Antibiotics for acute otitis media: a meta-analysis with individual patient data

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Summary

Background **Individual trials to test effectiveness of antibiotics in children with acute otitis media have been too small for valid subgroup analyses. We aimed to identify subgroups of children who would and would not benefit more than others from treatment with antibiotics.**

Methods **We did a meta-analysis of data from six randomised trials of the effects of antibiotics in children with acute otitis media. Individual patient data from 1643 children aged from 6 months to 12 years were validated and re-analysed. We defined the primary outcome as an extended course of acute otitis media, consisting of pain, fever, or both at 3–7 days.**

Findings **Significant effect modifications were noted for otorrhoea, and for age and bilateral acute otitis media. In children younger than 2 years of age with bilateral acute otitis media, 55% of controls and 30% on antibiotics still had pain, fever, or both at 3–7 days, with a rate difference between these groups of –25% (95% CI –36% to –14%), resulting in a number-needed-to-treat (NNT) of four children. We identified no significant differences for age alone. In children with otorrhoea the rate difference and NNT, respectively, were –36% (–53% to –19%) and three, whereas in children without otorrhoea the equivalent values were –14% (–23% to –5%) and eight.**

Interpretation **Antibiotics seem to be most beneficial in children younger than 2 years of age with bilateral acute otitis media, and in children with both acute otitis media and otorrhoea. For most other children with mild disease an observational policy seems justified.**

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See Comment page 1397

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Introduction

Acute otitis media is one of the most common childhood infections, the leading cause of doctors' consultations, and the most frequent reason for children to take antibiotics.[1] Evidence from systematic reviews, however, suggests that antibiotics provide only marginal benefit.[2,3] Furthermore, prescribing antibiotics is known to encourage clinic visits for subsequent episodes, intensify pressure on clinicians to prescribe, increase antibiotic use, and promote antibiotic resistance.[4–6]

Guidelines therefore recommend selective use of antibiotics for acute otitis media, especially in children aged 2 years or older. In children younger than 2 years, no consensus has been reached. Some guidelines recommend antibiotics for all these children,[7,8] whereas others advise antibiotics only for children under 2 years if they are severely affected or have persistent signs of disease or related comorbidity.[9,10]

Reliable identification of subgroups of children who do, and do not, benefit from treatment with antibiotics has not been straightforward, because individual trials have been too small for valid and reliable subgroup analyses. A meta-analysis of the individual data from original trials enables the opportunity to identify subgroups that are most likely to benefit. We therefore aimed to identify subgroups that might benefit most from such treatment.

Methods

Selection of trials

We did a systematic search of the Cochrane library, PubMed database, EMBASE, and the proceedings of the international symposia on recent advances in otitis media. We selected trials that (1) used random allocation of children, (2) included children aged 0–12 years with acute otitis media, (3) compared antibiotics with placebo or no treatment, and (4) had pain and fever as an outcome. All trials were assessed for four major quality criteria: proper randomisation methods; degree of follow-up; and blinding of the outcome assessor, patient, and care giver. All trials obtained informed consent and ethics approval.

The primary investigators of all selected trials were asked for the raw data of their trials. The data thus obtained were thoroughly checked for consistency, plausibility, integrity of randomisation, and follow-up. A few issues were queried with the responsible trial investigator or statistician, and all were resolved.

Outcome variables

The primary outcome was an extended course of acute otitis media, which was defined as pain, fever, or both at 3–7 days. We used this composite endpoint since both factors are relevant from clinical and patients' (or parental) perspectives. Fever was defined as temperature of 38°C or higher, and pain was assessed by parents and recorded in diary form (as either yes or no). Both outcome measures were dichotomised, since several trials measured them in this way. Fever and pain were also studied separately (as secondary outcomes). Additionally, the adverse effects of antibiotic treatment mentioned in every trial were analysed.

Independent predictors of an extended course of disease had been established in an earlier study within

the same setting (unpublished data).[11] We used these independent baseline predictors—ie, age (<2 *vs* ≥2 years), fever (yes *vs* no), and bilateral acute otitis media (yes *vs* no)—to investigate whether those at risk of an extended course had enhanced benefits from treatment with antibiotics. We also examined the effects of concurrent otorrhoea at baseline (yes *vs* no), both alone and in combination with the identified predictors, since this condition seems to be a clinically relevant outcome that occurs too infrequently to be identified as an independent predictor.

