Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tähtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011;364:116-26.

SUPPLEMENTARY METHODS

Recruitment

The study clinic was located at primary care level at the health center of Turku, Finland. The study project was scientifically and administratively supervised by the Department of Pediatrics, Turku University Hospital, Turku, Finland. The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All visits were free of charge and no compensation for participation was given.

Patients were recruited between March 2006 and December 2008 (excluding June and July) seven days a week from 8am to 8pm from Turku city area by nurse and physician suggestion, and by parental self-selection. As part of the recruitment process, most parents first contacted the study clinic by phone. Over the phone call, parents received information of the study, the consent of both parents was enquired, and the inclusion and exclusion criteria were initially assessed.

Exclusion criteria with detailed explanations and backgrounds.

1) Ongoing antimicrobial treatment.

   If antimicrobial treatment had ceased according to prescription the day before the enrollment visit, patient was eligible.

2) Acute otitis media with spontaneous perforation of tympanic membrane.

   Acute otitis media with spontaneous perforation of tympanic membrane has been shown to benefit from antimicrobial treatment.(1) Further, *Streptococcus pyogenes* is common in cases with acute otorrhea and this pathogen carries an increased risk of mastoiditis.(2)

3) Systemic or nasal steroid therapy within the 3 preceding days.

   Systemic or nasal steroids may affect the outcome of acute otitis media.(3-5)

4) Antihistamine therapy within the 3 preceding days.

   Antihistamines may affect the outcome of acute otitis media.(5)

5) Oseltamivir therapy within the 3 preceding days.

   Oseltamivir may affect the outcome of acute otitis media.(6).

6) Allergy to penicillin or amoxicillin.

   The active treatment was amoxicillin-clavulanate; penicillin and amoxicillin may have allergic cross-reactivity.

7) Tympanostomy tube present in tympanic membrane.

8) Severe infection requiring systemic antimicrobial treatment.

9) Documented Epstein-Barr virus infection within the 7 preceding days.

10) Down syndrome or other condition affecting middle ear diseases (e.g. cleft palate).

    These patients belong to special populations and their acute otitis media should be treated with antimicrobials.

11) Known immunodeficiency.

    As above.

12) Severe vomiting or another symptoms to violate per oral dosage.

13) Poor parental co-operation due to language or other reasons.

    Only patients whose parents could understand, speak, and read Finnish sufficiently were eligible. This was an important ethical principle because the study physician had to make sure that the parents understood and accepted that their child could also receive placebo.

14) Use of any investigational drugs during the 4 preceding weeks.

    A common principle to avoid unknown interactions.

Nasopharyngeal sampling, bacterial culture, and susceptibility testing

Nasopharyngeal sample was taken at enrollment visit and after study drug period. Samples were collected with dacron swabs (Copan diagnostics, Corona, CA USA) through the anterior nostrils from a depth of 6.5 cm on average. The swab was vigorously vortexed in 1 ml of sterilized 0.9% NaCl. Bacterial cultures were done by the study physician or the study nurse straight after the sampling in the patient study room. Two non-selective culture plates, a 5% sheep blood agar plate and a heated blood agar (chocolate agar) plate as well as a *Haemophilus* selective plate (a heated blood agar plate containing 300 mg/l of bacitracin) were inoculated as follows: a 10 µl loopful of sample suspension was transferred and spread over one-quarter of the culture plates, and then streaked onto four quadrants by using the same 10 µl loop. The *Streptococcus* selective agar plate, sheep blood agar containing 5 mg/l of colistin and 2.5mg/l of oxolinic acid was inoculated by pipetting 10µl of suspension onto the plate and then spreading the drop over the whole plate with a triangle loop. The culture plates were incubated in 5% CO_2 at +35°C and examined at 18-24 h and 36-48 h. Identification of bacterial isolates was performed by standard microbiological methods.(7)

Susceptibility of *Streptococcus pneumoniae* was first screened by the disk diffusion method with oxacillin disks.(7) In the case of decreased inhibition zone, the minimal inhibitory concentration of the strain was tested using penicillin G E-test. A penicillin MIC of 0,125-2 µg/ml was determined as intermediately resistant and an MIC of >2 µg/ml as resistant.(8) The bacteria were cultured on Mueller-Hinton II (Becton Dickinson Microbiology Systems, Cockeysville, Md.) susceptibility test agar plates supplemented with 5% sheep blood and incubated for 18-24h in 5% CO_2 at +35°C.(9) The control strain *S. pneumoniae* ATCC 49619 was tested together with the studied strains.

