by Subgroup**

- Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.
- For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.
- In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.
- In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

### **Adverse Events**

- In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. Adverse events

were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.

- Meta-analysis demonstrated that children treated with 7 to 10 day amoxicillin-clavulanate had an 18 percent (95 percent confidence intervals, 8 percent and 28 percent) greater rate of gastrointestinal adverse effects than children treated with 5-day azithromycin (although not reported in the studies, the clavulanate concentration was most likely 31.25 mg per 125 mg of amoxicillin, i.e., original formulation.)

### **Limitations of the Literature**

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears. Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.
- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.
- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.
- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea .
- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.

- Based on the exclusion factors of the investigations used in this analysis, the study findings are most applicable to children without comorbidities and with AOM of lesser severity.

## **Discussion**

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.<sup>12</sup> Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings.

Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

Overall, children over the age of two years had better outcomes with various antibiotic options than children under age two; laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to monitor response to treatment and outcomes more closely



when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.

Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

## **Future Research**

**Diagnosis of AOM** Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

**Influence of the PCV7 Vaccine on Microbiology/Epidemiology** Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

**Treatment Efficacy and Adverse Effects** Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability

of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the effect of children’s age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM. Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.

## Executive Summary

### Introduction

Acute Otitis Media (AOM)<sup>12</sup> is a viral and/or bacterial infection of the middle ear and represents the most common childhood infection for which antibiotics are prescribed in the United States. Timely and accurate diagnosis and management of AOM can have significant individual and public health consequences.

The 2001 AHRQ evidence report on the management of AOM analyzed the evidence on the initial management of uncomplicated AOM in children, focusing on the natural history of the disease and the use of antibiotics in management. Although the 2001 report provided valuable analysis of the literature on the management of uncomplicated AOM in children, it did not address issues related to diagnostic accuracy and precision, management of AOM in specific subgroups of children, or the impact of immunization with Heptavalent Pneumococcal Conjugate Vaccine (PCV7) on the microbiology of AOM, recommended for widespread use in 2000. Additionally, new trials of treatment continue to be published. The purpose of this current AHRQ evidence report is to examine and analyze the evidence on three broad areas of inquiry: 1) accuracy and consistency of the clinical diagnosis of AOM, 2) the impact of PCV7 on AOM microbial epidemiology, and 3) the comparative effectiveness of different treatment options for uncomplicated AOM in average risk children and in children with recurrent (defined as three or more episodes in six months or four or more episodes within 12 months) or persistent AOM.

### Methods

#### Key Questions

The American Academy of Pediatrics, the nominating organization, proposed six Key Questions aimed at assessing the comparative efficacy of interventions to treat uncomplicated and recurrent AOM in terms of treatment success, the safety of such treatments, and the effect on children in specific subgroups. In conjunction with a technical expert panel we refined these questions:

I. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?<sup>13</sup>

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<sup>12</sup>A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

<sup>13</sup>Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

II. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?

III. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?

IV. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?

V. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to the following: A. Laterality, i.e., unilateral vs. bilateral; B. Otorrhea or perforation; C. AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); D. Comorbidities, e.g., asthma; E. Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; F. Race; G. Ethnicity; H. Day care attendance?

VI. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ III and KQ IV?

## **Literature Searches**

Searches of PubMed and the Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center were conducted from January 1998 through July 2010 using the same search strategies used for the 2001 report, with the addition of terms for conditions not considered in the 2001 review (recurrent otitis media), new drugs, and the heptavalent vaccine. The Web of Science was also used to search for citations of the 2001 report and its peer-reviewed publications. Among the 8,945 titles identified were a number of recent, good-quality systematic reviews, which were included and which were examined for references. Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. For the efficacy and safety questions, we searched primarily for controlled trials or large observational studies aimed at identifying adverse effects.

## **Literature Review, Data Abstraction, and Analysis**

In total, the reviewers examined 8,945 titles for the draft version of this report; 739 titles were identified for further review. Of those, 72 articles that met the predetermined inclusion criteria were reviewed in detail for efficacy and safety results. Investigators abstracted data into standard evidence tables with abstraction checked by a second investigator. Studies were quality-rated by two investigators using established criteria. For randomized controlled trials (RCT), the Jadad criteria were used. QUADAS criteria were used to evaluate the studies that pertained to diagnosis. Data abstracted included parameters necessary to define study groups, inclusion/exclusion criteria, influencing factors, and outcome measures. Data for the analysis were abstracted by a biostatistician and checked by a physician reviewer. We used a sequential resolution strategy to match and resolve the screening and review results of the two reviewers.

For the assessment of treatment efficacy, pooled analysis was performed for comparisons for which three or more trials could be identified. The articles eligible for analysis for the Key Questions pertaining to treatment efficacy were grouped according to the specific treatment options they compared. Each comparison consisted of articles that were considered homogeneous from the standpoint of clinical practice. Since the question of treatment efficacy was addressed in the first evidence report published in 2001, we combined the articles identified in that report with articles newly identified for this evidence report that addressed the same populations and reported the same types of outcomes. We pooled data for comparisons that included three or more articles from the old and new searches and performed meta-analyses or quantitative syntheses. We used the Der Simonian and Laird random effects model to pool rate differences across studies. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the  $I^2$  statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the “minimal clinically important difference (MCID)” against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a “small” effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

## Results

### **Key Question I. Diagnosis of AOM: What Are the Operating Characteristics (Sensitivity, Specificity, and Likelihood Ratios) of Clinical Symptoms and Otoscopic Findings (Such As Bulging Tympanic Membrane) to Diagnose Uncomplicated AOM and to Distinguish It from OME?**

Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE). To address this Key Question, we searched for studies that examined clinicians’ accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together. A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1]) seemed to predict a clinical

diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).<sup>1</sup>

One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.

A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had “Type B” tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).

The prior review and three additional studies that we identified for this Key Question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians’ accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

## **Key Question II. What Has Been the Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology: What Organisms (bacterial and viral) are Associated with AOM Since the Introduction of PCV7; and What Are the Patterns of Antimicrobial Resistance in AOM Since the Introduction of PCV7?**

Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship

between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.

We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that *Haemophilus influenzae* (HF) has become more prevalent as a causative agent of AOM and *Streptococcus pneumoniae* (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.

We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.

The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine’s effect on these special populations.

### Key Question III. What Is the Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated AOM in Average Risk Children?

For the comparison of treatment success for children with uncomplicated AOM, we identified 63 comparisons of treatment options for uncomplicated AOM that encompassed different antibiotics and regimens. Our analyses yielded inconclusive results for many of these comparisons. For 12 comparisons, we reached stronger conclusions. Table S-1 shows key comparisons from the first AOM report, the present report, and where possible, combined results.

**Table S-1. Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media (AOM) in Average Risk Children in the 2001 Report and the Present Report**

Comparison	2001 Report		2010 Update			Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
<b>Drug vs. placebo, wait-and-see, and/or prescription-to-hold</b>						
Ampicillin or amoxicillin vs. placebo	5	12% (3%, 22%)	2	7	12%(5%, 18%)	Ampicillin or amoxicillin was more successful than placebo
Amoxicillin tid (7d) vs. prescription-to-hold) <sup>2</sup>	0	N/A	1	1	16% (6, 26)	Amoxicillin was more successful than prescription-to-hold (defined as success at day 3)
Antibiotic vs. prescription-to-	0	N/A	1	1	3% (-8, 14)	Inconclusive (defined as otalgia

Comparison	2001 Report		2010 Update			Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
hold) <sup>2</sup>						at day 4-6)
Amoxicillin 90mg/kg/d bid (10d) vs. wait-and-see <sup>3</sup>	0	N/A	1	1	15% (6, 24)	Amoxicillin was more successful (defined as success at day 12)
PcV vs. wait-and-see <sup>3</sup>	0	N/A	1	1	-3% (-14, 8)	Inconclusive (defined as success at day 14)
<b>Drug vs. drug</b>						
Ampicillin or amoxicillin vs. Ceftriaxone	3	3% (-2%, 9%)	1	4	0.1% (-7%, 7%)	Inconclusive
Amoxicillin 50mg/kg/d (bid, 10d) vs. erythromycin 40mg/kg/d (bid, 10d) <sup>4</sup>	0	N/A	1	1	0.6% (-3, 4)	Treatments were equivalent (when success defined as freedom from recurrence day 31-40)
Amoxicillin-clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d)	0	N/A	1	1	0% (-3.3, 3.3)	Treatments were equivalent (success d.12-14)
Amoxicillin-clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d) <sup>5</sup>	0	N/A	1	1	13% (5, 21)	Amoxicillin-clavulanate was more effective than cefaclor (success at day 28-34, as defined by clinical symptoms but not by culture)
Cefaclor vs. trimethoprim-sulfamethoxazole	3	-6% (-13, 2) (success at less than 14 d)	0	3	N/A	Inconclusive (defined as success at less than day 14); no new data but using MCID
Cefaclor vs. Ampicillin or amoxicillin	4	-5% (-15, 6) (success at d. 3-7)	0	4	N/A	Inconclusive (defined as success at day 3-7); no new data; no new data but using MCID
Cefixime vs.	4	0.1% (-3.9,	0	4	N/A	Treatments were



Comparison	2001 Report		Number of new trials	2010 Update		Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)		Total number of trials	Success rate difference	
Ampicillin or amoxicillin		4.2) (success at d. 10-15)				equivalent; no new data
Penicillin vs. ampicillin or amoxicillin	3	-5% (-11, 2) (success at d. 7-14)	0	3	N/A	Inconclusive (defined as success at day 7-14); no new data but using MCID
<b>High vs. Low Dose Treatment</b>						
Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d	1	1.5% (-3, 13)	0	1	N/A	Inconclusive(defined as persistent clinical cure with no recurrence at follow-up); no new data
High-dose amoxicillin bid vs. lower-dose amoxicillin tid	1	-4% (-14, 7)	0	1	N/A	Inconclusive (defined as success at day 15); no new data
Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days <sup>6</sup>	0	N/A	1	1	0.1% (-4.8, 4.6)	Treatments were equivalent (success d. 7-12)
<b>Short vs. Long Treatment Duration<sup>b</sup></b>						
Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)	3	3% (-2%, 9%) (success rate at 5-10d)	1	4	0% (-7%, 7%)	Inconclusive
Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)	2	N/A	3	5	3% (-2%, 7%)	Inconclusive
Cefaclor (7-10d) vs. Azithromycin (<5d)	1	N/A	2	3	-1% (-4%, 3%)	Treatments were equivalent
Amoxicillin (7d) vs. Azithromycin (1 dose)	0	N/A	1	1	1% (-1%, 4%)	Treatments were equivalent (defined as no new pain between day 6 and

Comparison	2001 Report		2010 Update			Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (≤5d)	5	2% (1, 5%) (success at 10-14d)	4	9	-0.3% (-6%, 6%)	Inconclusive
Amoxicillin-clavulanate 45/6.4 mg/kg/d (bid, 10d) vs. azithromycin 10 mg/kg/d (qd for 1 day), 5 mg/kg/d (qd for 4d) <sup>7</sup>	0	N/A	1	1	26% (6,36)	Longer-term amoxicillin-clavulanate is more successful than shorter-term azithromycin (at d. 12-14, when pathogen is H. influenzae)
Cefaclor 50mg/kg/d; bid 5 d) vs. cefaclor 40mg/kg/d; bid 10d)	0	N/A	1	1	0.7% (-3.5-4.9)	Treatments were equivalent

Table Notes: bid twice a day; CI confidence intervals; d day(s); kg kilograms (body weight); mg milligrams; NNT number needed to treat; PcV phenoxymethylpenicillin; qd once a day;

<sup>a</sup> Confidence intervals falling within the zone of indifference were considered to establish evidence of *no difference*, and confidence intervals outside the zone of indifference were considered to *establish difference*. If the confidence intervals crossed into the zone of indifference, an effect (positive or negative) of the treatment option on the outcome could not be established (*inconclusive*). For the 2010 systematic review, we used a *zone of clinical indifference of +/- 5%* for the difference in success rate between two treatment options.

<sup>b</sup>Short vs. long term duration refers to the length of treatment from the patient perspective, rather than from the perspective of drug action.

Meta-analyses of the comparison of ampicillin or amoxicillin vs. placebo indicates that nine children (95%CI: 6, 20) with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by day 14. For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. In four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95%CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95%CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group.

Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95%CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95%CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95%CI: -4, 3) between cefaclor (7-10 days) and azithromycin ( $\leq 5$  days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.

In pooled analysis, no difference (RD=-0.3%, 95%CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95%CI: 2, 17) and higher success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95%CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate  $>60$ mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid that in the 2001 Report were assessed as demonstrating equivalent clinical success rates are now assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

#### **Key Question IV. What Is the Comparative Effectiveness of Different Management Options for Recurrent Otitis Media (Uncomplicated) and Persistent Otitis Media or Relapse of AOM?**

In approaching this question, studies were divided into those that examined treatment and those that examined prevention.

The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of

evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.

Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95% CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.