Statistical analyses

Information was available for 72% of the potential subgroups (range 28–100%) and for 90% of the outcome variables (range 81–98%). To reduce bias and to increase statistical efficiency, we imputed the missing data for all trials using the linear regression method (multivariate analyses) available in SPSS (version 12.0).[11] Regression was based on the correlation between individual variables with missing values and all other variables, as estimated from the complete set of data. We imputed missing values only within trials. To decide whether pooling of data for analysis was justified, we assessed heterogeneity between studies using I^2, which describes the percentage of variation between studies due to heterogeneity rather than chance.[12] The range for I^2 lies between between 0% (ie, no observed heterogeneity) and 100%. The resulting I^2 was lower than 25% ($p>0\cdot30$) indicating that studies were sufficiently similar to justify pooling of data.

We calculated relative risks (RR), rate differences (RD), and NNT, with their 95% CI, for both the primary and secondary outcomes. To assess whether the effect of antibiotics was modified by age, bilateral acute otitis media, fever, otorrhoea, or a combination of these factors, we did a fixed-effect logistic regression analysis. In this model, the independent variables were: treatment with antibiotics (yes *vs* no); the potential-effect modifiers (age, bilateral acute otitis media, fever, otorrhoea, or combinations of these); and an interaction term (defined as use of antibiotics times potential-effect modifier). We also used a binary dummy variable to identify each study within the regression analysis. Dependent variables were an extended course (primary outcome), fever, and pain at 3–7 days (secondary outcomes). We calculated the c-index (area under the receiver operating curve) to measure the accuracy of each model. If a significant interaction effect was identified, we did stratified analyses of the rate ratios and rate differences within each stratum of the subgroups. The percentages of children with an extended course during each consecutive day within each of the identified subgroups were calculated for the five trials that asked parents to fill out diaries noting signs of the disease. Finally, we did sensitivity analyses, including only those trials that measured the outcomes on the same day, used the same dose regimen, or included placebo. All analyses were performed according to the intention-to-treat principle.

Role of the funding source

This study was sponsored by the Dutch College of General Practitioners and the Netherlands Organisation for Health Research and Development (grant number 4200.0010). This sponsor had no role in study design,

	Number of patients	Participants	Interventions	Duration of intervention	Outcomes
Ref 22	121	Children aged 6 months to 12 years visiting a GP with recurrent AOM	Amoxicillin with clavulanate vs placebo	7 days	Fever after 3 days Pain after 3 days Otorrhoea Otoscopy and tympanometry after 1 month
Ref 23	232	Children aged 3 to 10 years with AOM	Amoxicillin vs placebo	7 days	Symptoms noted by parents (including fever and ear pain) Home visits by researcher after 24 h and 5–7 days Otoscopy and tympanometry after 1 and 3 months
Ref 24	240	Children aged 6 months to 2 years visiting a GP with AOM	Amoxicillin vs placebo	10 days	Symptoms at day 4 assessed by a GP (including fever and earpain) Otoscopy and tympanometry after 6 weeks and 3 months
Ref 25	315	Children aged 6 months to 10 years visiting a GP with AOM	Immediate antibiotics (amoxicillin) vs delayed treatment	7 days	Symptoms noted by parents (including fever and earpain) Absence from school Consumption of paracetamol
Ref 26	512	Children aged 6 months to 5 years presenting to clinics or the emergency department with AOM	Amoxicillin vs placebo	10 days	Telephone follow-up at day 1, 2, 3, and between 10 and 14 days (including fever) Tympanometry at 1 and 3 months
Ref 27	223	Children aged 6 months to 12 years with AOM	Immediate antibiotics (amoxicillin) vs delayed treatment	10 days	Symptoms noted by parents (including fever and earpain) Analgesic consumption Nasopharyngeal carriage Adverse events Absence from school Tympanometry after 12 and 30 days

AOM=acute otitis media; GP=general practitioner.