Laboratory personnel analyzed all samples blind to treatment allocation, and without any data of the patients. Respectively, the study physicians were not informed of the results of bacterial culture unless an isolate of *Streptococcus pneumoniae* with decreased susceptibility to penicillin was found.

Otoscopic and tympanometric examination

All five study physicians were validated otoscopists (Drs. Tähtinen, Laine, and Ruohola, as well as two recidents of pediatrics at Turku University Hospital, Dr. Elina Lahti, M.D., Ph.D., and Dr. Raakel Luoto, M.D., Ph.D.). We first performed tympanometry (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA). After careful cerumen removal, we assessed and recorded systematically the findings of pneumatic otoscopy (Macroview otoscope model 23810, Welch Allyn, NY, USA): position, translucency, color, hyperemia, light reflex, and mobility of the tympanic membrane; possible air-fluid interfaces; and which ear had the worst otoscopic signs. Digital pneumatic video otoscopy was used to document the findings (Jedmed, St. Louis, MO, USA). We examined all patients in upright position which best reveals air-fluid interfaces. Of the five study physicians, the three of us (Drs. Tähtinen, Laine, and Ruohola) made over 90% of the diagnoses and had an excellent agreement (kappa values from 0.80 to 0.92). An ear-nose-throat specialist (Dr. Tuomo Puhakka, M.D., Ph.D., Turku University Hospital) assessed images and videos of 150 patients without knowing their symptoms and/or our diagnoses. He agreed in 95% of our diagnoses of acute otitis media.

Bilateral acute otitis media was diagnosed if a symptomatic patient had middle ear fluid and acute inflammatory signs on the tympanic membranes of both sides. If these diagnostic criteria were observed only on one side and the other side showed no otoscopic signs of pathology or only middle ear fluid, the case was defined to have unilateral acute otitis media.

Study drugs

Study drugs were produced by the University Pharmacy, Helsinki, Finland powdering and mixing amoxicillin-clavulanate tablets (Augmentin 875 mg; manufacturer Glaxo SmithKline Beecham; ATC Code: J01CR02) with lactose monohydrate powder. Each capsule of active treatment contained 68 mg of Augmentin tablet powder (respecting 40 mg of amoxicillin and 5.7 mg of clavulanate) and 572 mg of lactose monohydrate. Placebo capsules contained 640 mg of lactose monohydrate. Study drug powders and capsules were identical by appearance, taste, and smell. The concentrations of amoxicillin and clavulanate were analyzed in both active treatment and placebo capsules by the University Pharmacy. Finnish Medicines Agency monitored the quality of study drugs.

Allocation, concealment, assignment

The random allocation sequence was done with a computerized random-number generator by the Department of Biostatistics, University of Turku, Turku, Finland. The block length was 10 which was decided and known only by the biostatician. The allocation numbers were random four-digit numbers which were in non-consecutive order in the allocation list. The statistician gave the allocation list to the Hospital Pharmacy of Turku University Hospital, Turku, Finland. The pharmacist concealed the allocation by labeling the identical opaque study drug containers with allocation numbers. Another allocation list without the randomization code was given to the Pediatric Infectious Disease Ward in Turku University Hospital, Turku, Finland. The ward served as a call-center where the allocation list was kept. The ward's nursing staff assigned the study participants to their groups by providing the study personnel by phone the next allocation number in the list.

