

Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time

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Abstract

Objective: To conduct a systematic review comparing the effect of three interventions (prophylactic antibiotics, tympanostomy tube insertion and adenoidectomy) on otitis media recurrence, recurrence frequency and total recurrence time.

Methods: Literature on recurrent otitis media was identified using the PubMed and Scopus search engines for the period January 1990 to March 2011. A hand search of the reference lists of relevant articles and textbooks was conducted to identify additional studies. Randomised, controlled trials with a minimum of 40 children and follow up of at least 12 months were included.

Results: Eighteen publications were identified. Each was assessed using preset inclusion criteria; seven publications met these criteria.

Conclusion: Prophylactic antibiotics are effective in reducing otitis media recurrence, recurrence frequency and total recurrence time. Tympanostomy tube insertion failed to reduce the prevalence of otitis media recurrence, but reduced the recurrence frequency and total recurrence time. Adenoidectomy reduced otitis media recurrence; results on otitis media recurrence frequency differed but on average there was a reduction; however, the two studies with relevant data on total recurrence time had contradictory results.

Key words: Otitis Media; Prophylactic Antibiotics; Tympanostomy Tube; Adenoidectomy

Introduction

Otitis media is inflammation of the middle-ear cavity. It is caused by an infection of the mucous membrane of the middle-ear cleft. Both viral and bacterial infections can lead to otitis media: common viruses include respiratory syncytial virus and influenza A virus, while the two commonest bacterial species are *Haemophilus influenzae* and *Moraxella catarrhalis*. When organisms invade the mucosal membrane, they cause inflammation and oedema; exudate, and later pus, is secreted.¹

Otitis media is one of the commonest diseases of childhood, accounting for approximately one in four of all prescriptions for children under 10 years in the US.² By the age of one, 62 per cent of children will have had at least one episode of otitis media.² Many children suffer recurrent otitis media: approximately 46 per cent of children will have more than three episodes by the age of three years.² Although acute otitis media is often self-limiting (88 per cent of children experience symptomatic relief of pain and fever

by four to seven days without taking antibiotics), the condition can affect a child's intellectual, speech and language ability, as well as their school achievement.³ Studies show that the longer a child has otitis media, the poorer their performance in various tests assessing intelligence quotient and verbal and reading abilities.³ Therefore, it is important to prevent recurrent otitis media.

Currently, there are three main treatment modalities for recurrent otitis media: prophylactic antibiotics, adenoidectomy and tympanostomy tube insertion.⁴ Each of these treatments involves costs and risks. For antibiotics, risks include hypersensitivity and resistance. Surgical intervention carries the risk of anaesthetic complications and haemorrhage, while tympanostomy tube insertion can lead to eardrum scarring or perforation.⁵

This paper systematically reviews recent trials of recurrent otitis media treatment and prevention, with the aim of assessing the efficacy of the three main treatment methods.

Methods

Literature search

We conducted a thorough search of current, evidence-based research on recurrent otitis media, using the PubMed and Scopus search engines. Search terms included 'recurrent otitis media' and its synonym 'recurrent middle ear infection'.

A hand search of the reference lists of relevant articles and textbooks was conducted to identify additional studies missed during the database searches. Non-English language publications and unpublished studies were both excluded. The search was repeated throughout the duration of the study to update the study and to test reproducibility. Studies identified were published between January 1990 and March 2011.

Inclusion criteria

The inclusion criteria for this review are shown in Table I.

Publications were screened initially for potential relevance and then further assessed according to the preset inclusion criteria.

Outcomes

The first outcome assessed was the effect of different interventions on otitis media recurrence. Selected study data were retrieved, and the numbers or percentages of children who did not develop otitis media recurrence were compared in the intervention and control or placebo groups, to assess the effect of the intervention on this parameter.

The second outcome assessed was the effect of different interventions on the frequency of recurrent otitis media episodes. Again, selected study data were retrieved and the frequency of recurrent otitis media episodes during the follow-up period was compared in the intervention and control or placebo groups, to assess the effect of the intervention on this second parameter.

The third outcome assessed was the total time for which children suffered recurrent otitis media over the follow-up period. This parameter was compared in the intervention and control or placebo groups.

Results

Following an initial screening search, 18 publications were identified. Each was assessed using the preset

inclusion criteria. Only seven publications met these criteria.

The 11 papers not meeting the inclusion criteria, and the reasons for their exclusion, are summarised in Table II.

Description of studies

The properties of the seven studies that met the inclusion criteria are summarised in Table III.

Intervention

Mandel *et al.* investigated the effect of intervention on recurrent middle-ear effusion, but their study also produced data on the effectiveness of acute otitis media treatment.¹⁸ Relevant data were retrieved from the study for the current review. Paradise and colleagues' 1999 study randomised patients to undergo either adenotonsillectomy, adenoidectomy or placebo treatment.²⁰ In this study, only data from the adenoidectomy and placebo arms were used.

Studies investigating the effectiveness of antibiotic prophylaxis differed with regards to antibiotic type, dose and duration. The most commonly used antibiotic was amoxicillin. Teele *et al.* used sulfisoxazole 50 mg/kg per day and amoxicillin 20 mg/kg per day for six months.¹⁷ Koivunen *et al.* prescribed sulfafurazole 50 mg/kg per day for six months.²³ Mandel *et al.* used amoxicillin 20 mg/kg per day for one year.¹⁸ Casselbrant *et al.* used amoxicillin 20 mg/kg per day (once each evening) for the full duration of their study.²²

Participants

The age range of participants differed between studies, from infancy (Teale *et al.*) to 15 years (both of Paradise and colleagues' studies).^{17,19,20}

The number of participants in different studies varied hugely. All studies included more than 100 patients, apart from Le and colleagues', which randomised 57 patients.²¹ Of these 57 patients, 13 patients were enrolled due to chronic middle-ear effusion, while 44 were enrolled due to recurrent otitis media. Our review used data from these latter 44 patients. In Paradise and colleagues' earlier study, 213 children were enrolled but only 99 were randomised.¹⁹ Our review used data from these 99 randomised children.