The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **Key Question V. Do Treatment Outcomes in Key Question3 (KQ3) and KQ4 Differ by Characteristics of the Condition (AOM), Patient, Environment, and/or Health Care Delivery System?**

Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.

For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.

In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.

In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

### Key Question VI. What Adverse Effects Have Been Observed for the Treatments Whose Outcomes Are Addressed in KQ3 and KQ4?

We examined the incidence of adverse events in the RCTs identified for this report that compared the effectiveness of one or more treatment options. We also searched the FDA MedWatch Database for adverse events associated with use of medications for the treatment of AOM; however, none could be identified.

In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. However, Table S-2 shows the significant differences in adverse event rates that we noted (Table S-2 also shows the comparisons for the original report, those unique to the present report, and those that could be combined across both reports). Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.

Table S-2 Comparison of Rates of Adverse Events Between Drugs (Significant Differences Only)

Comparison	2011 Report		2010 Update			Conclusion
	Number of trials	AE rate Difference (95% CI)	Number of new trials	Total number of trials	AE rate difference (95% CI)	
<b>Uncomplicated AOM</b>						
<b>Overall Adverse Events</b>						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	19% (9%, 29%)	0	3	N/A	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (qd)	0	N/A	1	1	28% (17%, 39%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (bid)	0	N/A	1	1	19% (8%, 31%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. Ceftriaxone	0	N/A	1	1	16% (9%, 24%)	Amoxicillin-clavulanate associated with greater overall AE rate
<b>Gastrointestinal Adverse Events</b>						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	18% (8%, 28%)	0	0	N/A	Amoxicillin-clavulanate associated with greater rate of

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion
	Number of trials	AE rate Difference (95% CI)		Total number of trials	AE rate difference (95% CI)	
						GI AE
<b>Diarrhea</b>						
Ampicillin or amoxicillin vs. cefixime	5	-8% (-13, -4)	0	0	N/A	Cefixime associated with greater rate of diarrhea
Amoxicillin clavulanate vs. cefdinir	0		1	1	25% (15%, 35%) in Cef QD and 22% (11%, 32%) in Cef BID	Amoxicillin clavulanate associated with greater rate of diarrhea
Amoxicillin clavulanate vs. ceftriaxone	0		1	1	13% (6%, 20%)	Amoxicillin clavulanate associated with greater rate of diarrhea
<b>Recurrent Otitis Media</b>						
<b>Diarrhea</b>						
Amoxicillin-clavulanate vs. ciprofloxacin-dexamethasone ear drops	0	N/A				Greater for amoxicillin-clavulanate in 1 study, but equivalent in 41; no conclusion possible in 23 comparisons

Table notes: AE adverse event; bid twice a day; CI confidence interval; d day; NNT number needed to treat; qd once a day

Of the 44 RCTs newly identified for this report that compared the effectiveness of treatment options in uncomplicated AOM, there are 61 treatment comparisons. Of the 61 treatment comparisons, 42 included comparisons of the percent of cases that had experienced an adverse event between two treatment options. For treatment of uncomplicated AOM, five adverse event rate comparisons showed a significant difference between two treatment options. Amoxicillin-clavulanate was associated with diarrhea more often than was cefdinir (NNT=four) and more often than was ceftriaxone (NNT= seven). The adverse event rates ranged from 27% to 35% for amoxicillin-clavulanate and from 10% to 14% for the other treatment options. For mention of any adverse event, amoxicillin-clavulanate had a higher rate than cefdinir given once or twice daily and a higher rate than ceftriaxone. However, in one study, the dose of amoxicillin was 40mg/kg/day, whereas in the other study, it was 80mg/kg/day (the clavulanate dosage was 10mg/kg/day in both studies). Equivalence was demonstrated in 29 comparisons, leaving 99 comparisons inconclusive.

These findings complement the findings from the first review, which showed that for uncomplicated AOM, children treated with amoxicillin-clavulanate for seven to ten days had a 19% (95%CI: 9, 29; NNT=5) higher rate of overall adverse effects and a 18% (95%CI: 8, 28; NNT=6) higher rate of gastrointestinal adverse effects than children treated with five days of

azithromycin. (Although it was not specified in the studies, the original formulation was 31.25 mg clavulanate per 125 mg of amoxicillin). Eight children would need to be treated with azithromycin rather than amoxicillin-clavulanate to avoid a gastrointestinal adverse event. The original review also found that children treated with cefixime had an 8% (95%CI: 4, 13; NNT=12) greater rate of diarrhea than children treated with ampicillin or amoxicillin, so 12 children would need to be treated with ampicillin or amoxicillin rather than cefixime to avoid one case of diarrhea.

We also examined adverse event rates in children with presumed or explicitly defined ROM who were being given antibiotics for the treatment or prevention of AOM. Among the fourteen studies focused on children with ROM, persistent AOM, or AOM treatment failure, there were 21 treatment comparisons: eight involving the treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent AOM, and/or AOM with treatment failure and the remainder in children being given the drugs prophylactically for prevention of AOM. For *treatment* of AOM in children with ROM and/or persistent otitis media, and/or AOM with treatment failure, we found one study that identified a significant difference in adverse event rates. In that study, amoxicillin-clavulanate (amoxicillin 90mg/kg/day; clavulanate 6.4mg/kg/day) was associated with diarrhea more often than was ciprofloxacin-dexamethasone ear drops (NNT=5). However, in 41 other comparisons, the adverse event rates were equivalent. In 23 comparisons, a definitive conclusion was not possible. For studies that examined *prevention* of AOM in children with ROM, we did not find any significant differences in any of the adverse event rate comparisons.

## Conclusions

This section begins with a brief review of the limitations identified for this review. We then present our conclusions and recommendations for future research.

### Limitations

The conclusions that can be drawn from this review of the evidence are limited by a number of factors, some associated with specific questions and some that cross the entire body of literature.

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears.

- Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.

- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For

example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.

- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.

- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea.

- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.

## Discussion

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.<sup>12</sup> Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings. Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics



decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

While the 2001 evidence review identified only sufficient evidence to allow the assessment of the effects of age on treatment effectiveness, the current review identified information to assess the effect of laterality and otorrhea as well. The current review suggests that overall, children over the age of two years had better outcomes with various antibiotic options than children under age two and that laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to more closely monitor response to treatment and outcomes when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.

Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

## **Future Research Suggestions**

Based on the findings of this review, we provide the following suggestions for future research directions.

### **Diagnosis of AOM**

Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

### **Influence of the PCV7 Vaccine on Microbiology/Epidemiology**

Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

## **Treatment Efficacy and Adverse Effects**

Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.



## Version 5

# Executive Summary

## Introduction

Acute Otitis Media (AOM)<sup>14</sup> is a viral and/or bacterial infection of the middle ear and represents the most common childhood infection for which antibiotics are prescribed in the United States. Timely and accurate diagnosis and management of AOM can have significant individual and public health consequences.

The 2001 AHRQ evidence report on the management of AOM analyzed the evidence on the initial management of uncomplicated AOM in children, focusing on the natural history of the disease and the use of antibiotics in management. Although the 2001 report provided valuable analysis of the literature on the management of uncomplicated AOM in children, it did not address issues related to diagnostic accuracy and precision, management of AOM in specific subgroups of children, or the impact of immunization with Heptavalent Pneumococcal Conjugate Vaccine (PCV7) on the microbiology of AOM, recommended for widespread use in 2000. Additionally, new trials of treatment continue to be published. The purpose of this current AHRQ evidence report is to examine and analyze the evidence on three broad areas of inquiry: 1) accuracy and consistency of the clinical diagnosis of AOM, 2) the impact of PCV7 on AOM microbial epidemiology, and 3) the comparative effectiveness of different treatment options for uncomplicated AOM in average risk children and in children with recurrent (defined as three or more episodes in six months or four or more episodes within 12 months) or persistent AOM.

## Methods

### Key Questions

The American Academy of Pediatrics, the nominating organization, proposed six Key Questions aimed at assessing the comparative efficacy of interventions to treat uncomplicated and recurrent AOM in terms of treatment success, the safety of such treatments, and the effect on children in specific subgroups. In conjunction with a technical expert panel we refined these questions:

I. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?<sup>15</sup>

II. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?

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<sup>14</sup>A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

<sup>15</sup>Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

III. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?

IV. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?

V. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to the following: A. Laterality, i.e., unilateral vs. bilateral; B. Otorrhea or perforation; C. AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); D. Comorbidities, e.g., asthma; E. Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; F. Race; G. Ethnicity; H. Day care attendance?

VI. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ III and KQ IV?

## **Literature Searches**

Searches of PubMed and the Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center were conducted from January 1998 through July 2010 using the same search strategies used for the 2001 report, with the addition of terms for conditions not considered in the 2001 review (recurrent otitis media), new drugs, and the heptavalent vaccine. The Web of Science was also used to search for citations of the 2001 report and its peer-reviewed publications. Among the 8,945 titles identified were a number of recent, good-quality systematic reviews, which were included and which were examined for references. Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. For the efficacy and safety questions, we searched primarily for controlled trials or large observational studies aimed at identifying adverse effects.

## **Literature Review, Data Abstraction, and Analysis**

In total, the reviewers examined 8,945 titles for the draft version of this report; 739 titles were identified for further review. Of those, 72 articles that met the predetermined inclusion criteria were reviewed in detail for efficacy and safety results. Investigators abstracted data into standard evidence tables with abstraction checked by a second investigator. Studies were quality-rated by two investigators using established criteria. For randomized controlled trials (RCT), the Jadad criteria were used. QUADAS criteria were used to evaluate the studies that pertained to diagnosis. Data abstracted included parameters necessary to define study groups, inclusion/exclusion criteria, influencing factors, and outcome measures. Data for the analysis were abstracted by a biostatistician and checked by a physician reviewer. We used a sequential resolution strategy to match and resolve the screening and review results of the two reviewers.

For the assessment of treatment efficacy, pooled analysis was performed for comparisons for which three or more trials could be identified. The articles eligible for analysis for the Key Questions pertaining to treatment efficacy were grouped according to the specific treatment options they compared. Each comparison consisted of articles that were considered

homogeneous from the standpoint of clinical practice. Since the question of treatment efficacy was addressed in the first evidence report published in 2001, we combined the articles identified in that report with articles newly identified for this evidence report that addressed the same populations and reported the same types of outcomes. We pooled data for comparisons that included three or more articles from the old and new searches and performed meta-analyses or quantitative syntheses. We used the Der Simonian and Laird random effects model to pool rate differences across studies. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the  $I^2$  statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the “minimal clinically important difference (MCID)” against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a “small” effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

## Results

### **Key Question I. Diagnosis of AOM: What Are the Operating Characteristics (Sensitivity, Specificity, and Likelihood Ratios) of Clinical Symptoms and Otoscopic Findings (Such As Bulging Tympanic Membrane) to Diagnose Uncomplicated AOM and to Distinguish It from OME?**

Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE). To address this Key Question, we searched for studies that examined clinicians’ accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together. A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1]) seemed to predict a clinical diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%,

specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).<sup>1</sup>

One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.

A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had “Type B” tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).

The prior review and three additional studies that we identified for this Key Question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians’ accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Table S1 provides a summary of the findings for this Key Question.

## **Key Question II. What Has Been the Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology: What Organisms (bacterial and viral) are Associated with AOM Since the Introduction of PCV7; and What Are the Patterns of Antimicrobial Resistance in AOM Since the Introduction of PCV7?**

Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.

We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that *Haemophilus influenzae* (HF) has become more prevalent as a causative agent of AOM and *Streptococcus pneumoniae* (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.

We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.

The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine's effect on these special populations.

Table S1 provides a summary of the findings for this Key Question.

### **Key Question III. What Is the Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated AOM in Average Risk Children?**

For the comparison of treatment success for children with uncomplicated AOM, we identified 63 comparisons of treatment options for uncomplicated AOM that encompassed different antibiotics and regimens. Our analyses yielded inconclusive results for many of these comparisons. For 12 comparisons, we reached stronger conclusions. Table S1 provides a summary of the findings of this report and the original report for this Key Question.

Meta-analyses of the comparison of ampicillin or amoxicillin vs. placebo indicates that nine children (95%CI: 6, 20) with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by day 14. For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. In four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95%CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95%CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group.

Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95%CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.



Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95%CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95%CI: -4, 3) between cefaclor (7-10 days) and azithromycin ( $\leq 5$  days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.

In pooled analysis, no difference (RD=-0.3%, 95%CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95%CI: 2, 17) and higher success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95%CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate  $>60$ mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid that in the 2001 Report were assessed as demonstrating equivalent clinical success rates are now assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

#### **Key Question IV. What Is the Comparative Effectiveness of Different Management Options for Recurrent Otitis Media (Uncomplicated) and Persistent Otitis Media or Relapse of AOM?**

In approaching this question, studies were divided into those that examined treatment and those that examined prevention.

The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.

Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95%CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.

The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, cefibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Table S1 provides a summary of the findings for this Key Question.

### **Key Question V. Do Treatment Outcomes in Key Question3 (KQ3) and KQ4 Differ by Characteristics of the Condition (AOM), Patient, Environment, and/or Health Care Delivery System?**

Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media. Table S1 provides a summary of the findings of this report and the original report for this Key Question.

