EFFECTIVENESS OF SHORTENED COURSE (≤ 3 DAYS) OF ANTIBIOTICS FOR TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

A systematic review of randomized controlled efficacy trials

REPORT

DEPARTMENT OF CHILD AND ADOLESCENT HEALTH AND DEVELOPMENT

WORLD HEALTH ORGANIZATION

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Executive Summary

Background

The current World Health Organization (WHO) recommendation for antibiotic treatment of acute otitis media is to give oral co-trimoxazole (trimethoprim 4 mg/kg/sulfamethoxozole 20 mg/kg twice a day) or amoxicillin (15 mg/kg three times a day) for five days. On the basis of recent data, WHO now recommends antimicrobials for only three instead of five days in non-severe pneumonia. Participant countries are thus naturally interested to see whether a similar reduction in duration of antibiotic therapy is appropriate for acute otitis media. In this age of rising health-care costs, increasing concern about emergence of resistant bacteria from the overuse of antibiotics and poor compliance with medication following symptomatic relief, it is desirable to know the shortest duration of antibiotic treatment that would result in favourable outcomes for acute otitis media in children. The available relevant systematic reviews on this subject were performed through literature searches conducted eight to ten years ago, were primarily based on clinical outcomes and did not specifically address the efficacy of a three-day antibiotic course. The current systematic review was therefore conducted to update appropriately the evidence base including bacteriologic outcomes.

Methods

The objective of the review was to determine the effectiveness of a short course of antibiotics (less than four days) in comparison with a longer course (four days or greater) for the treatment of acute otitis media in children. Randomized controlled trials of the empiric treatment of acute otitis media, comparing two antibiotic regimens of different duration, were considered for inclusion in the review. The participants included children between the ages of four weeks to 18 years with a clinical diagnosis of acute otitis media and no history of immediate prior antibiotic use, immune deficiency, chronic disease or head and neck abnormalities. The types of intervention eligible for the review were empiric antibiotic therapy for less than four days (defined as the short course), compared with equal to or greater than four days (defined as the long course). The antibiotic choices could be the same or different in the two treatment arms. Trials providing non-antibiotic interventions (for example analgesics, decongestants, or both) were considered if the only difference between the treatment arms was antibiotic duration as defined above.

The primary outcome was treatment failure (lack of clinical resolution or relapse or recurrence of acute otitis media or bacteriologic failure - wherever culture results by tympanocentesis were available) at an evaluation point until one month (31 days) after initiation of therapy. Clinical resolution meant that the presenting signs and symptoms of acute otitis media had improved or resolved. Requirement of second antibiotic was considered treatment failure. Secondary outcomes were: (a) clinical or bacteriologic failure shortly after treatment, at 10 to 14 days; (b) the cumulative number of treatment failures, relapses and recurrences reported from time of diagnosis until a final evaluation point between one and three months; and (c) any adverse effects of therapy. Middle ear effusion was not classified as a treatment failure because of its documented persistence during the course of the disease, regardless of treatment.

Using a carefully designed search strategy, the trials were identified from simultaneous searches of the various medical databases (till 26 August 2007), reference lists of identified articles, hand searches of reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings, and with help from donor agencies, 'experts' and authors of recent reviews.

Data abstraction was done using preformed questionnaires. The trials were grouped by the pharmacokinetic behaviour of the antibiotic used in the short course arm as follows: (i) short-acting oral antibiotics, for example penicillin, amoxicillin, cefaclor, cefuroxime; (ii) oral azithromycin or other macrolides; or (iii) parenteral ceftriaxone. Quality assessment of the trials was performed using the three standard criteria – allocation concealment, completeness of follow-up and blinding.

Data entry and analysis were done with SPSS and STATA softwares. The presence of bias was evaluated by funnel plot, and confirmed by Begg's and Egger's methods. Pooled estimates [relative risk (RR) with 95% confidence intervals (CI)] were calculated by both fixed and random effects models but the latter was used for depiction. Formal tests of heterogeneity were performed, namely, the statistic Cochran Q and I-squared (variation in pooled estimate attributable to heterogeneity). Pre-specified sensitivity and subgroup analyses were planned to be conducted for the

following: (i) quality of trial (allocation concealment, completeness of follow-up, and blinding); (ii) age (<2 years or >2 years); (iii) perforated tympanic membrane (yes or no); (iv) recurrent otitis media (yes or no); (v) trial site (developed or developing country); (vi) pharmacokinetic behaviour of the antibiotic used in the short course treatment arm (as defined above); (vii) duration of treatment in the long course treatment arm (recorded as a continuous variable with attempt to stratify as <10 days, or ≥10 days); (viii) outcome assessment time (within 10 to 14 days, until 31 days, or until 32 to 90 days); (ix) co-interventions (yes or no); (x) compliance monitoring (yes or no); (xi) intention to treat analysis (yes or no); and (xii) microbiological isolates (*S. pneumoniae* and *H. influenzae* versus others). Separate sensitivity and subgroup analyses were also attempted to assess the robustness of outcome criteria by redefining clinical resolution to include cured, but not improved symptoms. As no analytic components were identified, which were exclusively conducted in the pre-specified strata for age group, perforated tympanic membrane, recurrent otitis media or microbiological isolates, these subgroup analyses were done separately for those studies providing disaggregated information for outcomes on these variables. The subgroup analyses for outcome assessment time were implicit in the primary and secondary outcomes evaluation. The contribution of these variables to heterogeneity was also explored by metaregression.

Results

Forty-six potentially eligible randomized controlled trials were identified. Among these, eight studies were excluded, as these were ineligible. Of the 38 trials satisfying the inclusion criteria, three were excluded by outcome. Thirty-five trials were finally evaluated, which provided 38 analytic components.

These studies were primarily conducted in developed countries (11 in Europe, 10 each in North America and Asia, and four were multicentric from different continents). The duration of antibiotic use in the long course arm was 10 days in 33 analytic components, 7-14 days in two analytic components, seven days in two analytic components, and five days in one analytic component. Of the 35 trials, three used short-acting oral antibiotics, 21 used azithromycin, and 11 used parenteral ceftriaxone in the short course arm. Among the short-acting oral antibiotics group, similar antibiotics had been used in the short and long course arms. In the 23 analytic components, which had used oral azithromycin in the short course arm, only four had employed macrolides in the long course arm while the remaining had administered short-acting oral antibiotics, either amoxicillin or amoxicillin-clavunate (n=14), or cephalosporins (n=5). In studies addressing parenteral ceftriaxone use in the short course group (n=12), only short-acting oral antibiotics had been employed in the long course arm, primarily amoxicillin or amoxicillin-clavunate (n=9).

Primary outcome (treatment failure until one month)

The funnel plot was symmetrical suggesting the absence of publication bias, which was confirmed using the Egger's (weighted regression) method (P for bias=0.994) and the Begg's (rank correlation) method (continuity corrected P= 0.763). There was no evidence of an increased risk of treatment failure with a shorter course of antibiotics (≤ 3 days). The overall relative risk for treatment failure with a short course of antibiotics in comparison to a longer course was 1.06 (95% CI 0.95 to 1.17, P=0.298; test for heterogeneity: Cochran Q=37.02, I^2=0.1%, P=0.468). Use of a short-acting oral antibiotic in the short course arm was associated with a significantly increased risk of treatment failure (2.27, 95% CI 1.04 to 4.99). The slightly increased risk of treatment failure with parenteral ceftriaxone (1.13, 95% CI 0.99 to 1.30) was not statistically significant; however, the lower limit of confidence interval was close to 1. On combined scrutiny of sensitivity, subgroup and metaregression analyses, azithromycin use in the short course arm and compliance monitoring emerged as significant predictors of heterogeneity. The adjusted risk of treatment failure was increased by 3.31 times (95% CI 1.11 to 9.89; P=0.034) when antibiotics other than azithromycin were used in the short course arm while compliance monitoring was associated with a 1.52 times lower (95% CI 1.01 to 2.28; P=0.046) risk of treatment failure. On influence analysis, no single analytic component had a substantial impact on the quantification of summary relative risk. When treatment failure was redefined to include subjects showing improvement, the risk of this outcome was significantly lower with the short course (0.83, 95% CI 0.70 to 0.98, P=0.024; test for heterogeneity: Cochran Q=50.5, I^2=46.5%, P=0.004). Limited data did not suggest that a short course of antibiotics resulted in an increased risk of: (i) treatment failure in culture positive cases or in high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media, and specific bacterial pathogens), (ii) bacteriologic failure, (iii) relapse, (iv) recurrence, or (v) persistent middle ear effusion.

Outcomes at 10 to 14 days and between one and three months

At an earlier evaluation point (10-14 days), there was no evidence of an increased risk of treatment failure, or of persistent middle ear effusion (data from six studies only). Limited data (three studies) evaluating outcomes between

1-3 months also did not suggest an increased risk of treatment failure, relapse, recurrence or persistent middle ear effusion with a shorter course of antibiotics.

Adverse effects

The risk of individuals reporting adverse effects was significantly lower with a short course of antibiotics (RR=0.58, 95% CI 0.48 to 0.70, P<0.001; test for heterogeneity: Cochran Q=13.34, I^2=0.0%, P=0.821). There was no evidence of heterogeneity in the three subgroups for the number of individuals reporting adverse effects. There was a suggestion that among the antibiotics used in the short course arm, oral azithromycin resulted in decreased risk of diarrhoea (0.54, 95% CI 0.33 to 0.89) and rash (0.53, 95% CI 0.32 to 0.90) whereas parenteral ceftriaxone might be associated with decreased risk of vomiting but an increased risk of injection site pain (single study data).

Strengths and limitations of review

This is an updated systematic review on the subject with pre-specified inclusion and exclusion criteria, which also incorporates relevant sensitivity, subgroup and metaregression analyses. Diligent efforts were made to include relevant non-English publications and the analyzed data did not reveal any evidence of publication bias. The main conclusion regarding the primary outcome (treatment failure at an evaluation point until one month after initiation of therapy) remained stable over a large spectrum of sensitivity and subgroup analyses performed and evidence of heterogeneity was unusual. Influence analysis, namely the effect of omitting one study at a time, did not reveal an overwhelming effect of any single trial. Bacteriologic failure was also analyzed to factor for the possibility of "Pollyanna phenomenon". Further, on sensitivity, subgroup and metaregression analyses, significant predictors of heterogeneity were identified (azithromycin use in short course arm and compliance monitoring).

The following limitations merit consideration. First, there were only four trials in which a head-to-head comparison of different durations of the same antibiotic was carried out. Of these, only two trials had used an antibiotic currently recommended by WHO for otitis media, namely, amoxicillin. The results of the vast majority of individual trials could therefore reflect the differences in pharmacokinetic and pharmacodynamic properties of the antibiotics used in the short and long course arms rather than the duration of drug use. Second, interpretation is confounded by the wide variation in diagnostic and outcome criteria. Third, in only three analytic components both bacteriologic diagnosis and outcome measures were available for all subjects. In the remaining trials diagnosis and outcomes were either assessed by clinical criteria only or diagnosis was based on bacteriologic culture but outcome was assessed clinically (five analytic components). This could undermine the true difference between the bacteriologic efficacies of two treatment courses because of the high rate of spontaneous cure in cases of clinically diagnosed acute otitis media. Fourth, there were only a few studies providing information on high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media and specific bacterial pathogens), which limited the statistical power to detect differences in treatment failure in such subjects. Fifth, the majority of trials (28 or 74% of analytic components) were conducted in developed countries, which could have a bearing on extrapolating these findings to developing countries. However, trial site was not a significant predictor of treatment failure, and thus extrapolation to developing countries may be appropriate. Finally, multiple subgroup and metaregression analyses were done for important pre-specified variables, which increased the possibility of false positive results. The identified significant predictors of treatment failure should therefore be considered as tentative rather than definitive.

A *post hoc* analysis was conducted to address the concern that the pooled results were biased due to pharmaceutical industry support in several trials. Among the 38 analytic components, two (5.3%) were funded by non-pharmaceutical sources, 13 (34.2%) by the pharmaceutical industry and in 23 (60.5%) the source of funding was not stated, which precludes a robust examination of the above hypothesis. There was no evidence of publication bias or differences in trial quality in relation to industry support (adequate allocation concealment 2/13 *vs.* 2/25, P=0.91; attrition below 10% 7/13 *vs.* 16/23, P=0.58; and double blinding 5/13 *vs.* 4/25, P=0.26). Stratified analysis indicated significant (P=0.010) heterogeneity for relative risk of treatment failure until one month between the two groups of industry-supported trials (RR 0.98, 95% CI 0.87 to 1.10, P=0.717) and other studies (RR 1.34, 95% CI 1.09 to 1.64, P=0.006). However, there was no evidence of heterogeneity when a similar analysis was done separately for trials using azithromycin or ceftriaxone in the short course arm. On univariable metaregression for the entire data set, industry support emerged as a significant predictor of lower risk (0.73, 95%CI 0.57, 0.94, P=0.015); however, with adjustment for other variables it did not remain a significant predictor (0.73, 95%CI -0.35, 1.52, P=0.384). There is thus no concrete evidence that the industry-supported trials biased the pooled results; however, this possibility cannot be totally excluded.

Conclusions

Overall, there is no evidence of an increased risk of treatment failure until one month with a short (≤ 3 days) course of antibiotics for treating acute otitis media in children. However, in the short course arm, azithromycin use was associated with a lower risk of treatment failure while short-acting oral antibiotics like oral amoxicillin and parenteral ceftriaxone may be associated with a higher risk of treatment failure. Overall, adverse effects were significantly lower with the short course; oral azithromycin resulted in a decreased risk of diarrhoea and rash whereas parenteral ceftriaxone was associated with a decreased risk of vomiting but an increased risk of injection site pain. Adequately designed trials need to be conducted, funded by sources other than the pharmaceutical industry, to confirm unequivocally the above findings in relation to a shortened course of azithromycin. A thorough decision tree analysis should also simultaneously explore the possibility of recommending short course azithromycin for treatment of uncomplicated acute otitis media in children in individual practice and in public health settings in the event that clinicians or other prescribers or parents decide to use antibiotics.

Background

Otitis media is one of the most common childhood infections, the leading cause of doctors' visits by children, and the most frequent reason children are prescribed antibiotics or undergo surgery in developed countries (1, 2). Although there is some debate regarding the utility and specific guidelines for prescribing antimicrobials in acute otitis media (2-8), these drugs are frequently employed in clinical practice.

The optimal duration of prescribed antibiotic treatment in acute otitis media is still unclear, and varies worldwide. Expert opinion has recommended a reduction in antimicrobial use from 10 to 5 days for the treatment of uncomplicated otitis media in children over the age of six years (9). Narrative and systematic reviews have assessed the quality of scientific evidence to support a shorter course of antibiotic treatment (3,10-12). Two earlier systematic reviews of randomized controlled trials (3,11,12) have evaluated the efficacy of varying durations of antibiotics for the treatment of acute otitis media in children. The authors of one review (11,12) concluded that five days of short-acting antibiotic was effective treatment in uncomplicated middle ear infections in children.

The existing World Health Organization (WHO) recommendation is to administer oral co-trimoxazole (trimethoprim 4 mg/kg/sulfamethoxozole 20 mg/kg twice a day) or amoxicillin (15 mg/kg three times a day) for five days in acute otitis media (13). Recent data on antibiotic therapy in pneumonia indicates that three days duration is sufficient to treat WHO-defined non-severe disease. Consequently, WHO now recommends antimicrobials for only three days (instead of five days) in non-severe pneumonia. Participant countries are thus naturally curious to see whether a similar reduction in antibiotic therapy is applicable in acute otitis media. In this age of rising health-care costs, increasing concern about emergence of resistant bacterial strains from the overuse of antibiotics, and poor compliance with medication following symptomatic relief, it is desirable to know the shortest duration of antibiotic treatment resulting in favourable outcomes (12). As the available relevant systematic reviews (3,11,12) were performed on literature searches conducted eight to ten years ago and did not specifically address the efficacy of a three-day antibiotic course, this evidence needs to be updated appropriately to aid revision of the existing WHO guidelines for antibiotic treatment of acute otitis media in children. Further, the earlier reviews were primarily based on clinical outcomes. The "Pollyanna phenomenon" demonstrates the difficulty in determining a real difference between two antimicrobial regimens when clinical outcome, rather than bacteriologic outcome, is the sole determinant of efficacy (14-16). In trials measuring efficacy by clinical response alone, antimicrobial regimens with excellent antibacterial activity will appear less effective than they really are and regimens with poor antibacterial activity will also appear to be effective. It is therefore important to analyze bacteriologic and clinical outcomes simultaneously. The current systematic review was therefore conducted to update the evidence on this subject including bacteriologic outcomes.

Methods

Objective

To determine the effectiveness of a short course of antibiotics (less than four days) in comparison to a longer course (four days or greater) for the treatment of acute otitis media in children. Subgroup analyses of children less than two years of age, children with a perforated eardrum and children with recurrent otitis media were conducted to address concerns that these groups may have less favourable outcomes.

Criteria for considering studies for this review

Types of studies

Randomized controlled trials addressing treatment of acute otitis media, comparing two antibiotic regimens of different duration, were considered for inclusion in the review.

Types of participants

Children between the ages of four weeks to eighteen years, with a clinical diagnosis of acute otitis media and no history of immediate prior antibiotic use, immune deficiency, chronic disease or head and neck abnormalities.

Types of intervention

Empiric antibiotic therapy of a treatment arm for less than four days (defined as short course), and of a comparison treatment arm for equal to or greater than four days (defined as long course). The antibiotic could be the same or different in the two treatment arms. Trials providing non-antibiotic interventions (for example, analgesics, decongestants, or both) were considered if the only difference between the treatment arms was antibiotic duration as defined above.

Types of outcome measures

The primary outcome was treatment failure, which included a lack of clinical resolution or relapse or recurrence of acute otitis media or bacteriologic failure (wherever culture results by tympanocentesis were available) at an evaluation point until one month (31 days) after initiation of therapy. Clinical resolution meant that the presenting signs and symptoms of acute otitis media had improved or resolved. Requirement of a second antibiotic was considered as treatment failure.

Secondary outcomes were: (a) clinical or bacteriologic failure shortly after treatment, at 10 to 14 days, because this time is most indicative of the bacteriologic effect of the drug, and it is important to distinguish between relapse and a new infection (recurrence) when considering treatment failure, as a new infection can occur even when treated with the most effective drug (15); (b) the cumulative number of treatment failures, relapses and recurrences reported from time of diagnosis until a final evaluation point between one and three months; and (c) any adverse effects of therapy. Middle ear effusion was not classified as a treatment failure because of its documented persistence during the course of the disease, regardless of treatment. Data were, however, sought on the number of children with persistent middle ear effusion at all evaluation points.

Search methods for identification of studies

The trials were identified by simultaneous searches of the various medical databases until 4 May 2007. The databases searched included PubMed (since 1966), EMBASE (since 1974), Cochrane Controlled Trials Register, Web of Science (WoS), Allied and Complementary Medicine (AMED) (since 1985), British Nursing Index (BNI) (since 1994), Cumulative

Index to Nursing and Allied Health Literature (CINAHL) (since 1982), DH Data (since 1983) and Kings Fund (since 1979). The search strategy employed for Medline was: (acute[All Fields] AND ("otitis media"[MeSH Terms] OR otitis media[Text Word]) OR ear infection[Text Word]) AND ("anti-bacterial agents"[TIAB] NOT Medline[SB]) OR "anti-bacterial agents"[MeSH Terms] OR "anti-bacterial agents"[Pharmacological Action] OR antibiotic[Text Word]OR antibiotic*) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR trial*) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent" [MeSH Terms]OR child*). There were no language restrictions, and we performed full text English translation of relevant non-English publications. Analogous strategies were used for other databases. The search strategy utilized for AMED, BNI, CINAHL, DH Data, EMBASE, and Kings Fund was (acute AND (otitis OR ear ADJ infection OR ear ADJ infections) AND (antibiotic OR antibiotics OR antibacterial OR antibacterials) AND (trial OR trials OR randomized OR randomized OR meta-analysis OR review) AND (Child OR children OR infant OR infants OR adolescent OR adolescents)). The search strategy employed for Cochrane Controlled Trials Register was (acute AND (otitis OR ear ADJ infection OR ear ADJ infections) AND (antibiotic OR antibiotics OR antibacterial OR antibacterials) AND (Child OR children OR infant OR infants OR adolescent OR adolescents)). The search strategy utilized for WoS was (acute and otitis and (antibiotic* OR antimicrob* OR antibacterial*) AND (child* OR infant*) AND (short* OR course)). These records were de-duplicated against the PubMed set. An update of this initial search was performed on 26August 2007.

The title and abstract of the studies identified in the computerized search were scanned to exclude studies that were obviously irrelevant. The full texts of the remaining studies were retrieved and relevant articles were identified. The reference lists of the identified articles were reviewed to search for citations that were not listed in the computerized databases. An electronic lateral search strategy was also employed for 10 publications considered to be most relevant for this systematic review. This was supplemented by hand searches of reviews, bibliographies of books and other unpublished relevant literature. Finally, donor agencies, 'experts' and authors of recent reviews were contacted for their knowledge of any additional trials. To avoid publication bias, efforts were made to include both published and unpublished trials, as far as possible.

Methodological quality assessment

In order to enhance the validity of the meta-analysis, the quality of the identified trials was assessed by the standard quality criteria with respect to the allocation concealment, follow-up and blinding (17). The scores assigned were as follows:
1. Allocation Concealment: A. adequate; B. unclear; C. inadequate; D. not used.
2. Completeness of follow-up: A. <3% of participants excluded; B. 3% to 9.9% of participants excluded; C. 10% to 19.9% of participants excluded; D. 20% or more of participants excluded.
3. Blinding: A. Double blinding; B. Single blinding; C. No blinding; D. unclear.

Data abstraction

Data abstraction was done using a preformed questionnaire (Annex 1). The data included in the review was derived from the published manuscript or as provided by the authors for unpublished studies (if required). The authors were contacted for clarification, if required (and if possible). Notable general and individual study-specific features in relation to data abstraction are summarized in Annex 2.

The trials were grouped by the pharmacokinetic behaviour of the antibiotic used in the short course arm, as follows: (i) short-acting oral antibiotics, for example penicillin, amoxicillin, cefaclor, cefuroxime; (ii) oral azithromycin or other macrolides; or (iii) parenteral ceftriaxone. Drug dose, route and treatment duration were documented. Data was also recorded on other aspects including the trial site, patient baseline characteristics, inclusion, exclusion and outcome criteria, co-interventions, compliance monitoring, intention to treat analysis, and adverse effects to summarize the generalizability of included studies and to facilitate subgroup analyses.

In 'multi-arm' trials, in order to examine heterogeneity characteristics, the shared group was split into two or more groups with smaller sample size, and two or more (reasonably independent) comparisons (18) or analytic components were included. Thus, some trials contributed more than one '*analytic component*' for the purpose of statistical analyses. This resulted in a greater number of 'analytic components' than the included trials.

Statistical analysis

Data entry and initial analysis were performed on SPSS (Version 13.0) software. Meta-analysis and metaregression were performed with user-written programmes on Stata (version 9.2) software. The presence of bias in the extracted data was evaluated quasi-statistically using the funnel plot. The effect measure was plotted against the inverse of the standard error of the effect size. In the absence of a bias, because of the sampling variability, the graph takes the form of an inverted funnel. In the presence of a bias, the corner of the funnel is distorted or missing. Formal statistical tests for funnel plot asymmetry, namely the Begg's and Egger's methods, were also conducted with the user-written "metabias" command in the STATA (version 9.2) software (19,20). Pooled estimates (relative risk with 95% confidence intervals) of the evaluated outcome measures for the short course *versus* the long course antibiotic therapy were calculated by the user-written "metan" command in STATA (version 9.2) software (19,21). This programme also computes the L'Abbe plot, a graphical technique of exploring heterogeneity (22), and formal tests of heterogeneity, namely the statistic Cochran Q and I-squared (variation in pooled estimate attributable to heterogeneity) (23).

The outcome variables were pooled by both fixed effects and random effects model assumptions. There are no comprehensive rules on when to use random effects and when to use fixed effects models; debate continues in the statistical community. The underlying assumption for the fixed-effects model is that each study estimates the same true population value for the effect of interest, and thus the differences between observed results of studies can be fully accounted for by sampling variation. Random-effects models assume that a distribution of population effects exists and is generated by a distribution of possible study effect situations. Thus outcomes of studies may differ both because of sampling variation and true differences in effects. Both random and fixed effects models can be appropriately applied to pooling of data and also for evaluating the sensitivity of results to differing model assumptions. The random effects model was preferred even with the presence of occasional heterogeneity.

Sensitivity and subgroup analyses (specified in advance) were planned to be conducted by disaggregating results for the following with the user written "metan" command ("by option") in STATA (version 9.2) software (19,21): (i) quality of trial (allocation concealment, completeness of follow-up, and blinding); (ii) age (<2 years or >2 years); (iii) perforated tympanic membrane (yes or no); (iv) recurrent otitis media (yes or no); (v) trial site (developed or developing country) – the trial sites were classified as developing countries if these were categorized in either the low or medium human development index as defined by the Human Development Report (24); (vi) pharmacokinetic behaviour of the antibiotic used in the short course treatment arm (as defined above); (vii) duration of treatment in the long course treatment arm (recorded as a continuous variable with attempt to stratify as <10 days, or $\geq$10 days); (viii) outcome assessment time (within 10 to 14 days, until 31 days, or until 32 to 90 days); (ix) co-interventions (yes or no); (x) compliance monitoring (yes or no); (xi) intention to treat analysis (yes or no); and (xii) microbiological isolates (*S. pneumoniae* and *H. influenzae* versus others). A separate sensitivity and subgroup analysis was also attempted to assess the robustness of outcome criteria by redefining clinical resolution to include cured, but not improved symptoms. As no analytic components were identified which were exclusively conducted in the pre-specified strata for age group, perforated tympanic membrane, recurrent otitis media or microbiological isolates, these subgroup analyses were performed separately for those studies providing disaggregated information for outcomes on these

variables. The subgroup analyses for outcome assessment time were implicit in the primary and secondary outcomes evaluation.

The contribution of these variables to heterogeneity was also explored by metaregression using the “metareg” command in STATA (version 9.2) software with the restricted maximum likelihood option (25). A variable was considered to be an important explanatory factor if statistical significance was consistently documented in the disaggregated analyses and in the metaregression. A greater credence was attached to the metaregression results, particularly those controlling for additional variables.

The influence of individual studies on the summary effect estimate was explored through the user-written “metainf” command in STATA (version 9.2) software. This command performs an influence analysis, in which the meta-analysis estimates are computed omitting one study at a time (19).

Results

Trial flow

Forty-six potentially eligible randomized controlled trials were identified (26-71). Among these, eight studies were excluded (26-33), as these were ineligible (Fig. 1). Of the 38 trials satisfying the inclusion criteria, three were excluded by outcome (34-36). Therefore 35 trials were finally evaluated, which provided 38 analytic components, in this systematic review.

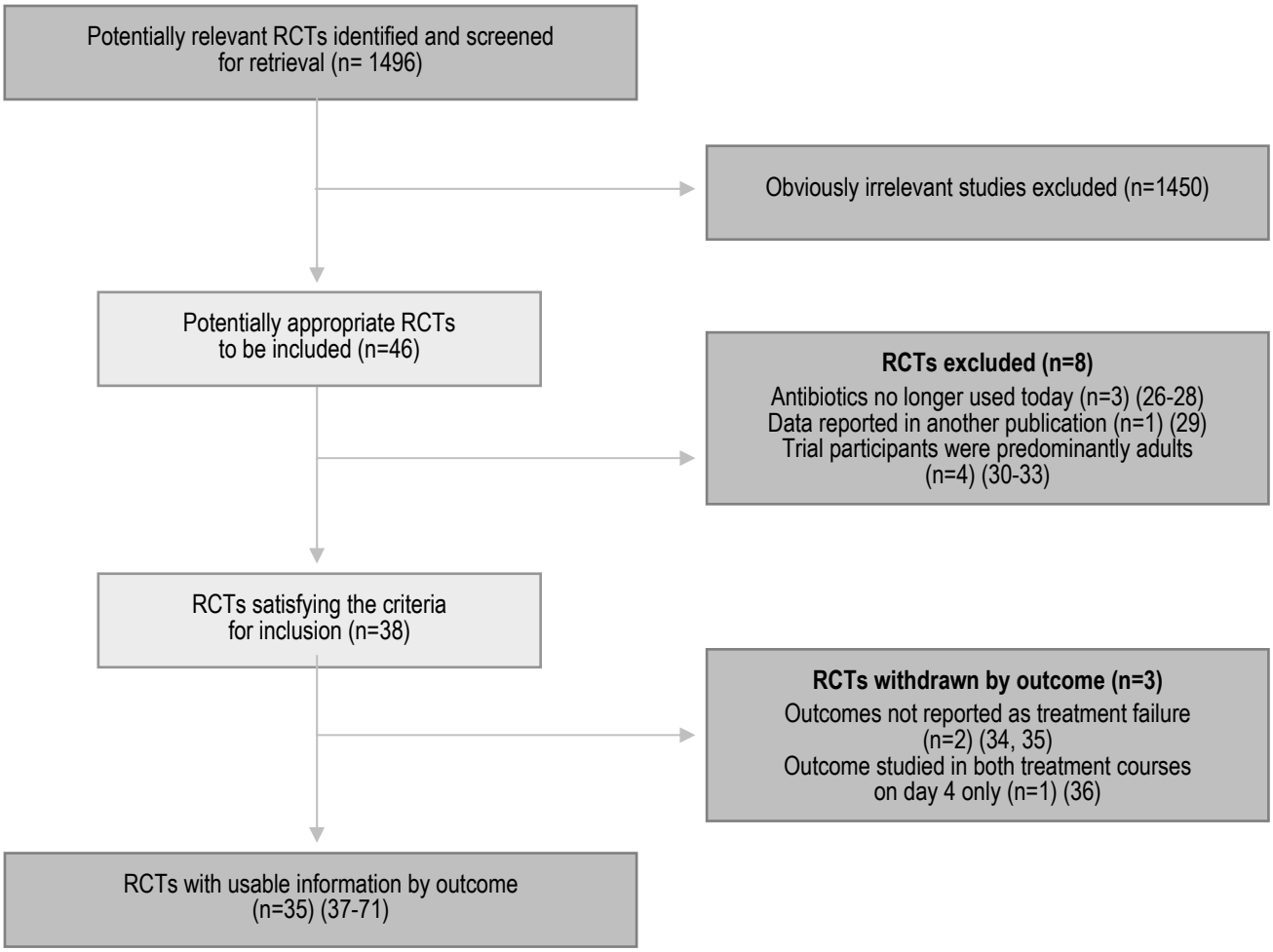

Fig. 1: Flow chart depicting the trial flow for selection of randomized control trials included in the meta-analysis

Study characteristics

Table 1 summarizes the baseline characteristics of the included trials. These studies were primarily conducted in developed countries (11 in Europe, 10 each in North America and Asia, and four were multicentric from different continents). Children more than 12 years old were included in one trial while no study was conducted exclusively in subjects below two years of age. The duration of antibiotic use in the long course arm was 10 days in 33 analytic components, 7-14 days in two analytic components, seven days in two analytic components, and five days in one analytic component. The details of the clinical diagnostic criteria employed for acute otitis media in individual studies are stated in Table 2. In most of the analytic components (22/36; 61%), apart from symptoms and signs of acute ear inflammation, presence of middle ear effusion was stated to be an essential diagnostic criterion. Presence of middle ear effusion was diagnosed by bulging of the tympanic membrane with or without impaired mobility, pneumatic otoscopy, or abnormal tympanogram.

Of the 35 trials, three used short-acting oral antibiotics, 21 used azithromycin, and 11 used parenteral ceftriaxone in the short course arm (Table 3). Within the short-acting oral antibiotics group, similar antibiotics had been used in the short and long course arms. In the 23 analytic components, which had used oral azithromycin in the short course arm, only four had employed macrolides in the long course arm while the remaining had administered short-acting oral antibiotics, either amoxicillin or amoxicillin-clavunate (n=14), or cephalosporins (n=5). Among those using parenteral ceftriaxone in the short course group (n=12), only short-acting oral antibiotics had been employed in the long course arm, primarily amoxicillin or amoxicillin-clavunate (n=9).

Table 4 summarizes the outcome criteria used for analyzing treatment efficacy in individual studies. Among 37 analytic components providing detailed information on treatment failure, 30 (81%) had relied on clinical outcome only; of these, four (13%) had utilized only nonresolution or persistence of symptoms to categorize the clinical outcome. In three analytic components, information on both clinical and bacteriologic failures was available for all subjects. Among the 19 analytic components providing information on relapse and/or recurrence, five had utilized both clinical and bacteriologic information.