Follow up

Both studies by Paradise *et al.* (1990 and 1999) adopted the same follow-up approach of having bi-weekly enquiries about day-to-day conditions and six-weekly nurse assessments.^{19,20} If otitis media was found, the patient was followed up every one to four weeks. Le *et al.* followed up their patients two to four weeks after their surgical procedure, and subsequently with three-monthly assessments.²¹ If otitis media was diagnosed, the patient was followed up monthly until that episode resolved.

Casselbrant *et al.* followed up patients with monthly examinations.²² If symptoms of otitis media or signs of

TABLE I
REVIEW INCLUSION CRITERIA

Randomised, controlled trial
Population >40 children
Age <15 years
Study of prophylactic Ab, adenoidectomy or TT
Prophylactic Ab given continuously for ≥1 mth
Follow-up period ≥12 mth
Ab = antibiotics; TT = tympanostomy tube insertion; mth = months

TABLE II
CHARACTERISTICS OF EXCLUDED STUDIES

Study	Design	Pts (n)	Interventions	Outcomes	Reason for exclusion
Hammaren-Malmi <i>et al.</i> ⁶	RT	217	Adenoidectomy + TT (or TTs)	OM episodes over 12 mth	No placebo
De Diego <i>et al.</i> ⁷	Prospective RCT	71	Azithromycin + amoxicillin	AOM episodes	No placebo
Mattila <i>et al.</i> ⁸	Prospective RT	306	TT ± adenoidectomy	AOM episode rate	No placebo
Marchisio <i>et al.</i> ⁹	RT	159	Amoxicillin + azithromycin	AOM episodes & rate	No placebo
El-sayed ¹⁰	Prospective RT	53	TT or sulfamethoxazole + trimethoprim	AOM episodes	No placebo
Valtonen <i>et al.</i> ¹¹	Follow-up study	281	TT	Re-tympanostomies (n), post-TT discharge episodes	Not relevant, no placebo, not randomised
Pereira <i>et al.</i> ¹²	Follow-up study	75	TT	Complications (n)	Not relevant, no placebo, not randomised
Autret-Leca <i>et al.</i> ¹³	RT	203	Amoxicillin + clavulanic acid	AOM at day 10 ± 2 days	Follow up <12 mth
Prellner <i>et al.</i> ¹⁴	RCT	76	Penicillin	AOM episodes	Ab prophylaxis not used continually
Roark & Berman ¹⁵	RCT	158	Amoxicillin	OM episodes/365 days at risk	Follow up <12 mth
Kaleida <i>et al.</i> ¹⁶	RCT	536	Amoxicillin + myringotomy	AOM episodes, time (%) with OM during FU	Min ab prophylaxis <1 mth

Pts = patients; RT = randomised trial; RCT = randomised, controlled trial; TT = tympanostomy tube insertion; OM = otitis media; AOM = acute otitis media; mth = months; Ab = antibiotic; Min = minimum

ENT illness were found, the patient was re-examined. Koivunen *et al.* did not arrange any follow up; rather, any patient who visited their doctor was assessed with reference to that patient's symptom diary and their doctor's notes.²³

Teele *et al.* followed up their patients at enrolment and then every four weeks until week 26.¹⁷ In addition, these patients also attended routine 'well child' clinics. The patients allocated to the sulfisoxazole arm of this study were asked to attend for an extra visit in week one for additional haematological tests. Mandel *et al.* examined their patients monthly for one year.¹⁸ If otitis media was diagnosed, the child was re-examined after 14 days.

Effect of interventions on otitis media recurrence

The first outcome we assessed was the effect of the three different interventions on preventing recurrence of otitis media.

Prophylactic antibiotics

Three studies (Teele *et al.*, Mandel *et al.* and Casselbrant *et al.*) assessed the effect of prophylactic antibiotics on the proportion of children not suffering otitis media recurrence.^{17,18,22}

Teele *et al.* reported data collected at six and 12 months after entry into the study.¹⁷ The group assessed

TABLE III
CHARACTERISTICS OF INCLUDED STUDIES

Study	Intervention	Pts (n)	Pt age range	Inclusion criteria	FU
Teele <i>et al.</i> ¹⁷	Ab vs placebo	117	0–1 yr	1 OM episode within 6 mth or 2 btwn 0 & 1 yr	1 yr
Mandel <i>et al.</i> ¹⁸	Ab vs placebo	111	7 mths to 12 yr	Functioning TT: AOM or middle-ear effusion once for ≥2 wk in prev 3 mth Non-functioning TT: ≥3 episodes or ≥3 cumulative mths of middle-ear effusion in prev 12 mth	1 yr
Paradise <i>et al.</i> ¹⁹	Adnd vs placebo	213	1–15 yr	≥3 OM episodes in 6 mth or ≥4 in 12 mth	3 yr
Paradise <i>et al.</i> ²⁰	Adnd vs adenotonsillectomy vs placebo	410	3–15 yr	≥3 OM episodes in 6 mth or ≥4 in 12 mth	3 yr
Le <i>et al.</i> ²¹	TT vs placebo	57	9–82 mth	≥4 OM episodes btwn 0 & 1 yr or ≥6 btwn 1 & 6 yr	3 yr
Casselbrant <i>et al.</i> ²²	TT vs Ab vs placebo	264	7–35 mth	≥3 OM episodes in 6 mth or ≥4 in 12 mth	2 yr
Koivunen <i>et al.</i> ²³	Adnd vs Ab vs placebo	180	10 mth to 2 yr	≥3 OM episodes in prev 6 mth	2 yr