For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.

In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.

In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

## Key Question VI. What Adverse Effects Have Been Observed for the Treatments Whose Outcomes Are Addressed in KQ3 and KQ4?

We examined the incidence of adverse events in the RCTs identified for this report that compared the effectiveness of one or more treatment options. We also searched the FDA MedWatch Database for adverse events associated with use of medications for the treatment of AOM; however, none could be identified.

In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. However, Table S1 shows the significant differences in adverse event rates that we noted in this report and the original report. Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.

Of the 44 RCTs newly identified for this report that compared the effectiveness of treatment options in uncomplicated AOM, there are 61 treatment comparisons. Of the 61 treatment comparisons, 42 included comparisons of the percent of cases that had experienced an adverse event between two treatment options. For treatment of uncomplicated AOM, five adverse event rate comparisons showed a significant difference between two treatment options. Amoxicillin-clavulanate was associated with diarrhea more often than was cefdinir (NNT=four) and more often than was ceftriaxone (NNT= seven). The adverse event rates ranged from 27% to 35% for amoxicillin-clavulanate and from 10% to 14% for the other treatment options. For mention of any adverse event, amoxicillin-clavulanate had a higher rate than cefdinir given once or twice daily and a higher rate than ceftriaxone. However, in one study, the dose of amoxicillin was 40mg/kg/day, whereas in the other study, it was 80mg/kg/day (the clavulanate dosage was 10mg/kg/day in both studies). Equivalence was demonstrated in 29 comparisons, leaving 99 comparisons inconclusive.

These findings complement the findings from the first review, which showed that for uncomplicated AOM, children treated with amoxicillin-clavulanate for seven to ten days had a 19% (95%CI: 9, 29; NNT=5) higher rate of overall adverse effects and a 18% (95%CI: 8, 28; NNT=6) higher rate of gastrointestinal adverse effects than children treated with five days of azithromycin. (Although it was not specified in the studies, the original formulation was 31.25 mg clavulanate per 125 mg of amoxicillin). Eight children would need to be treated with azithromycin rather than amoxicillin-clavulanate to avoid a gastrointestinal adverse event. The original review also found that children treated with cefixime had an 8% (95%CI: 4, 13; NNT=12) greater rate of diarrhea than children treated with ampicillin or amoxicillin, so 12 children would need to be treated with ampicillin or amoxicillin rather than cefixime to avoid one case of diarrhea.

We also examined adverse event rates in children with presumed or explicitly defined ROM who were being given antibiotics for the treatment or prevention of AOM. Among the fourteen studies focused on children with ROM, persistent AOM, or AOM treatment failure, there were 21 treatment comparisons: eight involving the treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent AOM, and/or AOM with treatment failure and the remainder in children being given the drugs prophylactically for prevention of AOM. For *treatment* of AOM in children with ROM and/or persistent otitis media, and/or AOM with treatment failure, we found one study that identified a significant difference in adverse event rates. In that study, amoxicillin-clavulanate (amoxicillin 90mg/kg/day; clavulanate 6.4mg/kg/day) was associated with diarrhea more often than was ciprofloxacin-dexamethasone ear drops (NNT=5). However, in 41 other comparisons, the adverse event rates were equivalent.

In 23 comparisons, a definitive conclusion was not possible. For studies that examined *prevention* of AOM in children with ROM, we did not find any significant differences in any of the adverse event rate comparisons.

**Table S1. Conclusions**

Gray shaded boxes contain questions that were added for the update report or conclusions that had no counterpart in the original report. Boldface text indicates changes to the original conclusions.

<b>Key Question</b>	<b>Strength of Evidence</b>	<b>Conclusion</b>
What is the natural history of AOM?		
		About 85 percent of children with AOM who are not initial treated with antibiotics have gotten better – had resolution of pain and fever - on their own within 7 days.
		In studies with close follow-up, few episodes of mastoiditis or other suppurative complications are reported in children with AOM who are not treated initially with antibiotics
Diagnosis: What are the operating characteristics of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?		
	Low	Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE)
		Only otalgia (ear pain) and ear rubbing seemed to predict a clinical diagnosis of AOM. AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain, ear rubbing, fever)
		Individual physical exam findings (cloudy, bulging, immobile, or red TM) were positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms
		Comparing the accuracy of otoscopic and tympanometric findings with that of tympanocentesis as the criterion standard to determine the presence of MEE, 97 percent of children with MEE on tympanocentesis had “Type B” tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM.
		Of cases of AOM diagnosed as or assumed to be AOM by general practitioners, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not (because the otolaryngologist diagnosed OME, viral otitis, or a normal TM). ENT-confirmed diagnoses were associated with both redness and bulging, vs. only redness.
		The studies suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms.
What Has Been the Impact of Pneumococcal Heptavalent Immunization on AOM Microbial Epidemiology?		
What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?	High	PCV7 is associated with an increased prevalence of Haemophilus influenzae as a causative agent of AOM and decreasing prevalence of Streptococcus pneumoniae (SP), although SP remains an important agent. The vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes.
What is the evidence for subpopulations of children	Very low	No studies analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in

Key Question	Strength of Evidence	Conclusion
according to prior antibiotic use?		the past
What are the effects of Antibiotics on AOM?		
What is the effect of the delayed treatment or wait-and-see approach compared with immediate antibiotic treatment?	Moderate	Comparing ampicillin or amoxicillin vs. placebo, immediate antibiotic therapy had higher clinical success than prescription-to-hold and wait-and-see in 2 studies; 2 studies demonstrated no difference in clinical success between immediate and delayed antibiotics; and 3 showed a marked decrease in antibiotic utilization in the delayed antibiotic group.
		<b>Compared with observational intervention without antibiotics, antibiotics have minimal to modest benefits during the initial treatment of AOM</b> for pain and fever resolution at 2 days, pain resolution at 2 to 7 days, contralateral otitis media, and clinical resolution at 7- to14-days. Antibiotic use did not affect tympanic membrane perforation, vomiting/diarrhea/rash, 1-month tympanometry, or recurrent AOM compared with delayed treatment.
Relative Effects of Different Antibiotic Regimens		
	Moderate	No difference in treatment success was seen with ampicillin or amoxicillin vs. ceftriaxone by day 14, although this finding was inconclusive utilizing an MCID of 5%
		No difference in failure rates was seen between ampicillin or amoxicillin and penicillin or cefixime
	Low	No difference was seen in clinical success rates between amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, or amoxicillin-clavulanate vs. amoxicillin-sulbactam
	Moderate	<b>No difference</b> was seen between amoxicillin-clavulanate and azithromycin in clinical success at day 14 (although this finding was inconclusive utilizing an MCID of 5%).
	Moderate	Amoxicillin-clavulanate (10 days) had <b>higher success rates</b> than cefaclor by day 34 when success was defined by clinical symptoms
		No difference was seen in clinical failure rates between trimethoprim-sulfamethoxazole and cefaclor
		No conclusions can be drawn on the effect of oral fluoroquinolones compared with other antibiotics because no comparative randomized controlled trials were found that addressed this question
High vs. low dose	Low	No difference was seen in clinical effect between high-dose amoxicillin-clavulanate and standard-dose amoxicillin-clavulanate or between <b>cefaclor 50 mg/kg/day and 40 mg/kg/day</b>
Bid vs. tid	Low	No difference was seen between high-dose amoxicillin two times a day vs. three times a day or between <b>amoxicillin-clavulanate 45/64/mg/kg/day</b> divided into two daily doses vs. <b>amoxicillin-clavulanate 40/10/mg/kg/day</b> divided into three daily doses
Longer term vs. shorter term treatment	High	Cefaclor (7-10 days) was equivalent to azithromycin ( $\leq 5$ days) in rate of clinical success at day-14
	Low	Amoxicillin-clavulanate (for 10 days) was shown to have <b>higher clinical success rates</b> than azithromycin (single dose, one day) by day 14 when the pathogen was HF
	Moderate	Ceftriaxone (short-duration single-dose) therapy was similar to amoxicillin-clavulanate (long-duration 7 to 10 day) therapy in clinical effect <b>at day 16</b>
		A short-acting oral antibiotic therapy of less than 2 days was not as effective as therapy lasting 7 days or longer
What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM		
Treatment	Low	No difference in effectiveness was seen for amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-

Key Question	Strength of Evidence	Conclusion
		clavulanate vs. azithromycin
Prevention	Low	Long-term antibiotics ( $\geq 6$ weeks) decreased episodes of AOM from 3 to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However nothing is known about the safety of long-term antibiotic administration and the potential consequences on bacterial resistance
Prevention	Low	Tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM
Prevention	Low	The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, cefitibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM
Do treatment outcomes for uncomplicated or recurrent AOM differ by characteristics of the condition, patient, environment, and/or health care delivery system, including but not limited to laterality; otorrhea or perforation; AOM severity; comorbidities; age groups,; race; ethnicity; day care attendance?		
		Antibiotic effects may be modified by age, laterality, and otorrhea
		Children over the age of 2 have better outcomes from AOM than children 2 years of age or younger, regardless of whether they are treated with antibiotics or not.
		No differences were seen in treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin
		Children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease
		Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner
		The effect of antibiotics (compared with placebo) was greater in children with otorrhea than in those without otorrhea.
What adverse effects have been observed for the treatments whose outcomes are addressed above?		
		Overall adverse events: amoxicillin-clavulanate was associated with a greater overall adverse event rate than azithromycin, <b>cefdinir</b> (qd and bid), and <b>ceftriaxone</b> . Gastrointestinal events: amoxicillin-clavulanate was associated with a greater rate than azithromycin.
		Diarrhea: Children treated with cefixime had an 8.4 percent greater rate of diarrhea than children treated with ampicillin or amoxicillin. <b>In children with uncomplicated AOM, amoxicillin-clavulanate was associated with a 22 percent-25 percent greater rate of diarrhea than cefdinir and a 13 percent greater rate than ceftriaxone.</b>

# Conclusions

This section begins with a brief review of the limitations identified for this review. We then present our conclusions and recommendations for future research.

## Limitations

The conclusions that can be drawn from this review of the evidence are limited by a number of factors, some associated with specific questions and some that cross the entire body of literature.

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears.

- Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.

- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.

- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.

- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea.

- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.

## Discussion

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.<sup>12</sup> Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings. Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

While the 2001 evidence review identified only sufficient evidence to allow the assessment of the effects of age on treatment effectiveness, the current review identified information to assess the effect of laterality and otorrhea as well. The current review suggests that overall, children over the age of two years had better outcomes with various antibiotic options than children under age two and that laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to more closely monitor response to treatment and outcomes when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.



Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

## **Future Research Suggestions**

Based on the findings of this review, we provide the following suggestions for future research directions.

### **Diagnosis of AOM**

Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

### **Influence of the PCV7 Vaccine on Microbiology/Epidemiology**

Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

### **Treatment Efficacy and Adverse Effects**

Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of

these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.

## Version 6 (“New” Version 3) Used for Focus Group 2 and Community

### Physicians

## Executive Summary

### Introduction

Acute Otitis Media (AOM)<sup>16</sup> is a viral and/or bacterial infection of the middle ear and represents the most common childhood infection for which antibiotics are prescribed in the United States. Timely and accurate diagnosis and management of AOM can have significant individual and public health consequences.

The 2001 AHRQ evidence report on the management of AOM analyzed the evidence on the initial management of uncomplicated AOM in children, focusing on the natural history of the disease and the use of antibiotics in management. Although the 2001 report provided valuable analysis of the literature on the management of uncomplicated AOM in children, it did not address issues related to diagnostic accuracy and precision, management of AOM in specific subgroups of children, or the impact of immunization with Heptavalent Pneumococcal Conjugate Vaccine (PCV7) on the microbiology of AOM, recommended for widespread use in 2000. Additionally, new trials of treatment continue to be published. The purpose of this current AHRQ evidence report is to examine and analyze the evidence on three broad areas of inquiry: 1) accuracy and consistency of the clinical diagnosis of AOM, 2) the impact of PCV7 on AOM microbial epidemiology, and 3) the comparative effectiveness of different treatment options for uncomplicated AOM in average risk children and in children with recurrent (defined as three or more episodes in six months or four or more episodes within 12 months) or persistent AOM.

### Methods

#### Key Questions

The American Academy of Pediatrics, the nominating organization, proposed six Key Questions aimed at assessing the comparative efficacy of interventions to treat uncomplicated and recurrent AOM in terms of treatment success, the safety of such treatments, and the effect on children in specific subgroups. In conjunction with a technical expert panel we refined these questions:

I. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?<sup>17</sup>

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<sup>16</sup>A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

<sup>17</sup>Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

II. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?

III. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?

IV. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?

V. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to the following: A. Laterality, i.e., unilateral vs. bilateral; B. Otorrhea or perforation; C. AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); D. Comorbidities, e.g., asthma; E. Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; F. Race; G. Ethnicity; H. Day care attendance?

VI. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ III and KQ IV?