Table 1. Baseline characteristics of the included studies

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Route$^{\mu}$, Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Route$^{\mu}$, Total daily dose (mg/kg), Number of days Treated, Number randomized
de Saintonge 1982 (37)	United Kingdom	24-120	Not mentioned, B, A , B, 1, 1	(1) No history of chronic ear disease. (2) Not more than one attack of otitis media in the preceding year and none in previous month. (3) No symptoms for more than a week. (4) No complications already present. (5) No acute exanthemata. (6) No concurrent serious medical problems. (7) No previous penicillin allergy.		Amoxicillin, 1, 25, 3, 42	Amoxicillin, 1, 25, 10, 42
Meistrup-Larsen 1983 (38)	Denmark	12-120	Not Mentioned, A, A, A, 1, 1	Children with diagnosis of AOM. (earache and red or inflamed tympanic membrane)	(1) Other treatment apart from acetylsalicylic acid already commenced. (2) Antibiotic treatment within the last month. (3) AOM within the last month. (4) Suspected chronic otitis media. (5) Treatment for secretory otitis media within last 12 months. (6) Suspected allergy to penicillin. (7) Concurrent disease requiring antibiotics, e.g. pneumonia or severe tonsillitis.	Penicillin, 1, 55, 2, 46	Penicillin, 1, 55, 7, 55
Puczynski 1987 (39)	United States of America	24-144	Not mentioned, B, A, A, 1, 3	Children with diagnosis of AOM.	(1) History of hypersensitivity to penicillin. (2) Antibiotic use within the previous 21 days. (3) Perforation of tympanic membrane. (4) History of acute otitis media in previous month. (5) History of chronic middle ear disease. (6) Concurrent disease requiring antimicrobial.	Amoxicillin, 1, 100, 1, 7	Amoxicillin, 1, 40, 10, 10

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Route[μ], Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Route[μ], Total daily dose (mg/kg), Number of days Treated, Number randomized
Varsano 1988 (40)	Israel	6-96	Not mentioned, B, A, D, 2, 1	Children treated for AOM.	(1) History of AOM during the preceding month. (2) Antibiotic therapy during the previous 2 weeks. (3) Eardrum perforation with or without otorrhea. (4) Myringotomy. (5) Conditions predisposing to recurrent ear infections, such as cleft palate, immunodeficiency, etc. (6) Known allergy to penicillins or cephalosporins.	Ceftriaxone, 2, 50, 1, 27	Amoxicillin, 1, 37.5, 7, 25
Pestalozza 1992 (41)	Italy	11-108	Not mentioned, D, C, A , 3, 3	Children with acute otitis media.	(1) Patients sensitive to macrolides or β lactams. (2) Receiving experimental drug or other antibiotics up to one month before treatment.	Azithromycin, 1, 10, 3, 15	Amoxicillin-clavulanate, 1, 50, 10, 15
Daniel 1993 (42)	Germany, Switzerland	0-108	Not mentioned, B, C, A, 1, 3	Clinical evidence of acute otitis media, demonstrated by presence of fluid accompanied by fever, pain or irritability.	(1) Known History of hypersensitivity to macrolide or penicillin. (2) Disorders of gastrointestinal tract, chronic otitis media, infectious mononucleosis, or any life-threatening condition. (3) Any antibiotic 48 hr before the study (unless infecting pathogen was resistant to that antibiotic). (4) Investigational drug within a month of study. (5) Treatment with long-acting penicillin within 6 weeks.	Azithromycin, 1, 10, 3, 105	Amoxicillin-clavulanate, 1, 30, 10, 54
Green 1993 (43)	United States of America	5-60	Not mentioned, A , A, C, 2, 2	Children with diagnosis of AOM.	(1) Weight <5 kg or >18.7 kg. (2) Use of antibiotics in previous 14 days. (3) AOM within the past month. (4) Chronic otitis media. (5) Myringotomy Tube. (6) Bleeding dyscrasia. (7) Serious underlying disease. (8) Concurrent infection. (9) Tympanic membranes that were heavily scarred, perforated, or obscured by purulent drainage. (10) Hypersensitivity to penicillins, cephalosporins, or lidocaine. (11) Parents not giving consent. (12) Normal tympanogram.	Ceftriaxone, 2, 50, 1, 128	Amoxicillin, 1, 40, 10, 133
Mohs 1993 (44)	Guatemala, Costa Rica, Panama, Egypt	24-144	Not randomized, B, C, A, 1, 3	Children with clinical diagnosis of acute otitis media.	(1) Patients treated with any antibiotic in two weeks period before entering the study unless failure of medication was documented. (2) Use of investigational drug within the previous month. (3) Infection requiring additional antibiotic. (4) Concurrent treatment with ergotamine, carbamazepine or digitalis glycosides. (5) History of chronic diarrhoea or other gastrointestinal disorders. (6) Known hypersensitivity to macrolides, penicillins or azithromycin. (7) Children with terminal illnesses or other conditions which could prevent completion of the evaluations.	Azithromycin, 1, 10, 3, 77	Amoxicillin, 1, 30, 10, 77
Schaad 1993 (45)	Switzerland	24-144	Not mentioned, B, C, A, 3, 3	Children suffering from AOM.	(1) Treatment with another investigational drug within four weeks, or other antibiotics within two weeks, before study enrolment (unless there was documented failure with treatment). (2) Known hypersensitivity to macrolides, azithromycin or β-lactam antibiotics. (3) Any evidence of GIT condition that could affect absorption of the study drugs.	Azithromycin, 1, 10, 3, 197	Amoxicillin-clavulanate, 1, 40, 10, 192

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Routeμ, Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Routeμ, Total daily dose (mg/kg), Number of days Treated, Number randomized
Chamberlain 1994 (46)	United States of America	18-72	Computer generated random numbers, C, B, C, 2, 3	Patients should have all the following - (1) Otalgia or fever. (2) Evidence of middle ear inflammation (redness or injection of tympanic membrane). (3) Clinical evidence of fluid or negative pressure in the middle ear (bulging or retracted tympanic membrane with decreased mobility by pneumatic otoscopy). (4) An abnormal tympanogram (type B or C).	(1) An immunocompromising disease. (2) Allergy to penicillins or cephalosporins. (3) Antibiotics within the last 10 days. (4) Otitis media within the last 30 days. (5) Chronic or recurrent otitis media. (6) Placement of pressure equalization tubes. (7) Focal infection other than otitis media. (8) Need for admission. (9) Ruptured tympanic membrane. (10) No telephone.	Ceftriaxone, 2, 50, 1, 39	Cefaclor, 1, 40, 10, 28
Principi 1995 (47)	Multicentric: Brazil, Chile, Germany, Italy, Republic of Korea, Spain, Turkey, Venezuela	6-144	Not mentioned, B, C, C, 2, 3	Children between the ages of 6 months and 12 years with a diagnosis of AOM (History and tympanic membrane changes at otoscopy)	(1) Children having terminal illness. (2) Use of another antimicrobial agent within two weeks prior to enrollment unless there was documented evidence of treatment failure. (3) Hypersensitivity to macrolides or penicillins. (4) Presence of an infection requiring additional antibiotic therapy. (5) Receipt of concurrent ergotamine, carbamazepine or digitalis glycosides. (6) History of chronic diarrhoea or other gastrointestinal disorders that could affect absorption of the study drug.	Azithromycin, 1, 10, 3, 243	Amoxicillin-clavulanate, 1, 40, 10, 240
Arguedas 1996 (48)	Costa Rica	72-144	Randomly allocated according to a computer-generated table of random numbers, A, C, B, 2, 1	Children with symptoms consistent with uncomplicated AOM and otoscopic and tympanometric signs indicative of otitis media.	(1) Perforated tympanic membrane. (2) Prior placement of a tympanostomy tube. (3) History of any significant reaction to a macrolide or β-lactam antibiotic. (4) Receipt of any other antimicrobial agent in the 72 hours prior to enrollment. (5) Presence of a serious underlying disease. (6) Malabsorption syndrome or other gastrointestinal disturbance that would preclude reliable administration and absorption of oral medication.	Azithromycin, 1, 10, 3, 51	Amoxicillin-clavulanate, 1, 40, 10, 49
Bauchner 1996 (49)	United States of America	3-72	Computer-generated number, B, C, C, 3, 3	Children with diagnosis of AOM.	(1) Diagnosis of AOM within 30 days prior to entry into study. (2) Antibiotic therapy within last 7 days. (3) Perforation of Tympanic membrane. (4) Presence of tympanostomy tubes. (5) Allergy to penicillins, cephalosporins, or lidocaine. (6) Recurrent otitis media. (7) Anatomic conditions predisposing to recurrent ear infections. (8) Parent or guardian unable or unwilling to understand and follow instructions. (9) Patients who lived in a household without a telephone.	Ceftriaxone, 2, 50, 1, 321	Amoxicillin -Clavulanate, 1, 50, 10, 327

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Route[µ], Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Route[µ], Total daily dose (mg/kg), Number of days Treated, Number randomized
Rodriguez 1996 (50)	Multicentre study: Guatemala	6-144	Not mentioned, B, C, B, 3, 3	Children with acute otitis media.	(1) Patients treated with any antibiotic in two weeks period before entering the study unless failure of medication was documented. (2) Use of investigational drug within the previous month. (3) Infection requiring additional antibiotic. (4) Concurrent treatment with ergotamine, carbamazepine or digitalis glycosides. (5) History of chronic diarrhoea or other gastrointestinal disorders. (6) Known hypersensitivity to macrolides, penicillins or azithromycin. (7) Children with terminal illnesses or other conditions that could prevent completion of the evaluations. (8) Chronic otitis media. (9) Perforated eardrum	Azithromycin, 1, 10, 3, 125	Cefaclor, 1, 40, 10, 134
Arguedas 1997 (51)	Costa Rica	6-144	Computer-generated numbers, A, C, B, 2, 1	Children with symptoms consistent with uncomplicated acute otitis media and otoscopic and tympanometric signs consistent with otitis media.	(1) Perforation with or without drainage. (2) Prior placement of tympanostomy tube. (3) History of any significant reaction to a macrolide. (4) Patients who had received another antimicrobial agent within 72 hrs before enrollment. (5) Patient with serious underlying disease and children with malabsorption syndrome or other gastrointestinal disturbances which would preclude reliable administration of oral medication.	Azithromycin, 1, 10, 1, 51	Clarithromycin, 1, 15, 10, 49
Barnett 1997 (52)	United States of America	3-36	Stratified by site and age using Metstat, B, B, C, 1, 1	Children diagnosed as AOM.	(1) Received antibiotic within the preceding 7 days. (2) Had an underlying anatomical anomaly of the head and neck. (3) Immunosuppressed. (4) Had a chronic illness. (5) Had an allergy to penicillins, sulfa drugs, or cephalosporins. (6) Had ever had tympanostomy tubes. (7) Did not have access to a telephone. (8) Spoke a language other than English, Portuguese, Spanish, or French.	Ceftriaxone, 2, 50, 1, 241	Trimethoprim-Sulphamethoxazole, 1, 48, 10, 243
Celik 1997 (53)	Turkey	6-636	Not mentioned, B, C, D, 3, 1	Symptom of acute otitis media with otoscopic findings.	(1) Pregnancy. (2) Hypersensitivity to medicines used in study. (3) Using any antimicrobial medicine during the last week. (4) No other disease that may obstruct the study (e.g. chronic kidney, liver disease). (6) Ergotamine, carbamazepine or digitatis intake.	Azithromycin, 1, 10, 3, 31	Cefuroxime, 1, 40, 10, 25
Ficnar 1997 (54)	Croatia	6-144	Not Mentioned, B, C, A, 3, 3	Children with diagnosis of acute otitis media.	(1) Patient with hypersensitivity to macrolides. (2) Severe renal or hepatic impairment. (3) Gastrointestinal disturbances which could affect drug absorption. (4) Acute viral infection. (5) Chronic otitis media. (6) Fibrocystic disease. (7) Immunocompromised patients. (8) Patients who had received more than one dose of any antibiotic 24 hours prior to entering the study or depot-penicillin in the past 2 weeks.	Azithromycin, 1, 10, 3, 54	Azithromycin, 1, 6, 5, 38

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Route$^{\mu}$, Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Route$^{\mu}$, Total daily dose (mg/kg), Number of days Treated, Number randomized
Varsano 1997 (55)	Israel	4-72	Randomized numbers in block of 16, B, C, B, 4, 1	Children treated for acute otitis media.	(1) History of AOM during the preceding month. (2) Antibiotic therapy during the previous 2 weeks. (3) Spontaneous perforation of the tympanic membrane. (4) Presence of tympanostomy tubes. (5) Conditions predisposing the patient to recurrent ear infections, such as craniofacial anomalies, Down's syndrome, or immunodeficiency. (6) Allergy to penicillins or cephalosporins.	Ceftriaxone, 2, 50, 1, 115	Amoxicillin-clavulanate, 1, 46.9, 10, 112
de Jose 1998 (56)	Multicentric: Spain	6-144	Not mentioned, B, C, B, 2, 3	Children with diagnosis of AOM.	(1) Treated with another antibiotic two weeks before the inclusion unless there was documented evidence of treatment failure. (2) Children with terminal illness or any other condition preventing them from completing the treatment. (3) Hypersensitivity to macrolides or penicillins. (4) Requiring treatment with another antimicrobial. (5) Concomitant treatment with ergotamine, carbamazepine or digitalis. (6) Children with chronic diarrhoea or any other gastrointestinal pathology that could affect the absorption of drug.	Azithromycin, 1, 10, 3, 64	Amoxicillin-clavulanate, 1, 40, 10, 62
Callejo1 1998 (57)	Spain	36-72	Not mentioned, B, C, B, 2, 3	Children with clinical diagnosis of otitis media.	(1) Hypersensitivity to macrolides or B-lactam antibiotics. (2) Disorders of the GIT. (3) Antibiotic use within past 14 days. (4) Chronic otitis media, Infectious mononucleosis or some other potentially fatal illness.	Azithromycin, 1, 10, 3, 0/18	Amoxicillin-clavulanate, 1, 40, 7-14, 2/22
Callejo2 1998 (57)	Spain	36-72	Not mentioned, B, C, B, 2, 3	Children with clinical diagnosis of otitis media.	(1) Hypersensitivity to macrolides or β lactam antibiotics. (2) Disorders of the GIT. (3) Antibiotic use within past 14 days. (4) Chronic otitis media, Infectious mononucleosis or some other potentially fatal illness.	Azithromycin, 1, 10, 3, 0/19	Cefaclor, 1, 40, 7-14, 2/15
Kara1 1998 (58)	Turkey	6-72	Not mentioned, B, C, A, 1, 3	Children with clinical symptoms and signs of acute otitis media.	(1) Acute ear infection history in past 3 months. (2) Antibiotic use during last 2 weeks. (3) Drug allergy.	Ceftriaxone, 2, 50, 1, 13	Amoxicillin, 1, 40, 10, 25
Kara2 1998 (58)	Turkey	6-72	Not mentioned, B, C, A, 1, 3	Children with clinical symptoms and signs of acute otitis media.	(1) Acute ear infection history in past 3 months. (2) Antibiotic use during last 2 weeks. (3) Drug allergy.	Ceftriaxone, 2, 50, 1, 12	Cefuroxime, 1, 30, 10, 25
Al Ghamdi 1999 (59)	Saudi Arabia	6-72	Not mentioned, B, D, B, 2, 1	Children diagnosed clinically as having AOM.	Antibiotic use in preceding 2 weeks.	Ceftriaxone, 2, 50, 1, 83	Amoxicillin-clavulanate, 1, 40, 10, 123
Cohen 1999 (60)	France	4-30	Telephonic computer-generated code, B, C, C, 1, 1	Newly diagnosed AOM. Diagnostic criteria for AOM - Presence of an effusion plus marked redness or marked bulging or moderate redness and bulging associated with fever and/or otalgia and/or irritability.	(1) Antibiotic treatment within 7 days before enrollment. (2) History of hypersensitivity to beta lactams. (3) Severe underlying disease. (4) Ruptured tympanic membrane. (5) Presence of tympanostomy tubes. (6) Previous inclusion into the study.	Ceftriaxone, 2, 50, 1, 255	Amoxicillin -Clavulanate, 1, 100, 10, 258
Dagan 2000 (61)	Israel	3-36	Not mentioned, B, B, C, 2, 1	(1) Had AOM as established on the basis of symptoms and signs. (2) Acute illness < 7 days duration. (3) Had an intact eardrum. (4) Had purulent, mucopurulent, or seropurulent fluid on tympanocentesis.	(1) They had received another antimicrobial agent within 72 hr before enrollment unless there was a clear clinical failure of the other antimicrobial agent. (2) Chronic otitis media. (3) Dry tap. (4) Concomitant infection requiring treatment with other systemic antimicrobial agent. (5) Underlying condition known to compromise their ability to handle bacterial infections as immunodeficiency.	Azithromycin, 1, 10, 3, 70	Cefaclor, 1, 40, 10, 68

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Routeμ, Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Routeμ, Total daily dose (mg/kg), Number of days Treated, Number randomized
Slapak 2000 (62)	Czech Republic	6-144	Microsoft Access 4.0. Sequential method 1:1 in blocks of 10, B, C, A, 1, 3	Children with diagnosis of acute otitis media.	(1) Allergy to macrolide. (2) Marked renal or hepatic dysfunction. (3) Gastrointestinal disorders which could affect absorption of drugs. (4) Syndromes with local or systemic infective complication. (4) Chronic otitis media. (5) Previous antibiotic use (during the last 7 days before inclusion in study or 4 weeks if it was long-acting penicillin injection).	Azithromycin, 1, 10, 3, 50	Clarithromycin, 1, 15, 10, 49
Kawalski1 2001 (63)	Poland	6-144	Using randomization schedule (sequential numbering), B, B, nm, 2, 1	Children with presence of middle ear effusion by pneumalic otoscopy and presence of at least one of the symptoms - ear pain, ear drainage, fever, irritability, vomitting or diarrhoea.	(1) History of allergy to macrolides and or beta -lactamase antibiotics and or clavulanic acid. (2) Marked renal or hepatic impairment. (3) Evidence of chronic diarrhoeal disease or other gastrointestinal disorder which might affect absorption. (4) Chronic otitis media. (5) Antimicrobial treatment (more than 1 daily dose) within 7 days before study enrollment or treatment with any long-acting penicillin injection within 4 weeks before study enrollment.	Azithromycin, 1, 10, 3, 29	Clarithromycin, 1, 15, 10, 53
Kawalski2 2001 (63)	Poland	6-144	Using randomization schedule (sequential numbering), B, B, nm, 2, 1	Children with presence of middle ear effusion by pneumalic otoscopy and presence of at least one of the symptoms - ear pain, ear drainage, fever, irritability, vomitting or diarrhoea.	(1) History of allergy to macrolides and or beta-lactamase antibiotics and or clavulanic acid. (2) Marked renal or hepatic impairment. (3) Evidence of chronic diarrhoeal disease or other gastrointestinal disorder which might affect absorption. (4) Chronic otitis media. (5) Antimicrobial treatment (more than 1 daily dose) within 7 days before study enrollment or treatment with any long-acting penicillin injection within 4 weeks before study enrollment.	Azithromycin, 1, 1, 3, 29	Amoxicillin-clavulanate, 1, 50, 10, 59
Arrieta 2003 (64)	Multicentric: United States of America, Latin America	6-72	Not mentioned, B, A, A, 1, 1	Children between 6 months and 6 yrs with recurrent otitis media. Recurrent AOM ≥1 episode within 30 days of enrollment, ≥ 3 episodes within 6 months of enrollment, ≥ 4 episodes within 12 months. AOM diagnosed with signs and middle ear effusion.	(1) Weight > 25kg. (2) Clinically significant cardiovascular, hepatic renal or hematological disease. (3) AOM requiring hospitalization or intravenous antibiotic. (4) History of hypersensitivity or intolerance to penicillin, penicillin derivatives or macrolides. (5) Treatment with systemic antibiotic for indications other than AOM within 30 days of enrollment. (6) Use of any investigational product within one month of enrollment. (7) Presence of tympanostomy tubes, cholesteatoma, retraction pockets, chronic perforation of the tympanic membrane, or inability to take oral medication.	Azithromycin, 1, 20, 3, 101	Amoxicillin- Clavulanate, 1, 96.4, 10, 99
Block 2003 (65)	United States of America	6-144	Randomly assigned 1:1, B, A, C, 1, 1	Children with diagnosis of AOM.	(1) Absence of AOM within the previous 30 days. (2) Weight > 40 kg. (3) AOM or any illness requiring systemic antimicrobial therapy <=30 days before study entry. (4) Significant interfering medical conditions as gastroenteritis. (5) Hypersensitivity to penicillins or macrolides. (6) Chronic or persistent otitis media. (7) Presence of tympanostomy tubes, prior ear surgery, cholesteatoma, or perforation of tympanic membrane.	Azithromycin, 1, 10, 1, 173	Amoxicillin-clavulanate, 1, 51.4, 10, 173

Study (Reference)	Location	Age Group (mo)	Method of randomization, Allocation concealment, Blinding, Loss to follow-up, Intention to treat, Compliance*	Inclusion criteria	Exclusion criteria	Antibiotic in short course, Routeμ, Total daily dose (mg/kg), Number of days treated, Number randomized	Antibiotic in long course, Routeμ, Total daily dose (mg/kg), Number of days Treated, Number randomized
Dunne 2003 (66)	United States of America	6-144	Computer-generated randomization list, B, A, A, 1, 1	Patients with typical signs and symptoms of AOM.	(1) History of hypersensitivity to β lactams, macrolides or azithromycin. (2) Phenylketonuric. (3) Treated with antibiotics in prior 30 days. (4) Had symptoms of otitis media for > 4 weeks. (5) Receiving antimicrobial prophylaxis.	Azithromycin, 1, 10, 3, 188	Amoxicillin-clavulanate, 1, 45, 10, 185
Oguz 2003 (67)	Turkey	6-144	Not mentioned, B, B, C, 3, 1	(1) Children with diagnosis of AOM. (2) No diagnosis of chronic otitis media. (3) No acute perforation of tympanic membrane. (4) Absence of allergy to study drugs.	(1) Antibiotics within 6 weeks. (2) Chronic disorder. (3) Inappropriate use of antibiotic used in the study.	Azithromycin, 1, 10, 3, 41	Cefaclor, 1, 40, 10, 37
Yamei 2003 (68)	China	12-144	Not mentioned, B, C, C, 3, 3	Children with acute otitis media.	(1) Known or suspected penicillin allergy. (2) AOM within 30 days or AOM twice within last 6 months. (3) Rupture of tympanic membrane. (4) Treated with antibiotics within last 7 days. (5) Unwillingness to take oral or injected drugs. (6) External ear inflammation, redness and pus. (7) With other serious infections, kidney failure, heart failure, immune deficiency or other life-threatening disease.	Ceftriaxone, 2, 50, 1, 118	Amoxicillin, 1, 40, 10, 118
Wang 2004 (69)	Taiwan, China	3-72	Not mentioned, B, C, D, 2, 1	Patients newly diagnosed with AOM.	(1) Received antibiotic treatment within last 7 days before enrollment. (2) Had ruptured tympanic membrane. (3) Presented with tympanostomy.	Ceftriaxone, 2, 50, 1, 51	Amoxicillin -Clavulanate, 1, 45, 10, 45
Arguedas 2005 (70)	Multicentric study: United States, Costa Rica, Chile, Finland	6-30	Not mentioned, B, A, A, 1, 1	Children 6-30 months of age if they had (1) At least one symptom or sign consistent with the diagnosis of AOM, and (2) Presence of middle ear effusion.	(1) Treatment with any antibiotic within 30 days before enrollment. (2) Symptoms or history of chronic or persistent otitis media, defined as antimicrobial use in the past 30 days for a previous otitis media episode. (3) Tympanosomy tubes in place. (4) History of hypersensitivity or intolerance to penicillin, penicillin derivatives or macrolide. (5) Tympanic membrane perforation of >24 hours. (6) Infection known to be caused by an organism resistant to azithromycin or amoxicillin. (7) Any other medical condition that was considered clinically significant by the investigators.	Azithromycin, 1, 30, 1, 158	Amoxycillin, 1, 90, 10, 154
Guven 2006 (71)	Turkey	6- 144	Not mentioned, B, B, B, 3, 3	(1) No antibiotic treatment within 2 weeks. (2) No diagnosis of chronic otitis media. (3) Purulent otorrhea for more than 24 h. (4) Absence of allergy history to any of the drugs used in study. (5) Absence of serious underlying disease that may impair response to treatment. (6) Written consent from the parents.		Azithromycin, 1, 10, 3, 94	Amoxicillin-clavulanate, 1, 51.4, 10, 86

*Allocation concealment: A – adequate; B – unclear; C – inadequate; D – not used.
Blinding: A – double blinding; B – single blinding; C – no blinding; D – unclear.
Loss to follow-up based on percentage of excluded participants: A: <3%; B: 3–9.9%; C: 10–19.9%; D: ≥20%.
Intention to treat: 1– used; 2 – not used; 3 – unclear; 4 – not mentioned.
Compliance: 1– yes; 2 – no; 3 – not mentioned.
μRoute: 1 – oral; 2 – parenteral. AOM –Acute otitis media
nm – not mentioned

Table 2. Clinical diagnostic criteria used for acute otitis media in individual studies

Study (Reference)	Clinical diagnostic criteria for acute otitis media
de Saintonge 1982 (37)	Acute painful condition of middle ear accompanied with signs of redness with bulging.
Meistrup-Larsen 1983 (38)	Red and inflamed tympanic membrane with ear pain.
Puczynski 1987 (39)	Symptoms of otalgia, irritability and fever, and accompanied by otoscopic findings such as loss of ossicular landmarks, and bulging and erythema of tympanic membrane. In addition mobility of the tympanic membrane and middle ear effusion were confirmed by pneumatic otoscopy and tympanometry.
Varsano 1988 (40)	Presence of erythema, white opacification or both, accompanied by fullness or bulging and impaired mobility of tympanic membrane associated with at least one of the symptoms of acute ear infection as irritability or otalgia or fever.
Pestalozza 1992 (41)	Presence of symptoms (irritability, otalgia, fever) and otoscopic findings (reddened eardrum, diminished light reflex, bulging eardrum, perforation of eardrum with or without discharge).
Daniel 1993 (42)	Presence of fluid accompanied by presence of pain, fever or irritability.
Green 1993 (43)	At least one symptom (irritability, otalgia or fever) and compatible otoscopic finding (discoloration, bulging, impaired mobility, or opacity other than scarring).
Mohs 1993 (44)	Based on history, clinical findings and where possible with bacteriologic confirmation.
Schaad 1993 (45)	Presence of at least two symptoms (earache, reduced general condition or headache or excitation, fever, conductive hearing impairment) and one sign (radial injection or diffuse redness of eardrum, bulging or rupture of tympanic membrane or otopyorrhea).
Chamberlain 1994 (46)	Patients should have all the following - (1) Otalgia or fever. (2) Evidence of middle ear inflammation (redness or injection of tympanic membrane). (3) Clinical evidence of fluid or negative pressure in the middle ear (bulging or retracted tympanic membrane with decreased mobility by pneumatic otoscopy). (4) An abnormal tympanogram (type B or C).
Principi 1995 (47)	Based on history and/or physical findings.
Arguedas 1996 (48)	Symptoms and otoscopic and tympanometric signs indicative of acute otitis media.
Bauchner 1996 (49)	1. The presence of specific signs, such as otalgia or hearing loss, or nonspecific findings, such as fever, lethargy, irritability, anorexia, vomiting, or diarrhoea; 2. Middle ear effusion demonstrated by pneumatic autoscopy; and 3. Results of tympanometry consistent with middle ear effusion.
Rodriguez 1996 (50)	Earache; erythema; fullness or bulging of the tympanic membrane; loss of tympanic membrane landmark; fever, lethargy and/or irritability.
Arguedas 1997 (51)	Symptoms and otoscopic and tympanometric signs indicative of acute otitis media.
Barnett 1997 (52)	Signs of acute illness plus an abnormal tympanic membrane with objective evidence of middle ear effusion.
Celik 1997 (53)	Symptoms of acute otitis media (earache, feeling of fullness in the ear, tinnitus, hearing loss) with abnormal otoscopic signs (redness of tympanic membrane, clearing of anatomic landmarks, bulging of tympanic membrane, decreased mobility in pneumatic otoscopy (if intact) or perforation with purulent or mucopurulent discharge).
Ficnar (54) 1997	Based on history and/or physical findings.
Varsano 1997 (55)	Characteristic otoscopic signs, as verified independently by two experienced pediatricians: Erythema and/or white opacification and impaired mobility accompanied by fullness or bulging of tympanic membrane associated with at least one of the symptoms of acute ear infection such as irritability, otalgia or fever >38^{0}C.
de Jose 1998 (56)	Based on history, clinical findings and where possible with bacteriologic confirmation.
Callejo1 1998 (57)	Not mentioned.
Callejo2 1998 (57)	Not mentioned.
Kara1 1998 (58)	Rapid and sudden onset of clinical symptoms and signs.
Kara2 1998 (58)	Rapid and sudden onset of clinical symptoms and signs.
Al Ghamdi 1999 (59)	Symptoms (fever, irritability and otalgia) and otoscopic findings (opacity or bulging or perforation)
Cohen 1999 (60)	Presence of middle ear effusion plus marked redness or marked bulging or moderate redness and bulging associated with fever and/or otalgia and/or irritability.
Dagan 2000 (61)	Based on symptoms and signs (erythema, fullness or bulging of the tympanic membrane).
Slapak 2000 (62)	Presence of discharge which was confirmed by otoscope. Presence of at least one of the following symptoms: earache, discharge from ear, temperature in axilla >38^{0}C or 38.5^{0}C rectally, uneasiness, vomiting or loose motion.
Kawalski1 2001 (63)	Symptoms (fever, irritability, otalgia, ear drainage, vomiting or diarrhoea) with middle ear effusion by pneumatic otoscopy.
Kawalski2 2001 (63)	Symptoms (fever, irritability, otalgia, ear drainage, vomiting or diarrhoea) with middle ear effusion by pneumatic otoscopy.
Arrieta 2003 (64)	Presence of middle ear effusion with at least one of the signs of acute inflammation (ear pain within previous 24 hours, marked redness, fullness or bulging of tympanic membrane).
Block 2003 (65)	Specific clinical signs and symptoms and documented by pneumatic otoscopy and spectral gradient acoustic reflectometry.
Dunne 2003 (66)	Symptoms with one of the following : bulging or marked erythema of tympanic membrane, loss of light reflex or tympanic membrane landmarks, or impaired tympanic mobility on biphasic pneumatic otoscopy.
Oguz 2003 (67)	Symptoms of acute otitis media like fever, irritability, etc. with discoloration (hyperemia or opacity), bulging or retraction, and signs of middle ear effusion.
Yamei 2003 (68)	Hyperemia of tympanic membrane plus one or more symptoms or signs.

Study (Reference)	Clinical diagnostic criteria for acute otitis media
Wang 2004 (69)	1. Presence of one or more specific signs or symptoms such as otalgia, hearing loss or nonspecific findings as fever ≥ 38^{0}C, lethargy, irritability, anorexia, vomiting or diarrhoea; 2. Middle ear infection – obvious redness as revealed by otoscopy findings and evidence of middle ear fluid; and 3. An abnormal tympanogram – results consistent with middle ear effusion.
Arguedas 2005 (70)	Presence of at least one symptom or sign (symptoms of ear pain or signs as marked redness or fullness or bulging of tympanic membrane) and the presence of middle ear effusion or acute perforation (<24 h) with visible purulent material in ear canal.
Guven 2006 (71)	Middle ear fluid, two or more local signs as erythema, fullness or bulging of tympanic membrane, loss of tympanic membrane landmark and acute perforation with purulent otorrhea.

