Suppl. Table 2

Study and year	Randomizing-procedure	Blinding	Intervention	Type of placebo	Additional treatment	Vaccine status
Ruohola et al. 2017	Computer-generated	Double blinded	Amoxicillin–clavulanate 40-5.7 mg/kg per day, divided into two daily doses) for 7 days.	Similar to active	Use of analgesic, antipyretic agents, analgesic ear drops and decongestant nose drops or sprays were allowed.	**≥1 dose of pneumococcal conjugate vaccine:** ABX group: 1.9%, placebo group: 2.5 %
Tähtinen et al. 2011	Computer-generated	Double blinded	Amoxicillin–clavulanate 40-5.7 mg/kg per day, divided into two daily doses for 7 days.	Similar to active	Use of analgesic, antipyretic agents, analgesic ear drops and decongestant nose drops or sprays were allowed.	**≥1 dose of pneumococcal conjugate vaccine:** ABX group: 1.9 %, placebo group: 2.5 %
Hoberman et al. 2011	Computer-generated	Double blinded	Amoxicillin–clavulanate 90-6.4 mg/kg daily in two doses for 10 days.	Similar to active	Acetaminophen as needed.	**≥2 dose of pneumococcal conjugate vaccine:** ABX group: 100 %, placebo group: 100 %
Neumark et al. 2007	Computer-generated	Open-label trial	Phenoxymethyl-penicillin 25mg/kg two times daily for five days.	N/A	Symptomatic treatment with paracetamol or NSAIDs, and drugs reducing the swelling of the nasal mucosa (e.g. xylomethazolin), and nasal steroids were allowed.	N/A
Le Saux et al. 2005	Computer-generated	Double blinded	Amoxicillin suspension (60 mg/kg) three times daily for 10 days.	Similar to active	5-day supply of ibuprofen (5 mg/kg per dose if body weight less than 10 kg, 10 mg/kg per dose if over 10 kg) to be given every 8 hours as required for pain or fever, and a 48-hour supply of codeine elixir (1 mg/kg) to be given as required for pain and fever.	N/A
McCormick et al. 2003	Computer-generated	The investigators, but not the parents, were blinded to enrollment status.	Amoxicillin: 90 mg/kg per day, 2 doses per day for 10 days. Subjects unable to take oral medication at follow-up received intramuscular ceftriaxone.	None	Ibuprofen, antihistamine, saline nose drops and/or cerumen removal drops as needed.	**Heptavalent pneumococcal vaccine status:** <u>Partial immunity*:</u> ABX group: 28 % WW group: 28 % <u>Full immunity*:</u> ABX group: 15 % WW group: 18 %

Suppl. Table 3

Study and year	Power-calculation	Adverse events	Compliance (medication)	Outcome	Success/failure criteria	Author conclusion
Ruohola et al. 2017	N/A	N/A	Yes, but data not shown	The **primary outcome** was the time to resolution of MEE (based on a pneumatic otoscopic assessment; both tympanic membranes had to have good mobility, complete or partial transparency and no visibly remnant effusion).	N/A	Immediate antimicrobial treatment does not significantly shorten the time to MEE resolution. The major reason for inadequate resolution and, thus, for the persistence of MEE is recurrence of AOM before MEE resolution.
Tähtinen et al. 2011	N/A	Diarrhea, Vomiting, Eczema (non-itchy exanthema + diaper dermatitis)	Yes, but data not shown	The **primary outcome** was the time to treatment failure, which was a composite outcome consisting of six independent components: a) no improvement in overall condition by the first scheduled visit (day 3); b) a worsening of the child's overall condition at any time; c) no improvement in otoscopic signs by the end-of treatment visit on day 8; d) perforation of the tympanic membrane at any time; e) severe infection (e.g., mastoiditis or pneumonia) necessitating systemic open-label antimicrobial treatment at any time; f) any other reasonfor stopping the study drug (e.g., an adverse event or nonadherence to the study drug) at any time. The **secondary outcomes** were a) time to the initiation of rescue treatment; b) developmentof contralateral acute otitis media; c) use of analgesic or antipyretic agents; d) resolution of symptoms.	**Failure** = primary outcome	Antimicrobial treatment reduces the risk of treatment failure by improving both overall condition and otoscopic signs.
Hoberman et al. 2011	Yes	Diarrhea, diaper dermatitis, oral trush, vomiting, rash	85 % (parent reported)	The **primary outcome** measures were a) the time to resolution of symptoms and the symptom burden over time. The time to resolution of symptoms was measured in two ways: the time to the first recording of an AOM-SOS score of 0 or 1 and the time to the second of two successive recordings of that score; b) The symptom burden over time (measured by calculating the mean AOM-SOS score in the two groups each day over the first 7 days of follow-up and the groups' weighted mean scores for that period.) The **secondary outcomes** were (a) clinical failure at day 4 to 5; (b) clinical failure at day 10 to 12; c) the use of acetaminophen; d) the occurrence of adverse events; e) nasopharyngeal colonization rates; f) the use of health care resources.	**Failure.** Clinical failure was defined, at or before the day 4–5 visit, as either a lack of substantial improvement in symptoms, a worsening of signs on otoscopic examination, or both. Clinical failure at the day 10–12 visit was defined as failure to achieve complete or nearly complete resolution of symptoms	Among children 6 to 23 months of age with acute otitis media, treatment with amoxicillin–clavulanate for 10 days affords a measurable short-term benefit, irrespective of the apparent severity of the illness. The benefit must be weighed against concern not only about the side effects of the medication but also about the contribution of antimicrobial treatment to the emergence of bacterial resistance.