## **Literature Searches**

Searches of PubMed and the Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center were conducted from January 1998 through July 2010 using the same search strategies used for the 2001 report, with the addition of terms for conditions not considered in the 2001 review (recurrent otitis media), new drugs, and the heptavalent vaccine. The Web of Science was also used to search for citations of the 2001 report and its peer-reviewed publications. Among the 8,945 titles identified were a number of recent, good-quality systematic reviews, which were included and which were examined for references. Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. For the efficacy and safety questions, we searched primarily for controlled trials or large observational studies aimed at identifying adverse effects.

## **Literature Review, Data Abstraction, and Analysis**

In total, the reviewers examined 8,945 titles for the draft version of this report; 739 titles were identified for further review. Of those, 72 articles that met the predetermined inclusion criteria were reviewed in detail for efficacy and safety results. Investigators abstracted data into standard evidence tables with abstraction checked by a second investigator. Studies were quality-rated by two investigators using established criteria. For randomized controlled trials (RCT), the Jadad criteria were used. QUADAS criteria were used to evaluate the studies that pertained to diagnosis. Data abstracted included parameters necessary to define study groups, inclusion/exclusion criteria, influencing factors, and outcome measures. Data for the analysis were abstracted by a biostatistician and checked by a physician reviewer. We used a sequential resolution strategy to match and resolve the screening and review results of the two reviewers.

For the assessment of treatment efficacy, pooled analysis was performed for comparisons for which three or more trials could be identified. The articles eligible for analysis for the Key Questions pertaining to treatment efficacy were grouped according to the specific treatment options they compared. Each comparison consisted of articles that were considered homogeneous from the standpoint of clinical practice. Since the question of treatment efficacy was addressed in the first evidence report published in 2001, we combined the articles identified in that report with articles newly identified for this evidence report that addressed the same populations and reported the same types of outcomes. We pooled data for comparisons that included three or more articles from the old and new searches and performed meta-analyses or quantitative syntheses. We used the Der Simonian and Laird random effects model to pool rate differences across studies. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the  $I^2$  statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the “minimal clinically important difference (MCID)” against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a “small” effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

## Results

Table S-3 presents the conclusions of the original report and this report.

### **Key Question I. Diagnosis of AOM: What Are the Operating Characteristics (Sensitivity, Specificity, and Likelihood Ratios) of Clinical Symptoms and Otoscopic Findings (Such As Bulging Tympanic Membrane) to Diagnose Uncomplicated AOM and to Distinguish It from OME?**

Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE). To address this Key Question, we searched for studies that examined clinicians’ accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together. A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear

rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1] seemed to predict a clinical diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).<sup>1</sup>

One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.

A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had “Type B” tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).

The prior review and three additional studies that we identified for this Key Question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians’ accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

## **Key Question II. What Has Been the Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology: What Organisms (bacterial and viral) are Associated with AOM Since the Introduction of PCV7; and What Are the Patterns of Antimicrobial Resistance in AOM Since the Introduction of PCV7?**

Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship

between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.

We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that *Haemophilus influenzae* (HF) has become more prevalent as a causative agent of AOM and *Streptococcus pneumoniae* (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.

We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.

The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine’s effect on these special populations.

### Key Question III. What Is the Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated AOM in Average Risk Children?

For the comparison of treatment success for children with uncomplicated AOM, we identified 63 comparisons of treatment options for uncomplicated AOM that encompassed different antibiotics and regimens. Our analyses yielded inconclusive results for many of these comparisons. For 12 comparisons, we reached stronger conclusions. Table S-1 shows key comparisons from the first AOM report, the present report, and where possible, combined results.

**Table S-1. Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media (AOM) in Average Risk Children in the 2001 Report and the Present Report**

Comparison	2001 Report		2010 Update			Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
<b>Drug vs. placebo, wait-and-see, and/or prescription-to-hold</b>						
Ampicillin or amoxicillin vs. placebo	5	12% (3%, 22%)	2	7	12%(5%, 18%)	Ampicillin or amoxicillin was more successful than placebo
Amoxicillin tid (7d vs. prescription-to-hold) <sup>2</sup>	0	N/A	1	1	16% (6, 26)	Amoxicillin was more successful than prescription-to-hold (defined as success at day 3)
Antibiotic vs. prescription-to-	0	N/A	1	1	3% (-8, 14)	Inconclusive (defined as otalgia)

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)		Total number of trials	Success rate difference	
hold) <sup>2</sup>						at day 4-6)
Amoxicillin 90mg/kg/d bid (10d) vs. wait-and-see <sup>3</sup>	0	N/A	1	1	15% (6, 24)	Amoxicillin was more successful (defined as success at day 12)
PcV vs. wait-and-see <sup>3</sup>	0	N/A	1	1	-3% (-14, 8)	Inconclusive (defined as success at day 14)
<b>Drug vs. drug</b>						
Ampicillin or amoxicillin vs. Ceftriaxone	3	3% (-2%, 9%)	1	4	0.1% (-7%, 7%)	Inconclusive
Amoxicillin 50mg/kg/d (bid, 10d) vs. erythromycin 40mg/kg/d (bid, 10d) <sup>4</sup>	0	N/A	1	1	0.6% (-3, 4)	Treatments were equivalent (when success defined as freedom from recurrence day 31-40)
Amoxicillin-clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d)	0	N/A	1	1	0% (-3.3, 3.3)	Treatments were equivalent (success d.12-14)
Amoxicillin-clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d) <sup>5</sup>	0	N/A	1	1	13% (5, 21)	Amoxicillin-clavulanate was more effective than cefaclor (success at day 28-34, as defined by clinical symptoms but not by culture)
Cefaclor vs. trimethoprim-sulfamethoxazole	3	-6% (-13, 2) (success at less than 14 d)	0	3	N/A	Inconclusive (defined as success at less than day 14); no new data but using MCID
Cefaclor vs. Ampicillin or amoxicillin	4	-5% (-15, 6) (success at d. 3-7)	0	4	N/A	Inconclusive (defined as success at day 3-7); no new data; no new data but using MCID
Cefixime vs.	4	0.1% (-3.9,	0	4	N/A	Treatments were



Comparison	2001 Report		Number of new trials	2010 Update		Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)		Total number of trials	Success rate difference	
Ampicillin or amoxicillin		4.2) (success at d. 10-15)				equivalent; no new data
Penicillin vs. ampicillin or amoxicillin	3	-5% (-11, 2) (success at d. 7-14)	0	3	N/A	Inconclusive (defined as success at day 7-14); no new data but using MCID
<b>High vs. Low Dose Treatment</b>						
Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d	1	1.5% (-3, 13)	0	1	N/A	Inconclusive(defined as persistent clinical cure with no recurrence at follow-up); no new data
High-dose amoxicillin bid vs. lower-dose amoxicillin tid	1	-4% (-14, 7)	0	1	N/A	Inconclusive (defined as success at day 15); no new data
Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days <sup>6</sup>	0	N/A	1	1	0.1% (-4.8, 4.6)	Treatments were equivalent (success d. 7-12)
<b>Short vs. Long Treatment Duration<sup>b</sup></b>						
Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)	3	3% (-2%, 9%) (success rate at 5-10d)	1	4	0% (-7%, 7%)	Inconclusive
Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)	2	N/A	3	5	3% (-2%, 7%)	Inconclusive
Cefaclor (7-10d) vs. Azithromycin (<5d)	1	N/A	2	3	-1% (-4%, 3%)	Treatments were equivalent
Amoxicillin (7d) vs. Azithromycin (1 dose)	0	N/A	1	1	1% (-1%, 4%)	Treatments were equivalent (defined as no new pain between day 6 and

Comparison	2001 Report		2010 Update			Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (≤5d)	5	2% (1, 5%) (success at 10-14d)	4	9	-0.3% (-6%, 6%)	Inconclusive
Amoxicillin-clavulanate 45/6.4 mg/kg/d (bid, 10d) vs. azithromycin 10 mg/kg/d (qd for 1 day), 5 mg/kg/d (qd for 4d) <sup>7</sup>	0	N/A	1	1	26% (6,36)	Longer-term amoxicillin-clavulanate is more successful than shorter-term azithromycin (at d. 12-14, when pathogen is H. influenzae)
Cefaclor 50mg/kg/d; bid 5 d) vs. cefaclor 40mg/kg/d; bid 10d)	0	N/A	1	1	0.7% (-3.5-4.9)	Treatments were equivalent

Table Notes: bid twice a day; CI confidence intervals; d day(s); kg kilograms (body weight); mg milligrams; NNT number needed to treat; PcV phenoxymethylpenicillin; qd once a day;

<sup>a</sup> Confidence intervals falling within the zone of indifference were considered to establish evidence of *no difference*, and confidence intervals outside the zone of indifference were considered to *establish difference*. If the confidence intervals crossed into the zone of indifference, an effect (positive or negative) of the treatment option on the outcome could not be established (*inconclusive*). For the 2010 systematic review, we used a *zone of clinical indifference of +/- 5%* for the difference in success rate between two treatment options.

<sup>b</sup>Short vs. long term duration refers to the length of treatment from the patient perspective, rather than from the perspective of drug action.

Meta-analyses of the comparison of ampicillin or amoxicillin vs. placebo indicates that nine children (95%CI: 6, 20) with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by day 14. For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. In four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95%CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95%CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group.

Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95%CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95%CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95%CI: -4, 3) between cefaclor (7-10 days) and azithromycin ( $\leq 5$  days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.

In pooled analysis, no difference (RD=-0.3%, 95%CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95%CI: 2, 17) and higher success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95%CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin, cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses. In addition, individual studies of amoxicillin-clavulanate  $>60$ mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid that in the 2001 Report were assessed as demonstrating equivalent clinical success rates are now assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

#### **Key Question IV. What Is the Comparative Effectiveness of Different Management Options for Recurrent Otitis Media (Uncomplicated) and Persistent Otitis Media or Relapse of AOM?**

In approaching this question, studies were divided into those that examined treatment and those that examined prevention.

The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of

evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.

Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95% CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.

The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### **Key Question V. Do Treatment Outcomes in Key Question3 (KQ3) and KQ4 Differ by Characteristics of the Condition (AOM), Patient, Environment, and/or Health Care Delivery System?**

Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.

For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.

In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.

In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

### Key Question VI. What Adverse Effects Have Been Observed for the Treatments Whose Outcomes Are Addressed in KQ3 and KQ4?

We examined the incidence of adverse events in the RCTs identified for this report that compared the effectiveness of one or more treatment options. We also searched the FDA MedWatch Database for adverse events associated with use of medications for the treatment of AOM; however, none could be identified.

In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. However, Table S-2 shows the significant differences in adverse event rates that we noted (Table S-2 also shows the comparisons for the original report, those unique to the present report, and those that could be combined across both reports). Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.

**Table S-2 Comparison of Rates of Adverse Events Between Drugs (Significant Differences Only)**

Comparison	2001 Report		2010 Update			Conclusion
	Number of trials	AE rate Difference (95% CI)	Number of new trials	Total number of trials	AE rate difference (95% CI)	
<b>Uncomplicated AOM</b>						
<b>Overall Adverse Events</b>						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	19%( 9%, 29%)	0	3	N/A	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (qd)	0	N/A	1	1	28% (17%, 39%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (bid)	0	N/A	1	1	19% (8%, 31%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. ceftriaxone	0	N/A	1	1	16% (9%, 24%)	Amoxicillin-clavulanate associated with greater overall AE rate
<b>Gastrointestinal Adverse Events</b>						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	18% (8%, 28%)	0	0	N/A	Amoxicillin-clavulanate associated with greater rate of GI AE

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion
	Number of trials	AE rate Difference (95% CI)		Total number of trials	AE rate difference (95% CI)	
<b>Diarrhea</b>						
Ampicillin or amoxicillin vs. cefixime	5	-8% (-13, -4)	0	0	N/A	Cefixime associated with greater rate of diarrhea
Amoxicillin clavulanate vs. cefdinir	0		1	1	25% (15%, 35%) in Cef QD and 22% (11%, 32%) in Cef BID	Amoxicillin clavulanate associated with greater rate of diarrhea
Amoxicillin clavulanate vs. ceftriaxone	0		1	1	13% (6%, 20%)	Amoxicillin clavulanate associated with greater rate of diarrhea
<b>Recurrent Otitis Media</b>						
<b>Diarrhea</b>						
Amoxicillin-clavulanate vs. ciprofloxacin-dexamethasone ear drops	0	N/A				Greater for amoxicillin-clavulanate in 1 study, but equivalent in 41; no conclusion possible in 23 comparisons

Table notes: AE adverse event; bid twice a day; CI confidence interval; d day; NNT number needed to treat; qd once a day

Of the 44 RCTs newly identified for this report that compared the effectiveness of treatment options in uncomplicated AOM, there are 61 treatment comparisons. Of the 61 treatment comparisons, 42 included comparisons of the percent of cases that had experienced an adverse event between two treatment options. For treatment of uncomplicated AOM, five adverse event rate comparisons showed a significant difference between two treatment options. Amoxicillin-clavulanate was associated with diarrhea more often than was cefdinir (NNT=four) and more often than was ceftriaxone (NNT= seven). The adverse event rates ranged from 27% to 35% for amoxicillin-clavulanate and from 10% to 14% for the other treatment options. For mention of any adverse event, amoxicillin-clavulanate had a higher rate than cefdinir given once or twice daily and a higher rate than ceftriaxone. However, in one study, the dose of amoxicillin was 40mg/kg/day, whereas in the other study, it was 80mg/kg/day (the clavulanate dosage was 10mg/kg/day in both studies). Equivalence was demonstrated in 29 comparisons, leaving 99 comparisons inconclusive.