Table 3. Grouping of antibiotics used in the short and long treatment courses

Antibiotic used in short course	Antibiotic used in long course	No. of analytic components
Short-acting oral antibiotic		
Amoxicillin – 2	Amoxicillin	2
Penicillin – 1	Penicillin	1
Oral Azithromycin	Amoxicillin	2
	Amoxicillin – Clavulanate	12
	Azithromycin	1
	Clarithromycin	3
	Cefaclor	4
	Cefuroxime	1
Parenteral Ceftriaxone	Amoxicillin	4
	Amoxicillin – Clavulanate	5
	Cefaclor	1
	Cefuroxime	1
	Trimethoprim – Sulfamethoxazole	1

Table 4. Outcome criteria used for analyzing treatment efficacy in individual studies

Study (Reference)	Failure	Relapse	Recurrence	1st follow-up visit (in days)	2nd follow-up visit (in days)	3rd follow-up visit	4th follow-up visit	5th follow-up visit
de Saintonge 1982 (37)	Rate of recovery considered unsatisfactory by general practitioner and who were consequently prescribed additional antibiotic on open basis.	nm	nm	3	13-16	4 weeks post-therapy	12 weeks post-therapy	6-18 months (na)
Meistrup-Larsen 1983 (38)	Nm	nm	nm	14	nd	nd	nd	nd
Puczynski 1987 (39)	Patient who did not show clinical improvement at the time of first return visit.	nm	nm	2-3	10-14	nd	nd	nd
Varsano 1988 (40)	Persistence or recurrence of fever and/or pain, associated with otoscopic signs of acute ear infection or spontaneous otorrhea, appearing during the first 10 days after commencement of therapy.	nm	Reappearance of clinical and otoscopic findings consistent with the diagnosis of AOM during days 10-30 of the study.	3	7	30 days	nd	nd
Pestalozza 1992 (41)	No change or worsening of pretreatment signs.	nm	nm	3-5	10-14	30 days	nd	nd
Daniel 1993 (42)	No apparent clinical response.	nm	nm	3-5	10-12	35 days (safety analysis)	nd	nd
Green 1993 (43)	Persistence or recurrence of symptoms within 10 days of initiating treatment.	Initial resolution of symptoms with recurrence in 11 through 30 days.	Initial resolution of AOM symptoms with recurrence in 31 through 90 days of initiating treatment.	3-5	11-17	55-65 days	90 days (Telephonic)	nd
Mohs 1993 (44)	The clinical response to treatment was classed as cured, improved, failed or relapsed, by comparison with the previous assessment.	The clinical response to treatment was classed as cured, improved, failed or relapsed, by comparison with the previous assessment.	nm	2-4	11-13	nd	nd	nd
Schaad 1993 (45)	No change in or worsening of symptoms from baseline.	When there was an improvement or disappearance of pretreatment signs or symptoms, followed by their worsening or reappearance.	nm	4-6	12-16	nd	nd	nd

Study (Reference)	Failure	Relapse	Recurrence	1st follow-up visit (in days)	2nd follow-up visit (in days)	3rd follow-up visit	4th follow-up visit	5th follow-up visit
Chamberlain 1994 (46)	Persistence of ear pain or fever longer than 48 hr.	Nm	Recurrence of ear pain or fever with clinical signs of acute otitis media either early (within 14 days) or late (at 15 to 90 days).	3 (Telephonic)	7-10	30 days	60 days (na)	90 days (na)
Principi 1995 (47)	No change or worsening of pretreatment signs and symptoms.	Initial improvement or disappearance of pretreatment signs and symptoms with subsequent reappearance or worsening.	nm	3-5	10-14	nd	nd	nd
Arguedas 1996 (48)	Bacteriologic and/or clinical failure. Bacteriologic failure - inability to sterilize the middle ear fluid in those patients who had persistent ear drainage or in whom repeated tympanocentesis was performed. Clinical failure - inability to clear the initial clinical symptoms of persistent ear drainage by end of therapy.	The presence of signs and symptoms of otitis media with effusion and isolation of the same pathogen within 7 days after completion of treatment.	The presence of signs and symptoms of otitis media with effusion more than 7 days after completion of treatment with no culture performed or with isolation of an organism other than the initial causative pathogen.	3-5	10-11	28-32 days post-therapy	55-60 days post-therapy	nd
Bauchner 1996 (49)	Worsening of signs of AOM.	nm	nm	3-5	14-16	nd	nd	nd
Rodriguez 1996 (50)	No disappearance, or worsening, of the pretreatment signs and symptoms.	Nm	nm	4-6	10-14	25-30 days (Optional)	nd	nd
Arguedas 1997 (51)	Bacteriologic and/or clinical failure. Bacteriologic failure - inability to sterilize the middle ear fluid in those patients who had persistent ear drainage or in whom repeated tympanocentesis was performed. Clinical failure - inability to clear the initial clinical symptoms of persistent ear drainage by end of therapy.	Presence of signs and symptoms of otitis media with effusion and isolation of the same pathogen within 7 days after completion of treatment.	Presence of signs and symptoms of otitis media with effusion more than 7 days after completion of treatment with no culture performed or with isolation of an organism other than the initial causative pathogen.	3-5	10-11	28-32 days post-therapy	55-60 days post-therapy (na)	nd
Barnett 1997 (52)	New signs of illness with presence of middle ear effusion.	nm	nm	3	14	28 days	nd	nd
Celik 1997 (53)	No change in the symptoms and signs of AOM at first follow-up visit.	If symptoms and findings of AOM diminished but increased at next visit.	nm	4-5	10-14	30 days	nd	nd
Ficnar 1997 (54)	Persistence or worsening of signs and symptoms of infection after at least 72 hrs of treatment.	nm	nm	3	10	3 weeks	nd	nd
Varsano 1997 (55)	Persistence or recurrence of AOM-related symptoms within 11 days of initiation of therapy.	Initial resolution of symptoms and their reappearance on days 12 through 30.	Resolution of symptoms within the first 11 days of onset of treatment and their reappearance on days 31-90.	3	11	30 days	60 days	90 days
de Jose 1998 (56)	Worsening or no change in signs or symptoms.	Improvement or disappearance of signs and symptoms and later worsening or reappearance.	nm	3-5	10-14	nd	nd	nd
Callejo1 1998 (57)	Signs and symptoms of primary action had not been modified.	Nm	nm	14-18	nd	nd	nd	nd
Callejo2 1998 (57)	Signs and symptoms of primary action had not been modified.	Nm	nm	14-18	nd	nd	nd	nd
Kara1 1998 (58)	Non-resolution of symptoms and clinical and tympanometric appearance of tympanic membrane.	Nm	nm	3	10	30 days	nd	nd
Kara2 1998 (58)	Non-resolution of symptoms and clinical and tympanometric appearance of tympanic membrane.	Nm	nm	3	10	30 days	nd	nd
Al Ghamdi 1999 (59)	No clinical improvement after 3-6 days	Nm	nm	10	60	nd	nd	nd

Study (Reference)	Failure	Relapse	Recurrence	1st follow-up visit (in days)	2nd follow-up visit (in days)	3rd follow-up visit	4th follow-up visit	5th follow-up visit
Cohen 1999 (60)	If between days 0 and 12 to 14, fever continued (37.5 °C) and/or if signs of otalgia and otoscopic signs persisted, worsened or recurred. Patients who experienced spontaneous otorrhea and/or other otitis complications and patients who underwent tympanocentesis or were given another antibiotic than the study drug at that time.	Nm	nm	12-14	28-42	nd	nd	nd
Dagan 2000 (61)	Bacteriologic failure - Any patient with positive culture after day 4 but before day 11. Otologic failure - persistence of initial fluid characteristics, coupled with signs of inflammation of the tympanic membrane.	Bacteriologic relapse - Culture at day 10 identical to culture at day 1. Otologic relapse - when after initial improvement, there was reaccumulation of pus in the middle ear and inflammation of the tympanic membrane associated with symptoms of otitis media at any time during follow-up.	nm	4-5	10	15-19 days	nd	nd
Slapak 2000 (62)	Failure requiring another antibiotic.	Nm	Symptoms of infection reappeared after initial improvement during 4 weeks after starting therapy.	3	10-12	6 weeks (Optional)	nd	nd
Kawalski1 2001 (63)	Persistence or progress of signs and symptoms of infection after at least 72 hours of treatment. Persistence - positive culture of an adequate specimen obtained after at least 72 hours of treatment.	Causative pathogen in culture of an adequate specimen obtained at any time after one negative culture.	Reappearance of signs and symptoms of infection within 4 weeks after start of treatment.	3	10-12	4 weeks	nd	nd
Kawalski2 2001 (63)	Persistence or progress of signs and symptoms of infection after at least 72 hours of treatment. Persistence - positive culture of an adequate specimen obtained after at least 72 hours of treatment.	Causative pathogen in culture of an adequate specimen obtained at any time after one negative culture.	Reappearance of signs and symptoms of infection within 4 weeks after start of treatment.	3	10-12	4 weeks	nd	nd
Arrieta 2003 (64)	No change, worsening of signs or symptoms or a requirement for additional antibiotic therapy for AOM.	Nm	nm	3-5 (Telephonic)	12-16	28-32 days	nd	nd
Block 2003 (65)	Patients who received other systemic antibiotic at any time prior to day 12-16 visit.	Nm	Patients who received other systemic antibiotics after the 12-16 days visit.	3-5 (Telephonic)	12-16	28-32 days	nd	nd
Dunne 2003 (66)	No change or worsening of signs and symptoms or requirement of additional antibiotic therapy for AOM.	Nm	nm	5 (Telephonic)	10	24-28 days	nd	nd
Oguz 2003 (67)	Persistence of clinical and otoscopic findings at 3rd to 5th day of evaluation visit of serous material during otoscopic examination.	Recurrence of clinical and otoscopic findings at day 10, after an initial period of improvement.	Recurrence of clinical and otoscopic findings in a patient during the 30-day follow-up period for whom cure or improvement had been detected on day 10.	3-5	10	30 days	nd	nd
Yamei 2003 (68)	After 72 hrs clinical manifestation without improvement or worsening.	Nm	nm	3-5	10-14		nd	nd
Wang 2004 (69)	If the symptoms and signs presented at baseline had not improved or had worsened on day 4 or if patient still showed symptoms or signs on day 11.	Nm	nm	4	11	28 days	nd	nd
Arguedas 2005 (70)	Worsening of symptoms of infection, no response to therapy or requirement for additional therapy for AOM (at 12-14 day visit).	Nm	Patient previously evaluated as cured or improved at 12-14 day visit who satisfied the criteria for failure between 2nd and 3rd follow-up visits.	4-6	12-14	25-28 days	nd	nd

Study (Reference)	Failure	Relapse	Recurrence	1st follow-up visit (in days)	2nd follow-up visit (in days)	3rd follow-up visit	4th follow-up visit	5th follow-up visit
Guven 2006 (71)	Failure to clear signs and symptoms.	After an initial period of improvement, recurrence of clinical and otoscopic findings on 11 to 13 day visit.	Recurrence of clinical and otoscopic findings in a patient during the 30 days follow-up period in whom cure or improvement had been detected at 11-13 day visit.	2-4	11-13	26-28 days	nd	nd

AOM - acute otitis media
na - not applicable for evaluating study outcome
nd - not done
nm - not mentioned

Quantitative data synthesis

Outcomes until one month

Primary outcome (Treatment failure until one month)

A total of 35 studies were finally eligible for analysis. Three of these studies had two treatment arms, so there were a total of 38 analytic components (refer to Methods section for details). The funnel plot (Fig. 2) for analytic components included in the analysis was symmetrical suggesting the absence of publication bias, which was confirmed using the Egger's (weighted regression) method (P for bias=0.994) and the Begg's (rank correlation) method (continuity corrected P= 0.763).

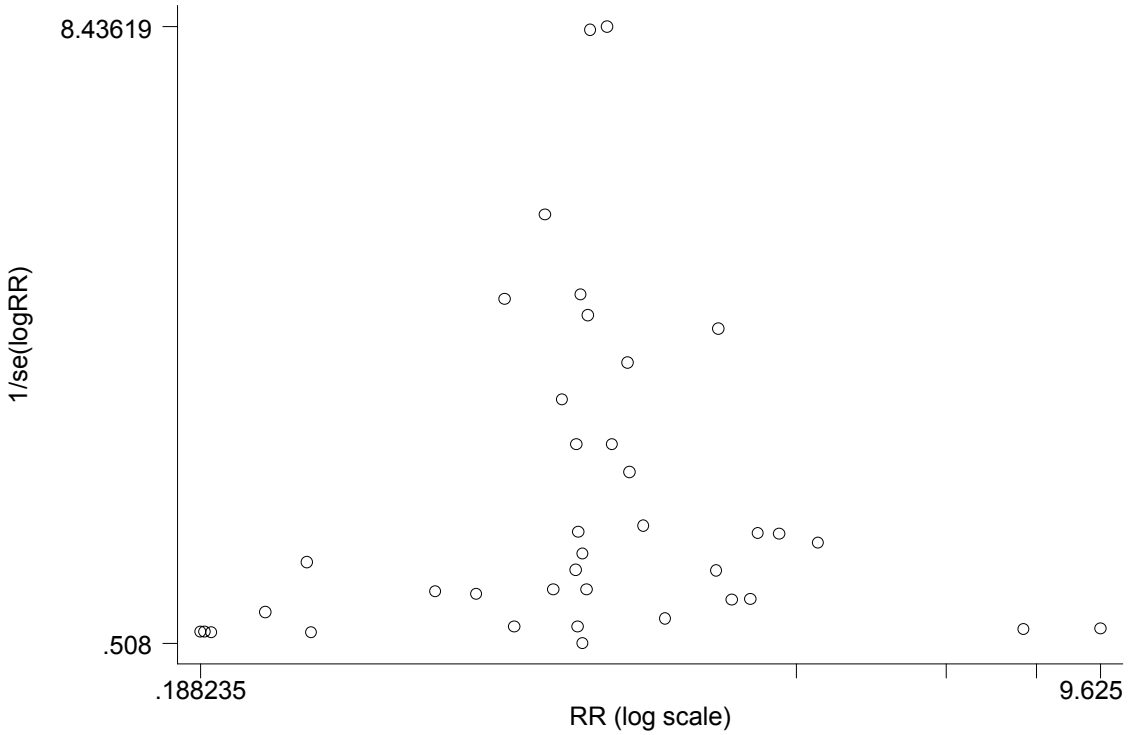

Fig. 2: Funnel plot of treatment failure until one month from random effects model for short course *versus* long course (analytic components = 38)

Overall, there was no evidence of an increased risk of treatment failure with a shorter course of antibiotics (≤3 days). The overall relative risk for treatment failure with a short course of antibiotics in comparison to a longer course was 1.06 (95% CI 0.95 to 1.17, P=0.298; test for heterogeneity: Cochran Q=37.02, I^2=0.1%, P=0.468) (Table 5 and Fig. 3). The L'Abbe plot also suggested a lack of heterogeneity (Fig. 4).

Table 5. Sensitivity and subgroup analyses of relative risk of primary outcome (Treatment failure until one month after intervention)

Stratification variable	No. #	Random effects model RR (95% CI)	P value	Tests for heterogeneity I^2 (%); Q (P value)	P value for heterogeneity in subgroups
Overall	*38*	*1.06 (0.95, 1.17)*	*0.298*	*0.10; 37.02 (0.468)*	*Not applicable*
Allocation concealment					
Adequate	4	1.20 (0.59, 2.41)	0.617	27.90; 4.16 (0.244)	
Others	34	1.05 (0.94, 1.16)	0.414	0.00; 32.29 (0.502)	0.452
Attrition					
<10%	23	1.03 (0.82, 1.30)	0.817	11.4; 24.84 (0.305)	
>10%	13	1.10 (0.97, 1.24)	0.135	0.00; 11.07 (0.523)	0.303
Blinding					
Double blind	9	0.98 (0.80, 1.19)	0.835	17.70; 9.72 (0.285)	
Others	29	1.12 (0.98, 1.27)	0.094	0.00; 25.40 (0.606)	0.168
Trial site					
Developing	10	0.96 (0.67, 1.38)	0.822	22.00; 11.54 (0.240)	
Developed	28	1.08 (0.97, 1.21)	0.152	0.00; 23.92 (0.635)	0.211
Short course antibiotic		2.27 (1.04, 4.99)	**0.040**	0.00; 1.16 (0.561)	
Short-acting oral	3	0.93 (0.79, 1.09)	0.350	0.00; 17.88 (0.713)	
Azithromycin	23	1.13 (0.99, 1.30)	0.071	0.00; 10.75 (0.464)	0.027
Parenteral Ceftriaxone	12				
Antibiotic duration in long course (days)					
< 10	3	1.45 (0.73, 2.88)	0.292	0.00; 1.16 (0.560)	
≥ 10	35	1.05 (0.94, 1.17)	0.394	3.00; 35.03 (0.419)	0.363
Cointervention use					
Yes	14	1.09 (0.89, 1.33)	0.423	0.00; 12.98 (0.449)	
Others	24	1.05 (0.92, 1.19)	0.491	3.90; 23.94 (0.407)	0.749
Compliance monitored					
Yes	19	1.00 (0.89, 1.12)	0.942	0.00; 10.86 (0.901)	
Others	19	1.34 (1.00, 1.79)	0.052	11.40; 20.31 (0.316)	0.015
Intention to treat analysis					
Used	14	1.01 (0.88, 1.16)	0.913	10.60; 14.54 (0.337)	
Others	24	1.17 (0.97, 1.42)	0.094	0.00; 20.72 (0.598)	0.185

Treatment failure refers to clinical failure or relapse or recurrence or bacteriologic failure until the last time point within one month of initiating intervention. Bacteriologic failure was amalgamated as a part of treatment failure for only one study as information was available distinct from clinical failure or relapse or recurrence.

- Number of analytic components.

Not done for age group (<2 years or >2 years), as there was no study exclusively on children below 2 years of age.
Not done for perforated tympanic membrane (yes or no), as there was no study exclusively on children with perforated tympanic membrane.
Not done for recurrent otitis media (yes or no), as there was only one study exclusively on children with recurrent otitis media.

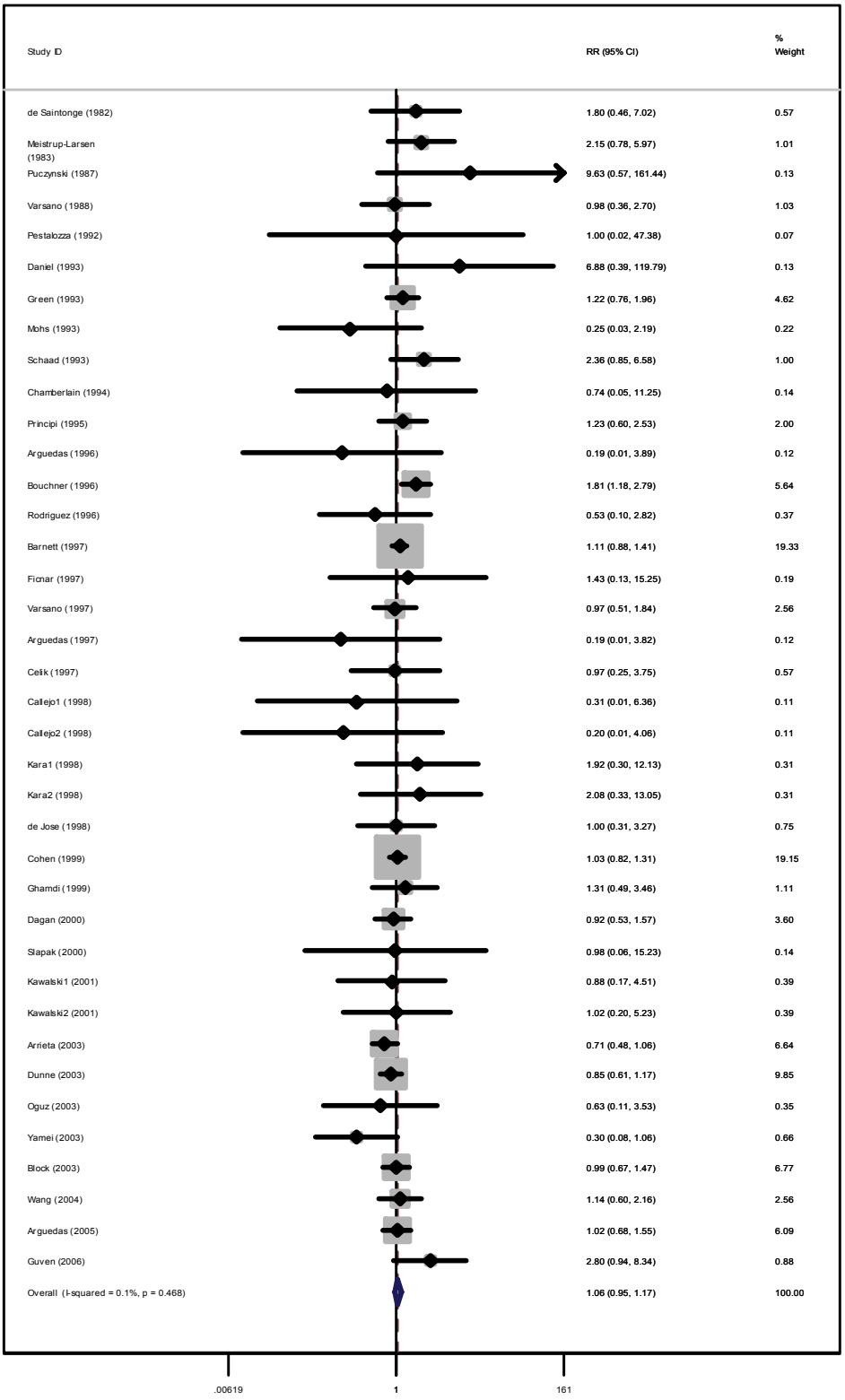

Fig. 3: Forest plot for treatment failure until one month from random effects model for short course *versus* long course (analytic components = 38)

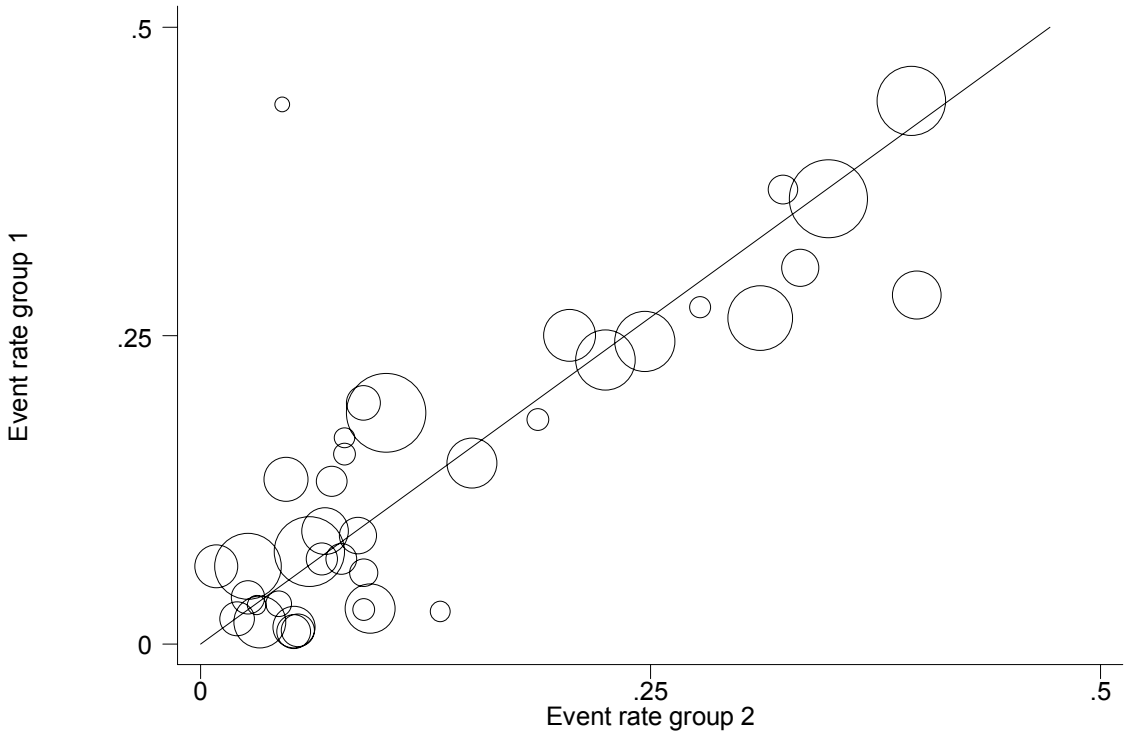

Fig. 4: L'Abbe plot for treatment failure until one month from random effects model for short course *versus* long course (analytic components = 38)

On conducting the pre-specified sensitivity and subgroup analyses, significant (P<0.05) heterogeneity was identified between the various subgroups of only two variables, namely pharmacokinetic behaviour of antibiotic used in the short course arm and compliance monitoring (Table 5 and Fig. 5-13). Use of a short-acting oral antibiotic in the short course arm was associated with a significantly increased risk of treatment failure, namely RR of 2.27 (95% CI 1.04 to 4.99, P=0.04; test for heterogeneity: Cochran Q=1.16, I^2=0.0%, P=0.561). The slightly increased risk of treatment failure with parenteral ceftriaxone (1.13, 95% CI 0.99 – 1.30) was not statistically significant; however, the lower confidence interval was close to 1.

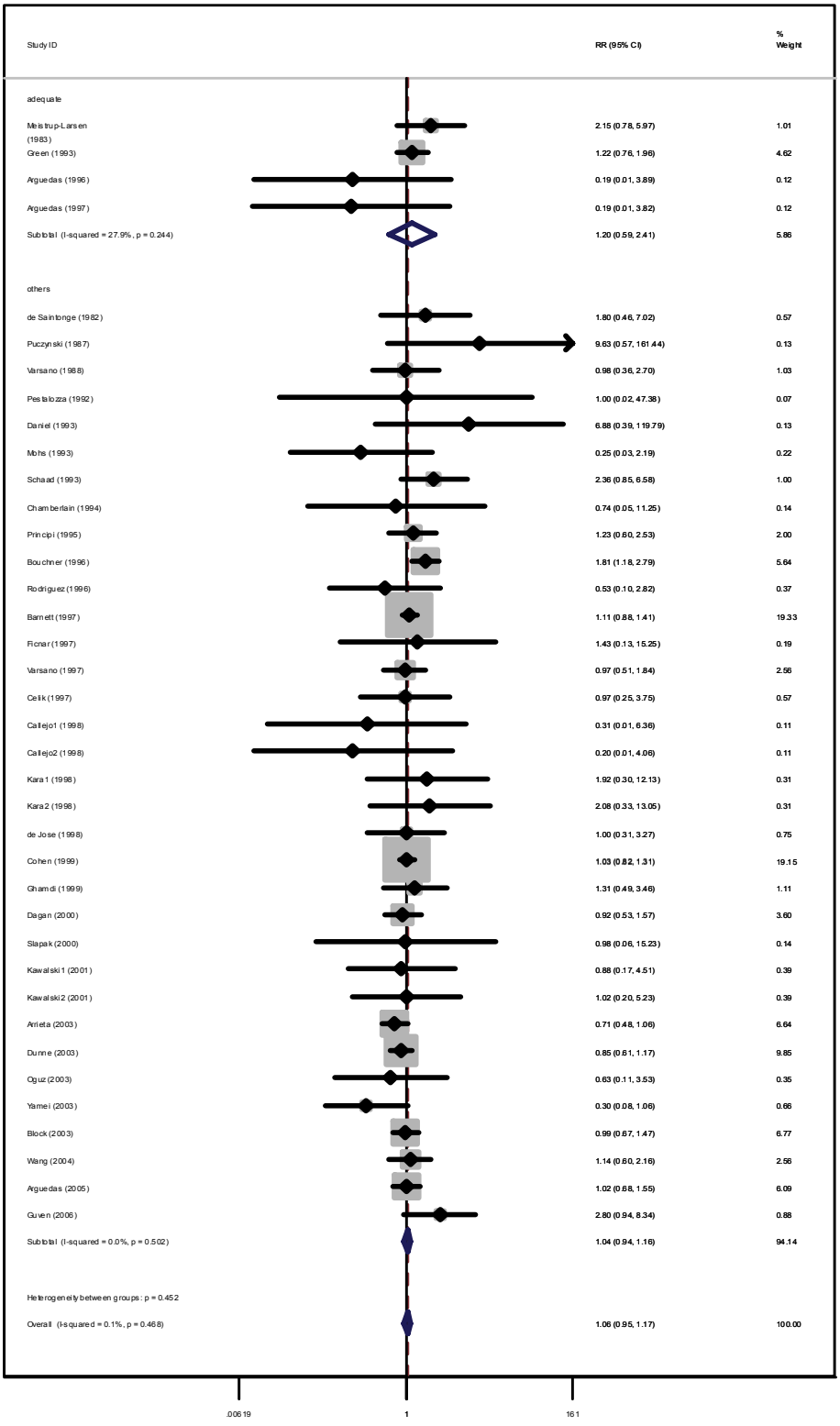

Fig. 5: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to allocation concealment (analytic components = 38)

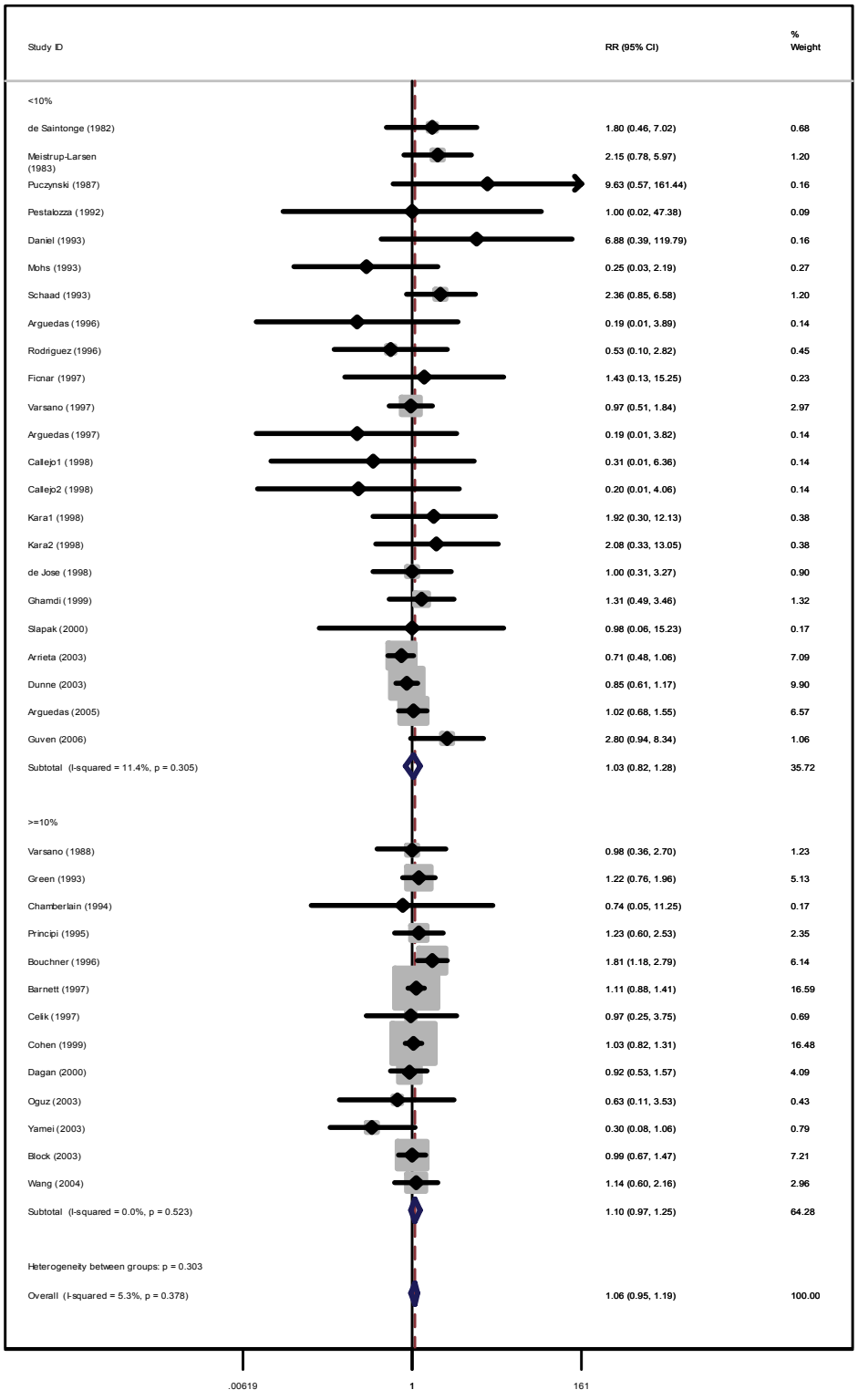

Fig. 6: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to attrition (analytic components = 36)

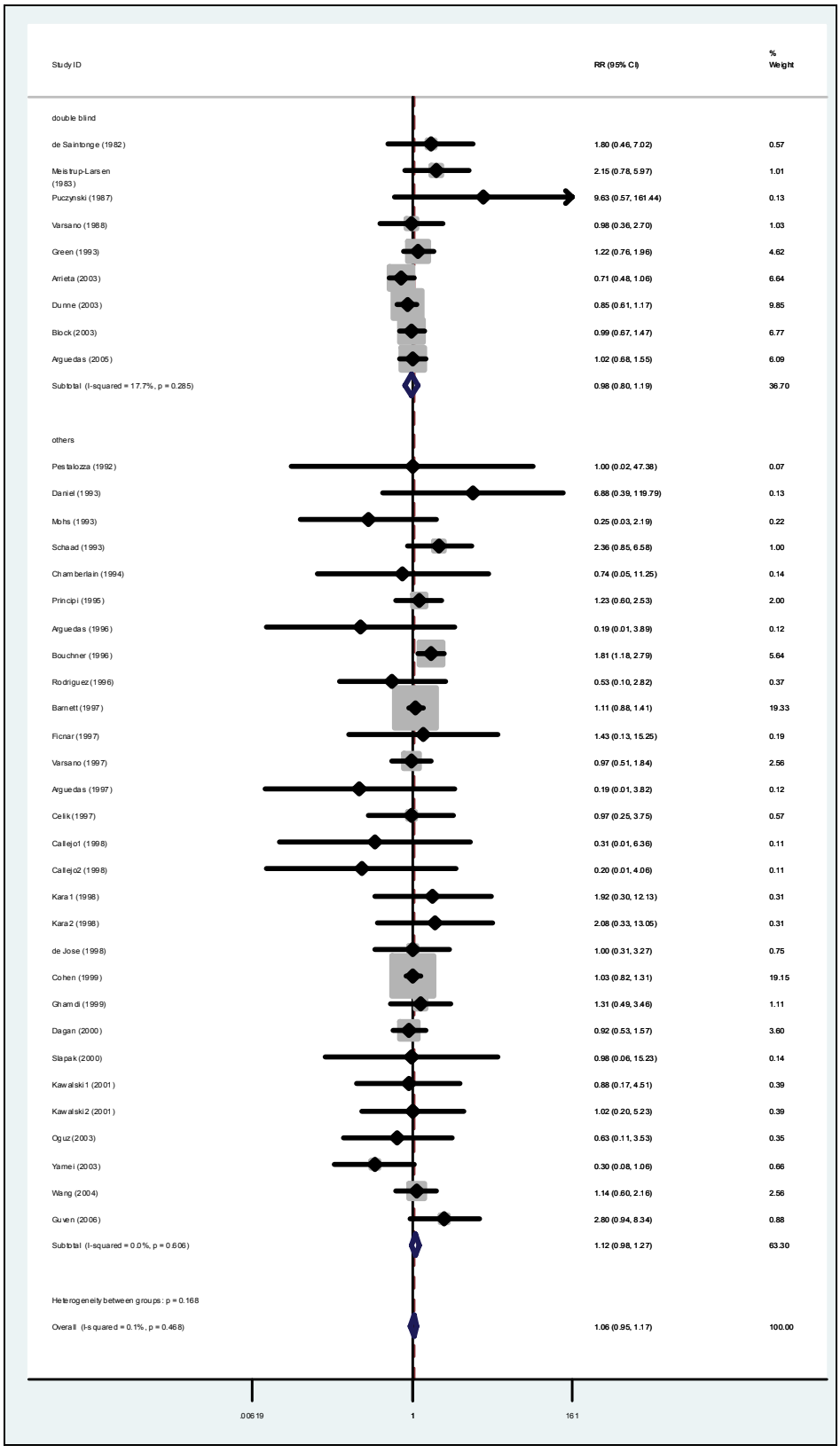

Fig. 7: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to blinding (analytic components = 38)

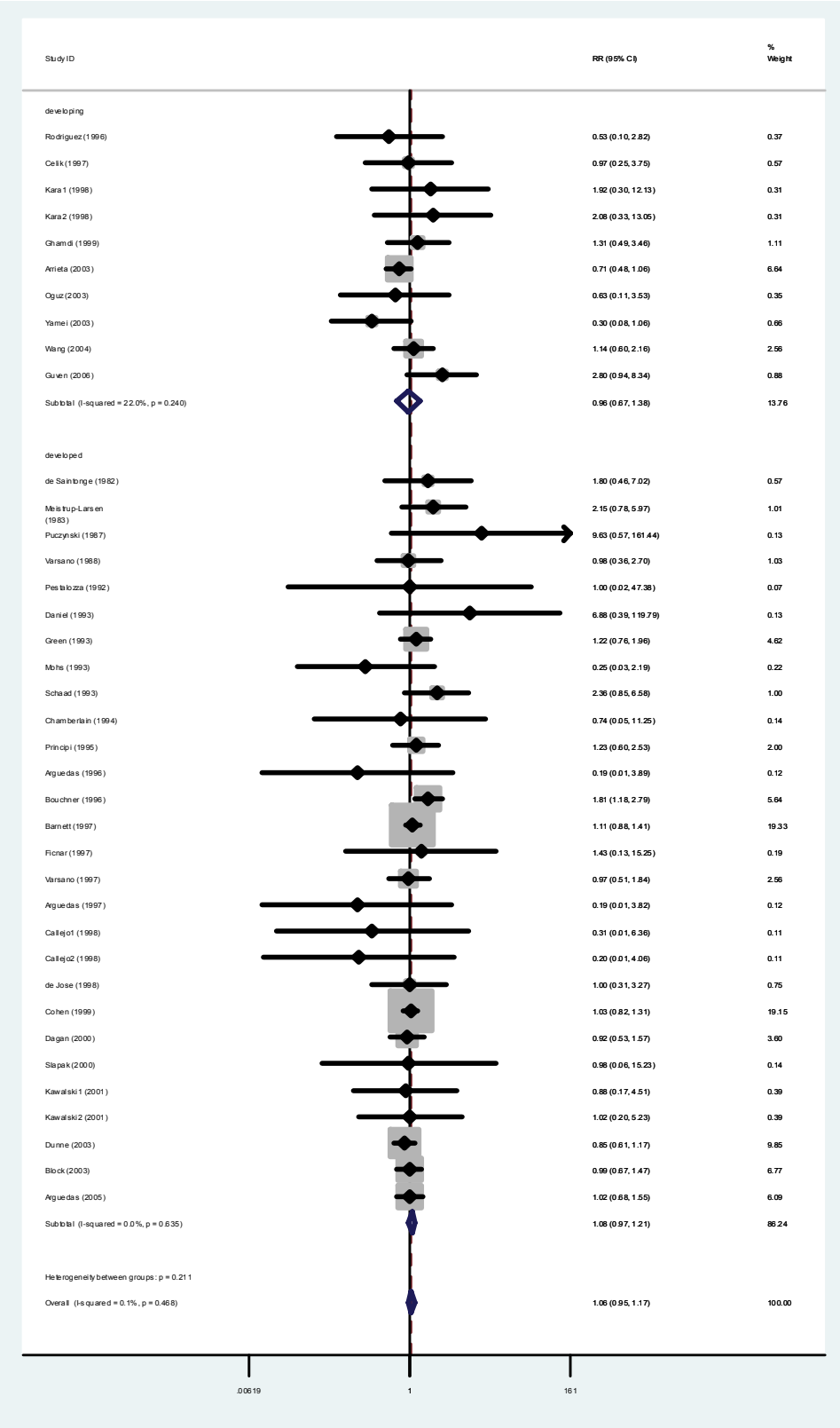

Fig. 8: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to country development status (analytic components = 38)