Each container had been packed with 98 capsules. The study nurse provided each patient with the amount of study drug capsules needed according to patient's weight. For example, if the weight was 12 kg, patient required 480 mg amoxicillin and 68.4 mg of clavulanate per day. This meant 12

capsules per day, i.e. 6 capsules every morning and evening. Thus, the patient needed 84 capsules for 7 days. The study nurse measured out the correct number of capsules needed, placed the extra capsules into an empty opaque container, labeled it with the allocation number, and stored the container behind locked doors in the study clinic. Parents administered study drugs at home by opening the capsules and mixing the powder content with a small amount of solid food.

Compliance to study drug was measured by two methods. In the diary method, we counted how many capsules parents had given during study drug period according to diary recordings and divided this number by the number of capsules that parents should have given based on the patient's weight. Secondly, we counted the number of returned empty capsules and divided this by the number of drug capsules we had given to parents.

Study drugs were not handled by the study physicians, who assessed the eligibility of patients, obtained informed consent, enrolled patients, cared for patients during the study, collected data, and assessed outcomes.

For the provision of a case of emergency, the hospital pharmacy made sealed opaque envelopes containing the randomization code for each allocation number separately. The envelopes were kept behind locked doors in the study clinic. None of the envelopes were opened before the completion of the study.

Rescue treatment

Rescue treatment was open-label antimicrobial treatment, primarily amoxicillin-clavulanate 40/5.7 mg/kg/day divided into two daily doses for 7 days. This was based, first, on the assumption that the majority of patients needing rescue treatment would belong to the placebo group and by using the same treatment as rescue treatment as in active arm of the study we could also obtain data of the effect of delayed antimicrobial treatment. Secondly, since strains of *Streptococcus pneumoniae* fully resistant to penicillin are rare in Finland, amoxicillin-clavulanate has excellent antimicrobial coverage on the bacterial pathogens of acute otitis media. Therefore, the Finnish guideline of the management of acute otitis media does not recommend using high-doses of amoxicillin or amoxicillin-clavulanate.(10) Nonetheless, the study physician could provide the patient also with high-doses of amoxicillin-clavulanate or intramuscular ceftriaxone, especially if the microbiologists had informed about an isolate of *Streptococcus pneumoniae* with decreased susceptibility to penicillin.

Statistical Analyses

In the analysis of the primary composite outcome (treatment failure), each patient was counted only once. The timing of treatment failure was the study day when the study physician confirmed any of the components for the first time. The incidence of each event component of the primary outcome was analyzed separately as a secondary outcome meaning that a patient could be included in more than one event category if the events were confirmed by the study physician at the same visit. The timing of rescue treatment was the study day when the study physician confirmed the need for rescue treatment although, for practical reasons, the rescue treatment might first have been given on the following day. When analyzing data regarding treatment failure and rescue treatment, for patients who did not have an event at latest at the end-of-treatment visit (day 8) data were censored on day 8 or at the last follow-up visit, whichever was the earliest.

When analyzing data regarding the treatment result of the overall condition and otoscopic signs at the end-of-treatment visit (day 8), for those patients who either received rescue treatment (n= 49) or withdrew (n=2) before that visit, the treatment result was carried forward from their last follow-up visit to the end-of-treatment visit.

Because of the high tendency of spontaneous resolution of symptoms, the assessment of treatment effect on the resolution of each symptom was based on diary recordings of those patients who had the symptom recorded in the diary at least once during the first 48 hours, instead of including all those patients who had the symptom before study entry. The symptom was determined to be resolved when it had not been recorded in the diary for two consecutive 24-hour periods. If the symptom was not resolved at latest at the end-of-treatment visit (day 8), the data were censored on day 8, at the time of the initiation of rescue treatment, at the last follow-up visit, or, if the diary was missing, on the study day with last diary recordings available, whichever was the earliest.

A subgroup analysis of the occurrence of treatment failure was done dividing the patients into two groups: unilateral and bilateral acute otitis media. The rate differences with 95% CIs between the amoxicillin-clavulanate and placebo groups are provided.