Table 1: **Characteristics of the six trials included in our meta-analysis**

data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search strategy identified nineteen trials that investigated the effectiveness of antibiotics in children with acute otitis media. After screening, nine trials were excluded, because randomisation was inadequate, the control group received another treatment, information about our selected outcomes was not available, or because they focused on special study populations, such as children with ventilation tubes.[13–21] Of the ten eligible trials, six research groups provided us with their data[22–27] and four did not.[28–31] The methodological quality of the six remaining studies was generally high. Five used adequate concealed allocations (blinded randomisations) and outcome assessments. Loss to follow-up was less than 10%. Table 1 shows the main characteristics of the six trials. The mean age of the children was 3·4 years (range 0–11); half were boys; about half had recurrent acute otitis media; and about a third had bilateral acute otitis media (table 2).

Our meta-analysis showed that, relative to placebo, overall RR for an extended course of acute otitis media at 3–7 days with antibiotics was 0·83 (95% CI 0·78–0·89). The rate difference between the control group and the antibiotics group was 13% (9–17), resulting in a NNT of eight children. Overall RR of fever at 3–7 days was 0·95 (0·92–0·98); the rate difference was 5% (2–8) and NNT was 20 children. The corresponding figures for children who had pain at 3–7 days were 0·86 (0·81–0·91); 11% (7–15); and ten children, respectively.

Our analyses showed that the effect of antibiotics was modified by age and bilateral disease, and by otorrhoea, notably for the primary outcome of pain, fever, or both at 3–7 days (table 3). In children aged less than 2 years with bilateral acute otitis media, more than half the control group and less than a third of the antibiotics group still had pain, fever, or both at 3–7 days, with a rate difference of about 25%. In children aged 2 years or older with bilateral disease the rate difference was about 12%. For age alone no differences were identified. The c-indices, calculated to gauge the accuracy of each model, were 0·63, 0·58 and 0·61, respectively, for age and bilaterality, age alone, and bilaterality alone.

About 60% of children with otorrhoea in the control group had pain, fever, or both at 3–7 days, whereas only about 25% of those given antibiotics had protracted illnesses. The rate difference, of about 36%; was much greater than that for those without otorrhoea, which was about 14%. Other factors, in combination with otorrhoea, such as age, bilateral disease, or both did not substantially alter this pattern—ie, children with otorrhoea seemed to benefit most from treatment with antibiotics, irrespective of other characteristics.

	Antibiotics (n=819)	Controls (n=824)	Total (n=1643)
Age <2 years	280 (34%)	287 (35%)	567 (35%)
Male sex	411 (50%)	411 (50%)	822 (50%)
Recurrent AOM	402 (49%)	429 (52%)	831 (51%)
Siblings*	455 (76%)	472 (78%)	927 (77%)
Winter season	623 (76%)	620 (75%)	1243 (76%)
Being breastfed†	244 (64%)	255 (64%)	499 (64%)
Passive smoking‡	214 (34%)	218 (33%)	432 (34%)
Crying§	407 (83%)	413 (83%)	820 (83%)
Coughing‡	460 (72%)	476 (72%)	936 (72%)
Runny nose¶	428 (77%)	429 (78%)	857 (78%)
Ear pain	723 (88%)	724 (88%)	1447 (88%)
Fever‖	282 (40%)	287 (41%)	569 (40%)
Bilateral AOM**	236 (35%)	220 (33%)	456 (34%)
Otorrhoea†	51 (19%)	65 (23%)	116 (21%)
Perforation‡‡	20 (8%)	19 (7%)	39 (7%)
Red tympanic membrane	751 (92%)	754 (92%)	1505 (92%)
Bulging tympanic membrane	343 (42%)	342 (42%)	685 (42%)

Data are number (%). AOM=acute otitis media. Overall number=*1207, †778, 1299, §984, ¶1105, ‖1411, **1328, ‡‡555. Percentages do not always add to 100% because of missing data for some characteristics.

Table 2: **Baseline characteristics of patients in the six trials**

With pain alone as the primary outcome, the effect of antibiotics was modified by age and bilateral disease together (p-value for interaction 0·01) (table 3). For children aged less than 2 years with bilateral acute otitis media, twice as many controls still had pain at 3–7 days, compared with those given antibiotics. For age alone no differences were identified.

Figure 1 shows the proportion of children with an extended course of disease in the subgroups for which antibiotics were of most benefit—ie, children younger than 2 years of age with bilateral disease, and those with otorrhoea. For both these subgroups, symptoms resolved faster in children who received antibiotics than in children randomised to the control group, but this difference disappeared after 4–5 days. Sensitivity analyses, including only those trials that measured the outcome at the same time during follow-up, used the same dose of antibiotics, or included a placebo, were in agreement with the overall results.