Ab = antibiotics; Adnd = adenoidectomy; TT = tympanostomy tube insertion; yr = years; mth = months; OM = otitis media; AOM = acute otitis media; btwn = between; prev = previous; FU = follow up

TABLE IV
ABSENCE OF OTITIS MEDIA RECURRENCE: EFFECT OF ANTIBIOTICS

Study	FU (mth)	Pts with no rec (%)			% Change*	
		Amox	Sulf	Placebo	Amox vs placebo	Sulf vs placebo
Teele <i>et al.</i> ¹⁷	6	70	47	32	119	47
	12	38	28	22	73	27
Mandel <i>et al.</i> ¹⁸	12	76.4	–	47.1	62	–
Casselbrandt <i>et al.</i> ²²	24	58	–	40	45	–

*((Treatment group – placebo group)/placebo group) × 100. FU = follow up; mth = months; Pts = patients; rec = recurrence; Amox = amoxicillin group; Sulf = sulfisoxazole group; Placebo = placebo group; – = not done

the effects of amoxicillin, sulfisoxazole and placebo. Results from this study are summarised in Table IV.

Mandel *et al.* reported data collected over the 12 months following entry into the study, for an amoxicillin group and a placebo group.¹⁸ The results from this study are summarised in Table IV.

Casselbrant *et al.* investigated the effect of amoxicillin over a two-year follow-up period. Their results are also summarised in Table IV.²²

Tympanostomy tube

One study, by Casselbrant *et al.* assessed the effect of tympanostomy tube insertion on prevention of otitis media recurrence over a two-year follow-up period.²² The results from this study are summarised in Table V.

Adenoidectomy

Two studies, both by Paradise and colleagues (1990 and 1999), assessed the effect of adenoidectomy on

TABLE V
ABSENCE OF OTITIS MEDIA RECURRENCE: EFFECT OF TYMPANOSTOMY

Study	FU (yr)	Pts with no rec (%)		% Change: TT vs ctrl*
		TT	Ctrl	
Casselbrant <i>et al.</i> ²²	2	35	40	–13

*Calculated as in Table IV. FU = follow up; yr = years; Pts = patients; rec = recurrence; TT = tympanostomy tube group; ctrl = control group

otitis media recurrence.^{19,20} The first study reported data collected over a three-year follow up; these results are summarised in Table VI.¹⁹

Paradise and colleagues' second study had two different groups: patients randomised into a three-way trial and patients randomised into a two-way trial.²⁰ Both groups were followed up over three years. The relevant data from this study (i.e. children treated with adenoidectomy, and controls) are summarised in Table VI.

Effect of interventions on otitis media frequency

The second outcome assessed in our review was the effect of the different interventions on the frequency of recurrent otitis media episodes.

Prophylactic antibiotics

Three studies (Mandel *et al.*, Casselbrant *et al.* and Koivunen *et al.*) assessed the effect of prophylactic antibiotics on the frequency of otitis media episodes.^{18,22,23}

Mandel *et al.* reported data from children treated with either amoxicillin or placebo, collected over 12 months.¹⁸ The results from this study are summarised in Table VII, expressed as the rate of otitis media episodes per person-year.

Casselbrant *et al.* measured the rate of otitis media episodes per person-year in children treated with either amoxicillin or placebo, over a two-year follow-up period.²² The results for the first and second

TABLE VI
ABSENCE OF OTITIS MEDIA RECURRENCE: EFFECT OF ADENOIDECTOMY

Study	FU yr	Pts with no rec (%)		% Change: adnd 1 vs ctrl 1*	Pts with no rec (%)		% Change: adnd 2 vs ctrl 2*
		Adnd 1	Ctrl 1		Adnd 2	Ctrl 2	
Paradise <i>et al.</i> ¹⁹	1	44	37	19	–	–	–
	2	51	19	168	–	–	–
	3	51	47	9	–	–	–
Paradise <i>et al.</i> ²⁰	1	31.1	21.5	45	29.5	22.4	32
	2	26.4	37.3	–29	50.0	38.2	31
	3	35.3	36.2	–2	65.2	47.7	37

*Calculated as in Table IV. FU yr = follow up year; Pts = patients; rec = recurrence; adnd = adenoidectomy group; ctrl = control group; – = not done

TABLE VII
OTITIS MEDIA RECURRENCE RATE*: EFFECT OF
ANTIBIOTICS^{18,22}

Study	FU (yr)	OM (episodes/ person-yr)		% Change: amox vs placebo [†]
		Amox	Placebo	
Mandel <i>et al.</i> ¹⁸	1	0.28	1.04	-73
Casselbrant <i>et al.</i> ²²	2	1.31	1.70	-23

*Number of otitis media episodes per person-year. [†]((Treatment group - placebo group)/placebo group) × 100. FU = follow up; yr = years; OM = otitis media; amox = amoxicillin group; placebo = placebo group

follow-up years did not differ substantially. These results are summarised in Table VII.

Koivunen *et al.* reported the number of episodes of acute otitis media in children treated with sulfafurazole and placebo.²³ The mean number of episodes was calculated from children who developed treatment failure during the study follow-up period. These study results are summarised in Table VIII.

Tympanostomy tube

Two studies (Casselbrant *et al.* and Le *et al.*) assessed the effect of tympanostomy tube insertion on the number of otitis media episodes.^{21,22}

Casselbrant *et al.* measured the number of otitis media episodes per person-year in children treated with tympanostomy tube or placebo, over two years of follow up.²² The results of the first and second follow-up year did not differ substantially. These results are summarised in Table IX.