These findings complement the findings from the first review, which showed that for uncomplicated AOM, children treated with amoxicillin-clavulanate for seven to ten days had a 19% (95%CI: 9, 29; NNT=5) higher rate of overall adverse effects and a 18% (95%CI: 8, 28; NNT=6) higher rate of gastrointestinal adverse effects than children treated with five days of azithromycin. (Although it was not specified in the studies, the original formulation was 31.25

mg clavulanate per 125 mg of amoxicillin). Eight children would need to be treated with azithromycin rather than amoxicillin-clavulanate to avoid a gastrointestinal adverse event. The original review also found that children treated with cefixime had an 8% (95%CI: 4, 13; NNT=12) greater rate of diarrhea than children treated with ampicillin or amoxicillin, so 12 children would need to be treated with ampicillin or amoxicillin rather than cefixime to avoid one case of diarrhea.

We also examined adverse event rates in children with presumed or explicitly defined ROM who were being given antibiotics for the treatment or prevention of AOM. Among the fourteen studies focused on children with ROM, persistent AOM, or AOM treatment failure, there were 21 treatment comparisons: eight involving the treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent AOM, and/or AOM with treatment failure and the remainder in children being given the drugs prophylactically for prevention of AOM. For *treatment* of AOM in children with ROM and/or persistent otitis media, and/or AOM with treatment failure, we found one study that identified a significant difference in adverse event rates. In that study, amoxicillin-clavulanate (amoxicillin 90mg/kg/day; clavulanate 6.4mg/kg/day) was associated with diarrhea more often than was ciprofloxacin-dexamethasone ear drops (NNT=5). However, in 41 other comparisons, the adverse event rates were equivalent. In 23 comparisons, a definitive conclusion was not possible. For studies that examined *prevention* of AOM in children with ROM, we did not find any significant differences in any of the adverse event rate comparisons.

## Conclusions

This section begins with a brief review of the limitations identified for this review. We then present our conclusions and recommendations for future research.

### Limitations

The conclusions that can be drawn from this review of the evidence are limited by a number of factors, some associated with specific questions and some that cross the entire body of literature.

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears.

- Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.

- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For

example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.

- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.

- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea.

- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.

## Discussion

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.<sup>12</sup> Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings. Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone



child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

While the 2001 evidence review identified only sufficient evidence to allow the assessment of the effects of age on treatment effectiveness, the current review identified information to assess the effect of laterality and otorrhea as well. The current review suggests that overall, children over the age of two years had better outcomes with various antibiotic options than children under age two and that laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to more closely monitor response to treatment and outcomes when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.

Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

## **Future Research Suggestions**

Based on the findings of this review, we provide the following suggestions for future research directions.

### **Diagnosis of AOM**

Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

### **Influence of the PCV7 Vaccine on Microbiology/Epidemiology**

Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further

research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

### **Treatment Efficacy and Adverse Effects**

Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.

**Table S3. Conclusions**

Gray shaded boxes contain questions that were added for the update report or conclusions that had no counterpart in the original report. Boldface text indicates changes to the original conclusions.

Key Question	Strength of Evidence	Conclusion
What is the natural history of AOM?		
		About 85 percent of children with AOM who are not initial treated with antibiotics have gotten better – had resolution of pain and fever - on their own within 7 days.
		In studies with close follow-up, few episodes of mastoiditis or other suppurative complications are reported in children with AOM who are not treated initially with antibiotics
Diagnosis: What are the operating characteristics of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?		
	Low	Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE)
		Only otalgia (ear pain) and ear rubbing seemed to predict a clinical diagnosis of AOM. AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain, ear rubbing, fever)
		Individual physical exam findings (cloudy, bulging, immobile, or red TM) were positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms
		Comparing the accuracy of otoscopic and tympanometric findings with that of tympanocentesis as the criterion standard to determine the presence of MEE, 97 percent of children with MEE on tympanocentesis had “Type B” tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM.
		Of cases of AOM diagnosed as or assumed to be AOM by general practitioners, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not (because the otolaryngologist diagnosed OME, viral otitis, or a normal TM). ENT-confirmed diagnoses were associated with both redness and bulging, vs. only redness.
		The studies suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms.
What Has Been the Impact of Pneumococcal Heptavalent Immunization on AOM Microbial Epidemiology?		
What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?	High	PCV7 is associated with an increased prevalence of Haemophilus influenzae as a causative agent of AOM and decreasing prevalence of Streptococcus pneumoniae (SP), although SP remains an important agent. The vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes.
What is the evidence for subpopulations of children according to prior antibiotic use?	Very low	No studies analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past
What are the effects of Antibiotics on AOM?		

Key Question	Strength of Evidence	Conclusion
What is the effect of the delayed treatment or wait-and-see approach compared with immediate antibiotic treatment?	Moderate	Comparing ampicillin or amoxicillin vs. placebo, immediate antibiotic therapy had higher clinical success than prescription-to-hold and wait-and-see in 2 studies; 2 studies demonstrated no difference in clinical success between immediate and delayed antibiotics; and 3 showed a marked decrease in antibiotic utilization in the delayed antibiotic group.
		<b>Compared with observational intervention without antibiotics, antibiotics have minimal to modest benefits during the initial treatment of AOM</b> for pain and fever resolution at 2 days, pain resolution at 2 to 7 days, contralateral otitis media, and clinical resolution at 7- to 14-days. Antibiotic use did not affect tympanic membrane perforation, vomiting/diarrhea/rash, 1-month tympanometry, or recurrent AOM compared with delayed treatment.
Relative Effects of Different Antibiotic Regimens		
	Moderate	No difference in treatment success was seen with ampicillin or amoxicillin vs. ceftriaxone by day 14, although this finding was inconclusive utilizing an MCID of 5%
		No difference in failure rates was seen between ampicillin or amoxicillin and penicillin or cefixime
	Low	No difference was seen in clinical success rates between amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, or amoxicillin-clavulanate vs. amoxicillin-sulbactam
	Moderate	<b>No difference</b> was seen between amoxicillin-clavulanate and azithromycin in clinical success at day 14 (although this finding was inconclusive utilizing an MCID of 5%).
	Moderate	Amoxicillin-clavulanate (10 days) had <b>higher success rates</b> than cefaclor by day 34 when success was defined by clinical symptoms
		No difference was seen in clinical failure rates between trimethoprim-sulfamethoxazole and cefaclor
		No conclusions can be drawn on the effect of oral fluoroquinolones compared with other antibiotics because no comparative randomized controlled trials were found that addressed this question
High vs. low dose	Low	No difference was seen in clinical effect between high-dose amoxicillin-clavulanate and standard-dose amoxicillin-clavulanate or between <b>cefaclor 50 mg/kg/day and 40 mg/kg/day</b>
Bid vs. tid	Low	No difference was seen between high-dose amoxicillin two times a day vs. three times a day or between <b>amoxicillin-clavulanate 45/64/mg/kg/day</b> divided into two daily doses vs. <b>amoxicillin-clavulanate 40/10/mg/kg/day</b> divided into three daily doses
Longer term vs. shorter term treatment	High	Cefaclor (7-10 days) was equivalent to azithromycin ( $\leq 5$ days) in rate of clinical success at day-14
	Low	Amoxicillin-clavulanate (for 10 days) was shown to have <b>higher clinical success rates</b> than azithromycin (single dose, one day) by day 14 when the pathogen was HF
	Moderate	Ceftriaxone (short-duration single-dose) therapy was similar to amoxicillin-clavulanate (long-duration 7 to 10 day) therapy in clinical effect <b>at day 16</b>
		A short-acting oral antibiotic therapy of less than 2 days was not as effective as therapy lasting 7 days or longer
What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM		
Treatment	Low	No difference in effectiveness was seen for amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin
Prevention	Low	Long-term antibiotics ( $\geq 6$ weeks) decreased episodes of AOM from 3 to 1.5 for every 12 months of treatment per otitis-prone child during

Key Question	Strength of Evidence	Conclusion
		active treatment. However nothing is known about the safety of long-term antibiotic administration and the potential consequences on bacterial resistance
Prevention	Low	Tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM
Prevention	Low	The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, cefbuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM
Do treatment outcomes for uncomplicated or recurrent AOM differ by characteristics of the condition, patient, environment, and/or health care delivery system, including but not limited to laterality; otorrhea or perforation; AOM severity; comorbidities; age groups,; race; ethnicity; day care attendance?		
		Antibiotic effects may be modified by age, laterality, and otorrhea
		Children over the age of 2 have better outcomes from AOM than children 2 years of age or younger, regardless of whether they are treated with antibiotics or not.
		No differences were seen in treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin
		Children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease
		Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner
		The effect of antibiotics (compared with placebo) was greater in children with otorrhea than in those without otorrhea.
What adverse effects have been observed for the treatments whose outcomes are addressed above?		
		Overall adverse events: amoxicillin-clavulanate was associated with a greater overall adverse event rate than azithromycin, <b>cefdinir</b> (qd and bid), and <b>ceftriaxone</b> . Gastrointestinal events: amoxicillin-clavulanate was associated with a greater rate than azithromycin.
		Diarrhea: Children treated with cefixime had an 8.4 percent greater rate of diarrhea than children treated with ampicillin or amoxicillin. <b>In children with uncomplicated AOM, amoxicillin-clavulanate was associated with a 22 percent-25 percent greater rate of diarrhea than cefdinir and a 13 percent greater rate than ceftriaxone.</b>

## Version 7 (“New” Version 4) Used for Focus Group 2 and Community

### Physicians

#### Executive Summary

Acute Otitis Media (AOM)<sup>18</sup> is a viral and/or bacterial infection of the middle ear and represents the most common childhood infection for which antibiotics are prescribed in the United States. Timely and accurate diagnosis and management of AOM can have significant individual and public health consequences.

The purpose of this current AHRQ evidence report is to update the 2001 evidence review on this topic by examining and analyzing the evidence on three broad areas of inquiry:

- 1) accuracy and consistency of the clinical diagnosis of AOM,
- 2) the impact of PCV7 on AOM microbial epidemiology, and
- 3) the comparative effectiveness and safety of different treatment options for uncomplicated AOM in average risk children and in children with recurrent (defined as three or more episodes in six months or four or more episodes within 12 months) or persistent AOM.

**Table S-1. Scope of the Report and Definitions**

<b>Disease Entity</b>	Uncomplicated AOM, including recurrent and persistent AOM <sup>19</sup>
<b>Patient Population</b>	Age 4 weeks to 18 years Exclude: patients with immunodeficiencies and craniofacial deficiencies including cleft palate
<b>Settings</b>	All types of providers and practice settings
<b>Interventions<sup>20</sup></b>	“Wait and see” approach/placebo

<sup>18</sup>A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

<sup>19</sup>Definition of AOM: A diagnosis of AOM requires (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation.

Elements of the definition of AOM are all of the following:

1. Recent, usually abrupt, onset of signs and symptoms of middle-ear inflammation and MEE
2. The presence of MEE that is indicated by any of the following:
  - a. Bulging of the tympanic membrane
  - b. Limited or absent mobility of the tympanic membrane
  - c. Air-fluid level behind the tympanic membrane
  - d. Otorrhea
3. Signs or symptoms of middle-ear inflammation as indicated by either
  - a. Distinct erythema of the tympanic membrane or
  - b. Distinct otalgia (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep)

Definition of Recurrent AOM (RAOM): A diagnosis of RAOM requires three or more episodes of acute otitis media within 6 months or four episodes within 12 months, including at least 1 episode during the preceding 6 months.