The principal investigator (Dr. Ruohola) developed the protocol in collaboration with Dr. Ruuskanen. The patient related data was gathered by the five study physicians (Drs. Tähtinen, Laine, Ruohola, as well as two residents of pediatrics at Turku University Hospital, Dr. Elina Lahti, M.D., Ph.D., and Dr. Raakel Luoto, M.D., Ph.D.). The microbiologic data was produced by two microbiologists (Dr. Huovinen, M.D., Ph.D., and Jalava, Ph.D.). The data was analyzed by Drs. Tähtinen and Ruohola in collaboration with statistician Tero Vahlberg, M.Sc., University of Turku. Drs. Tähtinen and Ruohola vouch for the data and the analyses. The manuscript was written by Drs. Tähtinen and Ruohola in collaboration with all other authors. All authors decided to publish the manuscript.

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SUPPLEMENTARY RESULTS

Supplement Table1. Baseline characteristics of the intention-to-treat population.

	Amoxicillin-clavulanate group (N=161)	**Placebo group (N=158)**
Demographics		
Mean age – mo (range)	16 (6–35)	16 (6–35)
Age – no. (%)		
6–11 mo	57 (35)	59 (37)
12–23 mo	78 (48)	65 (41)
24–35 mo	26 (16)	34 (22)
Male sex – no. (%)	92 (57)	90 (57)
Caucasian – no. (%)	159 (99)	158 (100)
Caucasian-African – no. (%)	2 (1)	0 (0)
Otitis media risk factors		
Recurrent otitis media in 1st degree relatives – no. (%)	90 (56)	98 (62)
Sibling(s) in the household – no. (%)	89 (55)	93 (59)
Daycare attendance – no. (%)	87 (54)	86 (54)
Exposure to environmental tobacco smoke – no. (%)*	57 (36)	48 (30)
Current use of pacifier – no. (%)	80 (50)	85 (54)
Mean duration of breastfeeding – mo (range)*	7 (0–19)	7 (0–30)
Otitis media history		
Mean number of previous episodes of acute otitis media (range)	2 (0–10)	2 (0–10)
Number of previous episodes of acute otitis media – no. (%)		
0	43 (27)	51 (32)
1–3	88 (55)	79 (50)
4–6	22 (14)	22 (14)
>6	8 (5)	6 (4)
Mean age at the first episode of acute otitis media – mo (range)†	9 (0–26)	10 (0–27)
Mean time from previous episode of acute otitis media – mo (range)‡	3 (0–22)	3 (0–15)
Time from previous episode of acute otitis media – no. (%)‡		
<1 mo	36 (23)	31 (20)
1–3 mo	41 (26)	45 (29)
>3 mo	38 (24)	29 (19)
Previous tympanostomy tubes – no. (%)	1 (1)	3 (2)
Adenoidectomy – no. (%)	1 (1)	2 (1)
Medical history		
Use of analgesics/antipyretics ≤24 h – no. (%)	79 (49)	87 (55)
Atopic eczema – no. (%)	16 (10)	12 (8)
Other medical condition – no. (%)∫	5 (3)	4 (3)
≥1 dose of pneumococcal conjucate vaccine – no. (%)	3 (2)	4 (3)
≥1 dose of influenza vaccine – no. (%)	17 (11)	24 (15)
≥1 dose of *Haemophilus influenzae* type b vaccine – no. (%)	161 (100)	158 (100)