Le *et al.* investigated the effect of tympanostomy tube insertion on the number of recurrent otitis media episodes, compared with controls, over a two-year follow-up period.²¹ As the study randomised individual ears rather than patients, the data were presented as mean episodes of otitis media per six months per ear. These study results are summarised in Table X.

Adenoidectomy

Three studies (Paradise and colleagues 1990 and 1999, and Koivunen *et al.*) assessed the effect of adenoidectomy on the number of otitis media episodes.^{19,20,23}

TABLE VIII
ACUTE OTITIS MEDIA RECURRENCE: EFFECT OF
ANTIBIOTICS²³

Study	FU (mth)	AOM (episodes/pt)		% Change: sulf vs placebo*
		Sulf	Placebo	
Koivunen <i>et al.</i> ²³	6	1.0	1.3	-23

*Calculated as in Table VII. FU = follow up; mth = months; AOM = acute otitis media; pt = patient; sulf = sulfafurazole group; placebo = placebo group

TABLE IX
OTITIS MEDIA RECURRENCE RATE*: EFFECT OF
TYMPANOSTOMY²²

Study	FU (yr)	OM (episodes/ person-yr)		% Change: TT vs placebo [†]
		TT	Placebo	
Casselbrant <i>et al.</i> ²²	2	1.39	1.70	-18

*Otitis media episodes per person-year. [†]Calculated as in Table VII. FU = follow up; yr = years; OM = otitis media; TT = tympanostomy tube group; placebo = placebo group

Both of Paradise and colleagues' studies assessed the mean number of otitis media episodes per patient per year in each of three follow-up years.^{19,20} The 1999 study had two patient groups: patients randomised into a three-way trial and patients randomised into a two-way trial.²⁰ Only the relevant data (i.e. children treated with adenoidectomy versus controls) are presented. The results from these two studies are summarised in Table XI.

Koivunen *et al.* measured the number of acute otitis media episodes in children treated with adenoidectomy or placebo.²³ The mean number of episodes was calculated from children who developed treatment failure during the study follow-up period. These study results are summarised in Table XII.

Effect of intervention on total time with otitis media

The third outcome assessed in our review was the effect of the three different interventions on the total time each child suffered with otitis media.

Prophylactic antibiotics

Three studies (Casselbrant *et al.*, Mandel *et al.* and Teele *et al.*) assessed the effect of prophylactic antibiotics on the total time each child suffered with otitis media.^{17,18,22}

Casselbrant *et al.* calculated the mean total time for which each child suffered with otitis media, expressed as a percentage of the total time between entry into the

TABLE X
OTITIS MEDIA RECURRENCE RATE*: EFFECT OF
TYMPANOSTOMY²¹

Study	FU (mth)	OM (episodes/6 mth/year)*		% Change: TT vs ctrl [†]
		TT	Ctrl	
Le <i>et al.</i> ²¹	1-6	0.6	1.8	-67
	7-12	0.7	1.1	-36
	13-18	1.0	0.9	11
	19-24	0.8	0.8	0

*Mean number of otitis media episodes per six-month interval per ear. [†]Calculated as in Table VII. FU = follow up; mth = months; OM = otitis media; TT = tympanostomy tube group; ctrl = control group

TABLE XI
OTITIS MEDIA RECURRENCE RATE*: EFFECT OF ADENOIDECTOMY^{19,20}

Study	FU yr	OM (episodes/ pt/yr)		% Change: adnd 1 vs ctrl 1 [†]	OM (episodes/ pt/yr)		% Change: adnd 2 vs ctrl 2 [†]
		Adnd 1	Ctrl 1		Adnd 2	Ctrl 2	
Paradise <i>et al.</i> ¹⁹	1	1.06	1.45	-27	-	-	-
	2	1.09	1.67	-35	-	-	-
	3	0.89	0.87	2	-	-	-
Paradise <i>et al.</i> ²⁰	1	1.8	2.1	-14.3	1.7	2.2	-23
	2	1.7	1.2	41.7	0.9	0.9	0
	3	1.3	1.5	-13.3	0.5	0.9	-44

*Mean number of otitis media episodes per patient per year. [†]Calculated as in Table VII. FU yr = follow up year; OM = otitis media; pt = patient; adnd = adenoidectomy group; ctrl = control group; - = not done

study and completion of two-year follow up, according to treatment assignment (amoxicillin or placebo).²² These study results are summarised in Table XIII.

Mandel *et al.* measured the percentage of time patients suffered with middle-ear effusion during the one-year follow-up period, and compared their amoxicillin and placebo groups.¹⁸ These study results are also summarised in Table XIII.

Teele *et al.* estimated the mean time their patients suffered with middle-ear effusion after entry into the study, expressed as days, and compared those treated with amoxicillin, sulfisoxazole and placebo.¹⁷ Data were given for the first six-month follow-up period and the full 12-month follow-up period. These study results are summarised in Table XIV.

Tympanostomy tube

Only one study, by Casselbrant *et al.* assessed the total time with otitis media for children treated with tympanostomy tube insertion versus placebo, expressed as a percentage, over a two-year follow-up period.²² These study results are summarised in Table XV.

Adenoidectomy

Two studies, both by Paradise and colleagues (1990 and 1999), assessed the effect of adenoidectomy on the total time with otitis media, expressed as a percentage of the total follow-up period.^{19,20} Both these

studies followed up children for three years, and presented a cumulative treatment group proportion (representing total days with otitis media/total days) for each follow-up year. The later study grouped patients into two different groups: patients randomised into a three-way trial and patients randomised into a two-way trial.²⁰ Only the relevant data (i.e. children treated with adenoidectomy versus controls) were used. The results from these two studies are summarised in Table XVI.

Discussion

Although all the papers included in this review were randomised, controlled studies of otitis media in children and assessed similar outcomes, there were multiple variables that made performing a meta-analysis difficult.