The most commonly described adverse effect of antibiotic treatment was diarrhoea, which ranged from 2% to 14% in controls and from 4% to 21% in those given antibiotics in each of the six trials that we analysed. Occurrence of rash ranged from 2% to 6% in the control groups, and from 1% to 8% in the antibiotic groups. One child from the control group developed meningitis at day 3,[24] but seemed to have received antibiotics at day 2 because of deterioration. No mastoiditis or other serious complications were mentioned in these six trials.

	Number (%)	Group given antibiotics (n=819)	Control group (n=824)	RD (95% CI)	NNT	RR (95% CI)	p value for interaction*
Pain, fever, or both at 3–7 days							
Age							
<2 years	567 (35%)	91 (33%)	137 (48%)	−15% (−23 to −7)	7	0·77 (0·68–0·89)	
≥2 years	1076 (65%)	107 (20%)	166 (31%)	−11% (−16 to −6)	10	0·86 (0·80–0·93)	0·83
Bilateral AOM							
No	872 (66%)	104 (24%)	132 (30%)	−6% (−12 to 0)	17	0·92 (0·85–1·00)	
Yes	456 (34%)	64 (27%)	104 (47%)	−20% (−28 to −11)	5	0·72 (0·62–0·84)	0·021
Age and bilateral AOM							
<2 years+bilateral AOM	273 (20%)	42 (30%)	74 (55%)	−25% (−36 to −14)	4	0·64 (0·62–0·80)	
<2 years+unilateral AOM	261 (20%)	45 (35%)	53 (40%)	−5% (−17 to 7)	20	0·92 (0·76–1·11)	
≥2 years+bilateral AOM	183 (14%)	20 (23%)	30 (35%)	−12% (−25 to 1)	9	0·84 (0·70–1·02)	
≥2 years+unilateral AOM	611 (46%)	59 (19%	79 (26%)	−7% (−14 to 0)	15	0·92 (0·85–1·01)	0·022
Otorrhea							
Yes	116 (21%)	12 (24%)	39 (60%)	−36% (−53 to −19%)	3	0·52 (0·37–0·73)	0·039
No	439 (89%)	61 (28%)	94 (42%)	−14% (−23 to −5%)	8	0·80 (0·70–0·92)	
Pain at 3–7 days							
Age, years							
< 2 years	567 (35%)	77 (28%)	115 (40%)	−12% (−20 to -4%)	9	0.83 (0·73–0·93)	
≥ 2 years	1076 (65%)	86 (16%)	142 (26%)	−10% (−15 to -5%)	10	0.88 (0·82–0·93)	0·76
Bilateral AOM							
No	872 (66%)	85 (20%)	102 (23%)	−3% (−8 to -2%)	34	0.96 (0·89–1·03)	
Yes	456 (34%)	48 (20%)	88 (40%)	−20% (−28 to -12%)	5	0.75 (0·66–0·85)	0·005
Age and bilateral AOM							
< 2 years+bilateral AOM	273 (20%)	32 (23%)	62 (46%)	−23% (−34 to -12%)	5	0.70 (0·58–0·84)	
< 2 years+unilateral AOM	261 (20%)	41 (31%)	42 (33%)	−2% (−13 to 9%)	50	0.99 (0·84–1·17)	
≥ 2 years+bilateral AOM	183 (14%)	16 (17%)	26 (30%)	−13% (−25 to 1%)	8	0.83 (0·71–0·99)	
≥ 2 years+unilateral AOM	611 (46%)	44 (15%)	59 (19%)	−4% (−10 to 2%)	25	0.95 (0·88–1·02)	0·009

AOM=acute otitis media. RD=rate difference. RR=rate ratio. NNT=number needed to treat. *p value for the interaction term (antibiotics x subgrouping variable) in the fixed effect regression analysis.