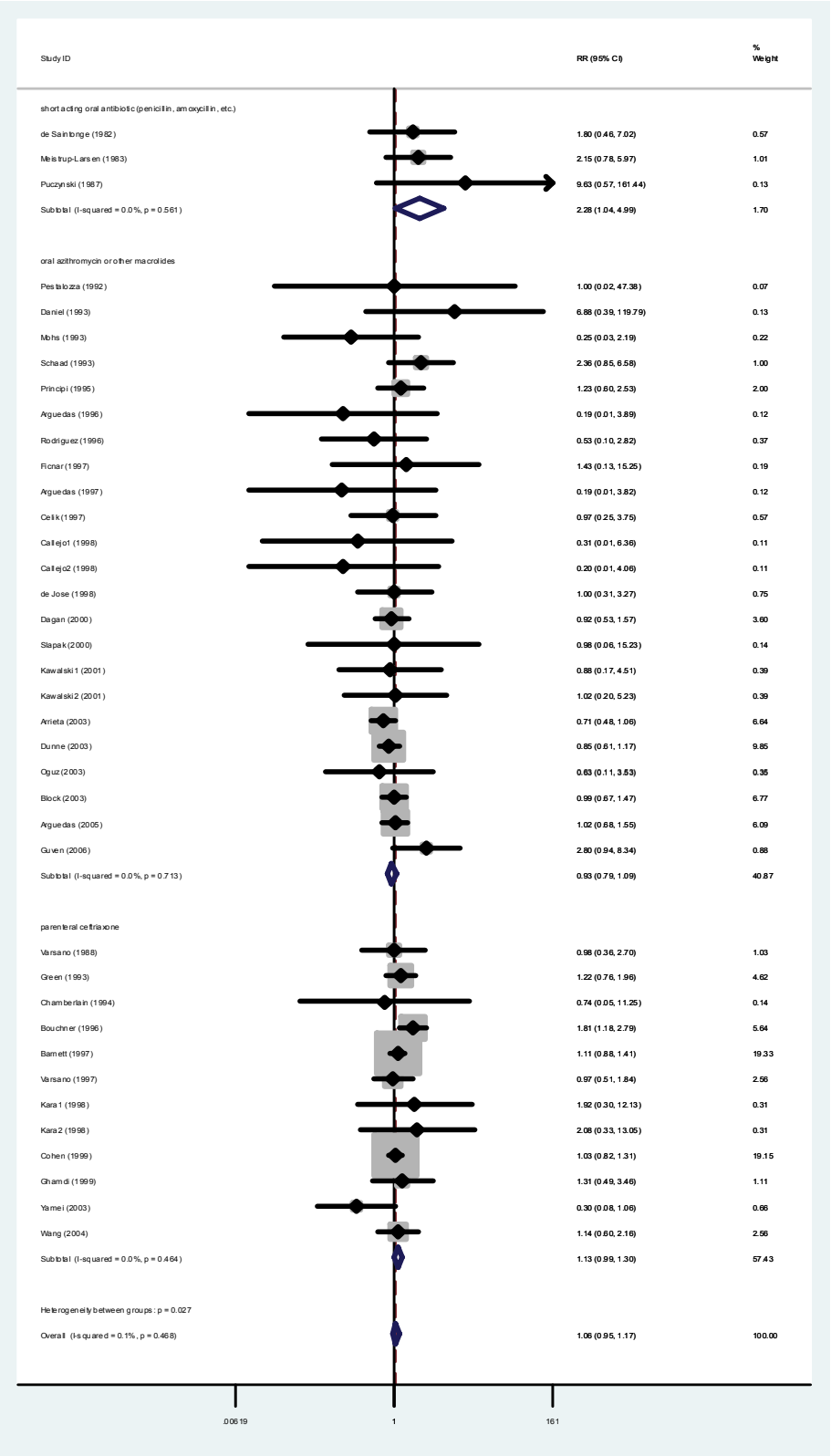

Fig. 9: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic used in short course (analytic components = 38)

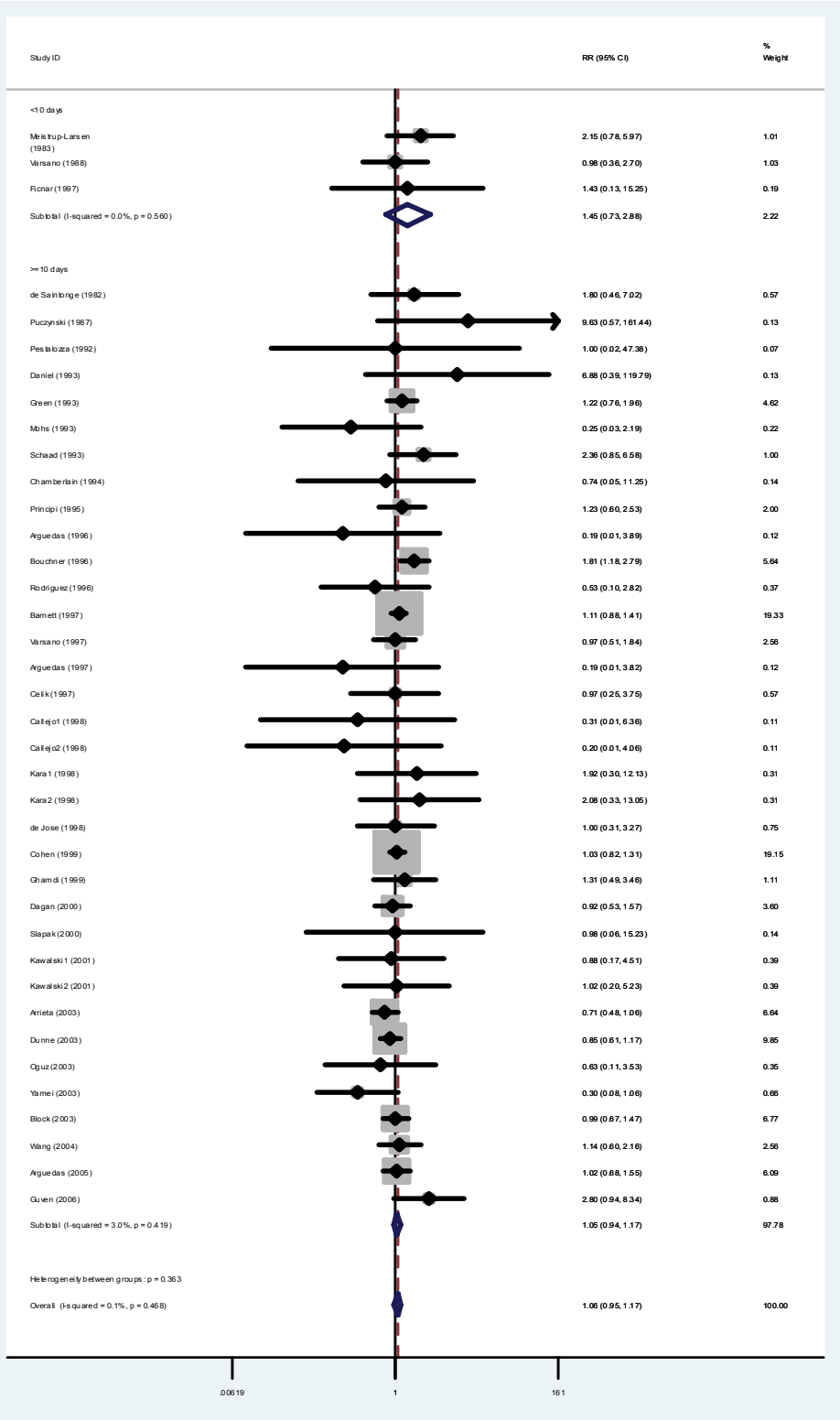

Fig. 10: Forest plot for treatment failure until one month from random effects model for short course versus long course in relation to duration of antibiotic treatment in long course (analytic components = 38)

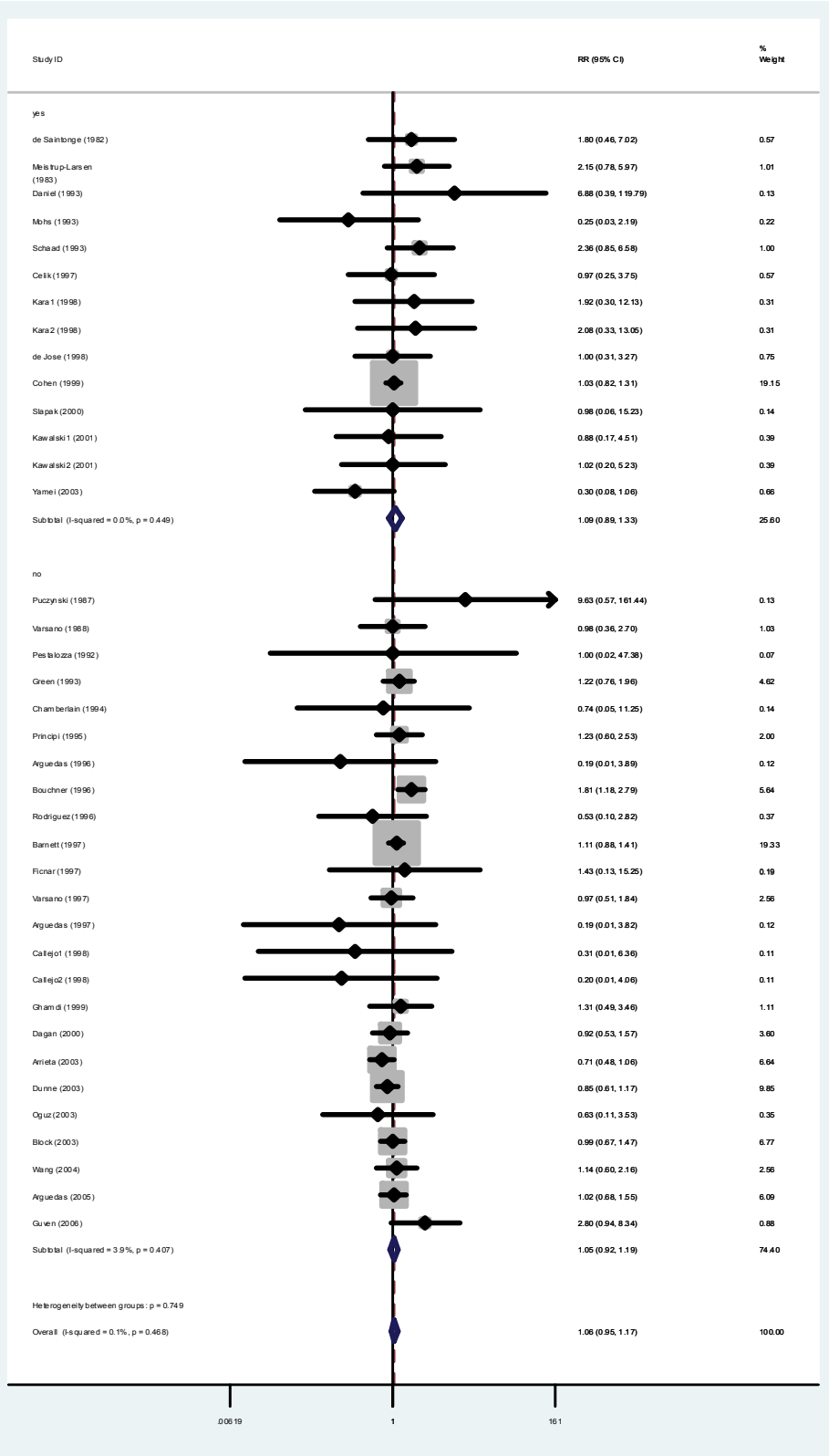

Fig. 11: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to co-intervention use (analytic components = 38)

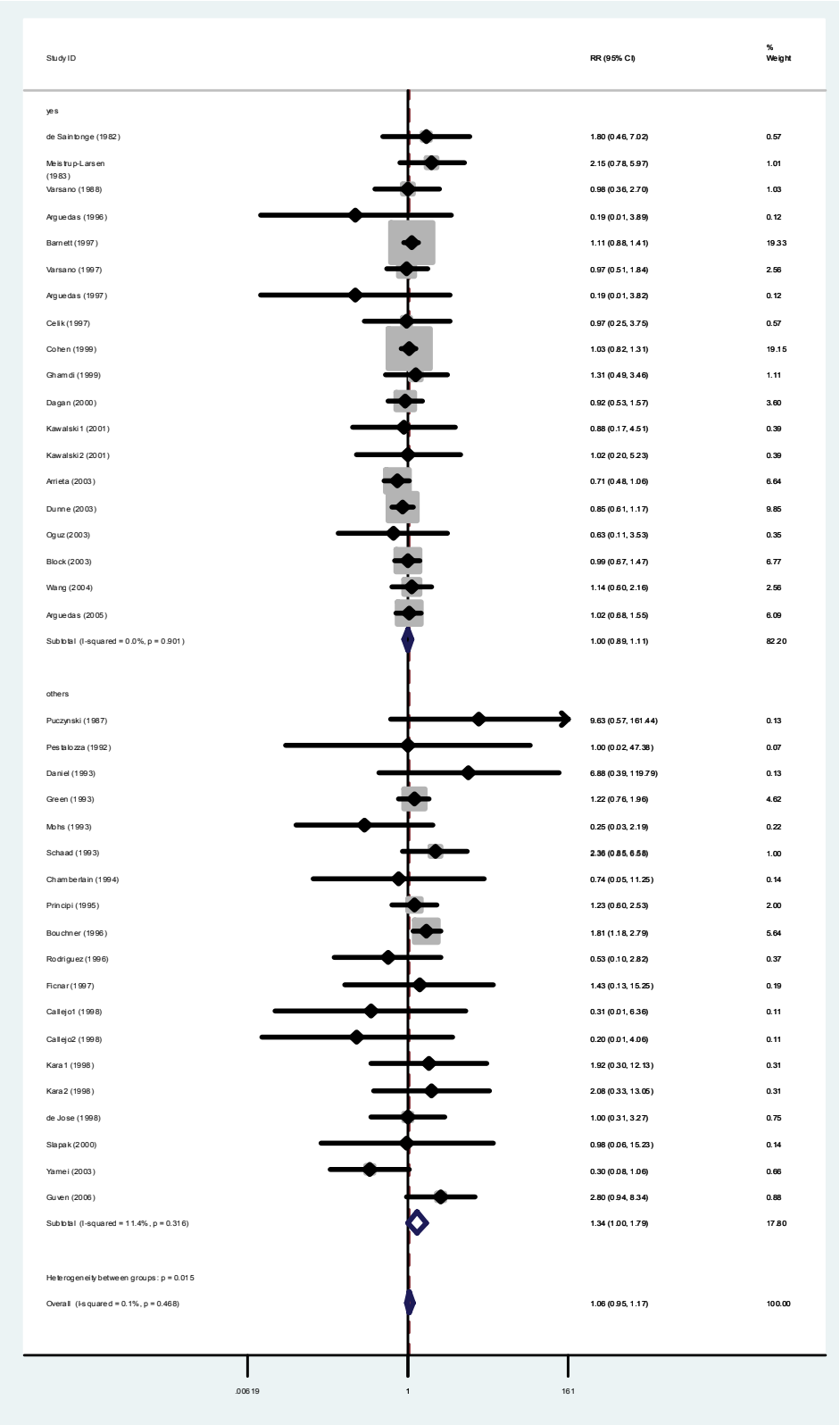

Fig. 12: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to compliance monitoring (analytic components = 38)

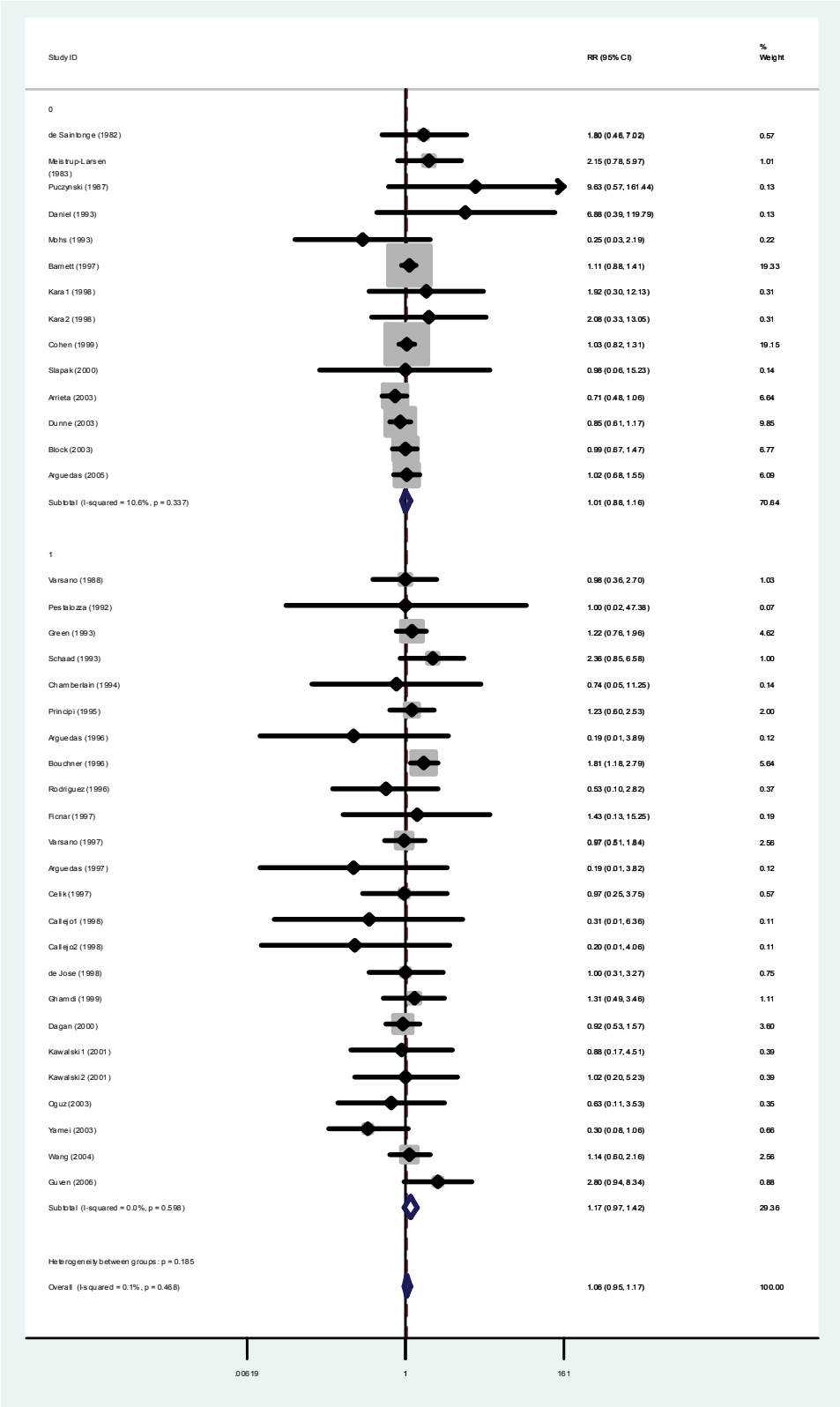

Fig. 13: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to intention to treat analysis (analytic components = 38)

On univariable metaregression, use of azithromycin in the short course arm and compliance monitoring were identified as significant predictors of heterogeneity (Table 6). On adjusting for additional variables, these two predictors of heterogeneity continued to be statistically significant (P<0.05). The risk of treatment failure was increased 3.31 times (95% CI 1.11 to 9.89; P=0.034) when antibiotics other than azithromycin were used in the short course arm. Compliance monitoring was associated with a 1.52 times lower (95% CI 1.01 to 2.28; P=0.046) risk of treatment failure (Table 6).

Table 6. Metaregression analyses for relative risk of primary outcome (Restricted Maximum Likelihood Method)

Study characteristic	Univariable analysis RR (95% CI); *I^2	P	Controlling for additional variables RR (95% CI)	P
Study quality				
Allocation concealment *(others vs. adequate)*	0.84 (0.52, 1.35); 0.01	0.456	*1.43 (0.70, 2.91)*	0.317
Attrition *(>10% vs. <10%)*(n=36)	1.13 (0.90, 1.43); 0.05	0.291	*1.03 (0.74, 1.42)*	0.873
Blinding *(others vs. double blind)*	1.16 (0.93, 1.45); 0.00	0.172	*1.00 (0.64, 1.58)*	0.982
Trial site (*developed vs. developing)*	1.21 (0.89, 1.65); 0.00	0.216	*1.15 (0.82, 1.63)*	0.404
Short course arm other antibiotics *vs.* oral short-acting	0.46 (0.20, 1.04); 0.00	0.062	*DR*	DR
Short course arm other antibiotics *vs.* azithromycin	1.25 (1.01, 1.55); 0.00	**0.045**	*3.31 (1.11, 9.89)*	**0.034**
Short course arm other antibiotics *vs.* parenteral ceftriaxone	0.85 (0.68, 1.05); 0.00	0.127	*2.71 (0.93, 7.88)*	0.066
Duration of long course antibiotic (≥ 10 *vs.* < 10 days)	0.73 (0.35, 1.50); 0.00	0.377	*0.99 (0.40, 2.45)*	0.982
Cointervention (*no vs. yes*)	0.94 (0.69, 1.27); 0.00	0.668	*1.11 (0.82, 1.51)*	0.475
Compliance monitoring (*others vs. yes*)	1.39 (1.05, 1.83); 0.00	0.021	*1.52 (1.01, 2.28)*	0.046
Intention to treat analysis (*others vs. yes*)	1.16 (0.92, 1.47); 0.00	0.196	*0.98 (0.66, 1.46)*	0.924

The number of analytic components in univariate model is 38 except where specifically stated otherwise.
* Proportion of residual variation due to heterogeneity, I-squared.
DR – Dropped in the analysis due to collinearity
Multivariate model – number of analytic components is 36 and the proportion of residual variation due to heterogeneity, I-squared is 0.0.
In the multivariate analysis, as a sensitivity exercise, on dropping the variable attrition from the model due to missing observation in two units, the following variable was found significant:
Compliance monitoring (*others vs. yes*): 1.50 (1.01, 2.23); P=0.046

Fig. 14 depicts the influence of omitting individual studies on summary estimates of relative risk by random effects model. It is obvious that no single analytic component had a substantial impact on the quantification of summary relative risk.

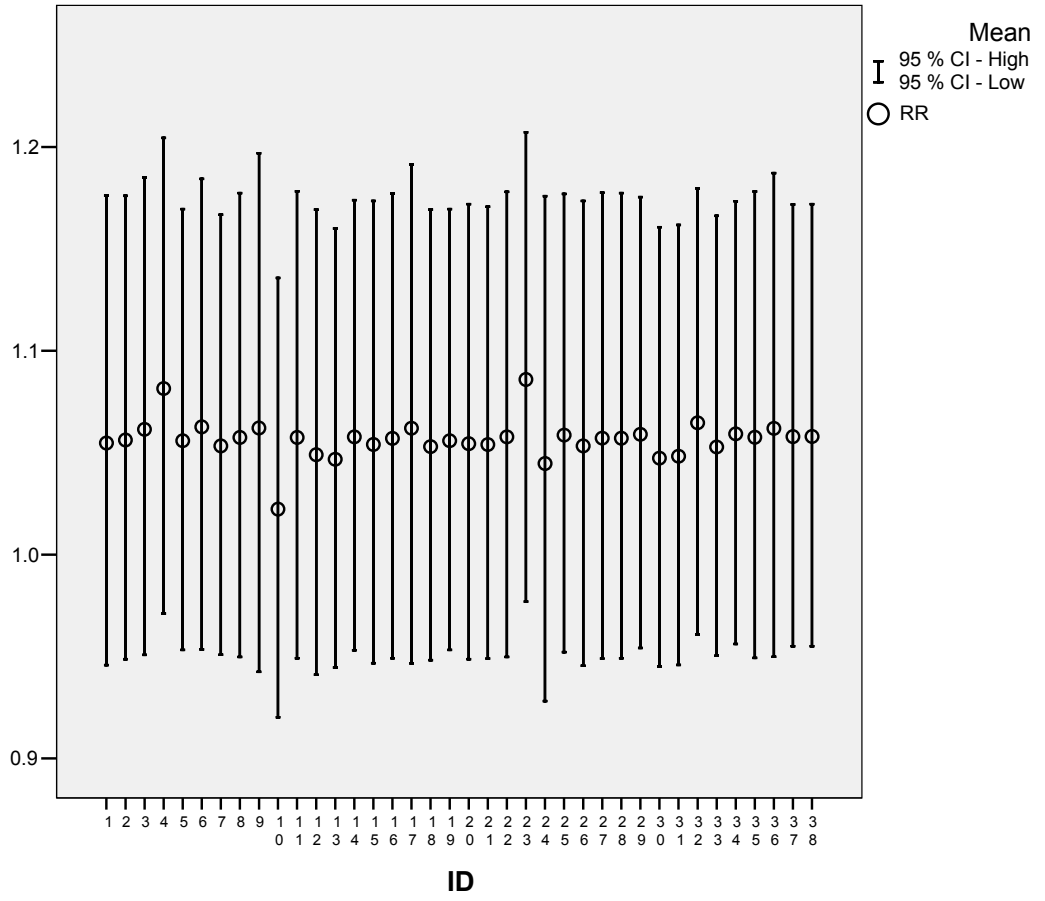

Fig 14: Influence analysis for treatment failure until one month from random effects model for short course versus long course (analytic components = 38)

Alternative definition for treatment failure (including subjects showing improvement as failure) until one month

When treatment failure was redefined to include subjects showing improvement, data until one month after intervention was available from 26 studies with 28 analytic components. The funnel plot (Fig. 15) for studies included in this analysis was symmetrical, suggesting the absence of publication bias, which was confirmed using the Egger's (weighted regression) method (P for bias=0.743) and the Begg's (rank correlation) method (continuity corrected P=0.890).

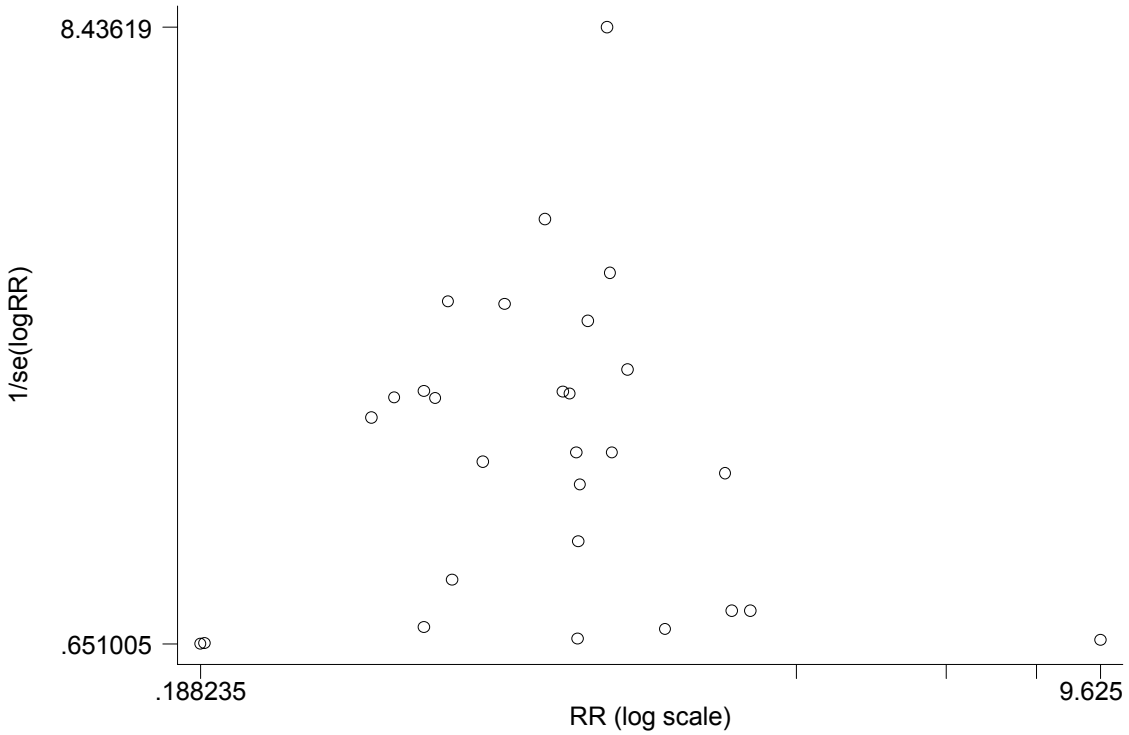

Fig. 15: Funnel plot of treatment failure until one month (using cured instead of improved definition) from random effects model for short course *versus* long course (analytic components =28)

The overall relative risk for treatment failure following short course antibiotic treatment in comparison to long course with this revised definition was 0.83 (95% CI 0.70 to 0.98, P=0.024; test for heterogeneity: Cochran Q=50.5, I^2=46.5%, P=0.004) (Table 7 and Fig.16). The L'Abbe plot also suggested heterogeneity (Fig. 17).

Table 7. Sensitivity and subgroup analyses of relative risk of treatment failure (Redefining subjects showing improvement as failure) until one month of intervention

Ratification variable	No. #	Random effects model RR (95% CI)	P value	Tests for heterogeneity I^2 (%); Q (P value)	P value for heterogeneity in subgroups
Overall	28	0.83 (0.70, 0.98)	**0.024**	46.50; 50.50 (**0.004**)	Not applicable
Allocation concealment					
Adequate	3	0.71 (0.20, 2.54)	0.595	30.70; 2.89 (0.236)	
Others	25	0.82 (0.69, 0.97)	**0.019**	48.30; 46.38 (**0.004**)	0.267
Attrition					
<10%	18	0.86 (0.70, 1.05)	0.122	28.90; 23.90 (0.122)	
>10%	8	0.94 (0.75, 1.17)	0.140	36.20; 10.97 (0.140)	0.292
Blinding					
Double blind	6	0.93 (0.74, 1.16)	0.499	19.20; 6.19 (0.289)	
Others	22	0.79 (0.64, 0.97)	**0.026**	52.20; 43.90 (**0.002**)	0.518
Trial site					
Developing	9	0.90 (0.69, 1.19)	0.460	32.90; 11.93 (0.154)	
Developed	19	0.79 (0.64, 0.98)	**0.028**	53.30; 38.57 (**0.003**)	1.000
Short course antibiotic					
Short-acting oral	1	9.63 (0.57, 161.44)	0.116	Not applicable	
Azithromycin or macrolides	19	0.73 (0.60, 0.88)	**0.001**	45.70; 33.13 (**0.016**)	
Parenteral Ceftriaxone	8	1.10 (0.93, 1.31)	0.277	0.00; 1.70 (0.975)	**<0.001**
Antibiotic duration in long course (days)					
< 10	2	1.04 (0.41, 2.64)	0.933	0.0; 0.08 (0.771)	
≥ 10	26	0.82 (0.70, 0.98)	**0.024**	50.20; 50.25 (**0.002**)	0.683
Cointervention use					
Yes	11	0.74 (0.55, 0.98)	**0.037**	51.10; 20.46 (**0.025**)	
Others	17	0.90 (0.74, 1.09)	0.268	40.50; 26.88 (**0.043**)	0.075
Compliance monitored					
Yes	13	0.80 (0.65, 0.99)	**0.044**	49.00; 23.52 (**0.024**)	
Others	15	0.88 (0.67, 1.14)	0.325	48.20; 27.01 (**0.019**)	1.000
Intention to treat analysis					
Used	10	0.90 (0.72, 1.12)	0.336	37.10, 14.30 (0.112)	
Others	18	0.79 (0.63, 0.99)	**0.039**	49.90, 33.96 (**0.008**)	0.135

- Number of analytic components.

Not done for age group (<2 years or >2 years), perforated tympanic membrane (yes or no), and recurrent otitis media (yes or no) as there was no or only a single study for one stratification of these subgroups.