In order to compare the effects of different interventions in the various studies, the percentage change in recurrence prevalence, otitis media frequency and total time with otitis media, for both the treatment group and the control or placebo group, were plotted on bar charts. In some studies investigating the effect of prophylactic antibiotics, children were treated for six months but were followed up for a longer period. The percentage change during the treatment period (or for an approximation of the duration of the treatment period) was used instead of the whole follow-up

TABLE XII
OTITIS MEDIA RECURRENCE RATE*: EFFECT OF ADENOIDECTOMY²³

Study	FU (mth)	OM (episodes/ pt/ yr)		% Change: adnd vs ctrl [†]
		Adnd	Ctrl	
Koivunen <i>et al.</i> ²³	6	1.3	1.3	0

*Mean number of otitis media episodes per patient per year. [†]Calculated as in Table VII. FU = follow up; mth = months; OM = otitis media; pt = patient; yr = year; adnd = adenoidectomy group; ctrl = control group

TABLE XIII
TIME WITH OTITIS MEDIA*: EFFECT OF ANTIBIOTICS^{18,22}

Study	FU (yr)	OM time (% of total FU)		% Change: amox vs placebo [†]
		Amox	Placebo	
Casselbrant <i>et al.</i> ²²	2	10	15	-33
Mandel <i>et al.</i> ^{18‡}	1	19.6	33.0	-41

*Mean time with otitis media, as percentage of total follow-up time. [†] $((\text{Treatment group} - \text{placebo group}) / \text{placebo group}) \times 100$. [‡]Otitis media indicated by presence of middle-ear effusion. FU = follow up; yr = years; OM = otitis media; amox = amoxicillin group; placebo = placebo group

TABLE XIV
TIME WITH OTITIS MEDIA*: EFFECT OF ANTIBIOTICS¹⁷

Study	FU (mth)	Amox OM time		Sulf OM time		Placebo OM time		% Change [†]	
		Days (mean ± SD)*	% [‡]	Days (mean ± SD)*	% [‡]	Days (mean ± SD)*	% [‡]	Amox vs placebo	Sulf vs placebo
Teele <i>et al.</i> ¹⁷	6	33.3 ± 34.5	18.5	53.9 ± 39.1	29.9	50.2 ± 40.6	27.8	-33	8
	12	62.8 ± 56.3	17.2	77.3 ± 55.0	21.2	73.3 ± 50.0	20.1	-14	5

*From entry into the study to end of follow up. †Calculated as in Table XIII. ‡Time with otitis media as percentage of total follow-up time. FU = follow up; mth = months; Amox = amoxicillin group; OM = otitis media; Sulf = sulfisoxazole group; Placebo = placebo group; SD = standard deviation

TABLE XV
TIME WITH OTITIS MEDIA*: EFFECT OF TYMPANOSTOMY

Study	FU (yr)	OM time (%) [*]		% Change: TT vs placebo [†]
		TT	Placebo	
Casselbrandt <i>et al.</i> ²²	2	6.6	15	-56

*Time with otitis media as percentage of total follow-up time. †Calculated as in Table XIII. FU = follow up; yr = years; TT = tympanostomy tube group; placebo = placebo group

period, if data were available for the treatment period. When data were not available, the percentage change for the whole follow-up period was used.

Effect of interventions on otitis media recurrence

Figure 1 shows the percentage change between the treatment group and the control or placebo group, for the absence of otitis media recurrence in each of the relevant studies.

It would appear that prophylactic antibiotics had the highest percentage change. This suggests that, of the three interventions reviewed, prophylactic antibiotics (studied by Teele *et al.*, Mandel *et al.* and Casselbrandt *et al.*) was the best method for reducing the proportion of children suffering otitis media recurrence.^{17,18,22} Adenoidectomy (as studied by Paradise

and colleagues in 1990 and 1999) also caused a small reduction in the prevalence of otitis media.^{19,20} Tympanostomy tube insertion (studied by Casselbrandt *et al.*), however, increased the prevalence of recurrence amongst treated children.²²

Effect of interventions on otitis media frequency

Figure 2 shows the percentage change between the treatment group and the control or placebo group, for the frequency of otitis media episodes in the relevant studies.

Different studies produced variable results for this comparison. The most consistent results were found in the studies on prophylactic antibiotics (Mandel *et al.*, Casselbrandt *et al.* and Koivunen *et al.*).^{18,22,23} All these studies showed a reduction in otitis media frequency in the treatment group compared with the control or placebo group. Both studies on tympanostomy tube insertion (Le *et al.* and Casselbrandt *et al.*) also showed a reduction in otitis media frequency in the treatment group compared with the control or placebo group.^{21,22} The results from the adenoidectomy studies were hard to interpret: one study (Paradise *et al.* 1999) showed a reduction in otitis media frequency; another (Koivunen *et al.*) showed no change; and a third (Paradise *et al.* 1990) showed an increase in otitis media frequency in the treatment group compared with the control or placebo group.^{19,20,23}

In an attempt to compare the effectiveness of the three types of intervention, the mean percentage

TABLE XVI
TIME WITH OTITIS MEDIA*: EFFECT OF ADENOIDECTOMY

Study	FU yr	OM time (% of FU year)		% Change: adnd 1 vs ctrl 1 [†]	OM time (% of FU year)		% Change: adnd 2 vs ctrl 2 [†]
		Adnd 1	Ctrl 1		Adnd 2	Ctrl 2	
Paradise <i>et al.</i> ¹⁹	1	15	28.5	-47	-	-	-
	2	17.8	28.4	-37	-	-	-
	3	15.1	16.7	-10	-	-	-
Paradise <i>et al.</i> ²⁰	1	22.4	29.9	-25	16.3	23.4	-30
	2	20	20.3	-1	11.9	12.2	-2
	3	19.3	16.6	16	9.8	9.7	1.0