Table 3: **Subgroup analyses with both the rate differences and rate ratios**

Discussion

Our meta-analyses of individual patient data showed that antibiotics are more beneficial in children aged less than 2 years with bilateral acute otitis media, and in those with both acute otitis media and otorrhoea—ie, in these groups three to four children have to be treated to prevent an extended course of the disease in one child. Although none of the trials included in this meta-analysis have had adequate power to produce precise effect estimates in clinically relevant subgroups, both McCormick[27] and Appelman[22] and their colleagues had suggested that children younger than 2 years might benefit most from antibiotics for otitis media. The results of our fixed-effect logistic regression analysis, however, showed that the effects of antibiotic treatment were not significantly modified by either age or bilateral disease alone. Additionally, the NNT was lower for the combined model than for individual components, indicating that targeting of both age and bilaterality would increase the benefits of antibiotic therapy. Moreover, the subgroups studied were based on a multivariate prognostic model, which showed that age and bilaterality were both independent predictors of an extended course of disease (unpublished data).

Although we need to understand the causal mechanism of the subgroups' effects before final conclusions can be drawn, we can postulate that, in children aged less than 2 years with bilateral acute otitis media and in those with otorrhoea, the infection is more often bacterial than viral. Indeed, Palmu and co-workers[32] have shown that culture-positive cases of acute otitis media are more often bilateral than are culture-negative events; middle ear effusion samples obtained through tympanic membranes with known pre-existing perforations were more likely to be culture-positive than were samples obtained through an intact membrane. Furthermore, perforations are more often caused by an infection with *Streptococcus pneumoniae* than with *Haemophilus influenzae* or *Moraxella catarrhalis*.[32] *S pneumoniae* is most common in young children.[32]

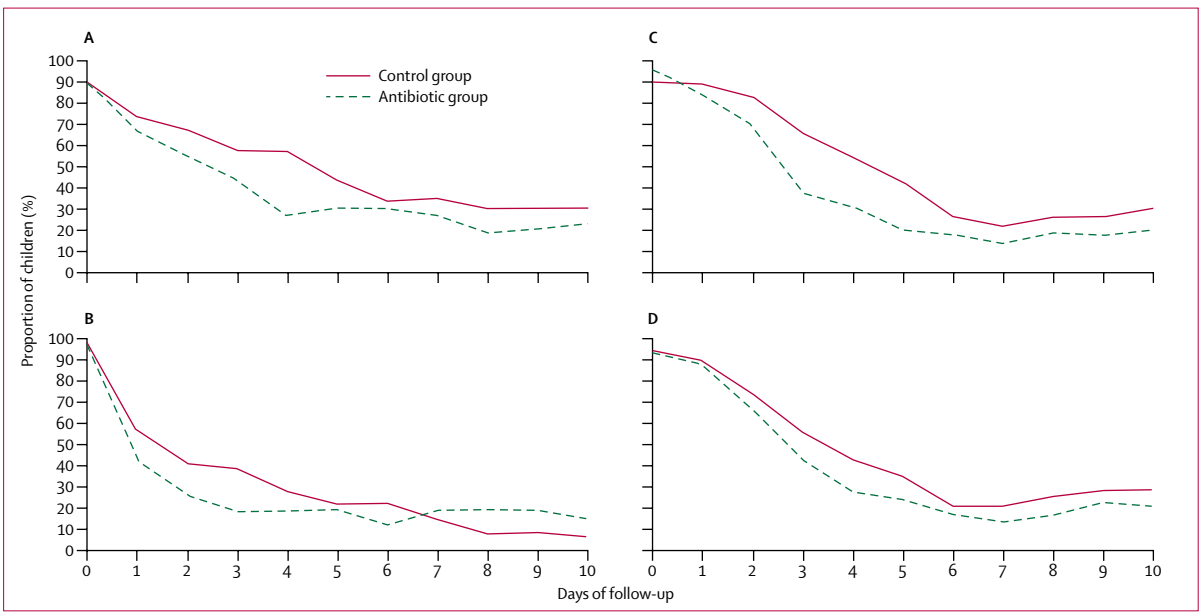

Figure 1: **Proportion of children with an extended course of acute otitis media**
A: ≤2 years with bilateral disease; B: ≥2 years with unilateral disease; C: with otorrhoea; and D: without otorrhoea.