Preceding symptoms		
Highest measured temperature ≤24 h – no. (%)		
<38°C (i.e. no fever)	97 (60)	112 (71)
38.0–38.9°C	40 (25)	28 (18)
39.0–39.9°C	21 (13)	15 (9)
≥40°C	3 (2)	3 (2)
Ear pain reported by parents – no. (%)	123 (76)	126 (80)
Ear pain reported by child – no. (%)	24 (15)	28 (18)
Ear rubbing – no. (%)	104 (65)	99 (63)
Poor appetite – no. (%)	99 (62)	91 (58)
Decreased activity – no. (%)	76 (47)	59 (37)
Irritability – no. (%)	127 (79)	126 (80)
Restless sleep – no. (%)	136 (84)	130 (82)
Excessive crying – no. (%)¶	113 (82)	115 (86)
Respiratory symptoms – no. (%)	156 (97)	156 (99)
Vomiting – no. (%)	2 (1)	3 (2)
Diarrhea – no. (%)	17 (11)	19 (12)
Otoscopic signs at enrollment		
Bilateral acute otitis media – no. (%)‖	60 (38)	67 (43)
Full or bulging tympanic membrane – no. (%)	149 (93)	144 (91)
Bulla formation – no. (%)	19 (12)	12 (8)
Pathogenic bacteria in nasopharyngeal sample – no. (%)**		
Any pathogenic bacteria††	150 (96)	153 (97)
Streptococcus pneumoniae‡‡	100 (64)	90 (57)
Haemophilus influenzae	31 (20)	48 (30)
Moraxella catarrhalis	117 (75)	115 (73)
Streptococcus pyogenes	2 (1)	1 (1)

* Data missing for one patient in the amoxicillin-clavulanate group.
† Data missing for 8 patients in the amoxicillin-clavulanate group and 12 patients in the placebo group.
‡ Data missing for 3 patients in the amoxicillin-clavulanate group and 2 patients in the placebo group.
ʃ In the amoxicillin-clavulanate group, two patients had asthma, one patient gastroesophageal reflux, one patient ventricular septal defect, and one patient operated duodenal atresia. In the placebo group, two patients had asthma, one patient ventricular septal defect, and one patient hydronefrosis.
¶ Data missing for 23 patients in the amoxicillin-clavulanate group and 24 patients in the placebo group.
‖ Data is missing for 2 patients in the amoxicillin-clavulanate group and 2 patients in the placebo group, because adequate view of contralateral tympanic membrane was not reached due to thick cerumen.
** Data missing for 4 patients in the amoxicillin-clavulanate group.
†† All strains were susceptible to amoxicillin-clavulanate.
‡‡ Strains with intermediate susceptibility to penicillin were detected in 18 and 21 of samples in the amoxicillin-clavulanate and placebo group, respectively. In the amoxicillin-clavulanate group, one strain of *Streptococcus pneumoniae* was fully resistant to penicillin.

Supplement Table 2. The frequency of each component and/or their combinations of treatment failure and the frequency of rescue treatment in the study groups according to study day. The treatment failure component(s) was the primary driver of the initiation of rescue treatment, but the final decision was made individually by the study physician based on both overall condition and otoscopic signs.

		Treatment failure		**Rescue treatment**	
Study day		**Amoxicillin-clavulanate group (N=161)**	**Placebo group (N=158)**	**Amoxicillin-clavulanate group (N=161)**	**Placebo group (N=158)**
2					
	Worsening of overall condition at any time	2	2	1	2
3					
	No improvement in overall condition by day 3	9	17	0	12*
	Worsening of overall condition	8	14	5†	12
	Perforation of tympanic membrane	1	2	1	2
	Any reason to stop the study drug‡	1	1	1	1
	No improvement in overall condition by day 3 and any reason to stop the study drug‡	1	0	1	0
	Worsening of overall condition and any reason to stop the study drug†	0	1	0	1
	Perforation of tympanic membrane and no improvement in overall condition by day 3	0	1	0	1
	Severe infection and worsening of overall condition	0	2	0	2
4					
	No improvement in overall condition by day 3∫	2	4	0	1
	Worsening of overall condition	2	1	1	1
	Any reason to stop the study drug‡	0	1	0	0
	Perforation of tympanic membrane and worsening of overall condition	0	1	0	1
5					
	Worsening of overall condition	0	4	0	3
6					
	Worsening of overall condition	1	1	0	1
	Perforation of tympanic membrane and worsening of overall condition	0	1	0	1
7					
	Worsening of overall condition	1	1	0	0
8					
	Worsening of overall condition	1	1	0	0
	No improvement in otoscopic signs by day 8	1	13	1	9
	Worsening of overall condition and no improvement in otoscopic signs by day 8	0	3	0	3