*Time with otitis media as percentage of follow-up year. †Calculated as in Table XIII. FU yr = follow-up year; OM = otitis media; adnd = adenoidectomy group; ctrl = control group

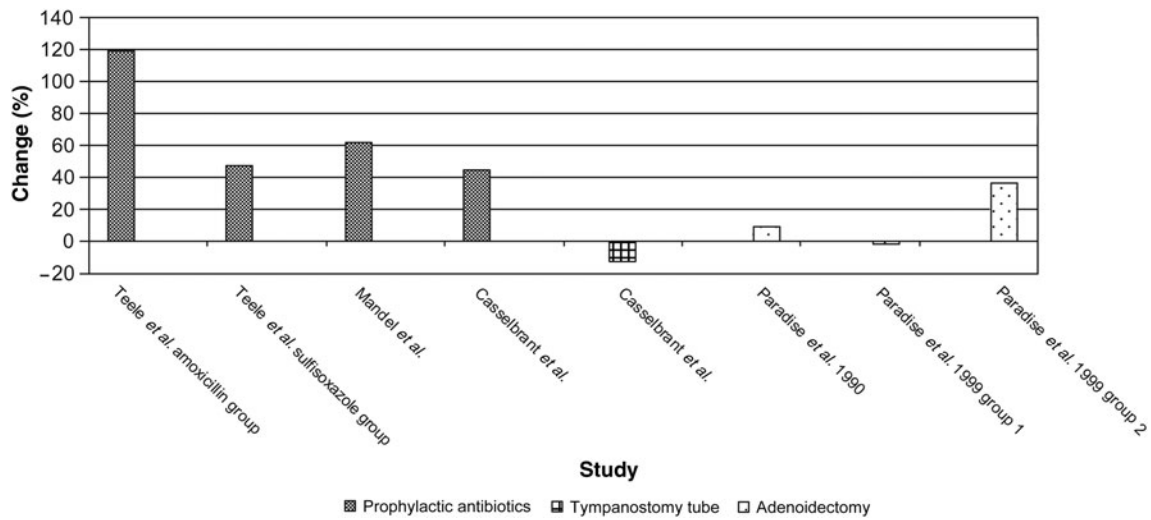


FIG. 1

Effect of different interventions on prevention of otitis media recurrence. The percentage change between the treatment group and the control or placebo group is shown for the relevant studies.

change in otitis media frequency was calculated for each type and plotted on a bar chart (Figure 3). This showed that prophylactic antibiotics were the most effective way of reducing otitis media frequency, of the three interventions reviewed. When judged solely on the basis of mean percentage change, tympanostomy tube insertion was superior to adenoidectomy in reducing otitis media frequency.

Effect of interventions on total otitis media time

Figure 4 shows the percentage change between the treatment group and the control or placebo group, for the total otitis media time in the relevant studies.

The largest percentage change in total otitis media time was seen for tympanostomy tube insertion (Casselbrant *et al.*).²² In other words, tympanostomy tube insertion seemed to be the best method (of the three interventions reviewed) for reducing the total amount of time a child suffered with recurrent otitis media episodes. Although prophylactic antibiotics (Teele *et al.*, Mandel *et al.* and Casselbrant *et al.*) did not show as great an effect compared with tympanostomy tube insertion, they still showed significant percentage changes (except for the sulfisoxazole arm of Teele *et al.*).^{17,18,22} Results from the two studies on adenoidectomy (Paradise and colleagues 1990 and

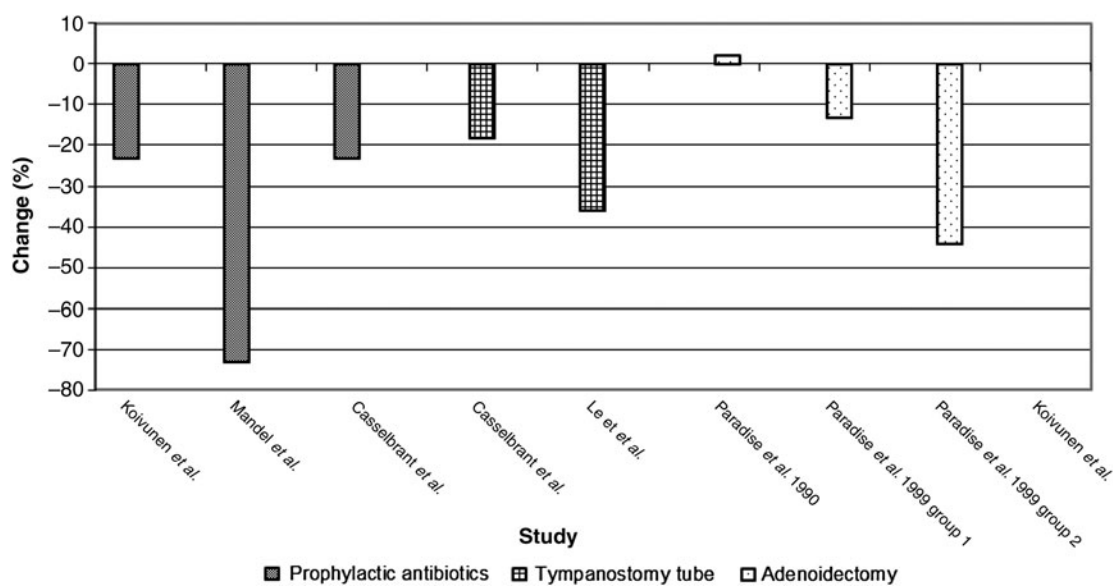


FIG. 2

Effect of different interventions on the frequency of otitis media episodes. The percentage change between the treatment group and the control or placebo group is shown for the relevant studies.