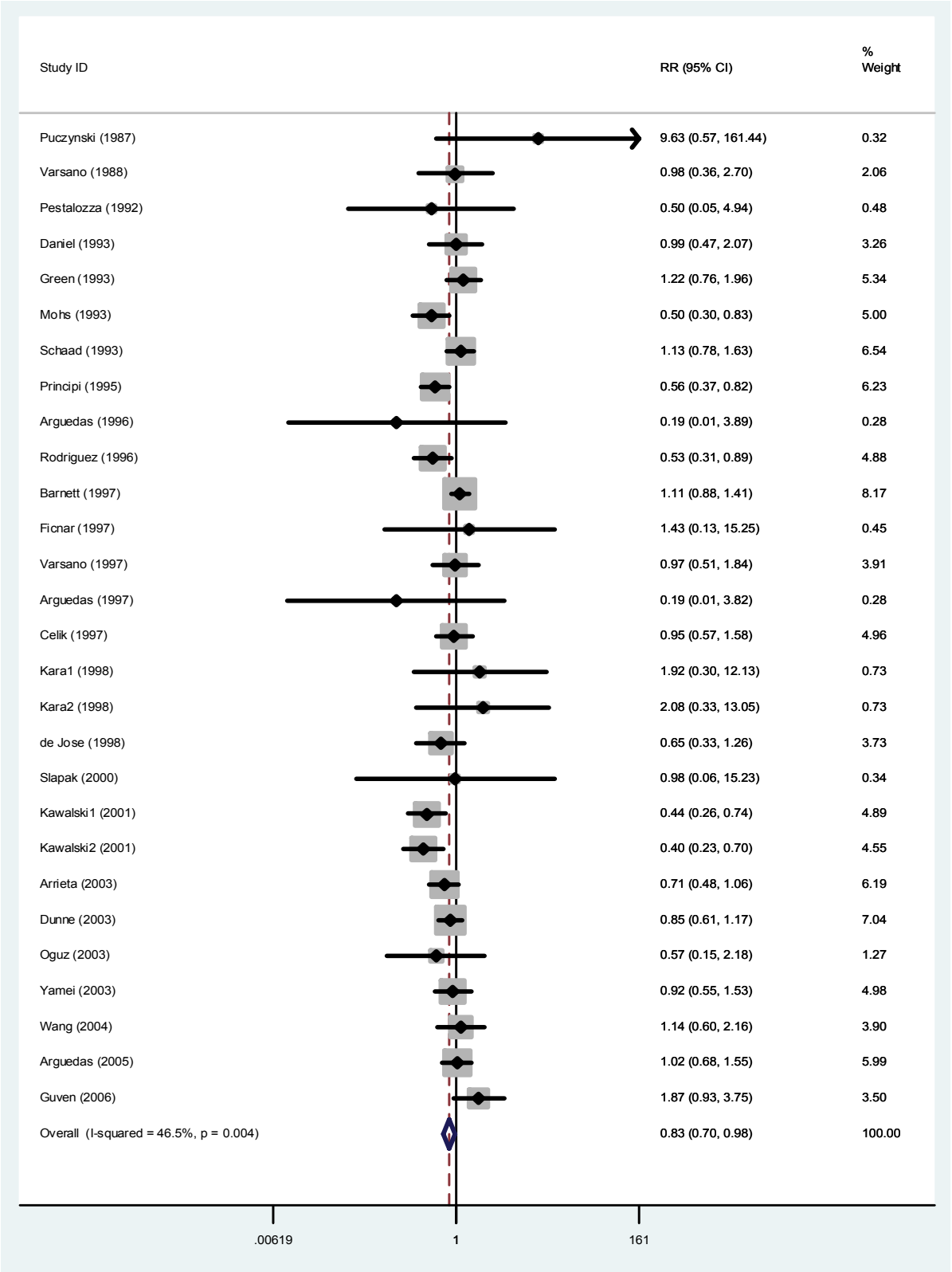

Fig. 16: Forest plot for treatment failure until one month (redefining subjects showing improvement as failure) from random effects model for short course *versus* long course (analytic components = 28)

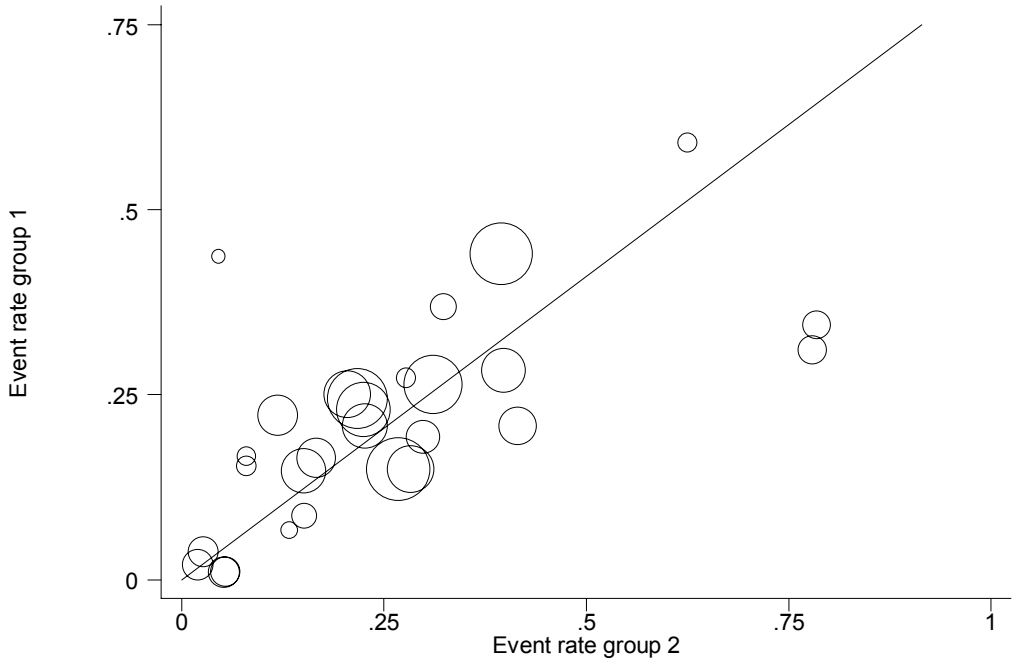

Fig. 17: L'Abbe plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course (analytic components = 28)

On conducting the pre-specified sensitivity and subgroup analyses, significant (P<0.05) heterogeneity was identified between the various subgroups of only one variable, namely, pharmacokinetic behaviour of the antibiotic used in the short course arm (Table 7 and Fig. 18-26). The relative risk of treatment failure was significantly lower when azithromycin was used in the short course [RR=0.73 (95% CI 0.60 to 0.0.88, P=0.001; test for heterogeneity: Cochran Q=33.13, I^2=45.7%, P<0.001)]. On univariable metaregression analysis, the pharmacokinetic behaviour of the antibiotic used in the short course arm was a significant predictor of heterogeneity. However, on multivariate analysis there was no significant predictor of heterogeneity (Table 8).

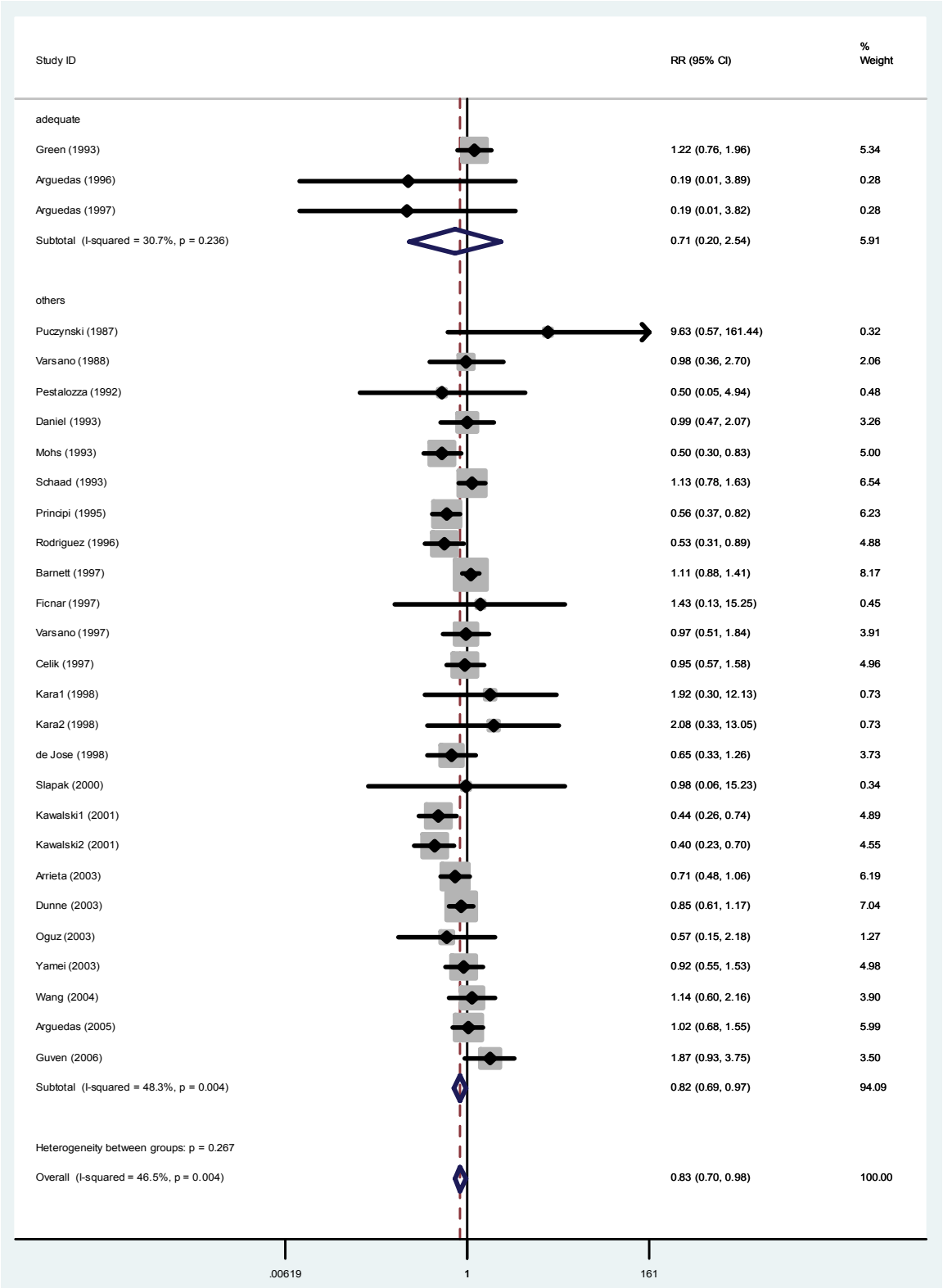

Fig. 18: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course versus long course in relation to allocation concealment (analytic components = 28)

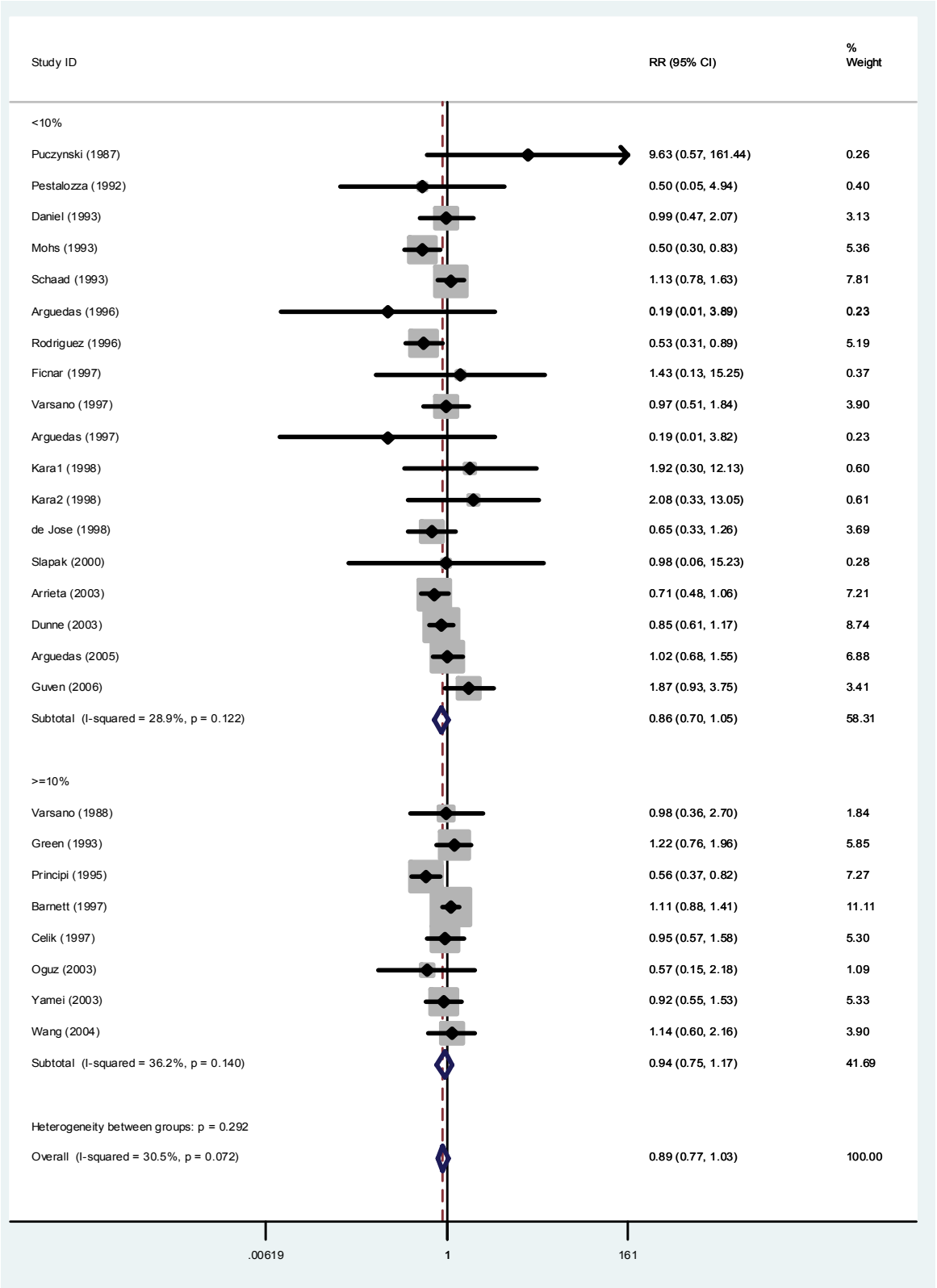

Fig. 19: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to attrition (analytic components = 26)

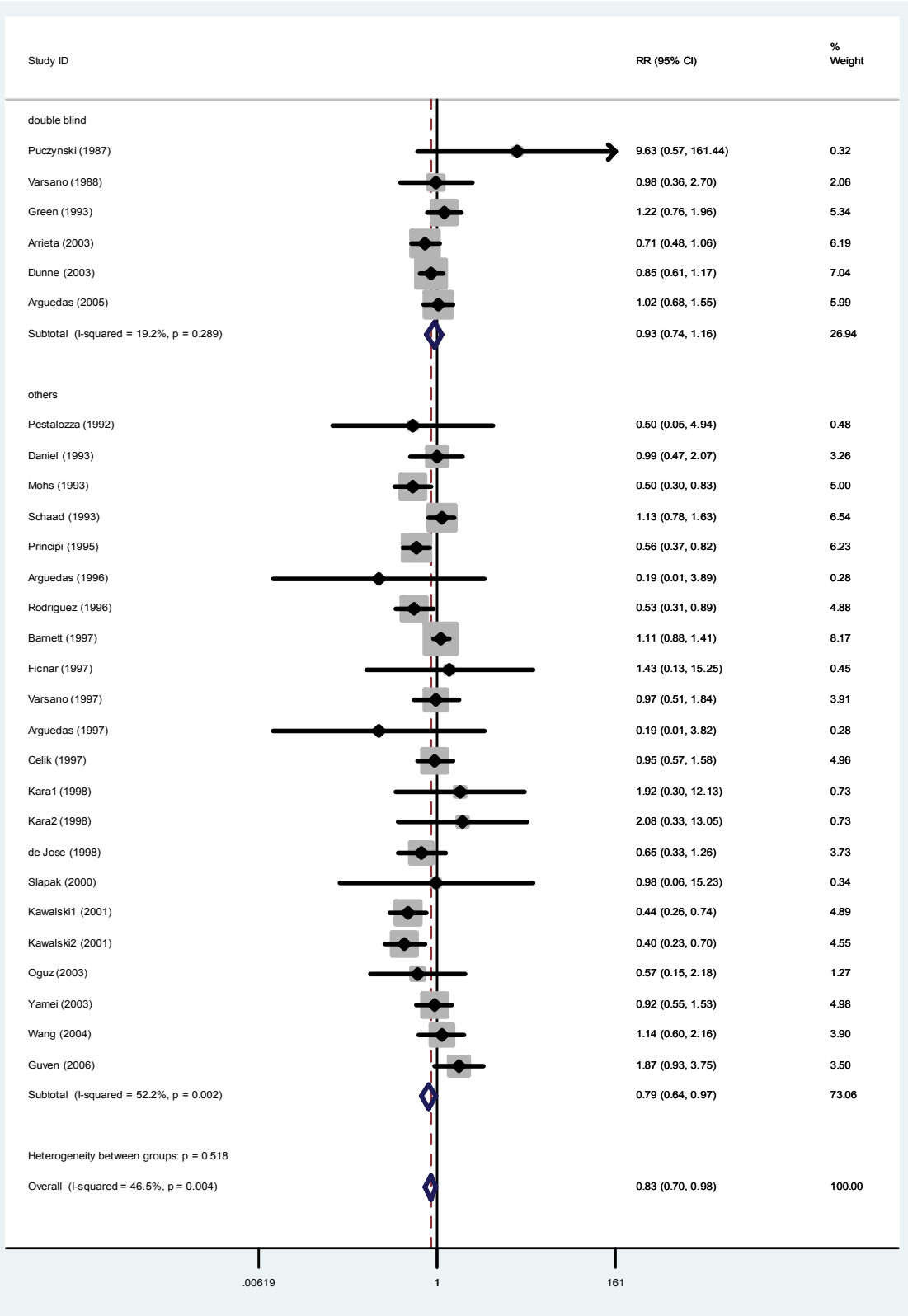

Fig. 20: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to blinding (analytic components = 28)

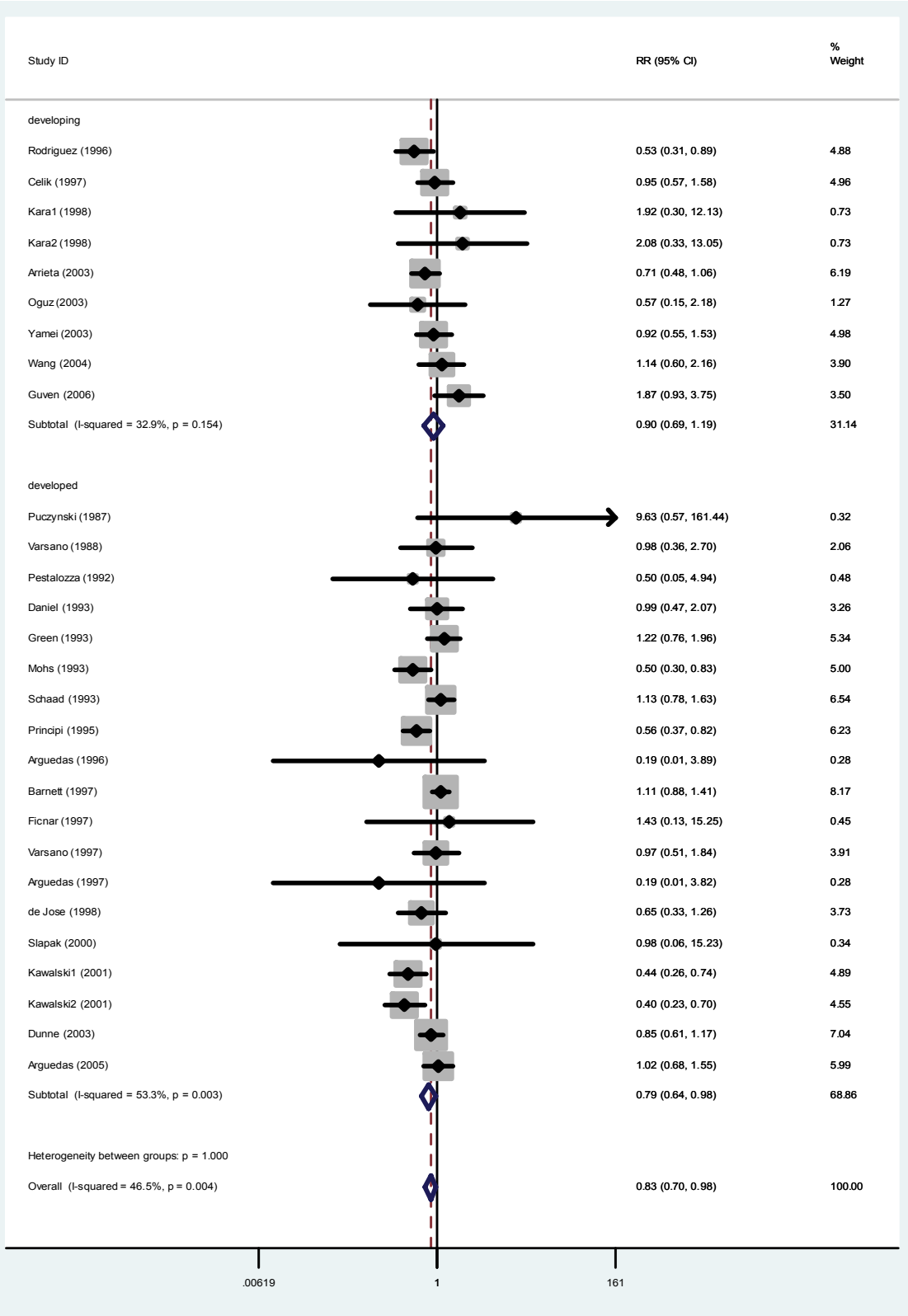

Fig. 21: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to country development status (analytic components = 28)

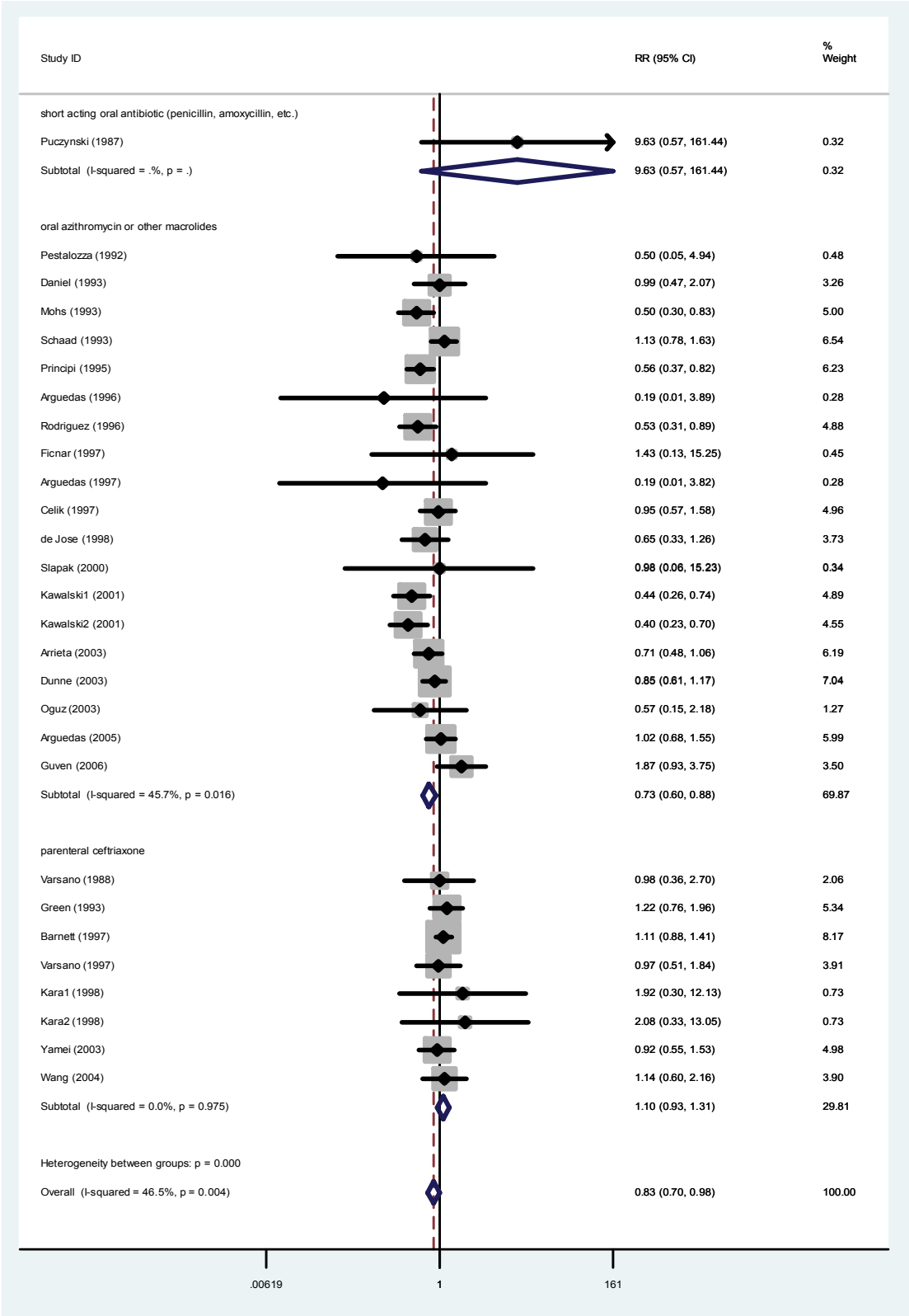

Fig. 22: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic used in short course (analytic components = 28)

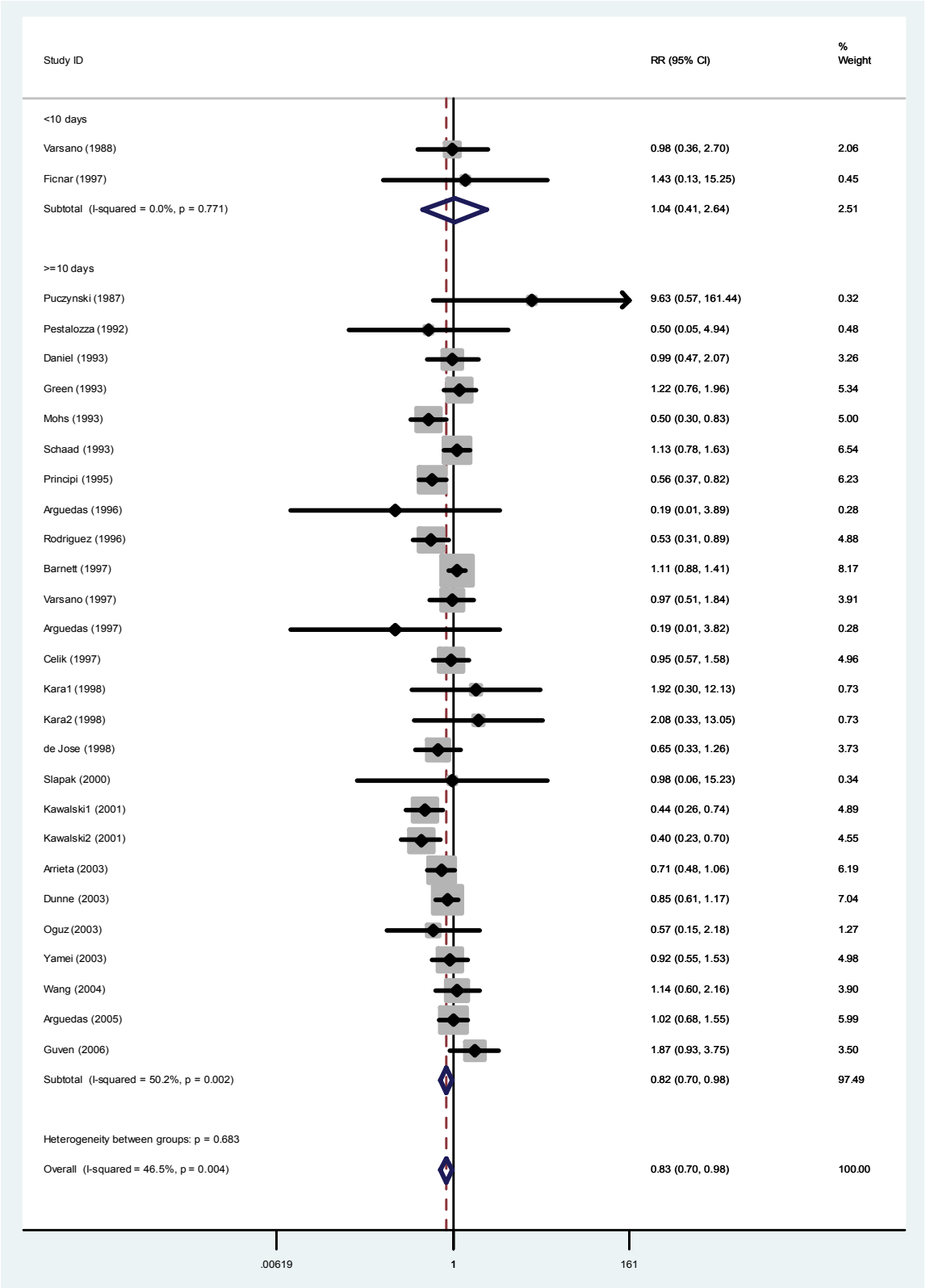

Fig. 23: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to duration of antibiotic use in long course (analytic components = 28)

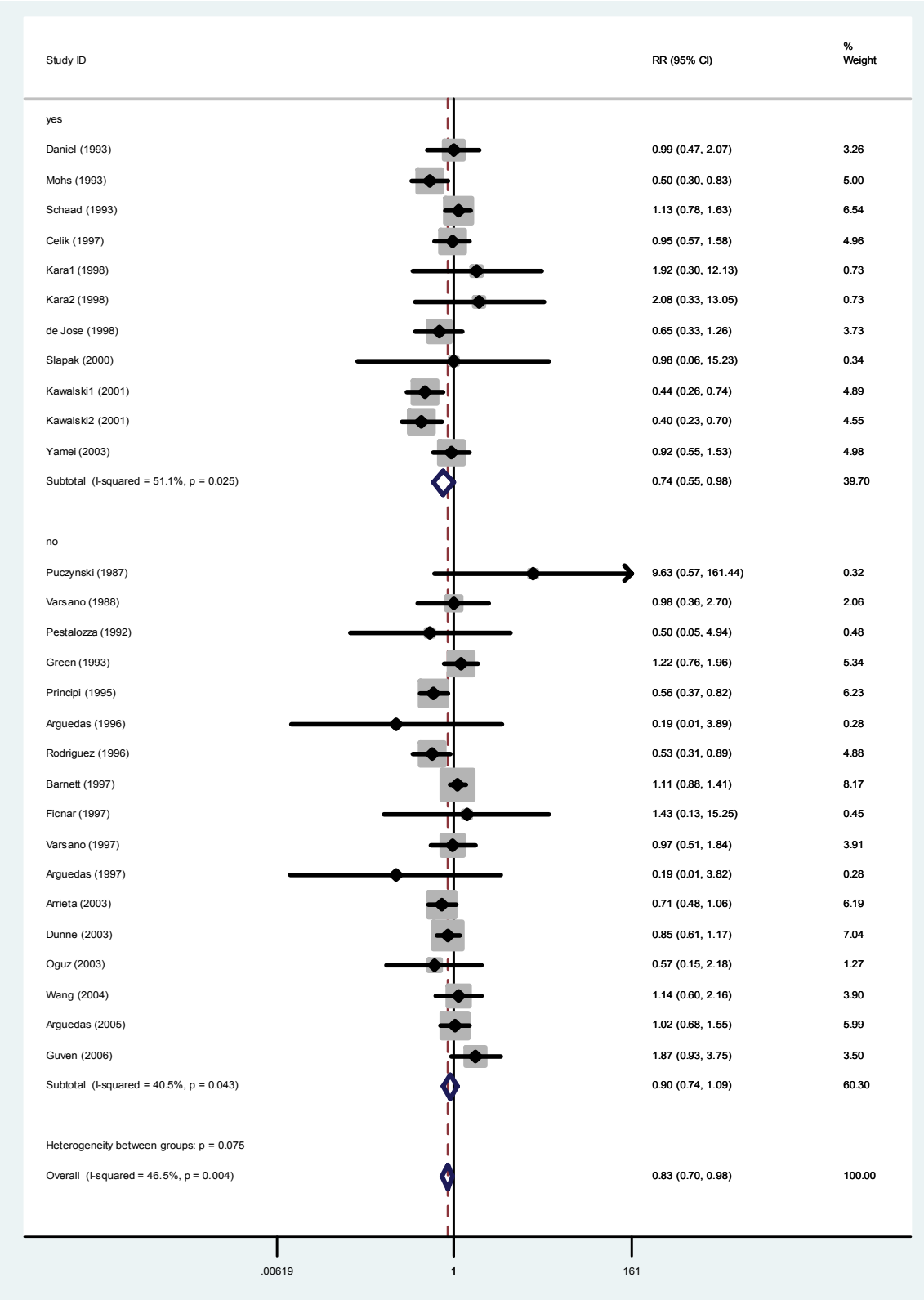

Fig. 24: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to co-intervention use (analytic components = 28)

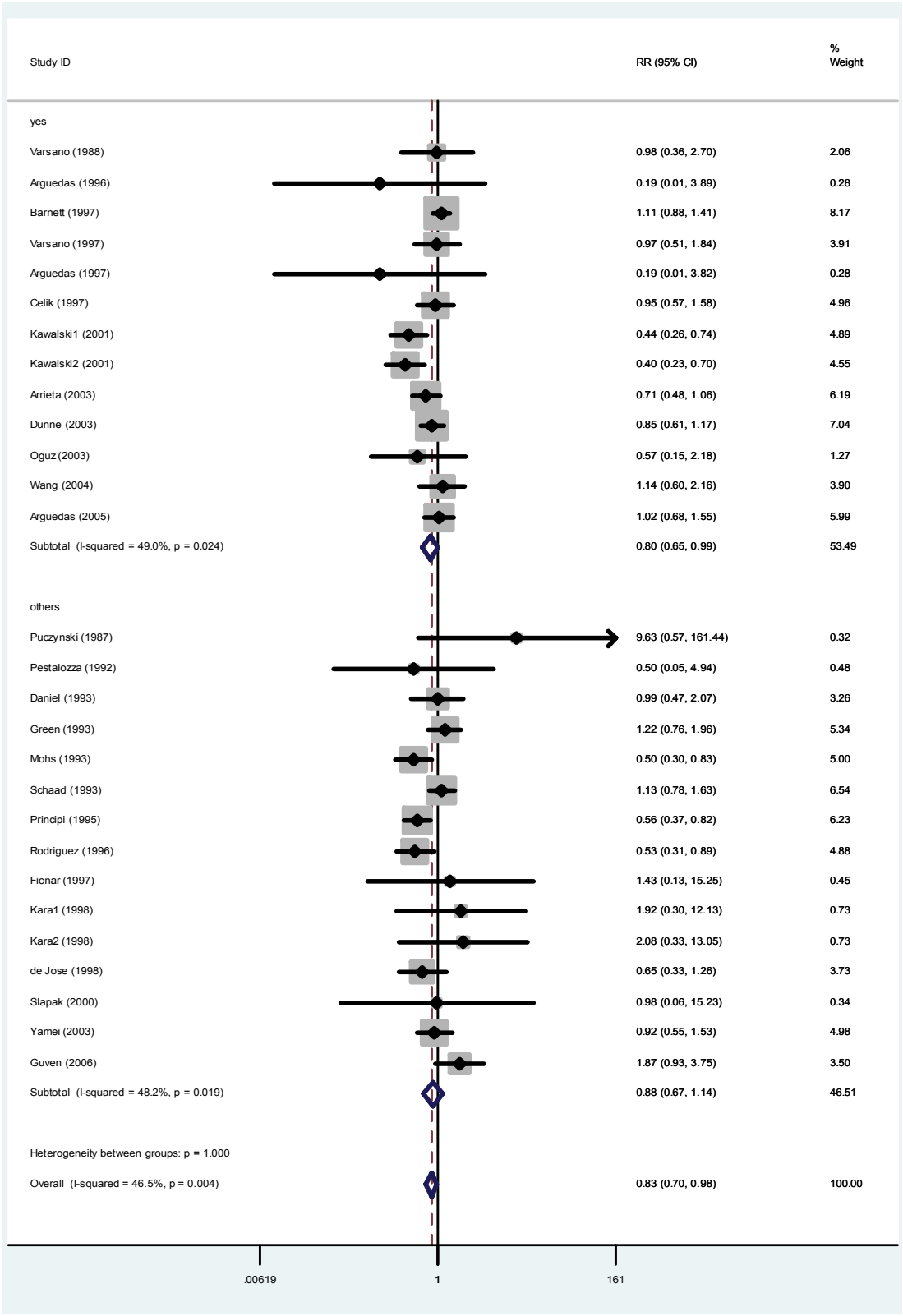

Fig. 25: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to compliance monitoring (analytic components = 28)