* For five of these twelve patients rescue treatment was not initiated on day 3, because the overall condition was not worrisome and the parents wanted to continue with the study drug. However, rescue treatment was initiated due to worsening of overall condition on day 5 for two patients, on day 7 for one patient, and on day 8 for one patient, and furthermore due to no improvement in otoscopic signs by day 8 for one patient.

† For one of these five patients the rescue treatment was not initiated on day 3, because the parents were reluctant to the initiation of rescue treatment and the otoscopic signs had improved. The study physician decided to set a control visit on day 4, and eventually rescue treatment was initiated due to worsening of overall condition on day 4.

‡ The study drug was stopped because the child refused to take the study drug.

∫ The first control visit was scheduled on study day 3. Nonetheless, for family reasons 26/319 (8%) patients had this visit on study day 4.

Supplement Table 3. A subgroup analysis of treatment failure rates in patients with unilateral and bilateral acute otitis media at entry.

Rate differences (95% CI) within the subgroups are between the treatment groups. Data of laterality is missing for 2 patients in the amoxicillin-clavulanate group and 2 patients in the placebo group, because adequate view of contralateral tympanic membrane was not reached due to thick cerumen.

Unilateral acute otitis media			**Bilateral acute otitis media**		
Amoxicillin-clavulanate group (N=99)	**Placebo group (N=89)**	**Rate difference (95% CI)**	**Amoxicillin-clavulanate group (N=60)**	**Placebo group (N=67)**	**Rate difference (95% CI)**
17 (17.2)	38 (42.7)	-25.5 (-38.5 to -12.5)	13 (21.7)	31 (46.3)	-24.6 (-41.2 to -8.0)

Supplement Table 4. Pathogenic bacteria in nasopharyngeal samples, no. (%).

All isolates were susceptible to amoxicillin-clavulanate.

	Before study drug		**After study drug**	
	Amoxicillin-clavulanate group (N=157)*	**Placebo group (N=158)**	**Amoxicillin-clavulanate group (N=143)**	**Placebo group (N=123)**
Any pathogenic bacteria	150 (96)	153 (97)	61 (43)	116 (94)
Streptococcus pneumoniae	100 (64)†	90 (57)‡	17 (12)∫	71 (58)¶
Haemophilus influenzae	31 (20)	48 (30)	25 (17)	31 (25)
Moraxella catarrhalis	117 (75)	115 (73)	27 (19)	91 (74)
Streptococcus pyogenes	2 (1)	1 (1)	0 (0)	0 (0)

* In four patients in the amoxicillin-clavulanate group no samples were taken due to parental request.