					and of otoscopic signs, without regard to the persistence or resolution of MEE.	
Neumark et al. 2007	N/A	Diarrhea, rash (data not shown in table 1), vomiting	83 %	**Primary outcomes:** a) pain at day 0, 1, 2 and 3 to 7; b) use of analgesics at day 0, 1, 2, 3, 4 to 7; c) fever > 38 °C at day 0, 1, 2 and 3 to 7; d) subjective recovery at day 14 and 3 months; e) perforations at 3 months; f) serous otitis media at 3 months	**Failure:** Absence of improvement or increasing symptoms after at least three days of treatment.	The benefit of antibiotic treatment of AOM is limited.
Le Saux et al. 2005	Yes	Diarrhea, rash, vomiting	N/A	The **primary outcome** measure was clinical resolution of symptoms, defined as absence of receipt of antimicrobial (other than the amoxicillin in the treatment group) at any time during the 14-day period. The initiation of antimicrobial therapy was based on persistence or worsening of symptoms, fever or irritability associated with otoscopic signs of unresolving acute otitis media, or development of signs or symptoms indicative of mastoiditis or invasive disease. **The secondary outcomes** included a) presence of fever and activity levels on days 1, 2 and 3; b) Occurrence of any rash or diarrhea in the 14 days after randomization was also ascertained; c) The presence of MEE was assessed by tympanometry, as described below, 1 and 3 months after diagnosis; d) the number of doses of analgesic (ibuprofen or acetominophen) and codeine over days 1, 2 and 3.	Not specified. Physician's clinical diagnosis of failure was accepted.	Among children 6 months to 5 years of age and those 2 to 5 years of age, amoxicillin had a modest treatment advantage over placebo in terms of clinical resolution rates at 14 days. In children 2 to 5 years, presence of middle ear fluid documented by tympanometry predicted a greater likelihood of success of antimicrobial therapy
McCormick et al. 2003	Yes	Allergy, diarrhea, and candidal infection.	Yes, mean number of ABX doses in WW group was 19	**Primary outcomes:** *a*) parent satisfaction with AOM care; *b*) resolution of AOM symptoms after treatment, including number of doses of symptom medication given; *c*) AOM failure (days 0-12) and recurrence (day 13-30) defined as returning to the office with acute ear symptoms, an abnormal tympanic and an AOM severity score higher than that at enrollment; *d*) nasopharyngeal carriage of *Streptococcus pneumoniae* strains resistant to ABX. **Secondary Outcomes**: *a*) minor adverse events caused by medication, such as allergy, diarrhea, and candidal infection; *b*) serious AOM-related adverse events such as invasive pneumococcal disease, mastoiditis, bacteremia, meningitis, perforation of the tympanic membrane, hospitalization, and emergency ear surgery; *c*) parent-child quality-of-life measures related to AOM.	**Failure**: AOM failure (days 0-12) and recurrence (day 13-30) defined as returning to the office with acute ear symptoms, an abnormal tympanic and an AOM severity score higher than that at enrollment.	Some children with nonsevere AOM may be observed with WW as long as they maintain nonsevere status and are kept comfortable with appropriate symptom management. Under these conditions, WW seems to be an alternative that is acceptable to parents, reduces the number and cost of ABX prescriptions, and reduces the percent of multidrug-resistant bacteria colonizing the nasopharynx of children after an episode of AOM.