*Definition of Persistent Otitis Media: Persistent otitis media is manifested by persistence during antimicrobial therapy of symptoms and signs of middle ear infection (treatment failure) and/or relapse of acute otitis media within 1 month of completion of antibiotic therapy. When two episodes of otitis media occur within 1 month, it may be difficult to distinguish recurrence of acute otitis media (i.e. a new episode) from persistent otitis media (i.e. relapse).*

<sup>20</sup>Antibiotics and other treatment modalities are considered individually for questions 3-6 on treatment outcomes;

	Antibiotic treatment (all classes, schedule, dosage, length, and mode)
	Delayed antibiotic
	Analgesics/other non-antibiotic medical therapies/surgery (including PE tubes)
<b>Influencing factors</b>	Age
	Race/ethnicity
	Laterality
	Otorrhea or perforation
	AOM severity
	Signs and physical symptoms (ear pulling, otorrhea, irritability, fever, tympanic membrane (TM) inflammation, retracted TM, middle ear effusion [MEE])
	Comorbidities (e.g., asthma)
	Day care attendance
	Environmental factors
	Practitioner
	Setting
	Parent/caretaker
	Examiner
	Recurrent OM/otitis prone
	Persistent/relapse OM (continued on next page)
	Diagnostic mode (otoscopy; tympanocentesis; pneumatic otoscopy/ tympanometry; acoustic reflectometry)
<b>Outcome measures</b>	Treatment failure
	Duration of symptoms or illness
	Presence of MEE by otoscopic findings (Bulging, cloudy, erythematous TM; air fluid level behind TM; Loss of landmarks; otorrhea)
	Presence of MEE by Pneumatic otoscopy/tympanometry (Limited or absent mobility of TM)
	Presence of MEE by acoustic reflectometry (presence of MEF)
	Presence of MEE by tympanocentesis
	Signs and symptoms of middle ear inflammation (MEI) by symptoms (otalgia, ear ness)
	Signs or symptoms of MEI by otoscopy (distinct TM erythema)
	Other symptoms (decreased hearing, fever)
	Invasive infections
	Bacteriological cure/failure
	Disease recurrence
	Adverse effects of treatment (e.g., diarrhea, vomiting, bacterial resistance) and method of assessment
	Quality of life or functional outcome
	Parental satisfaction
	Cost of outcomes, e.g., Days school/daycare missed
	Bacteriologic outcomes by nasopharyngeal Cultures
	Otologic complications- i.e., cholesteatoma
	PE tube placement
	Health care utilization
	Microbial epidemiology and antibiotic resistance <sup>21</sup>
<b>Time Period</b>	1998-2010 <sup>22</sup>
<b>Literature Sources</b>	Medline
	Web of Science
	Cochrane Database of Systematic Reviews
	Proceedings of International Society of Otolaryngology
	References
<b>Languages</b>	No restriction
<b>Study Design</b>	Randomized controlled trials, blinded and unblinded
	Non-randomized controlled trials, blinded and unblinded

<sup>21</sup>These outcomes are considered only for question 2 on PNC7 vaccine.

<sup>22</sup>Search for articles on recurrent and persistent AOM spanned 1966-2010

	Prospective and retrospective observational studies <sup>23</sup>
	Case-control studies <sup>6</sup>

**Table S-2. Search Criteria**

Key Question	Databases	Article Types	Timeframe	# Studies Reviewed	# Studies Included
1	PubMed, Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center	MAs, SRs, RCTs, large observational studies with measures of sensitivity/specificity	January 1998 through July 2010	14	6
2		MAs, SRs, RCTs, large observational studies that compared microbiology in the same populations before and after introduction of the or across vaccinated and unvaccinated populations		69	8
3		MAs, SRs, RCTs		123	58
4		MAs, SRs, RCTs			
5		MAs, SRs, RCTs, and large observational studies that assessed populations of interest			
6					

<sup>23</sup>Where RCTs unavailable to answer a particular question



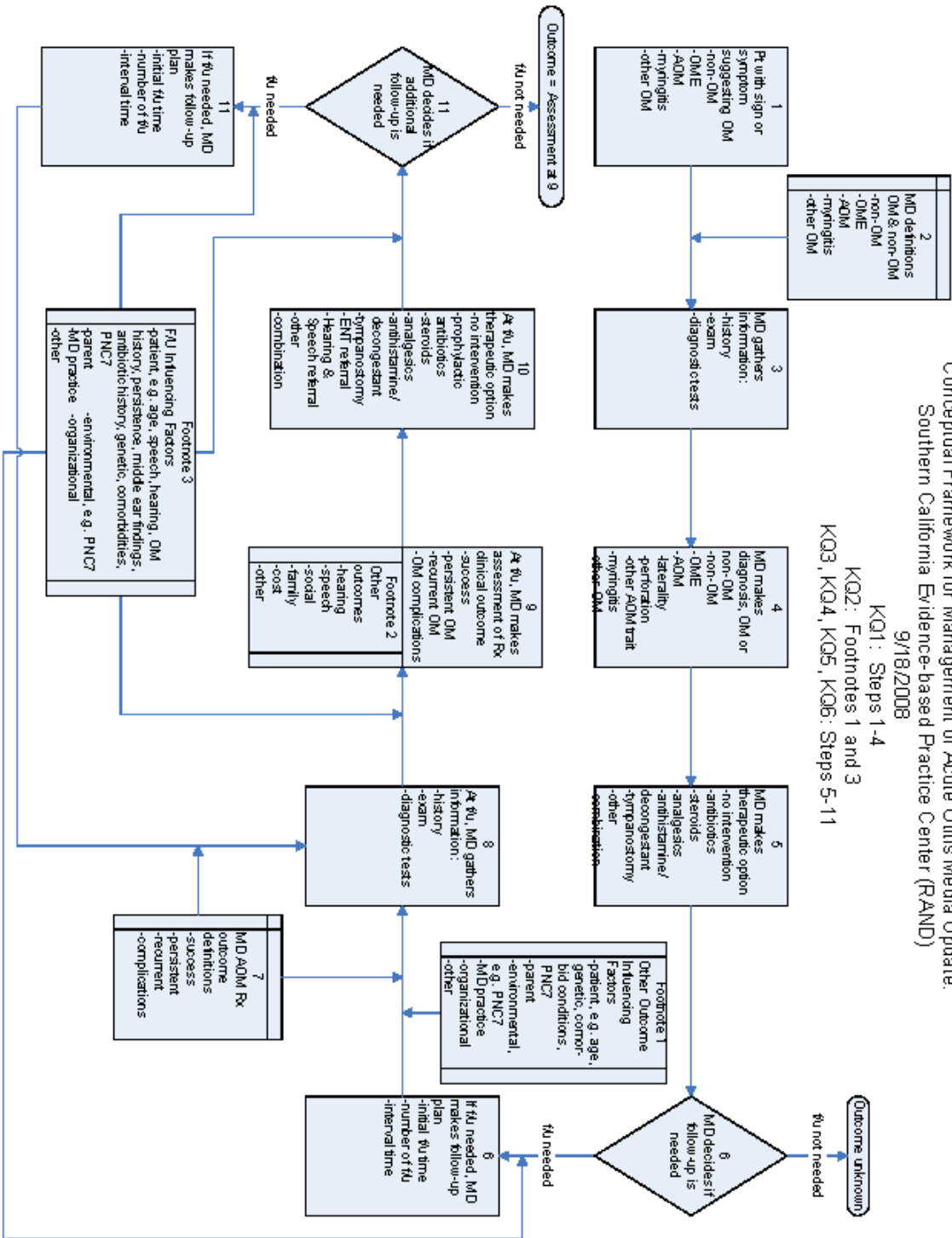
Conceptual Framework for Management of Acute Otitis Media Update:  
 Southern California Evidence-based Practice Center (RAND)

9/18/2008

KQ1: Steps 1-4

KQ2: Footnotes 1 and 3

KQ3, KQ4, KQ5, KQ6: Steps 5-11



## Results

Table S-7 compares the conclusions of the original report and this report.

### **Key Question 1. Diagnosis of AOM: What Are the Operating Characteristics (Sensitivity, Specificity, and Likelihood Ratios) of Clinical Symptoms and Otoscopic Findings (Such As Bulging Tympanic Membrane) to Diagnose Uncomplicated AOM and to Distinguish It from OME?**

The prior review and three additional studies that we identified for this Key Question did not directly or completely answer the question:

- However, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms(see Table S-3).
- Studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians' accuracy in identifying all three clinical criteria in one patient is moderate, at best.
- The overall quality of evidence for this Key Question is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Table S-3 Studies Included in KQ1**

<b>Author, Year</b>	<b>Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics</b>	<b>Examiner Group(s) and Sample Size</b>	<b>Comparison(s) Influencing Diagnostic Methods (Dx), cutpoints Gold Standards (GS), cutpoints</b>	<b>Findings</b>	<b>Quality<sup>a</sup></b>
Saeed, 2004 <sup>39</sup>	<p><u>Time</u> Recruitment period: Sept 1995-May 1998</p> <p><u>Place:</u> pediatric clinics</p> <p><u>Affiliation</u> University of Texas Medical Branch, Galveston</p> <p><u>Inclusion</u> Clinical diagnosis of AOM by:</p> <ul style="list-style-type: none"> <li>- acute symptoms</li> <li>- acute TM inflammation</li> <li>- evidence of MEE by pneumatic otoscopy and/or tympanometry</li> </ul> <p><u>Exclusion</u></p> <ul style="list-style-type: none"> <li>- ear or nasopharynx defects</li> <li>- tympanostomy tubes</li> <li>- major medical condition</li> <li>- antibiotic treatment w/in 7 days of enrollment</li> </ul>	<p><u>Examiner(s)</u> Pneumatic otoscopy- Pediatrician/investigator</p> <p>Tympanometry- research assistant</p> <p>Tympanostomy- same</p> <p>Pediatrician/investigator as otoscopy examiner</p> <p><u>Group</u> children with a dx of AOM and findings from otoscopy, tympanometry, and tympanocentesis available</p> <p><u>Sample size</u> N=81 participants, 130 ears</p>	<p><u>Comparisons</u></p> <p>1. Pneumatic otoscopy Dx- : no AOM Dx+ : AOM Tympanostomy GS- : no MEE GS+ : MEE present</p> <p>2. Tympanogram Dx- :Type A (normal) Dx+ Type B (abnormal) Tympanostomy GS- : no MEE GS+ :MEE present</p>	<p><u>Comparisons</u></p> <p>1. Tympanogram Sensitivity: 97% Specificity: 7% PPV 88% NPV: 25% falsely low true negatives b/c GS test not performed on normal ears</p> <p>2. Pneumatic otoscopy Sensitivity: 100% Specificity: 5% PPV 86% NPV: 100% falsely low true negatives b/c GS test not performed on normal ears</p>	<p><u>Study Quality Assessment</u> Rothman scale: 4</p> <p>QUADAS: 11 y, y, y, y, n, n, y, y, y, y, n, y, y, y</p>

Author, Year	Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics	Examiner Group(s) and Sample Size	Comparison(s) Influencing Diagnostic Methods (Dx), Gold Standards (GS), cutpoints	Findings	Quality <sup>a</sup>
	<ul style="list-style-type: none"> <li>- treatment of AOM w/in 30 days</li> <li>- allergy to study medication</li> </ul> <p><u>Patient Characteristics</u></p> <ul style="list-style-type: none"> <li>- mean age 19.2 months, age range 3-72 months</li> <li>- part of clinical trial (double blind RCT) to evaluate adjunctive drugs in AOM with AOM from pediatric clinics</li> <li>- all participants received IM ceftriaxone.</li> </ul>				
Legros, 2007 <sup>40</sup>	<p><u>Time</u> Recruitment period: December 04-March 05 and October 05-January 06</p> <p><u>Place</u> GP clinics</p> <p><u>Affiliation</u> Angers Medical School, France</p> <p><u>Inclusion</u></p> <ul style="list-style-type: none"> <li>- children from 1-4 years old who had been suspected of having AOM or diagnosed with AOM by GP</li> <li>- Parents had to agree to see ENT within 48 hours at another location</li> </ul> <p><u>Exclusion</u></p> <ul style="list-style-type: none"> <li>- chronic ear pathology</li> </ul> <p><u>Patient Characteristics</u></p> <ul style="list-style-type: none"> <li>- mean age 27.1</li> </ul>	<p><u>Examiner(s)</u> GP clinical exam: by GP ENT clinical diagnosis: by ENT</p> <p><u>Group</u> first 6 children either suspected or diagnosed with AOM by a GP</p> <p><u>Sample Size</u> N=104 participants, 137 ears</p>	<p><u>Comparisons</u></p> <p>1. GP clinical diagnosis/suspicion Dx- : no AOM Dx+ : AOM ENT clinical diagnosis GS- : no AOM GS+ : has AOM</p> <p>2. GP clinical diagnosis/suspicion when eardrum only partially visible or not visible (subset of #1) Dx- : no AOM Dx+ : AOM ENT clinical diagnosis GS- : no AOM GS+ : has AOM</p>	<p>1. GP clinical diagnosis/suspicion 137 AOM diagnoses/suspicions by GPs of these, 122 based on visible/partially visible TMs (54 had redness and bulging of TM; 32 had redness only), 13 based on non-visible TM, 2 based on otorrhea</p> <p>Of the 137: ENTs diagnosed- 107 as AOM, and 30 as not AOM. of these 30, --- 16 as OME, 4 as viral otitis, and 10 as normal</p> <p>2. Study also gives descriptions of what happened with the cases based on non-visible TMs. 19 of the 24 cases of</p>	<p><u>Study Quality Score</u> Rothman scale: 4 QUADAS: 13 y, y, y, u, y, y, y, y, y, u, y, y, y</p>