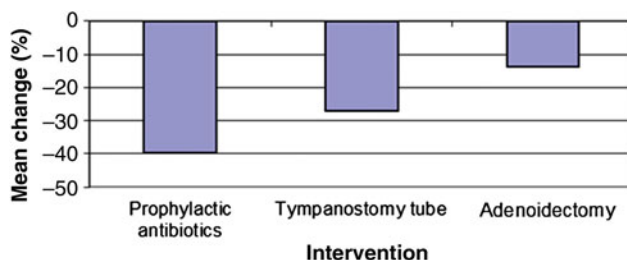


FIG. 3

Mean percentage change (comparing intervention and control or placebo groups) for otitis media frequency, for the three interventions.

1999) were hard to interpret.^{19,20} Although the 1990 study indicated that adenoidectomy was not as effective in reducing total otitis media time, compared with tympanostomy tube insertion and prophylactic antibiotics, there was still a beneficial effect in this respect.¹⁹ However, Paradise and colleagues' 1999 study indicated that adenoidectomy increased, rather than reduced, the total otitis media time.²⁰

Children under two years

It is appropriate to discuss separately the treatment of children under the age of two years. Only two studies investigated children below this age: Teele *et al.* and Koivunen *et al.*^{17,23} Teele *et al.* compared antibiotics with placebo, and their results contributed to our assessment of our first and third outcomes.¹⁷ They found that antibiotic prophylaxis was able to reduce both the recurrence of otitis media and the total otitis media time. However, there were no other data available for these two outcomes, for the other two treatment methods. Koivunen *et al.* compared antibiotics

versus adenoidectomy versus placebo.²³ Their results were used in our assessment of our second outcome: they found that antibiotics reduced the frequency of otitis media episodes but adenoidectomy did not, compared with placebo. No data were available on the effect of tympanostomy tube insertion on otitis media frequency, in children under two years.

Based on these studies, we conclude that, in children under two years, antibiotic prophylaxis is useful in reducing the prevalence of otitis media recurrence, the frequency of otitis media episodes, and the total time spent with otitis media. Adenoidectomy failed to show any benefit in reducing otitis media frequency. There were no data supporting the effectiveness of tympanostomy tube insertion in children under two years.

Factors affecting study results and inter-study variation

The effectiveness of treatments in the reviewed studies was inconsistent. While some studies showed a huge beneficial effect, others demonstrated only a modest

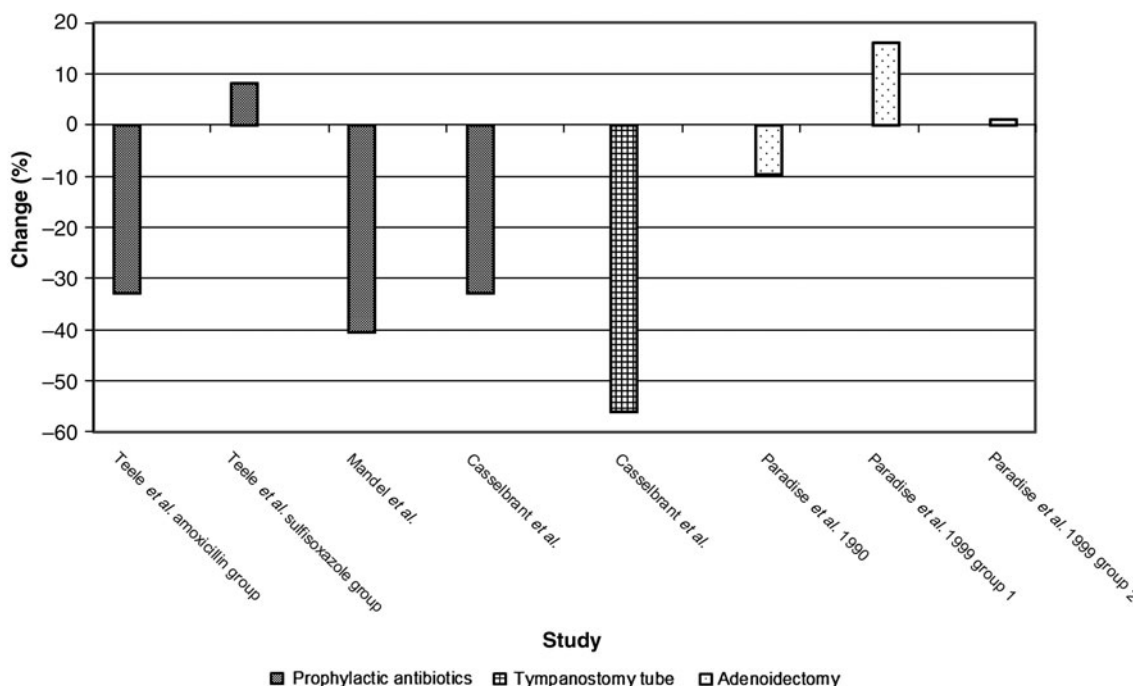


FIG. 4

Effect of different interventions on the total time spent with otitis media. The percentage change between the treatment group and the control or placebo group is shown for the relevant studies.

change. Some studies contradicted each other regarding the effects of a particular treatment.

One reason behind this inconsistency was that the follow-up period was longer than the treatment period in some studies. For example, Casselbrant *et al.* only reported data from the end of a two-year follow-up period, while the duration of function of a tympanostomy tube is usually six to 12 months.^{22,24} Therefore, for a certain part of the follow-up period, children treated with tympanostomy tubes were not protected. Thus, this was not a true assessment of the therapeutic effectiveness of tympanostomy tube insertion.