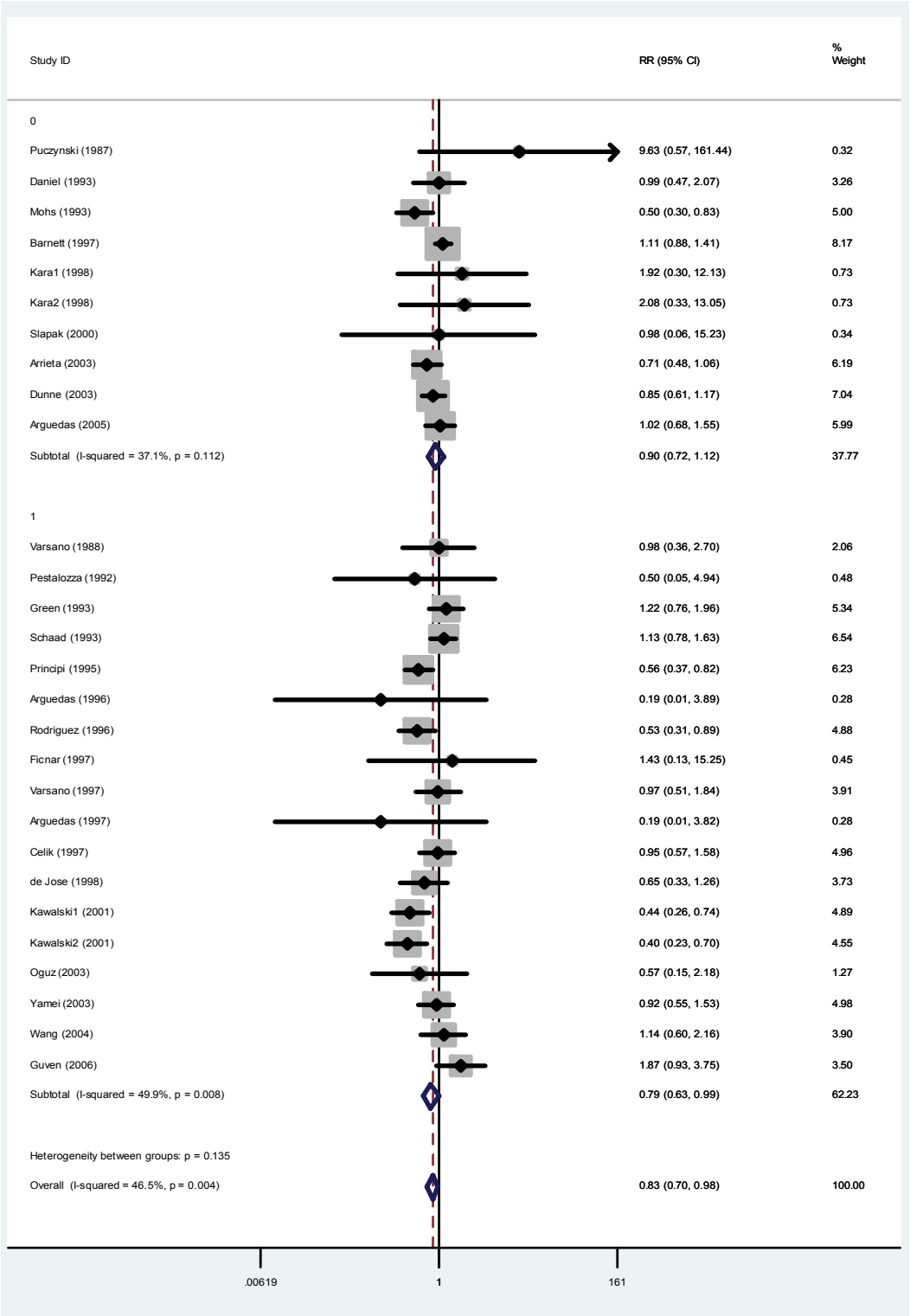

Fig. 26: Forest plot for treatment failure (redefining subjects showing improvement as failure) until one month from random effects model for short course *versus* long course in relation to intention to treat analysis (analytic components = 28)

Table 8. Metaregression analyses for relative risk of treatment failure (Redefining subjects showing improvement as failure) by Restricted Maximum Likelihood Method

Study characteristic	Univariable analysis RR (95% CI); *I^2	P	Controlling for additional variables RR (95% CI)	P
Study quality				
Allocation concealment *(others vs. adequate)*	0.82 (0.38, 1.71); 0.47	0.568	1.22 (0.34, 4.45)	0.743
Attrition *(>10% vs. <10%)*(n=26)	1.09 (0.78, 1.51); 0.31	0.612	0.88 (0.51, 1.52)	0.634
Blinding *(others vs. double blind)*	0.83 (0.55, 1.24); 0.48	0.339	0.81 (0.38, 1.71)	0.550
Trial site (*developed vs. developing)*	0.87 (0.59, 1.28); 0.48	0.455	0.94 (0.59, 1.51)	0.790
Short course arm other antibiotics *vs.* oral short-acting	0.09 (0.00, 1.74); 0.45	0.106	0.15 (0.01, 3.86)	0.230
Short course arm other antibiotics *vs.* azithromycin/macrolides	1.54 (1.10, 2.16); 0.30	**0.015**	1.61 (0.91, 2.86)	0.096
Short course arm other antibiotics *vs.* parenteral ceftriaxone	0.67 (0.48, 0.94); 0.32	**0.023**	DR	DR
Duration of long course antibiotic *(≥ 10 vs. < 10 days*)	0.78 (0 .26, 2.40); 0.48	0.652	1.09 (0.27, 4.41)	0.898
Cointervention (*no vs. yes*)	1.22 (0.86, 1.74); 0.45	0.258	0.90 (0.53, 1.51)	0.660
Compliance monitoring (*others vs. yes*)	1.10 (0.76, 1.58); 0.48	0.605	1.03 (0.58, 1.83)	0.926
Intention to treat analysis (*others vs. yes*)	0.87 (0.60, 1.27); 0.46	0.463	1.05 (0.59, 1.88)	0.856

The number of analytic components in univariate model is 28 except where specifically stated otherwise.
* Proportion of residual variation due to heterogeneity, I-squared.
DR – Dropped in the analysis due to colinearity.
Multivariate model – number of analytic components is 26 and the proportion of residual variation due to heterogeneity, I-squared is 0.32.
In the multivariate analysis, as a sensitivity exercise, on dropping the variable attrition from the model due to missing observation in two units, no variable was significant.

Clinical treatment failure until one month in culture positive otitis media

There was no increased risk of clinical treatment failure with the use of a shorter course of antibiotics when the analysis was restricted to studies (48, 61, 64, 70, 71) providing relevant information on culture positive cases of otitis media (Fig. 27). The overall relative risk for treatment failure with a short course of antibiotics in comparison to a longer course was 1.05 (95% CI 0.75 to 1.46, P=0.796; test for heterogeneity: I^2=20%, P=0.287). In one study (64), about two thirds of the subjects had recurrent otitis media and the rest persistent otitis media. However, disaggregated culture information was not provided for recurrent and persistent otitis media. As a subgroup analysis, exclusion of this study did not alter the findings (RR=1.23, 95% CI 0.75 to 2.02, P=0.418; test for heterogeneity: I^2=22.1%, P=0.278).

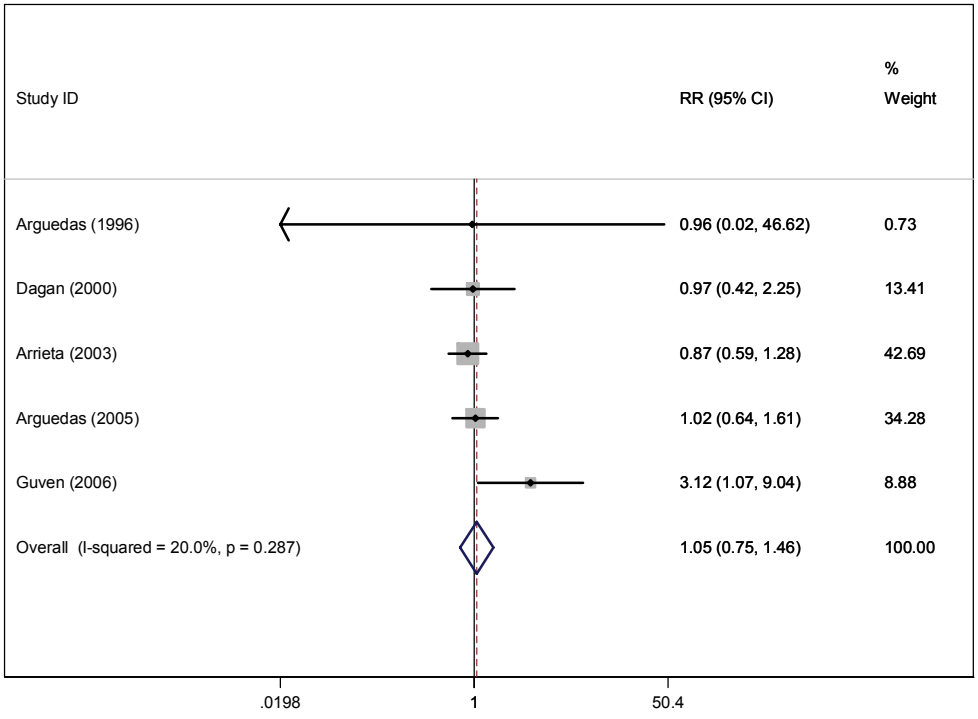

Fig. 27: Forest plot of clinical treatment failure until one month in culture-positive cases of otitis media

Bacteriologic failure until one month

Bacteriologic cultures from the middle ear had been performed in all subjects at recruitment and after initiation of antibiotic therapy in only three analytic components (61, 63). In addition, in four analytic components (47, 54, 57) cultures were available at the two time points in only a small proportion of recruited subjects. Overall, there was no evidence of an increased risk of bacteriologic failure (Fig. 28) with the use of a shorter course of antibiotics (RR=0.97, 95% CI 0.66 to 1.44, P=0.880; test for heterogeneity: I^2=0.0%, P=0.912). The findings were similar when both the above subgroups were analyzed separately and there was no evidence of heterogeneity in the subgroups (RR=1.0, 95% CI 0.67 to 1.50, P=0.999; test for heterogeneity: I^2=0.0%, P=0.996 for subgroup with cultures available for all subjects at both time points, and RR=0.66, 95% CI 0.15 to 2.86, P=0.575; test for heterogeneity: I^2=0.0%, P=0.625 for subgroup with cultures available for only a small proportion of subjects at both time points).

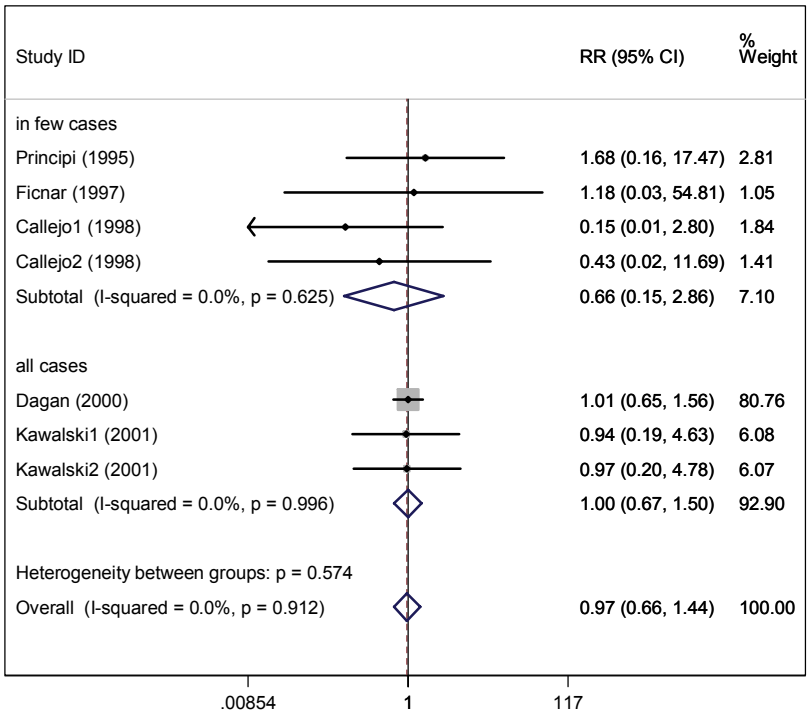

Fig. 28: Forest plot for bacteriologic failure until one month from random effects model for short course *versus* long course (analytic components = 7). All cases = Bacteriologic cultures performed in all subjects at recruitment and after initiation of antibiotic therapy; In few cases = Bacteriologic cultures were available at two time points in only a small proportion of recruited subjects.

Treatment failure in high-risk groups

We had initially considered performing subgroup analyses of primary outcome among groups known to be associated with a high risk of treatment failure, namely children below two years of age, perforated eardrum, recurrent otitis media and specific bacterial pathogens. However, subgroup analyses and metaregression could not be performed for the primary outcome because of the paucity of studies conducted exclusively in these high-risk groups. Nevertheless, stratified information for these high-risk groups could be collected from some individual studies.

There was no study conducted exclusively in children below two years of age. In only five trials, data was available separately for children below and above two years of age (45, 47, 65, 66, 70). There was no evidence of an increased risk of treatment failure with short course antibiotics in children below two years of age (Table 9 and Fig. 29).

Table 9. Sensitivity and subgroup analyses of relative risk of primary outcome (Treatment failure until one month of intervention) with information for stratification variables extracted from available individual studies

Stratification variable	No. #	Random effects model RR (95% CI)	P value	Tests for heterogeneity I^2 (%); Q (P value)	P value for heterogeneity in subgroups
Age (years)					
< 2	5	*0.87 (0.61, 1.25)*	0.454	35.30; 6.18 (0.186)	
> 2	5	*0.96 (0.63, 1.48)*	0.864	25.70; 5.39 (0.250)	0.758
Perforated eardrum					
Yes	4	0.80 (0.39, 1.63)	0.535	0.00; 2.77 (0.428)	
No	1	1.31 (0.60, 2.87)	0.499	Not applicable	0.365
Recurrent otitis media					
Yes	4	0.70 (0.48, 1.03)	0.070	0.00; 0.10 (0.992)	
No	3	1.07 (0.65, 1.76)	0.784	0.00; 1.92 (0.382)	0.186
Isolated microorganisms					
S. pneumoniae or *H. influenzae*	8	1.03 (0.81, 1.33)	0.797	0.00; 6.10 (0.528)	
Others	7	0.97 (0.49, 1.88)	0.916	0.00; 4.98 (0.546)	1.000

Treatment failure refers to clinical failure or relapse or recurrence or bacteriologic failure until the last time point within one month of initiating intervention.

For perforated eardrum, in one study the last time point was at 60 days. The definition of failure was either persistent perforation or clinical failure.

The definition of failure for isolated microorganisms included clinical or bacteriologic failure.

- Number of analytic components.

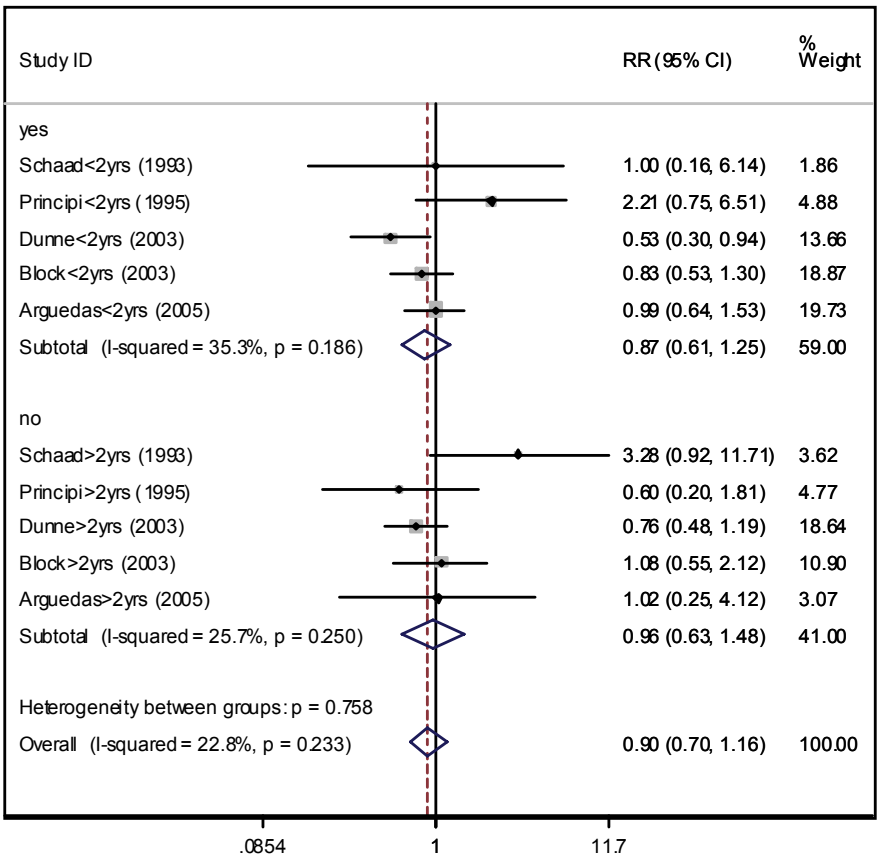

Fig. 29: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to age of subjects with information derived from individual studies (analytic components = 10). Yes = age < 2 years and no = age > 2 years

In a single study, treatment failure outcome was given separately for children with perforated and non-perforated eardrums (47). However, in three other analytic components (44, 45, 59) information was available for subjects with perforated eardrums. There was no evidence of an increased risk of treatment failure with short course antibiotics in children with perforated eardrums (Table 9 and Fig. 30).

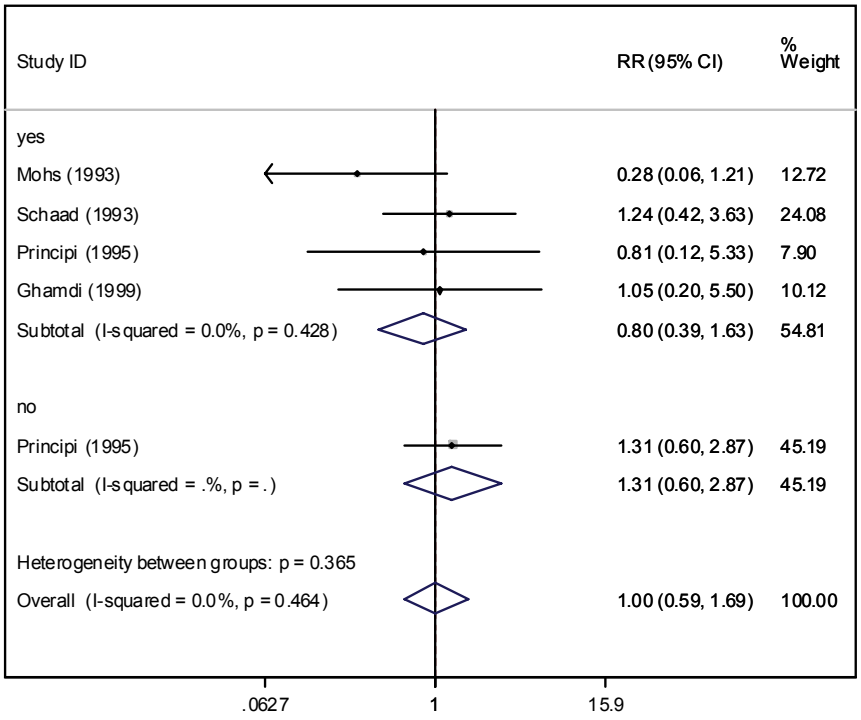

Fig. 30: Forest plot for failure until 2 months from random effects model for short course *versus* long course in relation to perforated eardrum with information derived from individual studies (analytic components = 5)

In three trials, data was available separately for subjects with recurrent and non-recurrent otitis media (44, 47, 55). An additional trial provided information only for children with recurrent otitis media (64). There was no evidence of an increased risk of treatment failure with short course antibiotics in children with recurrent otitis media (Table 9 and Fig. 31).

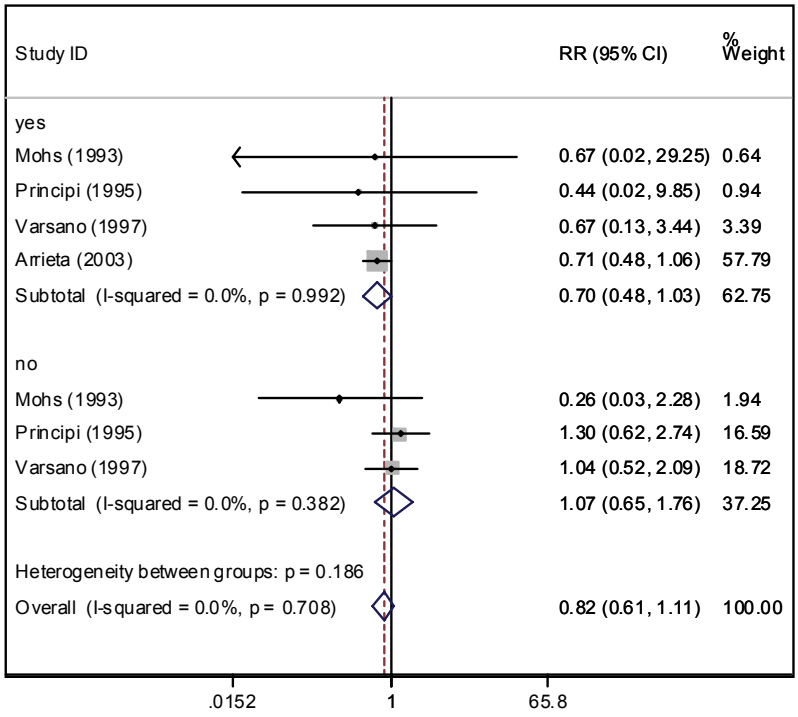

Fig. 31: Forest plot for treatment failure until one month from random effects model for short course *versus* long course in relation to recurrent otitis media with information derived from individual studies (analytic components = 7)

Information on treatment outcomes in relation to bacterial pathogens (*Streptococcus pneumoniae* or *H. influenzae*, and others) was available from 15 analytic components (39, 48, 61, 63, 64, 70, 71). There was no evidence of an increased risk of treatment failure with short course antibiotics with any specific group of bacterial pathogens (Table 9 and Fig. 32). The findings remained unchanged when the study (64) including a small proportion of subjects with persistent otitis media was excluded (overall RR = 1.06, 95% CI 0.79 to 1.43, P=0.674; test for heterogeneity: I^2=0.0%, P=0.833; *Streptococcus pneumoniae* or *H. influenzae* RR = 1.05, 95% CI 0.73 to 1.51, P=0.787; test for heterogeneity: I^2=5.0%, P=0.389; and other bacterial pathogens RR = 1.23, 95% CI 0.60 to 2.51, P=0.566; test for heterogeneity: I^2=0.0%, P=0.964).

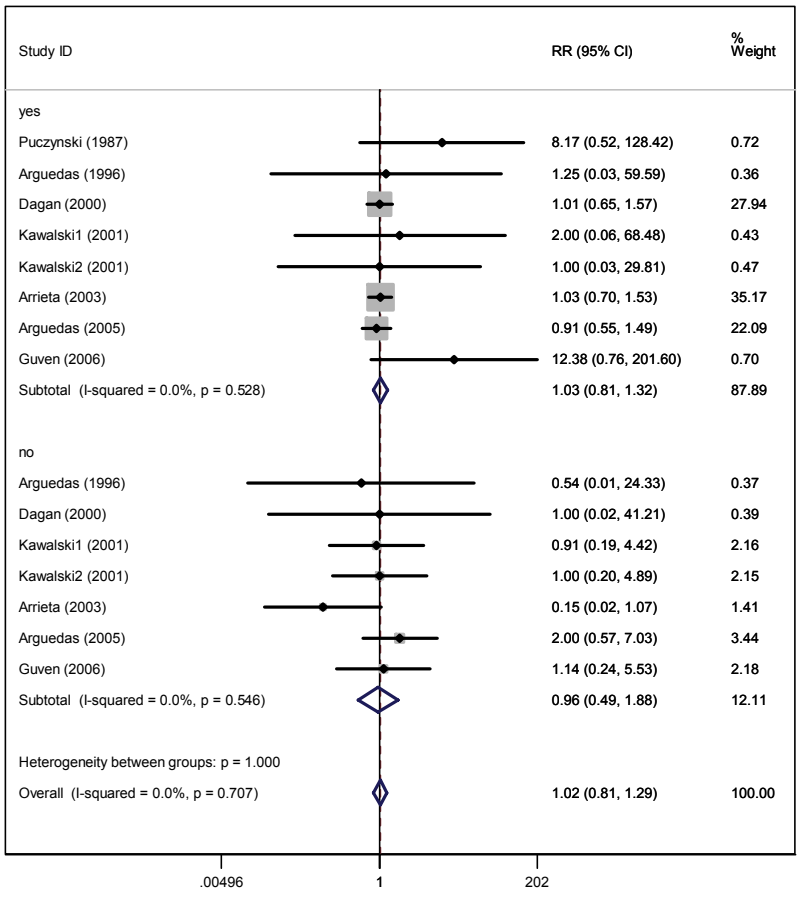

Fig. 32: Forest plot for treatment (clinical or bacteriologic) failure until one month from random effects model for short course *versus* long course in relation to microbiological isolates (Yes=*Streptococcus pneumoniae* or *Hemophilus influenzae,* No=Other pathogens) with information derived from individual studies (analytic components = 15)

Persistent middle ear effusion

Data on persistent middle ear effusion until one month was available from six studies (48, 51, 55, 66, 67, 71). Except for one study (55), which had used parenteral ceftriaxone, other trials had prescribed azithromycin in the short course arm. Overall, there was no evidence of an increased risk for persistent middle ear effusion with the short course antibiotic treatment (RR=0.86; 95% CI 0.72 to 1.02, P > 0.05; test for heterogeneity: I^2=0.0%, P=0.457). There was no evidence of heterogeneity (P=0.165) between the two subgroups (Fig. 33). However, the risk for persistent middle ear effusion was significantly lower when azithromycin was used as the short course antibiotic (RR=0.81, 95% CI 0.67 to 0.98, P= 0.031; test for heterogeneity: I^2=0.0%, P=0.601).

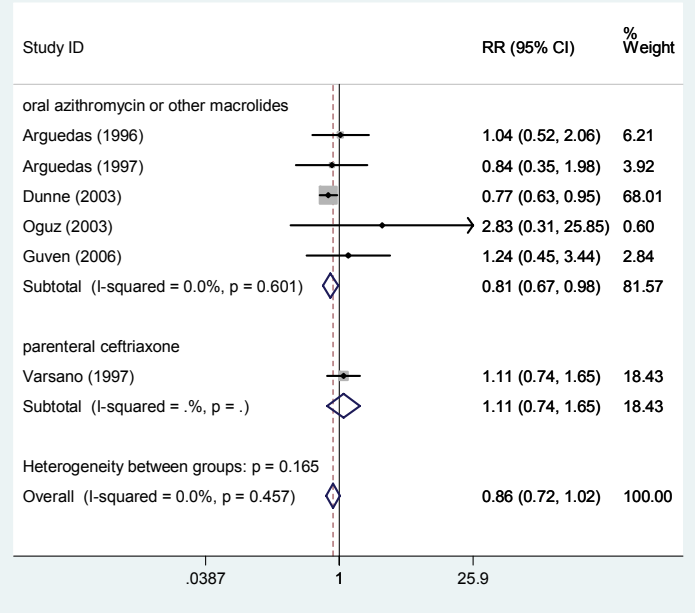

Fig. 33: Forest plot for persistent middle ear effusion until one month from random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short course (analytic components = 6). The P value for azithromycin/macrolide was 0.031, and for parenteral ceftriaxone and overall >0.05.

Relapse

Overall, there was no evidence of an increased risk for relapse until one month with short course antibiotics (RR=0.99; 95% CI 0.73 to 1.34, P > 0.05; test for heterogeneity: I^2=0.0%, P=0.992). There was no evidence of heterogeneity (P=0.472) in the subgroups according to the pharmacokinetic behaviour of the antibiotic used in the short course treatment arm (Fig. 34).

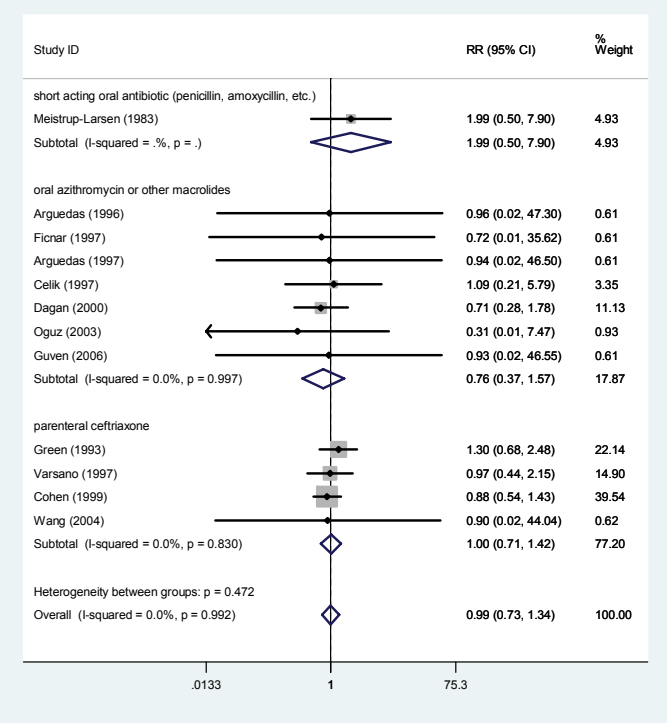

Fig. 34: Forest plot for relapse until one month from random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short course (analytic components = 12).
The P value was > 0.05 for all the three subgroups.

Recurrence

Overall, there was no evidence of an increased risk for recurrence until one month with short course antibiotics (RR=1.33; 95% CI 0.66 to 2.70, P > 0.05; test for heterogeneity: I^2=0.0%, P=0.771). There was no evidence of heterogeneity (P=0.272) in the subgroups according to the pharmacokinetic behaviour of the antibiotic used in the short course treatment arm (Fig. 35).

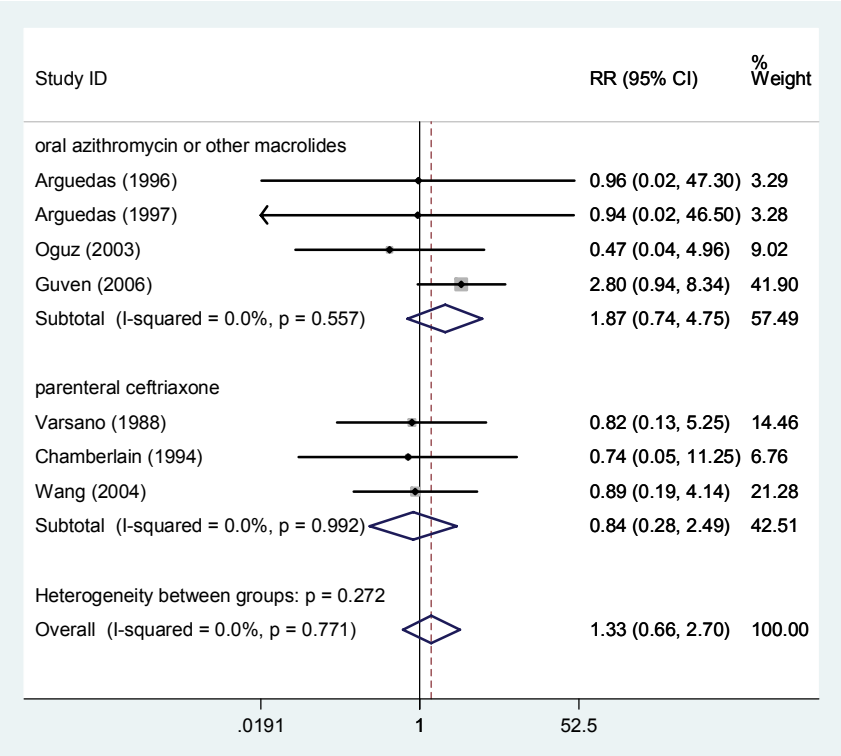

Fig. 35: Forest plot for recurrence until one month from random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short course (analytic components = 7).
The P value was > 0.05 for both the subgroups.

Outcomes at 10 to 14 days

Clinical or bacteriologic failure

There was no evidence of an increased risk of treatment failure at an earlier evaluation point (at 10-14 days) in children treated with a short course of antibiotics (overall RR=1.12; 95% CI 0.97 to 1.30, P= 0.130; test for heterogeneity: Cochran Q=18.25, I^2= 0.0%, P=0.939) (Table 10 and Fig. 36). On conducting the pre-specified subgroup analyses, significant (P<0.05) heterogeneity was not identified between the various strata of any variable (Table 10 and Fig. 37-44). Similarly, on metaregression no variable was identified as a significant predictor of heterogeneity (Table 11).