Author, Year	Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics	Examiner Group(s) and Sample Size	Comparison(s) Influencing Diagnostic Methods (Dx), Gold Standards (GS), cutpoints	Findings	Quality <sup>a</sup>
Laine, 2010 <sup>1</sup>	<p><u>Time:</u> November 2006-December 2008</p> <p><u>Place:</u> Outpatient setting</p> <p><u>Affiliation:</u> Turku University Hospital, Finland</p> <p><u>Inclusion:</u> Parental suspicion of AOM in child based on symptoms</p> <p><u>Patient Characteristics:</u> 6-35 months</p>	<p><u>Examiner:</u> Study physician validated to assess TM findings</p> <p><u>Group:</u> Children presenting to an outpatient setting with a parental suspicion of AOM by symptoms</p> <p><u>Sample Size:</u> N= 469 children. 237 with AOM by study physician exam and 3 criteria, 232 without.</p>	<p><u>Comparisons:</u></p> <p><b>1. Parental Suspicion</b> Dx-: no AOM Dx +: AOM</p> <p><b>2. Ear-related symptoms</b> (pain, rubbing, fever, non-specific symptoms, respiratory symptoms)</p>	<p>non-visible TMs did not have a contralateral ear w/ AOM. Of these, the main signs noted by GP for diagnosis were night cries, irritability, pain, ear pulling, and fever.</p> <p>GP diagnoses/suspicious based on 42 visible/partially visible eardrums: 24 GP diagnoses/suspicious of AOM 18/24 were confirmed by the ENT</p> <p>1. Parental suspicion was correct for 51% of all children, 48% of children without a previous AOM diagnosis, and 52% of children with a previous AOM diagnosis.</p> <p>2. The occurrence, duration, and severity of ear-related symptoms were not associated with AOM diagnosis</p>	<p>Rothman scale: 4 QUADAS: 12 n,y,y,y,y,y,y,y,y,y,y,y</p>

**Key Question 2. What Has Been the Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology: What Organisms (bacterial and viral) are Associated with AOM since the Introduction of PCV7; and What Are the Patterns of Antimicrobial Resistance in AOM Since the Introduction of PCV7?**

- Since the introduction of PCV7, the observational studies generally report that Haemophilus influenzae (HF) has become more prevalent as a causative agent of AOM and Streptococcus pneumoniae (SP) has become less prevalent, although SP remains an important agent as well.
- The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results (Table S-4).
- We found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.
- The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect.
- The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine's effect on these special populations.

**Table S-4 Studies Included in KQ2**

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
Intervention/Post-vaccine vs. Control/Pre-vaccine							
Casey, 2004 <sup>47</sup>	<b>31% vs. 48%</b>	<b>57% vs. 38%</b>	1% vs. 4%	no serotype analysis	no serotype analysis	no serotype analysis	S. pyogenes: 1995-1997- 3% 1998-2000- 3% 2001-2003- 2%
<b>Differences in bold are significant at the p&lt;0.05 level</b>	<b>1995-1997- 48%</b> <b>1998-2000- 44%</b> <b>2001-2003- 31%</b>	<b>1995-1997: 38%</b> <b>1998-2000: 43%</b> <b>2001-2003: 57%</b>	1995-1997: 4% 1998-2000: 5% 2001-2003: 1%				No growth (not included in total): <sup>a</sup> includes S. epidermidis. S. aureus and diphtheroids were considered non-pathogens
	Proportion by Susceptibility: <u>Susceptible:</u> 1995-1997- 54% 1998-2000- 58% 2001-2003- 72%	Proportion by Susceptibility: : B-lactamase positive: <b>1995-1997- 46%</b> <b>1998-2000- 33%</b> <b>2001-2003- 55%</b>					1995-1997- 47% 1998-2000- 44% 2001-2003- 42%
	<u>Intermediate-susceptibility:</u> 1995-1997- 12% 1998-2000- 18% 2001-2003- 14%	B-lactamase negative: 1995-1997- 54% 1998-2000- 67% 2001-2003- 45%					
	<u>Resistant:</u> 1995-1997- 34% 1998-2000- 24% 2001-2003-						

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	14%						
Block, 2004 <sup>46</sup>	31% vs. 48% p=0.007	56% vs. 41% p=0.001	11% vs. 9% (B-lactamase)	36% vs. 70% p=0.005	32% vs. 22% 1, 11, 15A, 29, and 33F	32% vs. 8% p=0.005 6A and 19A	S. Pyogenes 2% vs. 2%  <u>Otitis prone</u> All SP- 85% vs. 43% PNSP- 81% vs. 53% Gram Negative- 78% vs. 45%  <u>Antibiotics within 30 days</u> All SP- 62% vs. 58% PNSP-75% vs. 70% Gram Negative- 85% vs. 61%  <u>Antibiotics within 3 days</u> All SP- 27% vs. 34% PNSP- 38% vs. 41% Gram Negative- 38% vs. 24%  <u>Male</u> All SP- 67% vs. 59% PNSP- 75% vs. 60% Gram Negative- 58% vs. 51%  <u>Day-care attendees</u> All SP-57% vs. 31% PNSP-63% vs. 40% Gram Negative- 69% vs. 29%
	Proportion by Susceptibility: <u>Susceptible:</u> 12% vs. 23% <u>Intermediate:</u> 13% vs. 16% <u>Resistant:</u> 6% vs. 9%	Proportion by Susceptibility: Non- B lactamase 20% vs. 18%					
	PCV7 Serogroups: % of SP isolates that were nonsusceptible 27% vs. 46%	B-lactamase 36% vs. 23%					
	Non-PCV7 Serogroups: % of SP isolates that were nonsusceptible 18% vs. 1%						
	PCV7 Related Serogroups: % of SP isolates that were nonsusceptible 27% vs. 5%						
Veenhoven, 2003 <sup>50</sup>	22% vs. 35% (re-calculated	35% vs. 43% PCV7: 21/60	13% vs. 11%	31% vs. 42%	70% vs. 58%		P. aeruginosa 10% vs. 17% PCV7: 9/60

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	to exclude negative cultures)	Control: 23/54	PCV7: 8/60 Control: 6/54	PCV7: 4/13 Control: 8/19  vaccine serotypes: 4, 6B, 9V, 14, 18c, 19F, 23F	PCV7: 9/13 Control: 11/19  non-vaccine serotypes not specified		Control: 6/54  S. aureus 34% vs. 17% (p=0.004) PCV7: 26/60 Control: 9/54 Group A Strep 10% vs. 7% PCV7: 6/60 Control: 4/54
McEllistrem, 2005 <sup>48</sup>	All cases were SP  % that were PNSP: Overall nonsusceptible 1999: 62% 2000: 63% 2001: 50% 2002: 59%; p=0.21  <u>Intermediate</u> 1999: 23% 2000: 22% 2001: 19% 2002: 23%; p=0.74  <u>Resistant</u> 1999: 39% 2000: 41% 2001: 31% 2002: 35%; p=0.32  By number of PCV7 doses: 2-4 doses vs. ≤1 dose <u>Overall</u> - 56% vs. 60% p=.64 <u>Intermediate</u> - 22% vs. 22%; p=.88 <u>Resistant</u> 33% vs. 37% p=.64  PCV7 Serogroups: % of SP	All cases were SP	All cases were SP	52% vs.. 76% <sup>a</sup>  1999: 76% 2000: 74% 2001: 50% 2002: 52% p<0.01  By number of PCV7 doses: 2-4 doses vs. ≤1 dose 41% vs. 70% p<0.01	32% vs.. 12%  1999: 12 2000: 13 2001: 30 2002: 32 p<0.01  By number of PCV7 doses: 2-4 doses vs. ≤1 dose 35% vs. 18% p<0.01	13% vs. 10%  1999: 10 2000: 10 2001: 13 2002: 13 p<0.29  By number of PCV7 doses: 2-4 doses vs. ≤1 dose 19% vs. 10% p=0.05	Subgroups:  <u>Antibiotic within 30 days % of SP isolates that were nonsusceptible</u> 1999: 65% 2000: 65% 2001: 65% 2003: 56% p=.23  2-4 doses 67% ≤1 dose- 63% p=.62

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	isolates that were nonsusceptible 1999: 70% 2000: 71% 2001: 66% 2003: 88% p=.12  2-4 doses 89% ≤1 dose- 70% p=.08  Non-PCV7 Serogroups: % of SP isolates that were nonsusceptible 1999: 27% 2000: 12% 2001: 14% 2003: 23% p=.75  2-4 doses 24% ≤1 dose- 28% p=.86						
Eskola, 2009 <sup>51</sup> <b>Comparisons in bold are significant at the p&lt;0.05 level</b>	<b>23% vs. 33%</b> (p<0.001)	<b>27% vs.. 23%</b> (p=0.02)  Denominator : all AOM episodes	32% vs.. 30%  Denominator : all AOM episodes	<b>40% vs. 60%</b> (p<0.001)  Denominator : all S.pne isolates  vaccine serotypes: 4, 6B, 9V, 14, 18c, 19F, 23F (also separately analyzed)	<b>46% vs. 23%</b> (p<0.001)  Denominator : all S.pne isolates  non-vaccine serotypes: 3, 11, 15, 16, 22, 33, 35, 38, and others combined: 7, 10, 12, 28, 34, pool G	<b>15% vs. 20%</b>  Denominator : all S.pne isolates  vaccine-related serotypes: 6A, 9N, 18B, 19A, 23A (also separately analyzed)	
Brook, 2009 <sup>49</sup>	44% vs. 54%  1993-1998: 54% 2001-2006:	24% vs. 18%  Proportion by	12% vs. 10%	Not reported	Not reported	S. pyogenes  10% vs. 14%	Methicillin-sensitive S. aureus  1993-1998: 8%



Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	44%	Susceptibility :					2001-2006: 8%
	Proportion by Susceptibility:	B-lactamase positive: 1993-1998: 67%					Methicillin-resistant S. aureus
	<u>Susceptible:</u> 1993-1998: 52%	2001-2006: 50%					<b>1993-1998: 0%</b>
	2001-2006: 73%	B-lactamase negative: 1993-1998: 33%					<b>2001-2008: 10%</b>
	<u>Intermediate-Susceptibility</u> 1993-1998: 33%	2001-2006: 50%					p<0.05
	2001-2006: 23%						
	<u>Resistant</u> 1993-1998: 15%						
	2001-2006: 4%						

**Key Question III. What Is the Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated AOM in Average Risk Children?**

**Table S-5. Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media (AOM) in Average Risk Children in the 2001 Report and the Present Report**

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)		Total number of trials	Success rate difference	
<b>Drug vs. placebo, wait-and-see, and/or prescription-to-hold</b>						
Ampicillin or amoxicillin vs. placebo	5	12% (3%, 22%)	2	7	12%(5%, 18%)	Ampicillin or amoxicillin was more successful than placebo (NNT 9[6,20]) Quality of evidence=moderate
Amoxicillin tid (7d) vs. prescription-to-hold) <sup>2</sup>	0	N/A	1	1	16% (6, 26)	Amoxicillin was more successful than prescription-to-hold (defined as success at day 3) (NNT 6 [4, 17])
Antibiotic vs. prescription-to-hold) <sup>2</sup>	0	N/A	1	1	3% (-8, 14)	Inconclusive (defined as otalgia at day 4-6)
Amoxicillin 90mg/kg/d bid (10d)	0	N/A	1	1	15% (6, 24)	Amoxicillin was more successful (defined as

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)		Total number of trials	Success rate difference	
vs. wait-and-see <sup>3</sup>						success at day 12) (NNT 7 [4,17])
PcV vs. wait-and-see <sup>3</sup>	0	N/A	1	1	-3% (-14, 8)	Inconclusive (defined as success at day 14)
<b>Drug vs. drug</b>						
Ampicillin or amoxicillin vs. Ceftriaxone	3	3% (-2%, 9%)	1	4	0.1% (-7%, 7%)	Inconclusive Quality of evidence=moderate
Amoxicillin 50mg/kg/d (bid, 10d) vs. erythromycin 40mg/kg/d (bid, 10d) <sup>4</sup>	0	N/A	1	1	0.6% (-3, 4)	Treatments were equivalent (when success defined as freedom from recurrence day 31-40)
Amoxicillin-clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d)	0	N/A	1	1	0% (-3.3, 3.3)	Treatments were equivalent (success d.12-14)
Amoxicillin-clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d) <sup>5</sup>	0	N/A	1	1	13% (5, 21)	Amoxicillin-clavulanate was more effective than cefaclor (success at day 28-34, as defined by clinical symptoms but not by culture)
Cefaclor vs. trimethoprim-sulfamethoxazole	3	-6% (-13, 2) (success at less than 14 d)	0	3	N/A	Inconclusive (defined as success at less than day 14); no new data but using MCID
Cefaclor vs. Ampicillin or amoxicillin	4	-5% (-15, 6) (success at d. 3-7)	0	4	N/A	Inconclusive (defined as success at day 3-7); no new data; no new data but using MCID
Cefixime vs. Ampicillin or amoxicillin	4	0.1% (-3.9, 4.2) (success at d. 10-15)	0	4	N/A	Treatments were equivalent; no new data
Penicillin vs. ampicillin or amoxicillin	3	-5% (-11, 2) (success at d. 7-14)	0	3	N/A	Inconclusive (defined as success at day 7-14); no new data but using MCID
<b>High vs. Low Dose Treatment</b>						
Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d	1	1.5% (-3, 13)	0	1	N/A	Inconclusive(defined as persistent clinical cure with no recurrence at follow-up); no new data
High-dose amoxicillin	1	-4% (-14, 7)	0	1	N/A	Inconclusive (defined