The main strength of our study was that, by re-analysing the data of six trials, we were able to include 1643 children, which gave us the power to identify subgroups that could benefit most from treatment with antibiotics. Nevertheless, some of our findings deserve further discussion. First, only six of the ten eligible randomised, controlled trials could be included in our meta-analysis. The main characteristics of the four trials for which individual patient data were not available were, however, much the same as those in the six included trials. Moreover, the overall results of our subset of six trials are very similar to the overall results reported by the Cochrane review[3] that did include all trials. A funnel plot of the included studies (data not shown) also indicated that publication bias was unlikely.

Second, we could not do a pooled analysis with respect to failure rates since these rates were defined and measured differently in each of the six included trials. We did, however, undertake subgroup analyses of failure rate within each trial, and subsequently pooled these results for the six trials. The results were in accord with the pooled results for the subgroups—ie, the largest effect of antibiotics was in children aged younger than 2 years with bilateral acute otitis media (rate difference –8%, 95% CI –17% to 0%), and the smallest effect was in children aged 2 years or older with unilateral acute otitis media (rate difference –3%, –7% to 1%).

Third, the severity of the pain was estimated by parents and not further quantified in the trials, which could have resulted in an incorrect estimation of the real pain. Analysis with fever alone, however, showed much the same trend. Moreover, the fact that in many children the complaints at days 3–7 were mild should be taken into account in interpretation of reported NNTs and in the decision to initiate antibiotic therapy in individual patients.

Fourth, the results are based on child participants, who might not be representative of those visiting general practitioners. For example, the most severely affected children might be under-represented. However, because we had access to raw data from six trials, we had high numbers of children from specific high-risk groups, which are often under-represented in single trials. Furthermore, the children we included seem representative of those with acute otitis media visiting general practitioners, since the percentages of those aged less than 2 years and 2 years or older were much the same as those from a national survey in Netherlands of children with acute otitis media in primary care (ie, 35% *vs* 33%, and 65% *vs* 67%, respectively).[33]

Fifth, the rate of mastoiditis was so low that we could not obtain a precise estimate for risk of this complication. The trials done so far, however, showed that initially withholding antibiotics from children with acute otitis media does not increase suppurative complications. Whether restrictive antibiotic use increases acute mastoiditis at the population level remains unresolved, but the potential increase is only two cases per 100 000 person-years and should be weighed against potential adverse effects.[1]

Sixth, since not all trials used the most objective diagnostic methods (eg, pneumatic otoscopy or tympanometry) some children in our meta-analysis might not have had ear infections. Sensitivity analyses

with the three trials that did use these diagnostic methods were, however, in accord with the overall results.

Seventh, we did not study all possible subgroups. We selected established predictors of an extended course of disease (unpublished data) and some clinically relevant variables, and did stratified analyses only for those variables that showed a significant p value for the interaction in the fixed regression model. We might therefore have missed a subgroup. Our approach is, however, in agreement with recommendations for study of subgroups.[34] The strength of this approach is that our prognostic analyses revealed only a few relevant subgroups, limiting the number of subgroup analyses and subsequent false-positive findings (type I error) that could be caused by multiple testing. Furthermore, other subgroups that might benefit more from treatment with antibiotics (eg, children with Down syndrome or cleft palate) could not be studied in this meta-analysis of individual patient data, because these subgroups were excluded in the individual trials. The experience of many clinicians that these subgroups of children benefit more from treatment with antibiotics has not yet been evidenced in randomised controlled trials.

Eighth, we did not adjust for potential confounding due to differences between trials. We did, however, examine whether such confounding had occurred in our study, and noted that children aged less than 2 years were most likely to have fever and an abnormal tympanic membrane at baseline. We therefore used the Mantel Haenszel technique to adjust for these potential confounders in our subgroup analyses. Since the effect estimates were not altered by adjustments, crude effect estimates are presented.

We conclude that antibiotics are beneficial in relieving residual pain or fever at 3–7 days in children younger than 2 years of age with bilateral acute otitis media, and in children with acute otitis media and otorrhoea. For most other children with mild disease an observational policy seems justified.

Contributors

M M Rovers designed and planned the study, and gathered, analysed, and interpreted the data. P Glasziou and A W Hoes contributed to the initial idea and design of the study, interpreted the data, and supervised the study. C L Appelman, P Burke, D McCormick, R A Damoiseaux, I Gaboury, and P Little provided the data of the original trials, contributed to the protocol, and interpreted the data. The manuscript was prepared by M M Rovers, and all authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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