Table 10. Sensitivity and subgroup analyses of relative risk of treatment failure at 10-14 days of intervention

Stratification variable	No. #	Random effects model RR (95% CI)	P value	Tests for heterogeneity I^2 (%); Q (P value)	P value for heterogeneity in subgroups
Overall	*30*	*1.12 (0.97, 1.30)*	*0.130*	*0.00; 18.25 (0.939)*	*Not applicable*
Allocation concealment					
Adequate	2	0.19 (0.02, 1.60)	0.126	0.00; 0.00 (0.993)	
Others	28	1.13 (0.98, 1.32)	0.104	0.00; 15.56 (0.961)	0.101
Attrition					
<10%	18	1.18 (0.91, 1.53)	0.216	0.00; 13.64 (0.692)	
>10%	10	1.10 (0.91, 1.33)	0.316	0.00; 4.35 (0.887)	0.694
Blinding					
Double blind	5	1.17 (0.89, 1.55)	0.265	0.00; 3.28 (0.512)	
Others	25	1.12 (0.97, 1.30)	0.278	0.00; 14.88 (0.924)	0.767
Trial site					
Developing	10	0.98 (0.67, 1.44)	0.929	0.00; 5.61 (0.778)	
Developed	20	1.15 (0.98, 1.35)	0.092	0.00; 12.15 (0.879)	0.486
Short course antibiotic					
Short-acting oral	1	9.63 (0.57, 161.44)	0.116	Not applicable	
Azithromycin	20	1.13 (0.90, 1.41)	0.297	0.00; 10.84 (0.929)	
Parenteral					
Ceftriaxone	9	1.11 (0.90, 1.36)	0.325	0.00; 5.19 (0.737)	0.329
Cointervention use					
Yes	12	1.10 (0.84, 1.44)	0.487	0.70; 11.08 (0.436)	
Others	18	1.13 (0.94, 1.36)	0.181	0.00; 7.13 (0.982)	0.851
Compliance monitored					
Yes	16	1.12 (0.96, 1.32)	0.163	0.00; 4.13 (0.997)	
Others	14	1.12 (0.71, 1.76)	0.624	8.00; 14.13 (0.365)	1.000
Intention to treat analysis					
Used	12	1.15 (0.97, 1.37)	0.113	0.00; 8.05 (0.709)	
Others	18	1.04 (0.78, 1.41)	0.775	0.00; 9.97 (0.905)	0.627

Treatment failure refers to clinical or bacteriologic failure until 10 to 14 days of initiating intervention. Bacteriologic failure was amalgamated as a part of treatment failure for only one study as information was available distinct from clinical failure or relapse or recurrence.

- Number of analytic components.

Not done for age group (<2 years or >2 years), perforated tympanic membrane (yes or no), recurrent otitis media (yes or no) and duration of antibiotic use in long course (<10 or ≥10 days) as there was no or only a single study for one stratification of these subgroups.

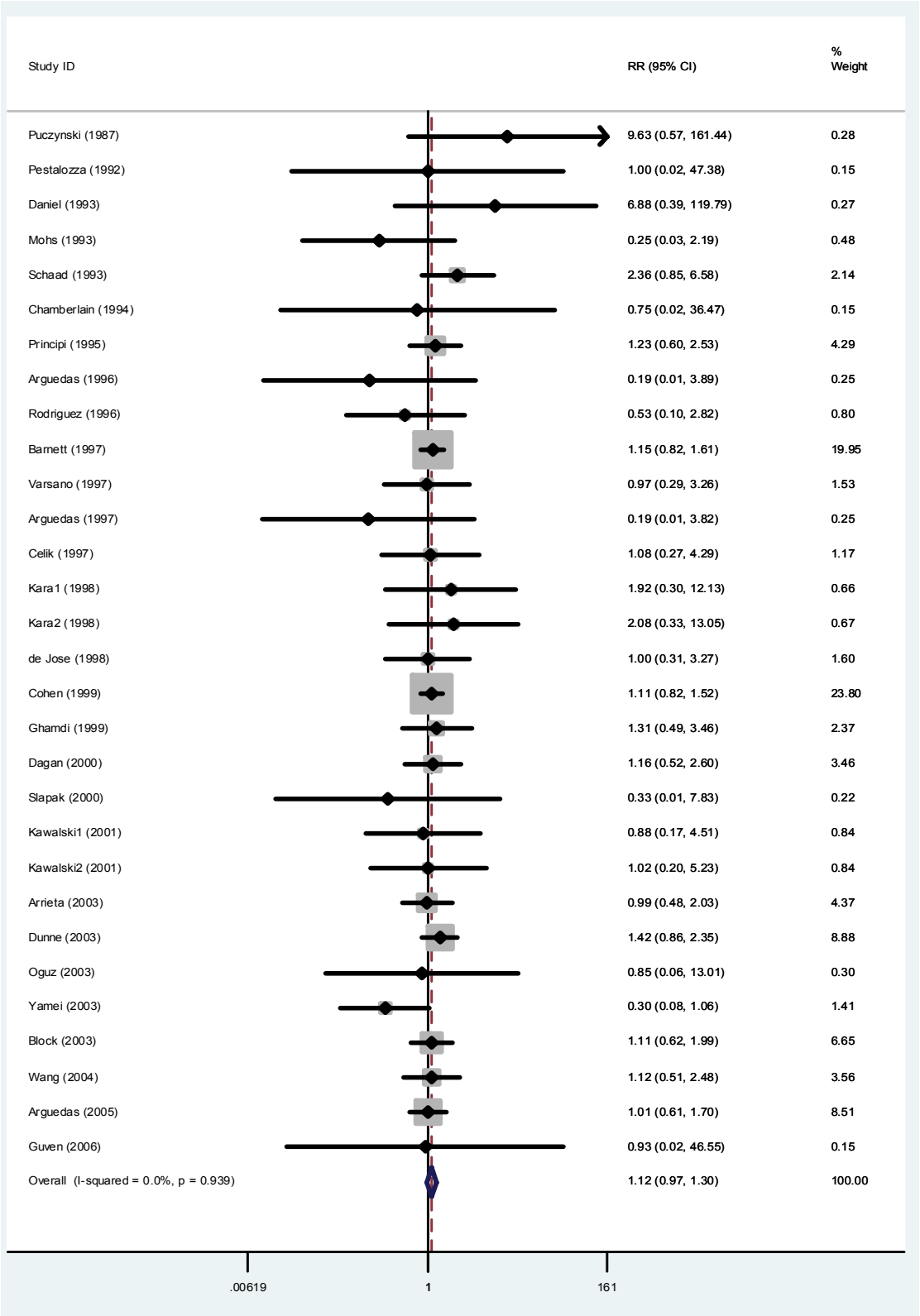

Fig. 36: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course (analytic components =30)

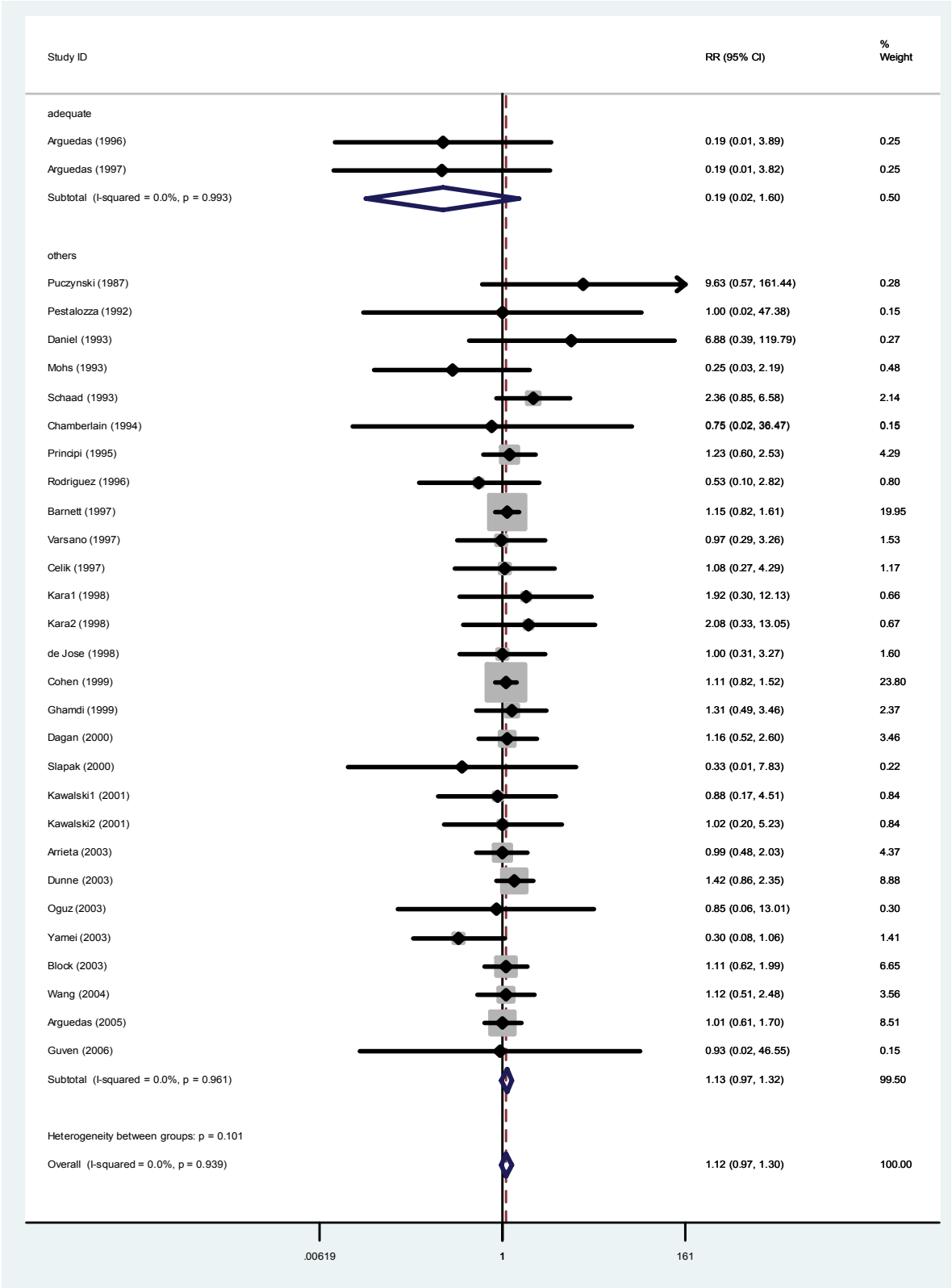

Fig. 37: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to allocation concealment (analytic components =30)

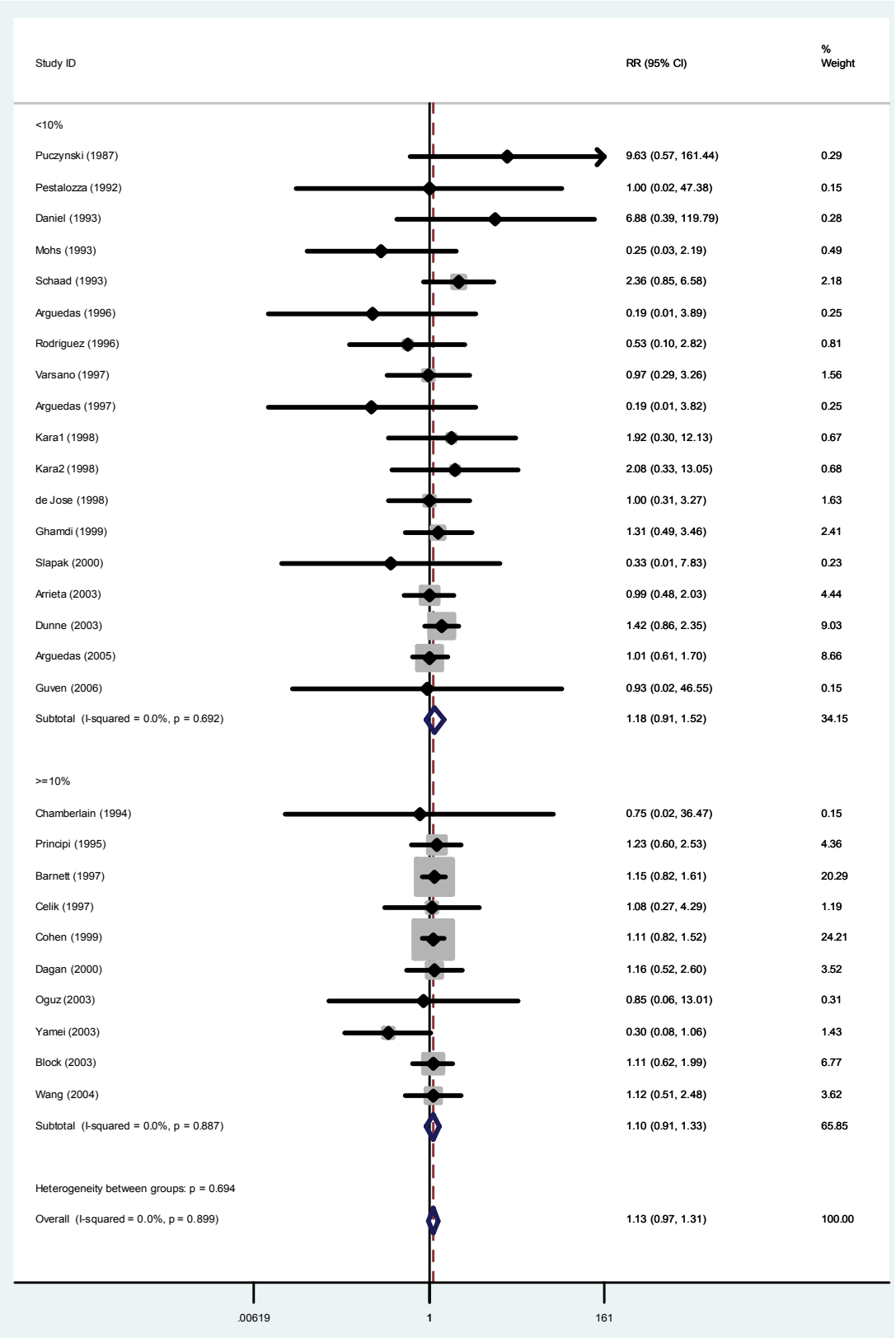

Fig. 38: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to attrition (analytic components = 28)

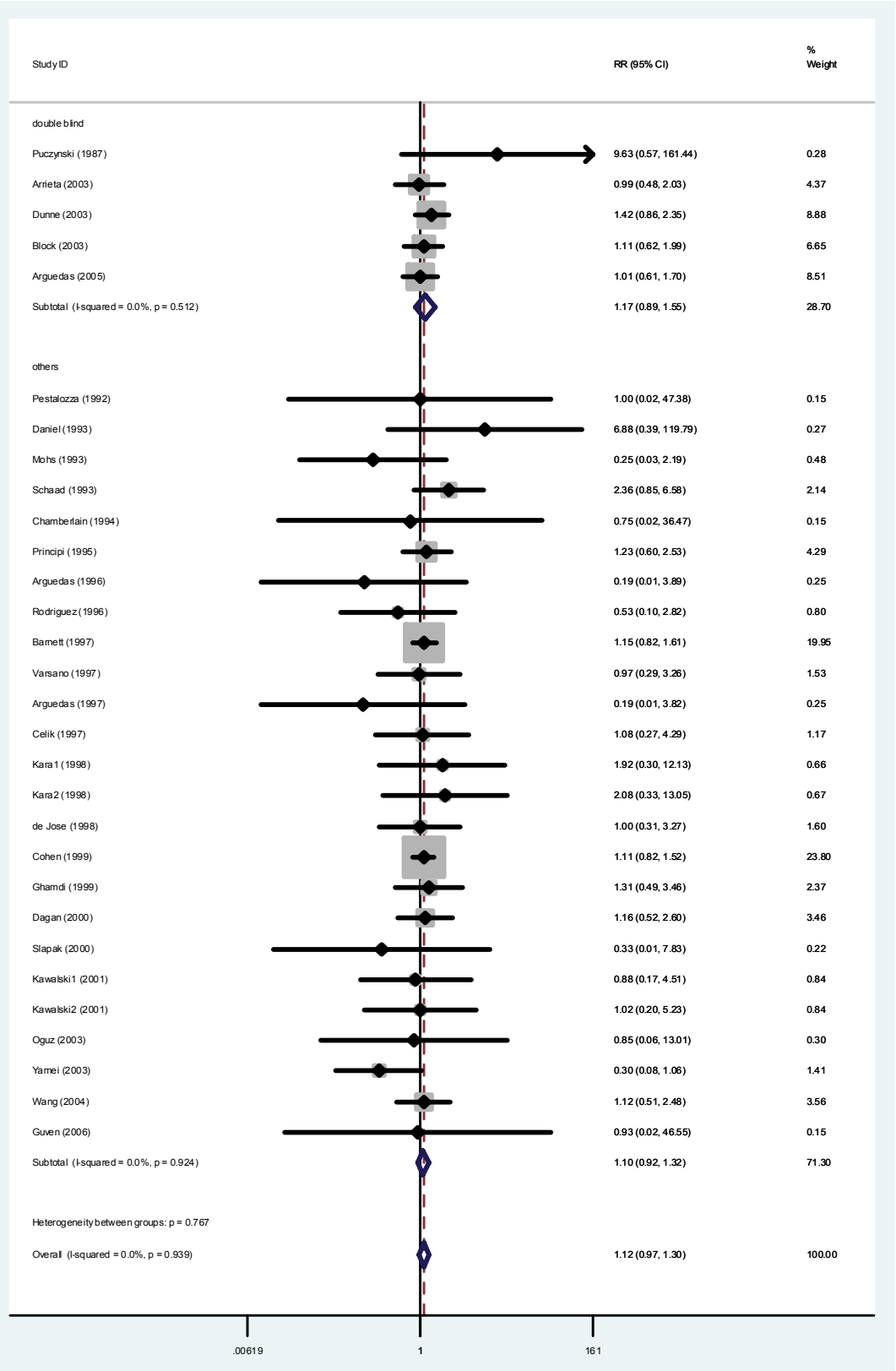

Fig. 39: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to blinding (analytic components =30)

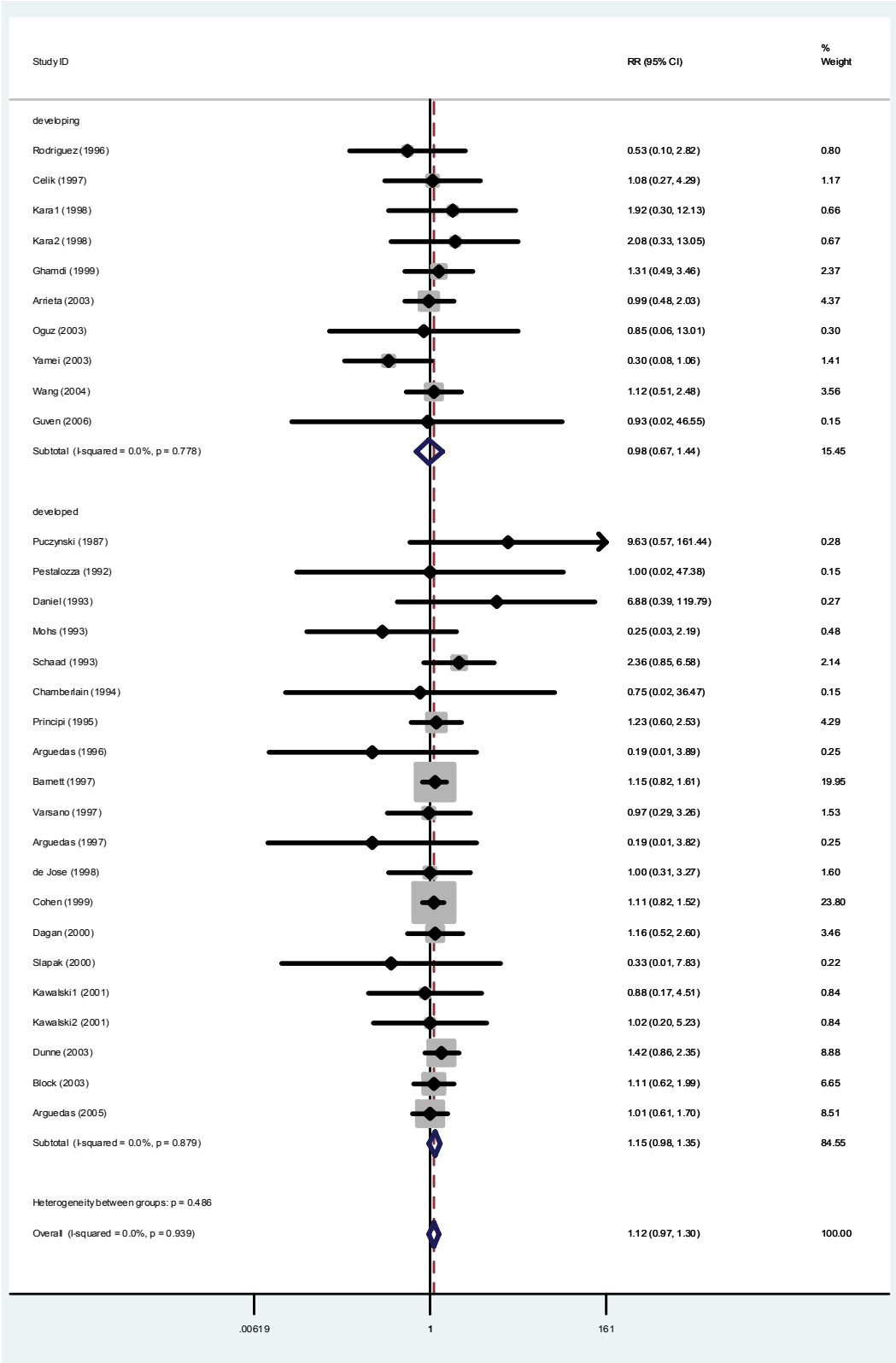

Fig. 40: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to country development status (analytic components =30)

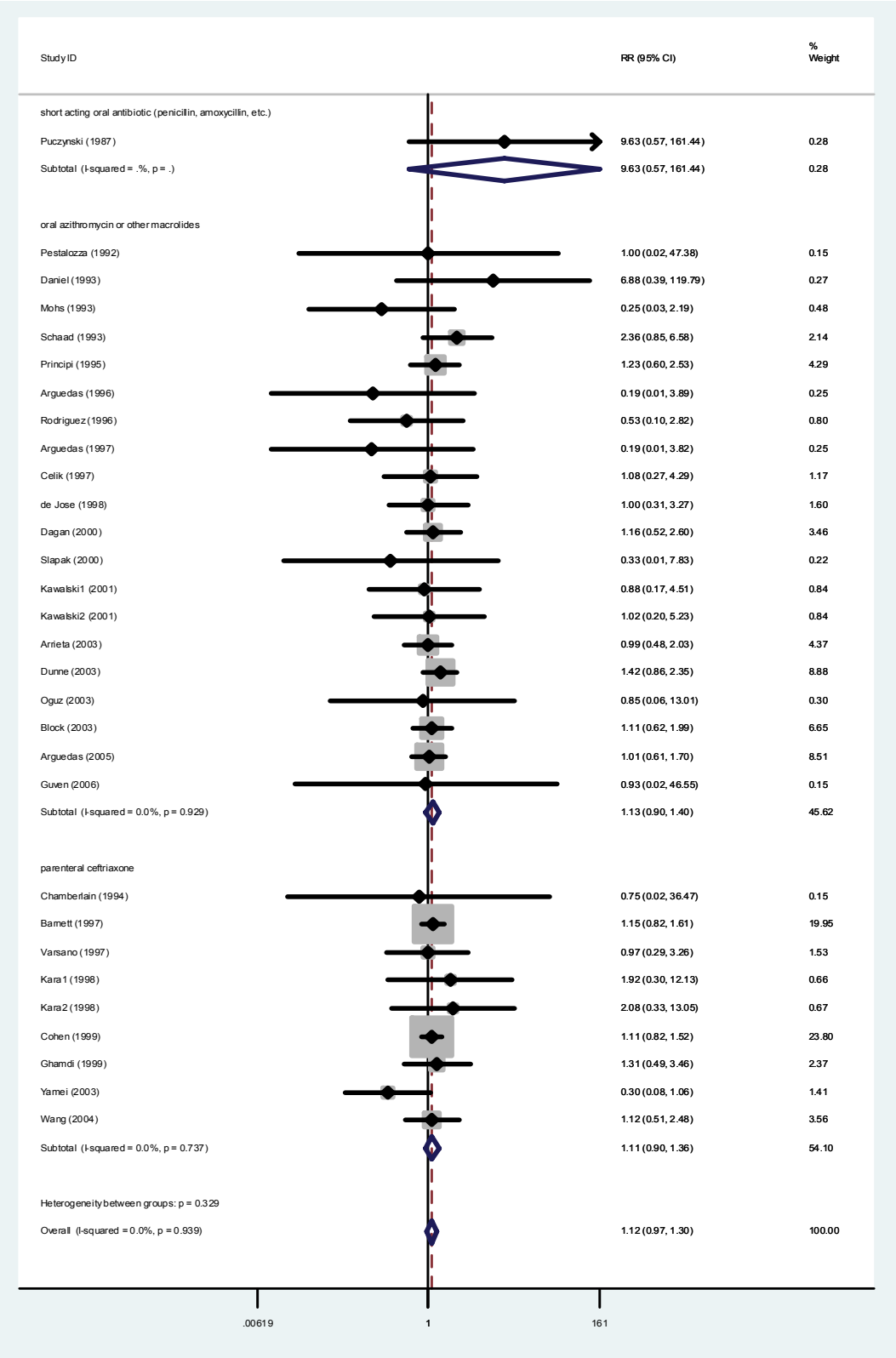

Fig. 41: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic used for short course (analytic components =30)

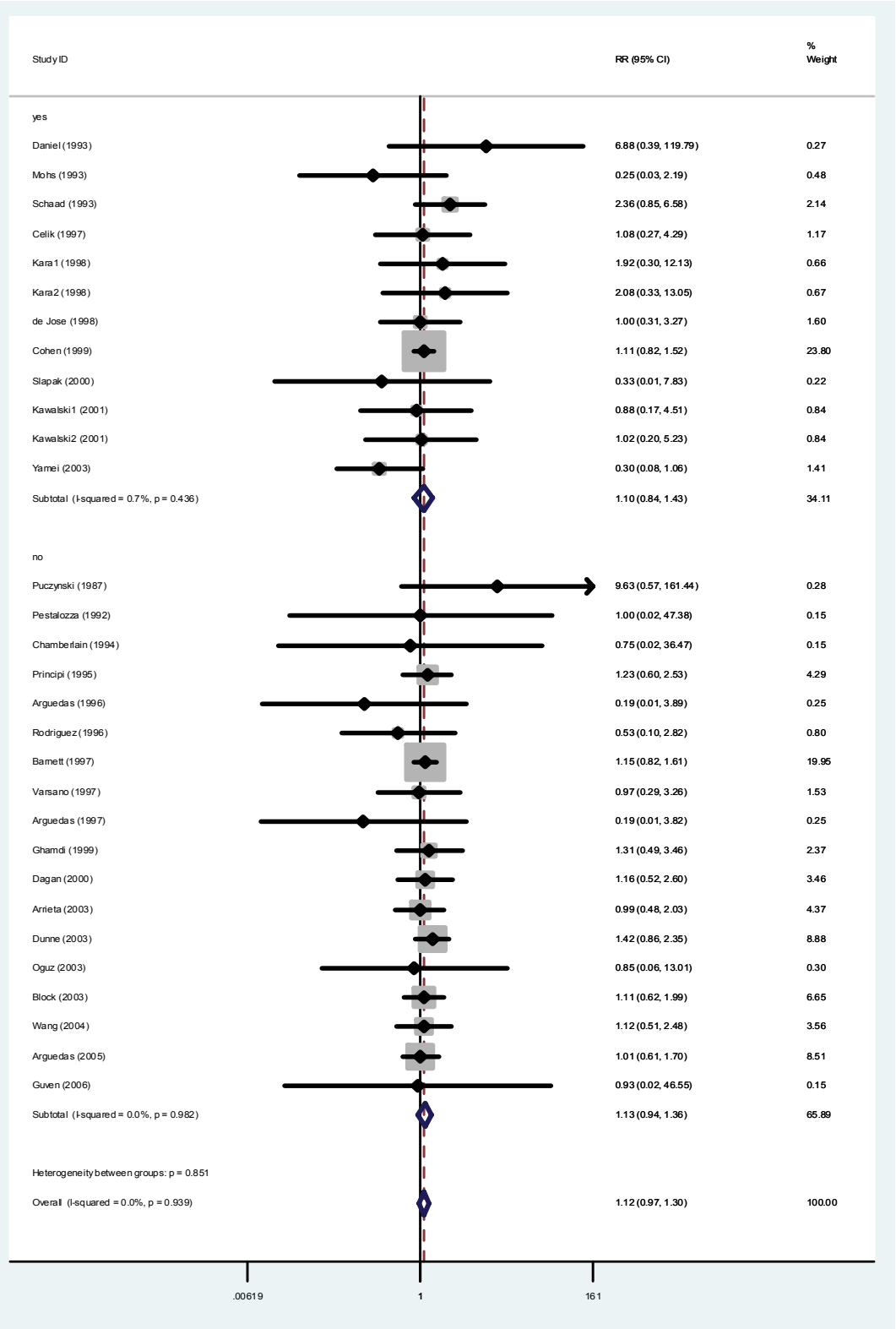

Fig. 42: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to cointervention use (analytic components =30)

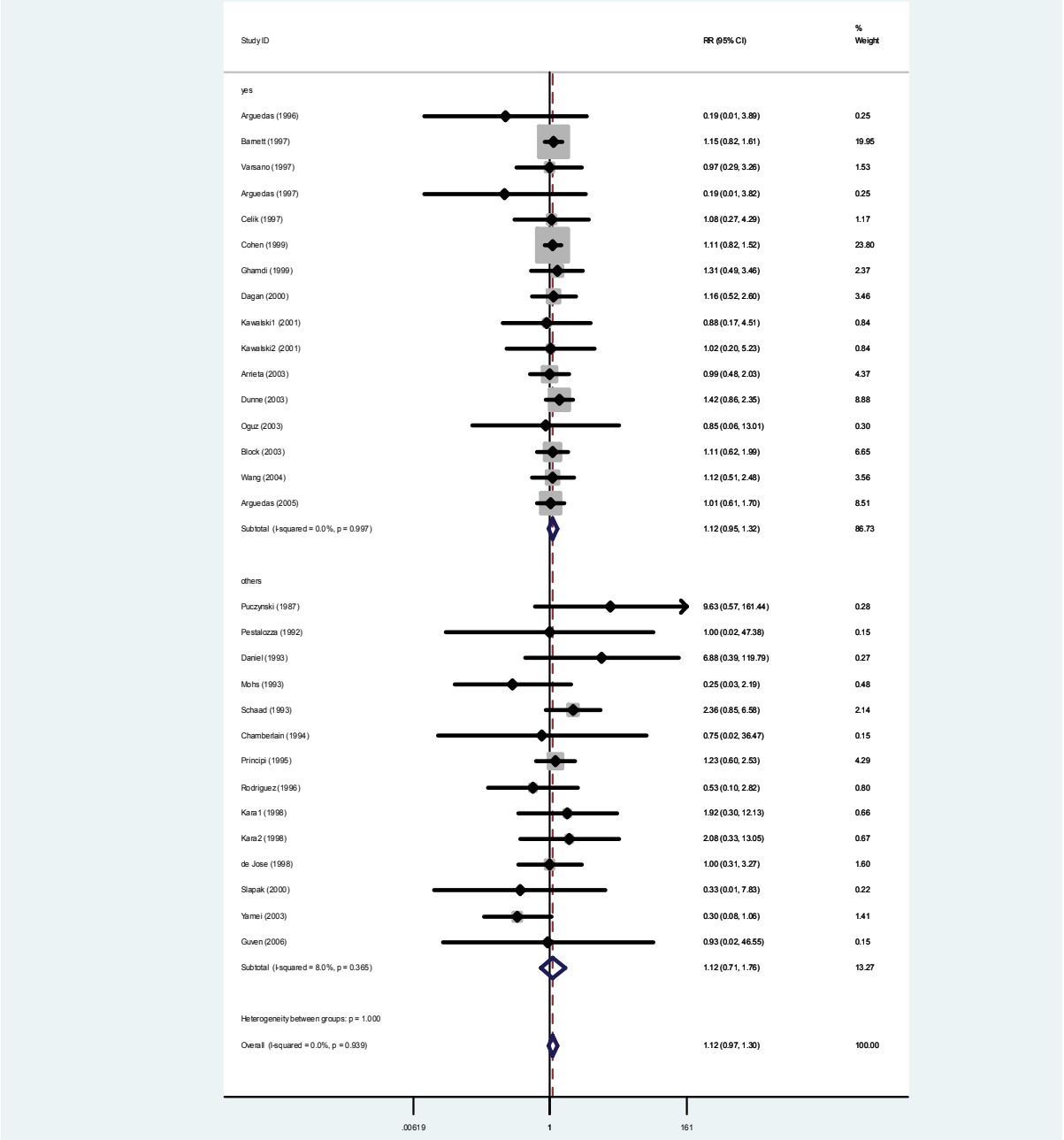

Fig. 43: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to compliance (analytic components =30)

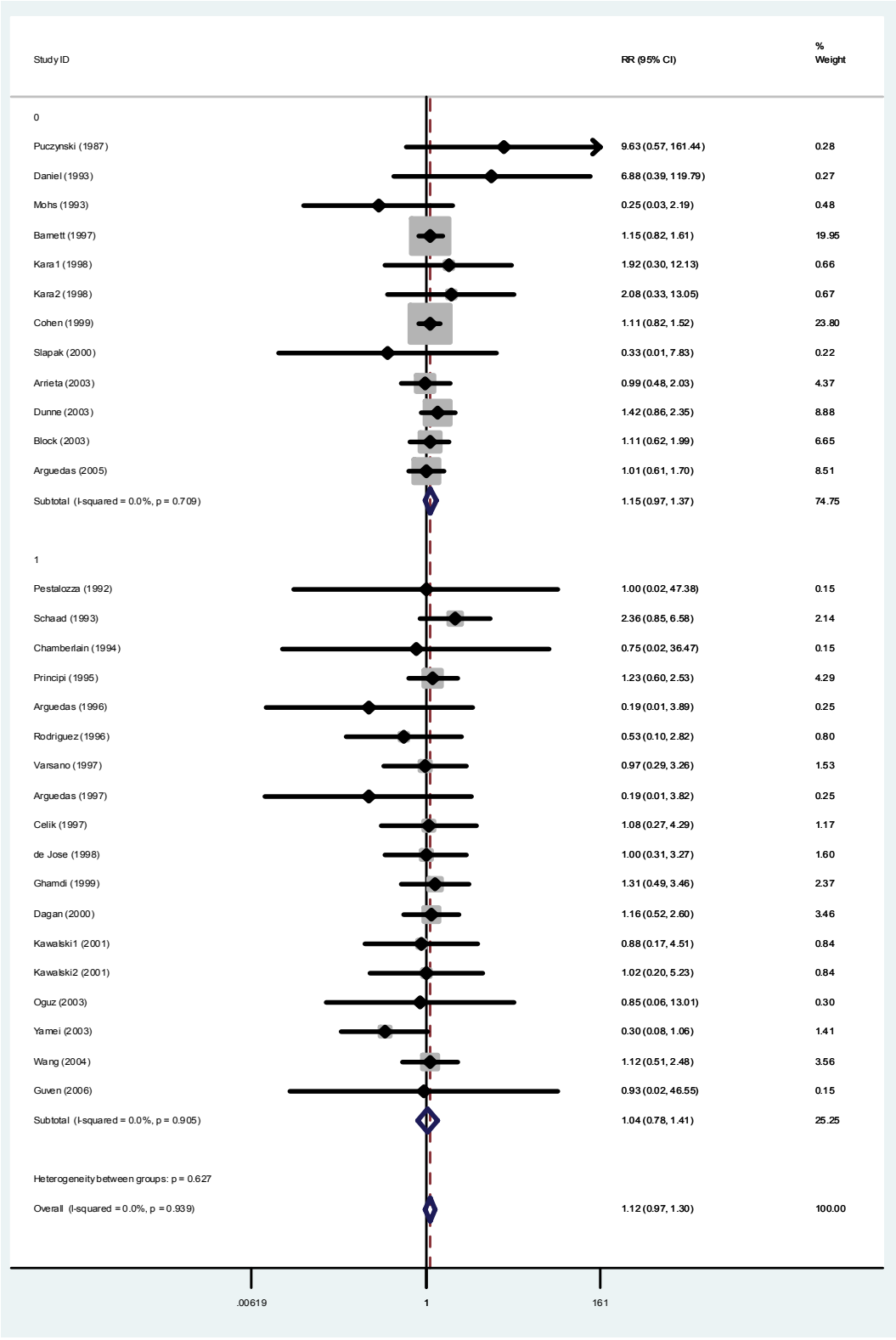

Fig. 44: Forest plot for treatment failure at 10-14 days from random effects model for short course *versus* long course in relation to intention to treat analysis (analytic components =30).
Abbreviations: 0=intention to treat analysis used; 1=others.