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion <sup>a</sup>
	Number of trials	Success rate difference (95% CI)		Total number of trials	Success rate difference	
bid vs. lower-dose amoxicillin tid						as success at day 15); no new data
Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days <sup>6</sup>	0	N/A	1	1	0.1% (-4.8, 4.6)	Treatments were equivalent (success d. 7-12)

#### Short vs. Long Treatment Duration<sup>b</sup>

Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)	3	3% (-2%, 9%) (success rate at 5-10d)	1	4	0% (-7%, 7%)	Inconclusive Quality of evidence: moderate
Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)	2	N/A	3	5	3% (-2%, 7%)	Inconclusive Quality of evidence: moderate
Cefaclor (7-10d) vs. Azithromycin (<5d)	1	N/A	2	3	-1% (-4%, 3%)	Treatments were equivalent Quality of evidence: high
Amoxicillin (7d) vs. Azithromycin (1 dose)	0	N/A	1	1	1% (-1%, 4%)	Treatments were equivalent (defined as no new pain between day 6 and 11)
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (≤5d)	5	2% (1, 5%) (success at 10-14d)	4	9	-0.3% (-6%, 6%)	Inconclusive Quality of evidence: moderate
Amoxicillin-clavulanate 45/6.4 mg/kg/d (bid, 10d) vs. azithromycin 10 mg/kg/d (qd for 1 day), 5 mg/kg/d (qd for 4d) <sup>7</sup>	0	N/A	1	1	26% (6,36)	Longer-term amoxicillin-clavulanate is more successful than shorter-term azithromycin (at d. 12-14, when pathogen is H. influenzae)
Cefaclor 50mg/kg/d; bid 5 d) vs. cefaclor 40mg/kg/d; bid 10d)	0	N/A	1	1	0.7% (-3.5-4.9)	Treatments were equivalent

Table Notes: bid twice a day; CI confidence intervals; d day(s); kg kilograms (body weight); mg milligrams; NNT number needed to treat; PcV phenoxymethylpenicillin; qd once a day;

<sup>a</sup>Confidence intervals falling within the zone of indifference were considered to establish evidence of *no difference*, and confidence intervals outside the zone of indifference were considered to *establish difference*. If the confidence intervals crossed into the zone of indifference, an effect (positive or negative) of the treatment option on the outcome could not be established

(*inconclusive*). For the 2010 systematic review, we used a *zone of clinical indifference of +/- 5%* for the difference in success rate between two treatment options.

<sup>b</sup>Short vs. long term duration refers to the length of treatment from the patient perspective, rather than from the perspective of drug action.

#### **Key Question 4. What Is the Comparative Effectiveness of Different Management Options for Recurrent Otitis Media (Uncomplicated) and Persistent Otitis Media or Relapse of AOM?**

##### **Treatment:**

- The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin.
- The overall quality of evidence for these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.

##### **Prevention:**

Several prior systematic reviews addressed the prevention of AOM in children with ROM.

- One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95%CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance.
- The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.
- The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM.
- The overall quality of evidence for each of these comparisons is considered low, meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

#### **Key Question 5. Do Treatment Outcomes in Key Question3 (KQ3) and KQ4 Differ by Characteristics of the Condition (AOM), Patient, Environment, and/or Health Care Delivery System?**

- Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.
- For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.
- In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.
- In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

**Key Question 6. What Adverse Effects Have Been Observed for the Treatments Whose Outcomes Are Addressed in KQ3 and KQ4?**

**Table S-6 Comparison of Rates of Adverse Events Between Drugs (Significant Differences Only)**

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion
	Number of trials	AE rate Difference (95% CI)		Total number of trials	AE rate difference (95% CI)	
<b>Uncomplicated AOM</b>						
<b>Overall Adverse Events</b>						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	19% (9%, 29%)	0	3	N/A	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (qd)	0	N/A	1	1	28% (17%, 39%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (bid)	0	N/A	1	1	19% (8%, 31%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin clavulanate vs. ceftriaxone	0	N/A	1	1	16% (9%, 24%)	Amoxicillin-clavulanate associated with greater overall AE rate
<b>Gastrointestinal Adverse Events</b>						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	18% (8%, 28%)	0	0	N/A	Amoxicillin-clavulanate associated with greater rate of GI AE
<b>Diarrhea</b>						
Ampicillin or amoxicillin vs. cefixime	5	-8% (-13, -4)	0	0	N/A	Cefixime associated with greater rate of diarrhea
Amoxicillin clavulanate vs. cefdinir	0		1	1	25% (15%, 35%) in Cef QD and 22% (11%, 32%) in Cef BID	Amoxicillin clavulanate associated with greater rate of diarrhea
Amoxicillin clavulanate vs. ceftriaxone	0		1	1	13% (6%, 20%)	Amoxicillin clavulanate associated with greater rate of diarrhea
<b>Recurrent Otitis Media</b>						
<b>Diarrhea</b>						
Amoxicillin-clavulanate vs. ciprofloxacin-dexamethasone ear drops	0	N/A				Greater for amoxicillin-clavulanate in 1 study, but equivalent in 41; no conclusion possible in 23

Comparison	2001 Report		Number of new trials	2010 Update		Conclusion
	Number of trials	AE rate Difference (95% CI)		Total number of trials	AE rate difference (95% CI)	

Table notes: AE adverse event; bid twice a day; CI confidence interval; d day; NNT number needed to treat; qd once a day

### Conclusions

**Table S-7. Conclusions**

Gray shaded boxes contain questions that were added for the update report or conclusions that had no counterpart in the original report. Boldface text indicates changes to the original conclusions.

Key Question	Strength of Evidence	Conclusion
What is the natural history of AOM?		
		About 85 percent of children with AOM who are not initially treated with antibiotics have gotten better – had resolution of pain and fever - on their own within 7 days.
		In studies with close follow-up, few episodes of mastoiditis or other suppurative complications are reported in children with AOM who are not treated initially with antibiotics
Diagnosis: What are the operating characteristics of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?		
	Low	Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE)
		Only otalgia (ear pain) and ear rubbing seemed to predict a clinical diagnosis of AOM. AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain, ear rubbing, fever)
		Individual physical exam findings (cloudy, bulging, immobile, or red TM) were positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms
		Comparing the accuracy of otoscopic and tympanometric findings with that of tympanocentesis as the criterion standard to determine the presence of MEE, 97 percent of children with MEE on tympanocentesis had "Type B" tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM.
		Of cases of AOM diagnosed as or assumed to be AOM by general practitioners, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not (because the otolaryngologist diagnosed OME, viral otitis, or a normal TM). ENT-confirmed diagnoses were associated with both redness and bulging, vs. only redness.
		The studies suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms.
What Has Been the Impact of Pneumococcal Heptavalent Immunization on AOM Microbial Epidemiology?		
What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications),	High	PCV7 is associated with an increased prevalence of Haemophilus influenzae as a causative agent of AOM and decreasing prevalence of Streptococcus pneumoniae (SP), although SP remains an important agent. The vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes.

Key Question	Strength of Evidence	Conclusion
with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?		
What is the evidence for subpopulations of children according to prior antibiotic use?	Very low	No studies analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past
What are the effects of Antibiotics on AOM?		
What is the effect of the delayed treatment or wait-and-see approach compared with immediate antibiotic treatment?	Moderate	Comparing ampicillin or amoxicillin vs. placebo, immediate antibiotic therapy had higher clinical success than prescription-to-hold and wait-and-see in 2 studies; 2 studies demonstrated no difference in clinical success between immediate and delayed antibiotics; and 3 showed a marked decrease in antibiotic utilization in the delayed antibiotic group.
		<b>Compared with observational intervention without antibiotics, antibiotics have minimal to modest benefits during the initial treatment of AOM</b> for pain and fever resolution at 2 days, pain resolution at 2 to 7 days, contralateral otitis media, and clinical resolution at 7- to 14-days. Antibiotic use did not affect tympanic membrane perforation, vomiting/diarrhea/rash, 1-month tympanometry, or recurrent AOM compared with delayed treatment.
Relative Effects of Different Antibiotic Regimens		
	Moderate	No difference in treatment success was seen with ampicillin or amoxicillin vs. ceftriaxone by day 14, although this finding was inconclusive utilizing an MCID of 5%
		No difference in failure rates was seen between ampicillin or amoxicillin and penicillin or cefixime
	Low	No difference was seen in clinical success rates between amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, or amoxicillin-clavulanate vs. amoxicillin-sulbactam
	Moderate	<b>No difference</b> was seen between amoxicillin-clavulanate and azithromycin in clinical success at day 14 (although this finding was inconclusive utilizing an MCID of 5%).
	Moderate	Amoxicillin-clavulanate (10 days) had <b>higher success rates</b> than cefaclor by day 34 when success was defined by clinical symptoms
		No difference was seen in clinical failure rates between trimethoprim-sulfamethoxazole and cefaclor
		No conclusions can be drawn on the effect of oral fluoroquinolones compared with other antibiotics because no comparative randomized controlled trials were found that addressed this question
High vs. low dose	Low	No difference was seen in clinical effect between high-dose amoxicillin-clavulanate and standard-dose amoxicillin-clavulanate or between <b>cefaclor 50 mg/kg/day and 40 mg/kg/day</b>
Bid vs. tid	Low	No difference was seen between high-dose amoxicillin two times a day vs. three times a day or between <b>amoxicillin-clavulanate 45/64/mg/kg/day</b> divided into two daily doses vs. <b>amoxicillin-clavulanate 40/10/mg/kg/day</b> divided into three daily doses
Longer term vs. shorter term treatment	High	Cefaclor (7-10 days) was equivalent to azithromycin ( $\leq 5$ days) in rate of clinical success at day-14
	Low	Amoxicillin-clavulanate (for 10 days) was shown to have <b>higher clinical success rates</b> than azithromycin (single dose, one day) by day 14 when the pathogen was HF
	Moderate	Ceftriaxone (short-duration single-dose) therapy was similar to amoxicillin-clavulanate (long-duration 7 to 10 day) therapy in clinical effect <b>at day 16</b>
		A short-acting oral antibiotic therapy of less than 2 days was not as effective as therapy lasting 7 days or longer

Key Question	Strength of Evidence	Conclusion
What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM		
Treatment	Low	No difference in effectiveness was seen for amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin
Prevention	Low	Long-term antibiotics ( $\geq 6$ weeks) decreased episodes of AOM from 3 to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However nothing is known about the safety of long-term antibiotic administration and the potential consequences on bacterial resistance
Prevention	Low	Tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM
Prevention	Low	The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, cefbuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM
Do treatment outcomes for uncomplicated or recurrent AOM differ by characteristics of the condition, patient, environment, and/or health care delivery system, including but not limited to laterality; otorrhea or perforation; AOM severity; comorbidities; age groups; race; ethnicity; day care attendance?		
		Antibiotic effects may be modified by age, laterality, and otorrhea
		Children over the age of 2 have better outcomes from AOM than children 2 years of age or younger, regardless of whether they are treated with antibiotics or not.
		No differences were seen in treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin
		Children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease
		Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner
		The effect of antibiotics (compared with placebo) was greater in children with otorrhea than in those without otorrhea.
What adverse effects have been observed for the treatments whose outcomes are addressed above?		
		Overall adverse events: amoxicillin-clavulanate was associated with a greater overall adverse event rate than azithromycin, <b>cefdinir</b> (qd and bid), and <b>ceftriaxone</b> . Gastrointestinal events: amoxicillin-clavulanate was associated with a greater rate than azithromycin.
		Diarrhea: Children treated with cefixime had an 8.4 percent greater rate of diarrhea than children treated with ampicillin or amoxicillin. <b>In children with uncomplicated AOM, amoxicillin-clavulanate was associated with a 22 percent-25 percent greater rate of diarrhea than cefdinir and a 13 percent greater rate than ceftriaxone.</b>



### **Limitations of the Review**

The conclusions that can be drawn from this review of the evidence are limited by a number of factors, some associated with specific questions and some that cross the entire body of literature.

- Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears.
- Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.
- The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.
- The inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.
- Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea.
- Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.

### **Future Research Suggestions**

Based on the findings of this review, we provide the following suggestions for future research directions.

#### **Diagnosis of AOM**

- Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation.

#### **Influence of the PCV7 Vaccine on Microbiology/Epidemiology**

- Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine.
- Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.
- More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7.
- A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.<sup>8</sup> These new data support the need for ongoing surveillance of AOM isolates.
- Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13.
- It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

### **Treatment Efficacy and Adverse Effects**

- The usefulness of the conclusions in this review to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system.
- Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed.
- Greater knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition.
- In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.
- Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.