The subject selection also varied between studies. Although many studies used three or more episodes of otitis media in six months as the inclusion criterion, some studies did not. For example, Teele *et al.* included infants who had had one otitis media episode within six months or two episodes in the first year of life, while Le *et al.* included children with four or more otitis media episodes before one year of age, or six or more episodes between one and six years of age.^{17,21} These two studies required fewer otitis media episodes to qualify for study inclusion, compared with the three or more episodes within a six-month period required by other studies. It could be argued that, using stringent inclusion criteria, children who were more prone to recurrence were more likely to be recruited. This could affect the outcome of children receiving placebo treatment. The effectiveness of different interventions could also vary in children with differing tendencies to recurrence. Therefore, the inclusion criteria variation in the various studies reviewed could potentially have affected our results.

Inclusion and exclusion criteria have an important influence on study outcomes. Apart from Teele *et al.*, all the studies had exclusion criteria.¹⁷ Various conditions are known to predispose children to otitis media. For example, cleft palate and Down's syndrome patients have impaired eustachian tube function and are known to have a higher incidence of middle-ear diseases.^{25,26} In addition to increasing the risk of otitis media, these anatomical abnormalities may influence how such children respond to treatment. Other conditions such as immunodeficiency, asthma and chronic sinusitis would also increase the risk of otitis media. Many of these conditions were listed as exclusion criteria in some of the studies, but consistency was lacking. Such inconsistent exclusion criteria may mean that children with differing recurrence tendencies are included in different studies, and this may influence treatment effectiveness outcome measures.

Another factor which could lead to inconsistency between study results was the way in which new otitis media episodes were treated. Most studies used antibiotics to treat each new episode of otitis media that occurred during follow up, and in the prophylactic antibiotic group the prophylactic antibiotic was paused. However, the type of antibiotics and the dose and duration of treatment differed in each study. For example,

Teele *et al.* treated otitis media with either co-trimoxazole, cefaclor or erythromycin, while Paradise and colleagues (1990) first treated patients with ampicillin or amoxicillin and used erythromycin ethylsuccinate combined with sulfisoxazole acetyl as an alternative.^{17,19} Differences in treatment protocols between studies could affect the duration of otitis media episodes, and could thus affect the total otitis media time during the follow-up period. In addition, in surgical treatment groups these antibiotics were given in addition to the original surgical intervention. Therefore, these patients received double protection, which could possibly have affected their otitis media frequency. However, since treatment was only given if a new episode developed, the prevalence of initial otitis media recurrence would not have been affected.

It is also worth mentioning that Le *et al.* randomised individual ears, instead of individual children, to receive their study treatment.²¹ The benefit of this method is that variables such as genotype, allergies and environmental factors will be the same in the treatment and control groups. However, if a child developed a new episode of otitis media in one ear, it would be impossible to isolate the affected ear during oral antibiotic treatment.

The nature of otitis media should also come under consideration when comparing study results. Risk factors for otitis media include gender and season.²⁷ Boys have a significantly higher prevalence of both single episode otitis media and recurrent otitis media, compared with girls. However, since all the reviewed studies were randomised, the effect of gender should not have significantly affected their results. Although otitis media occurs throughout the year, it is more frequent during the autumn and winter months. Seasonal variation might affect the results of studies of prophylactic antibiotic effectiveness. Some studies only treated patients with antibiotics for six months. The prevalence of new otitis media episodes could also differ depending on the season in which placebo testing was conducted. If placebo testing was conducted during the summer and active treatment during the winter, the differences in both the prevalence of initial otitis media recurrence and the frequency of recurrent episodes would be smaller, compared with the differences observed if placebo testing was conducted during the winter and active treatment during the summer.

As mentioned above, otitis media is often self-limiting. Eighty-eight per cent of children have symptomatic relief from pain and fever within 4 to 7 days, without taking any antibiotics.² Follow-up methods varied between studies, with most studies following up their patients at monthly intervals; therefore, it is possible that some otitis media episodes may have occurred in between follow-up appointments, and thus may not have been recorded.

The incidence of otitis media in children also changes as they grow. The peak incidence is found in

children aged between six and 18 months, and thereafter gradually reduces.²⁸ The ages of children entered into the reviewed studies varied, as did the study follow-up periods. For some studies with longer follow-up periods, the otitis media incidence changed during the follow-up period as the child grew. This could potentially make the effectiveness of intervention appear to decrease as follow-up progressed, as the otitis media incidence would also fall in the control or placebo group.

Conclusions

Despite the above limitations, it is still safe to make the following conclusions from the data extracted from the seven studies reviewed.

Firstly, we conclude that prophylactic antibiotics are effective in improving all three otitis media outcomes assessed in this review. Treatment with prophylactic antibiotics reduces the prevalence of otitis media recurrence, the frequency of otitis media episodes, and the total time each child spends with otitis media. The effectiveness of prophylactic antibiotics was greater than that of tympanostomy tube insertion and adenoidectomy, in terms of reduction in otitis media recurrence and otitis media episode frequency.

Secondly, tympanostomy tube treatment fails to prevent recurrence of otitis media. However, it is effective in reducing the frequency of otitis media episodes and the total time spent with otitis media.

Thirdly, adenoidectomy is effective in reducing otitis media recurrence. Data on otitis media frequency differed amongst studies, but the mean result from the three relevant studies indicated that adenoidectomy reduces the frequency of otitis media episodes. The two studies assessing the effect of adenoidectomy on total otitis media time had contradictory results, and it was therefore hard to draw a conclusion. Adenoidectomy has no benefit in the treatment of otitis media in children under the age of two years.

In the future, it would be beneficial if a standard protocol were adopted for all studies, with standard inclusion and exclusion criteria (including a narrower inclusion age), a standard treatment protocol for new otitis media episodes, and a standard follow-up method. The adoption of such a protocol would limit the various factors that can affect study results.

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