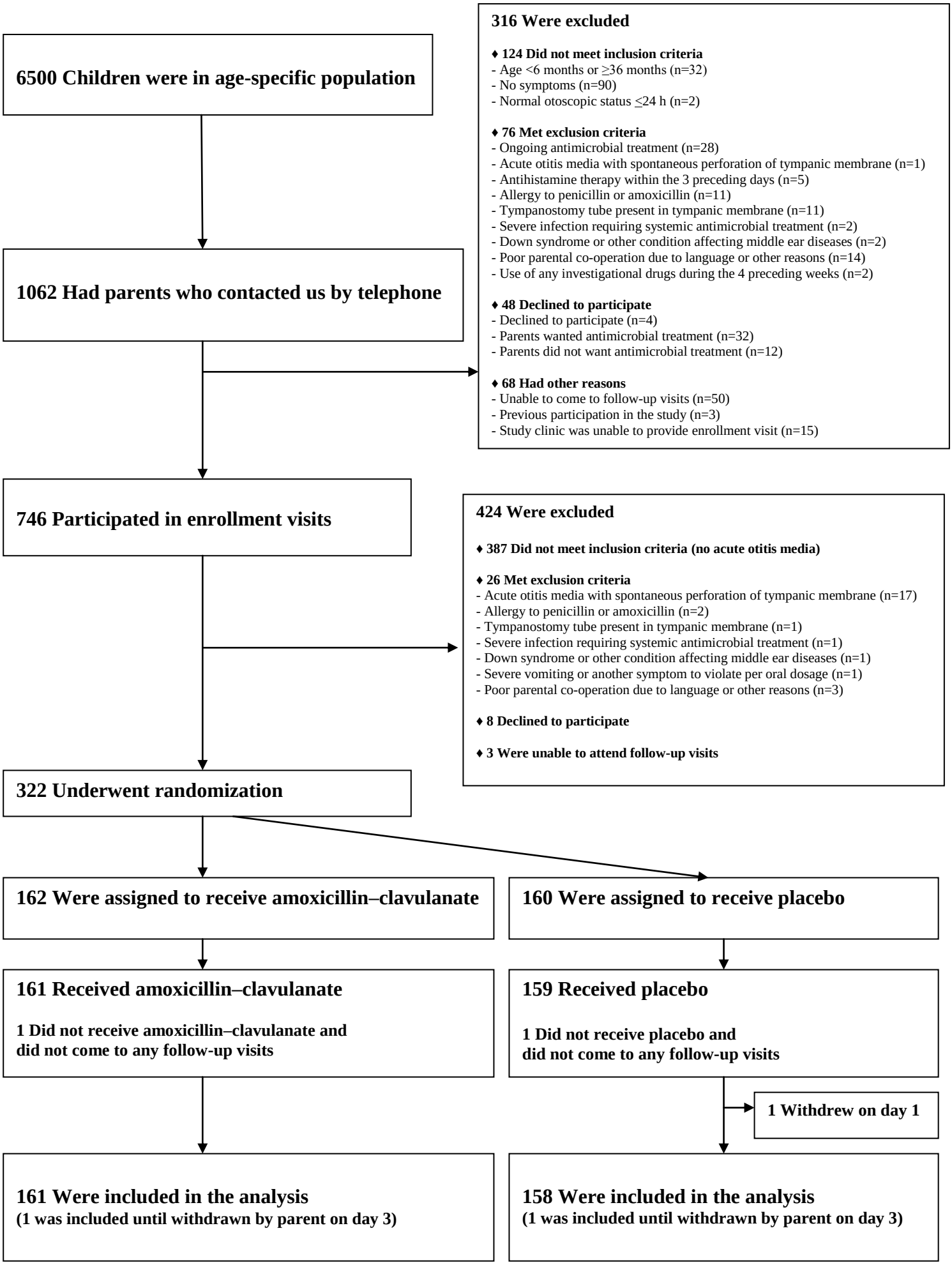
† Intermediate susceptibility to penicillin was detected in 18 isolates. One isolate was fully resistant to penicillin, MIC 3 mg/L.

‡ Intermediate susceptibility to penicillin was detected in 21 isolates.

∫ Intermediate susceptibility to penicillin was detected in 9 isolates. Two isolates were fully resistant to penicillin, both having MIC 4 mg/L.

¶ Intermediate susceptibility to penicillin was detected in 10 isolates.

Supplement Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.



Supplement Figure 2. The Kaplan-Meier curves in Panels A-I show the treatment effect on the resolution of nine symptoms. Each symptom was recorded in the diary every 6 hours during the first 24 hours and after that every morning and evening. Fever was defined as temperature $\geq 38^{o}$C. Analyses included those patients who had the symptom recorded in the diary at least once during the first 48 hours. The symptom was determined to be resolved when it had not been recorded for two consecutive 24-hour periods. On X axis, 1 denotes the time of the first dose of study drug on the study day 1.