Table 11. Metaregression analyses for relative risk of treatment failure at 10-14 days (Restricted Maximum Likelihood Method)

Study characteristic	Univariable analysis RR (95% CI); *I²	P	Controlling for additional variables RR (95% CI)	P
Study quality				
Allocation concealment *(others vs. adequate)*	5.96 (0.64, 55.45); 0.00	0.112	8.13 (0.73, 90.00)	0.084
Attrition *(>10% vs. <10%)*(n=28)	0.93 (0.67, 1.30); 0.00	0.679	0.82 (0.51, 1.33)	0.408
Blinding *(others vs. double blind)*	0.94 (0.67, 1.33); 0.00	0.722	1.34 (0.47, 3.78)	0.567
Trial site (*developed vs. developing)*	1.17 (0.76, 1.80); 0.00	0.463	1.19 (0.68, 2.09)	0.521
Short course arm other antibiotics *vs.* oral short-acting	0.12 (0.01, 2.22); 0.00	0.146	DR	DR
Short course arm other antibiotics *vs.* azithromycin/macrolides	1.00 (0.73, 1.36); 0.00	0.977	9.30 (0.41, 210.10)	0.150
Short course arm other antibiotics *vs.* parenteral ceftriaxone	1.03 (0.75, 1.41); 0.00	0.852	10.86 (0.40,298.33)	0.148
Cointervention (no *vs.* yes)	1.03 (0.74, 1.43); 0.00	0.852	1.04 (0.68, 1.58)	0.859
Compliance monitoring (*others vs. yes*)	1.01 (0.64, 1.60); 0.00	0.968	0.84 (0.41, 1.70)	0.608
Intention to treat analysis (*others vs. yes*)	0.91 (0.63, 1.30); 0.00	0.587	0.94 (0.46, 1.92)	0.850

The number of analytic components in univariate model is 30 except where specifically stated otherwise.
* Proportion of residual variation due to heterogeneity, I-squared.
DR – Dropped in the analysis due to colinearity.
Multivariate model – number of analytic components is 28 and the proportion of residual variation due to heterogeneity, I-squared is 0.0.

Persistent middle ear effusion

Data on persistent middle ear effusion until 10-14 days was available from six studies (48, 51, 55, 66, 67, 71). Overall, there was no evidence of an increased risk for persistent middle ear effusion with the short course (RR=1.02, 95% CI 0.92 to 1.14, P=0.668; test for heterogeneity: I^2= 0.0%, P=0.910) (Fig. 45).

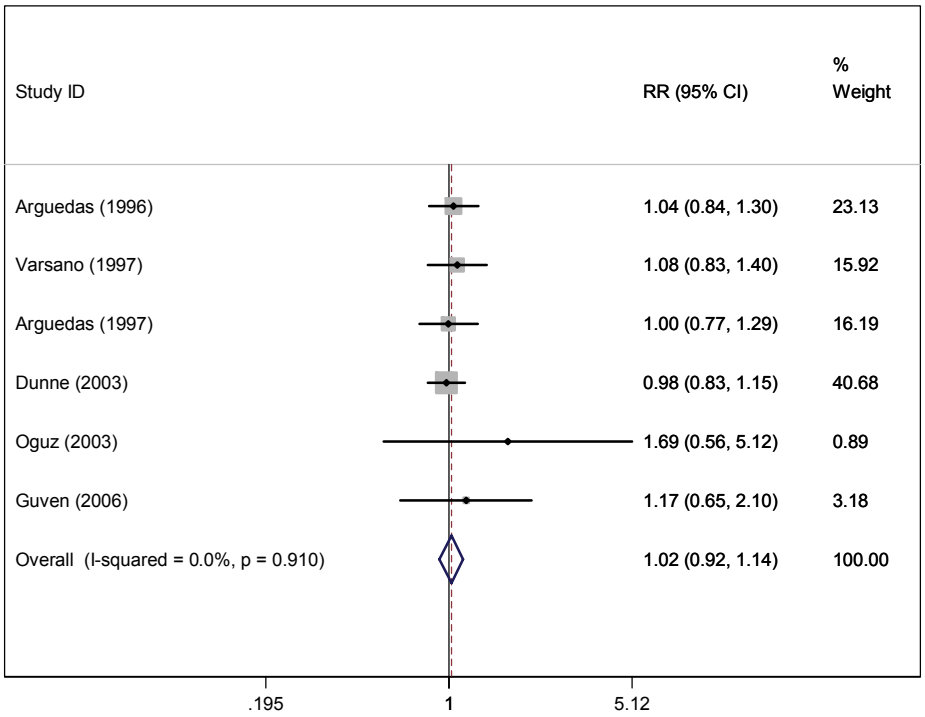

Fig. 45: Forest plot for persistent middle ear effusion at 10-14 days from random effects model for short course *versus* long course (analytic components =6). Test of RR=1; P=0.668.

Outcomes between one and three months

Data on the cumulative number of treatment failures, relapses and recurrences reported from time of diagnosis until a final evaluation point between one and three months could be extracted from three studies only.

Treatment failure

Relevant data was available from only three studies (37, 43, 55). There was no evidence of an increased risk of treatment failure between one and three months in children treated with a short course of antibiotics (overall RR=0.84; 95% CI 0.66 to 1.08, P= 0.171; test for heterogeneity: I^2= 0.0%, P=0.379) (Fig. 46).

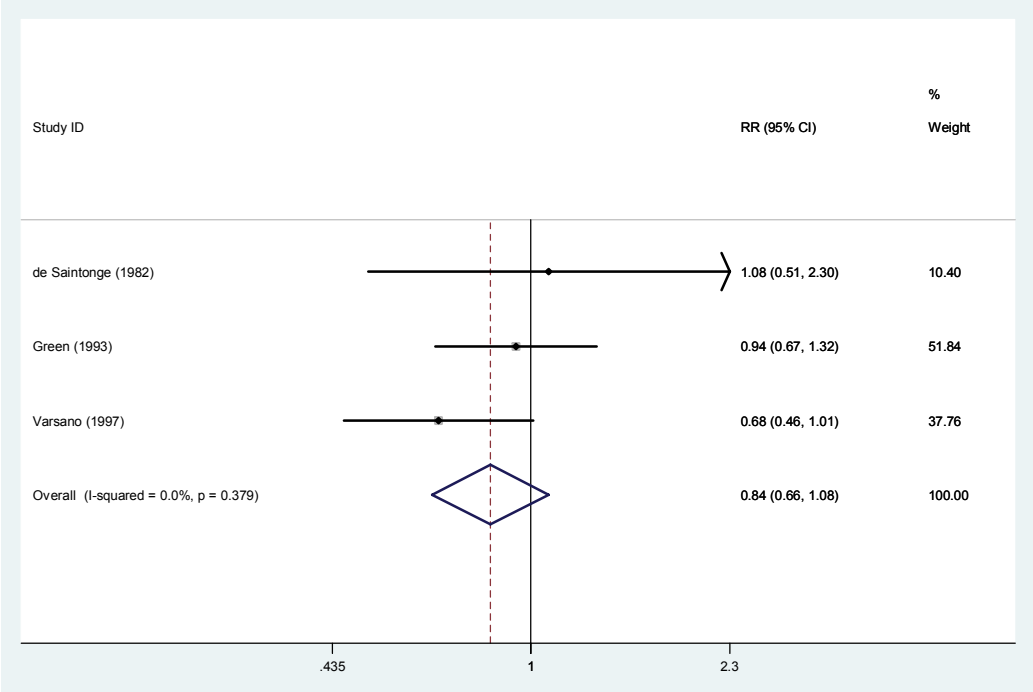

Fig. 46: Forest plot for treatment failure between 1-3 months from random effects model for short course *versus* long course (analytic components =3). Test of RR=1; P=0.171.

Relapse

There was no evidence of an increased risk for relapse between one and three months with short course antibiotics (RR=1.18; 95% CI 0.72 to 1.95, P=0.514; test for heterogeneity: I^2=0.0%, P=0.660) (Fig. 47).

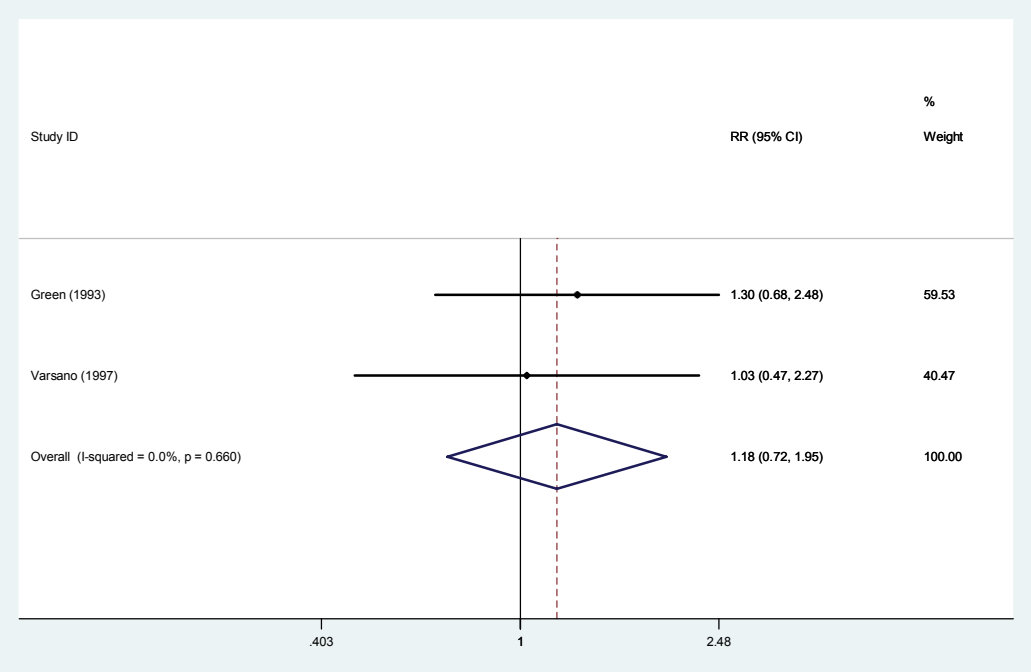

Fig. 47: Forest plot for relapse between 1-3 months from random effects model for short course *versus* long course (analytic components =2). Test of RR=1; P=0.514.

Recurrence

There was a significantly lower risk for recurrence in patients treated with a short course as compared to a long course between one and three months (RR=0.56; 95% CI 0.36 to 0.85, P=0.007; test for heterogeneity: I^2=0.0%, P=0.670) (Fig. 48).

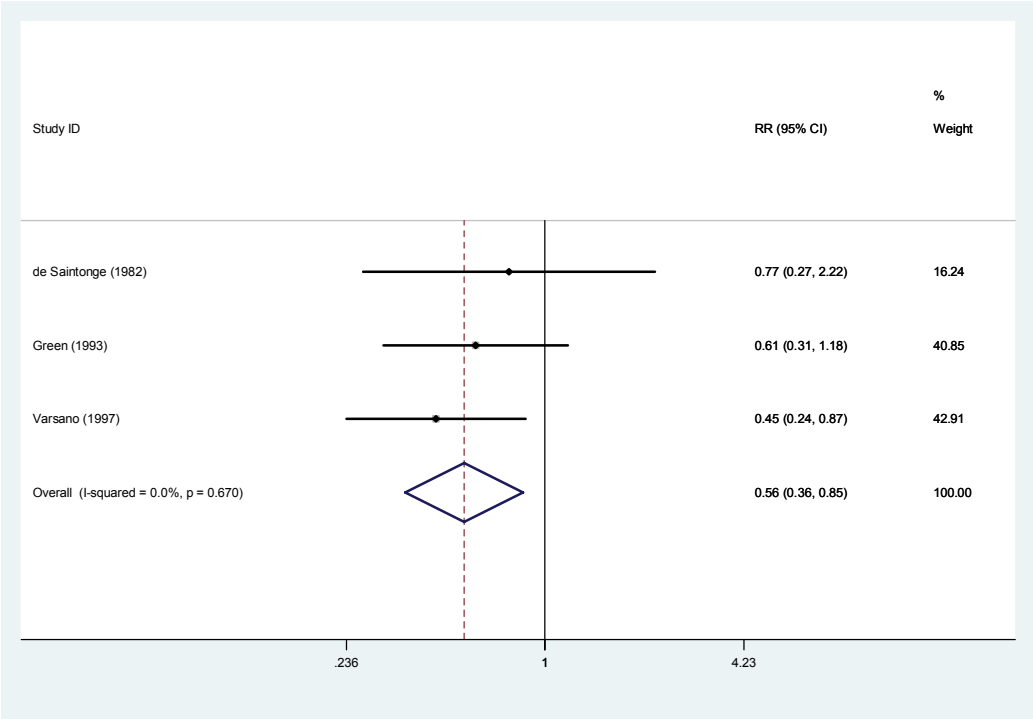

Fig. 48: Forest plot for recurrence between 1-3 months from random effects model for short course versus long course (analytic components =3). Test of RR=1; P=0.007.

Persistent middle ear effusion

Overall, there was no evidence of an increased risk for persistent middle ear effusion with a short course between one and three months (RR=0.79, 95% CI 0.42 to 1.49, P=0.469; test for heterogeneity: I^2= 0.0%, P=0.958) (Fig. 49).

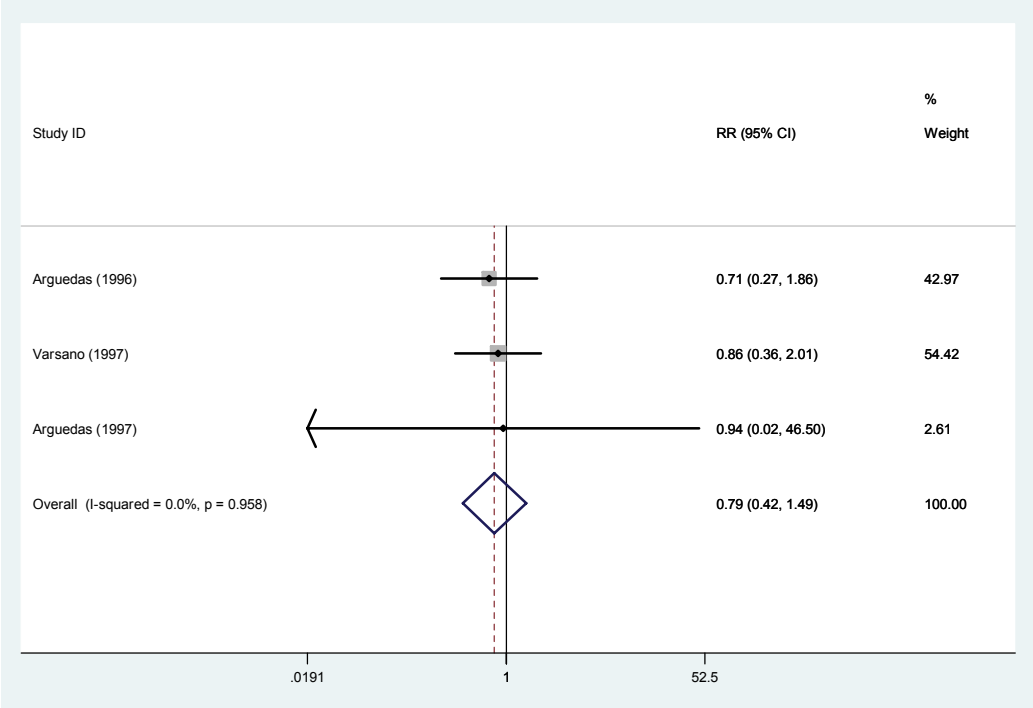

Fig. 49: Forest plot for persistent middle ear effusion between 1-3 months from random effects model for short course versus long course (analytic components =3). Test of RR=1; P=0.469.

Adverse effects

Apart from the duration of treatment, adverse effects of therapy could also be related to the pharmacokinetic behaviour of the antibiotic employed in the short course arm. We therefore also performed a stratified analysis for the risk of adverse effects according to the type of antibiotic utilized in the short course arm (Table 12).

Table 12. Relative risk (Random Effects Model) of adverse effects in relation to pharmacokinetics of antibiotic in short arm

Adverse Drug Effect	No. #	Random effects model RR (95% CI)	P value	Tests for heterogeneity I^2 (%); Q (P value)	P value for heterogeneity in subgroups
Individuals reporting adverse effects					
Short-acting oral	1	4.00 (0.47, 34.31)	0.206	Not applicable	
Azithromycin	12	0.62 (0.49, 0.79)	**<0.001**	0.00; 6.32 (0.851)	
Parenteral Ceftriaxone	7	0.51 (0.38, 0.68)	**<0.001**	0.00; 2.90 (0.822)	
Overall	20	0.58 (0.48, 0.70)	**<0.001**	0.00; 13.34 (0.821)	0.127
Diarrhoea					
Short-acting oral	1	4.00 (0.47, 34.31)	0.206	Not applicable	
Azithromycin	15	0.54 (0.33, 0.89)	**0.015**	64.80; 39.82 (**<0.001**)	
Parenteral Ceftriaxone	4	0.63 (0.21, 1.85)	0.395	94.20; 51.40 (**<0.001**)	
Overall	20	0.61 (0.38, 0.97)	**0.036**	81.20; 101.14 (**<0.001**)	**0.007**
Vomiting					
Azithromycin	11	0.72 (0.49, 1.06)	0.100	0.00; 2.24 (0.994)	
Parenteral Ceftriaxone	1	0.08 (0.01, 0.61)	**0.015**	Not applicable	
Overall	12	0.67 (0.46, 0.98)	**0.038**	0.00; 6.84 (0.812)	**0.032**
Rash					
Azithromycin	12	0.53 (0.32, 0.90)	**0.019**	0.00; 6.08 (0.868)	
Parenteral Ceftriaxone	5	1.13 (0.71, 1.78)	0.614	0.00; 3.96 (0.412)	
Overall	17	0.82 (0.58, 1.15)	0.244	0.00; 15.34 (0.500)	**0.021**
Abdominal Pain					
Azithromycin	9	1.32 (0.67, 2.60)	0.426	5.10; 8.43 (0.392)	
Overall	9	1.32 (0.67, 2.60)	0.426	5.10; 8.43 (0.392)	Not applicable
Others					
Azithromycin	11	0.74 (0.43, 1.28)	0.282	0.00; 9.93 (0.446)	
Parenteral Ceftriaxone	1	37.38 (2.32, 601.15)	**0.011**	Not applicable	
Overall	12	0.90 (0.43, 1.87)	0.772	41.60; 18.85 (0.064)	**0.003**
Laboratory abnormalities					
Azithromycin	8	0.98 (0.61, 1.60)	0.947	0.00; 6.13 (0.525)	
Parenteral Ceftriaxone	1	0.64 (0.25, 1.65)	0.354	Not applicable	
Overall	9	0.90 (0.59, 1.38)	0.631	0.00; 6.75 (0.563)	0.430

- Number of analytic components.

Overall, the risk of *individuals reporting adverse effects* was significantly lower in the short course as compared to the long course (RR=0.58, 95% CI 0.48 to 0.70, P<0.001; test for heterogeneity: Cochran Q=13.34, I^2=0.0%, P=0.821) (Table 12 and Fig. 50). There was no evidence of heterogeneity in the three subgroups for the number of individuals reporting adverse effects.

Overall, the risk of *diarrhoeal episodes* was significantly lower in the short course as compared to the long course (RR=0.61, 95% CI 0.38 to 0.97, P=0.036; test for heterogeneity: Cochran Q=101.14, I^2=81.2 %, P<0.001) (Table 12 and Fig. 51). There was significant heterogeneity in the three subgroups (P=0.007). The risk of diarrhoeal episodes was the least in the group receiving oral azithromycin in the short course arm (RR=0.54, 95% CI 0.33 to 0.89, P=0.015).

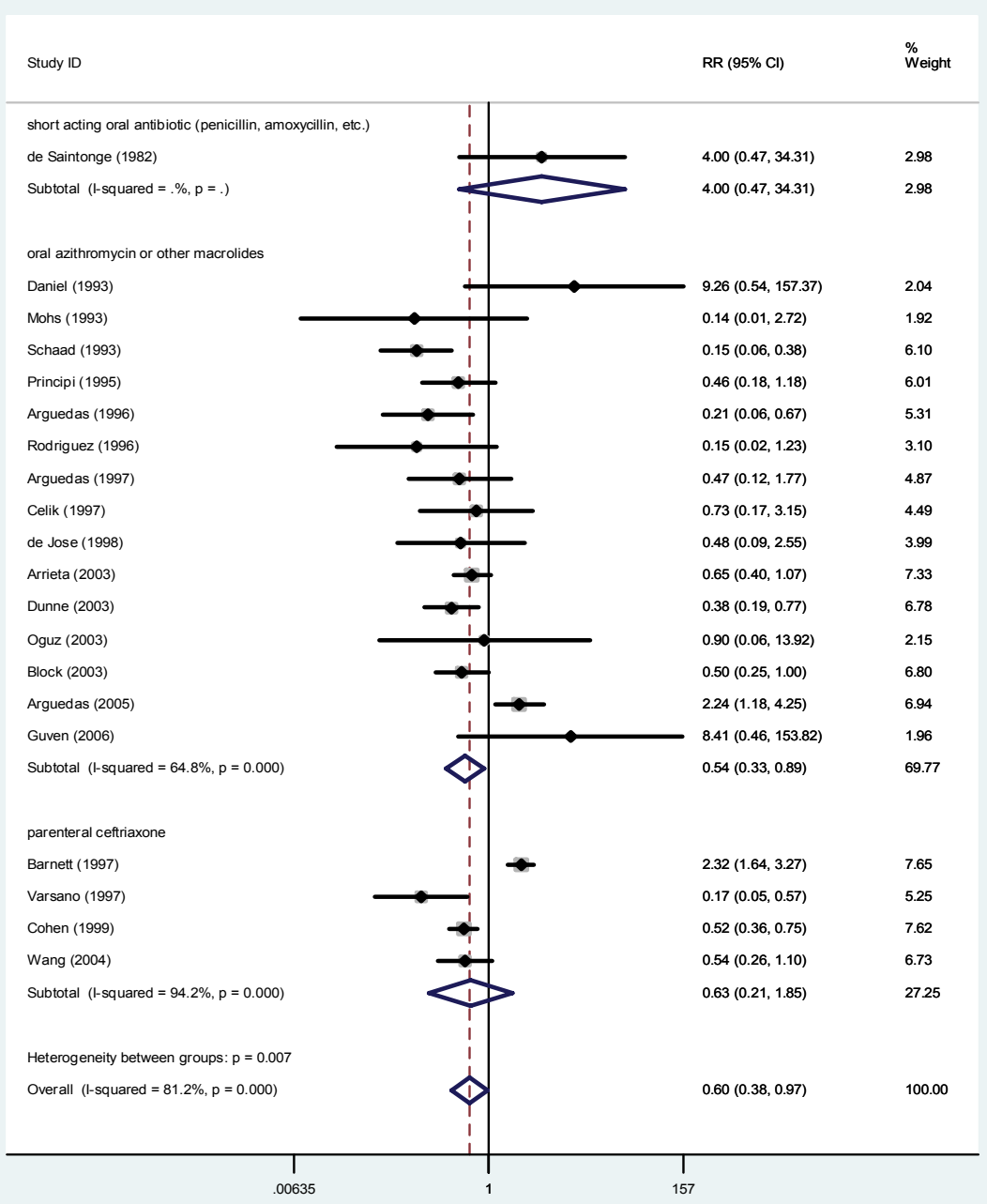

Fig. 51: Forest plot for diarrhoea by random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short arm (analytic components = 20)

Overall, the risk of *vomiting episodes* was significantly lower in the short course as compared to the long course (RR=0.67, 95% CI 0.46 to 0.98, P=0.038; test for heterogeneity: Cochran Q=6.84, I^2=0 %, P=0.812) (Table 12 and Fig. 52). There was significant heterogeneity in the two subgroups (P=0.032). The risk of vomiting episodes was significantly lower in the only study in which parenteral ceftriaxone was used in the short course arm (RR=0.08, 95% CI 0.01 to 0.61, P=0.015) but there was no difference in risk of vomiting episodes in the group prescribed azithromycin in the short course arm (RR=0.72, 95% CI 0.49 to 1.06, P=0.100).

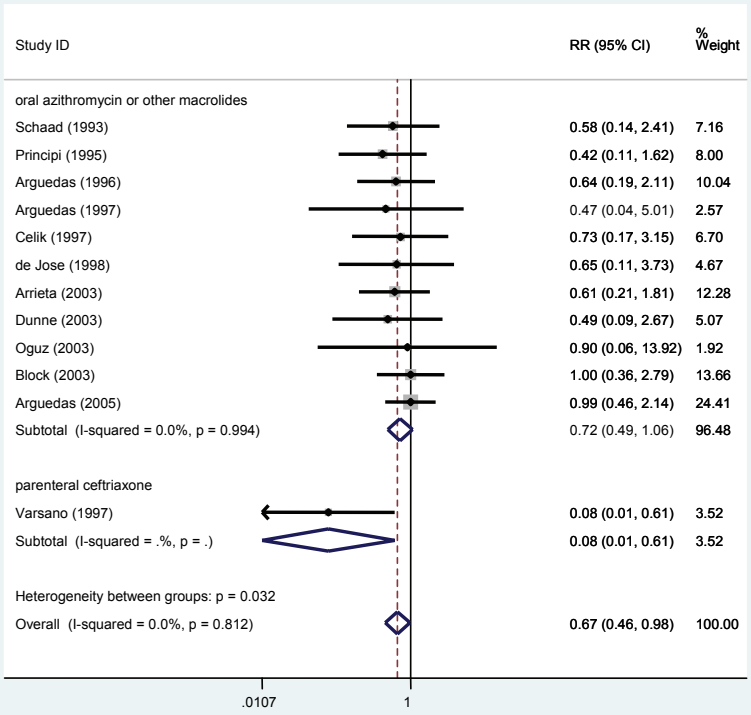

Fig. 52: Forest plot for vomiting by random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short arm (analytic components = 12)

Overall, there was no evidence of an increased risk of *rash* in the short course as compared to the long course (RR=0.82, 95% CI 0.58 to 1.15, P=0.244; test for heterogeneity: Cochran Q=15.34, I^2=0 %, P=0.500) (Table 12 and Fig. 53). There was significant heterogeneity in the two subgroups (P=0.021). The risk of rash was significantly lower in the group receiving oral azithromycin in the short course arm (RR=0.53, 95% CI 0.32 to 0.90, P=0.019).

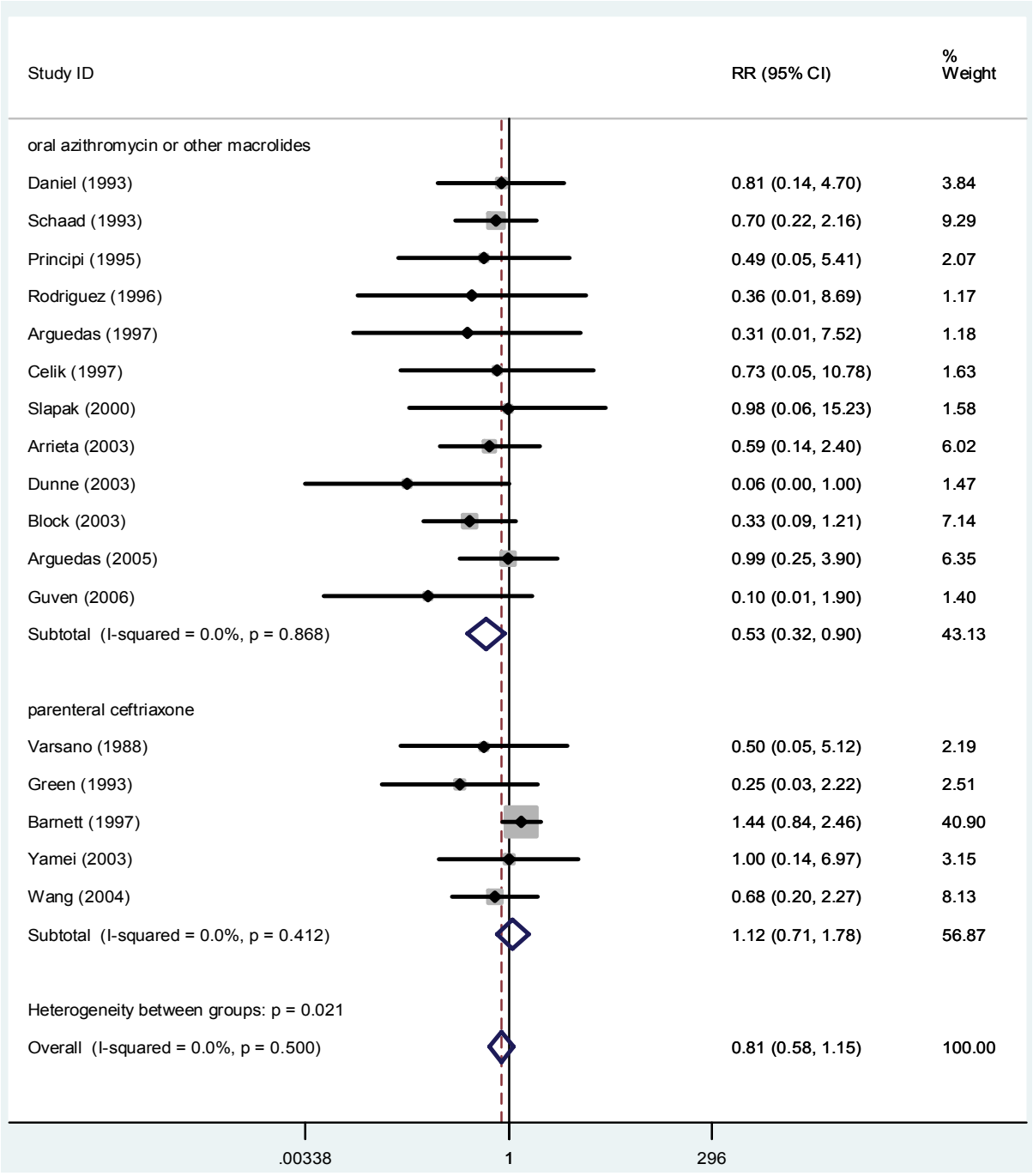

Fig. 53: Forest plot for rash by random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short arm (analytic components = 17)

There was no evidence of an increased risk of *abdominal pain* in the short course as compared to the long course (RR=1.32, 95% CI 0.67 to 2.60, P=0.426; test for heterogeneity: Cochran Q=8.43, I^2=5.1 %, P=0.392) (Table 12 and Fig. 54). Data for this outcome was available only for oral azithromycin use in the short course arm.

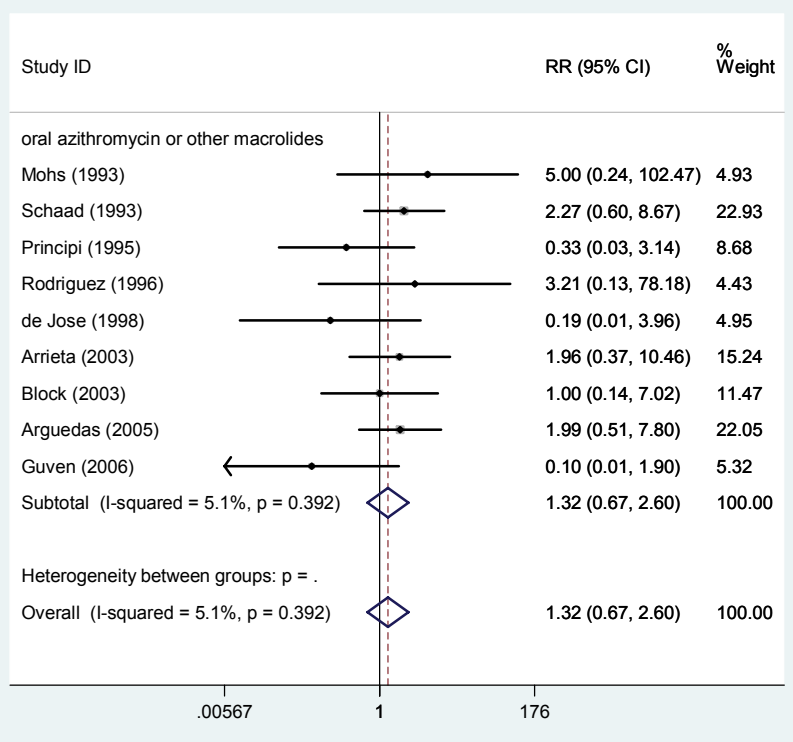

Fig. 54: Forest plot for abdominal pain by random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short arm (analytic components =9)

Overall, there was no evidence of an increased risk of *other adverse effects* in the short course as compared to the long course (RR=0.90, 95% CI 0.43 to 1.87, P=0.772; test for heterogeneity: Cochran Q=18.85, I^2=41.6 %, P=0.064) (Table 12 and Fig. 55). There was significant heterogeneity in the two subgroups (P=0.003). The risk of other adverse effects, primarily pain at the injection site, was significantly higher in the single study in which parenteral ceftriaxone was used in the short course arm (RR=37.38, 95% CI 2.32 to 601.15, P=0.011).

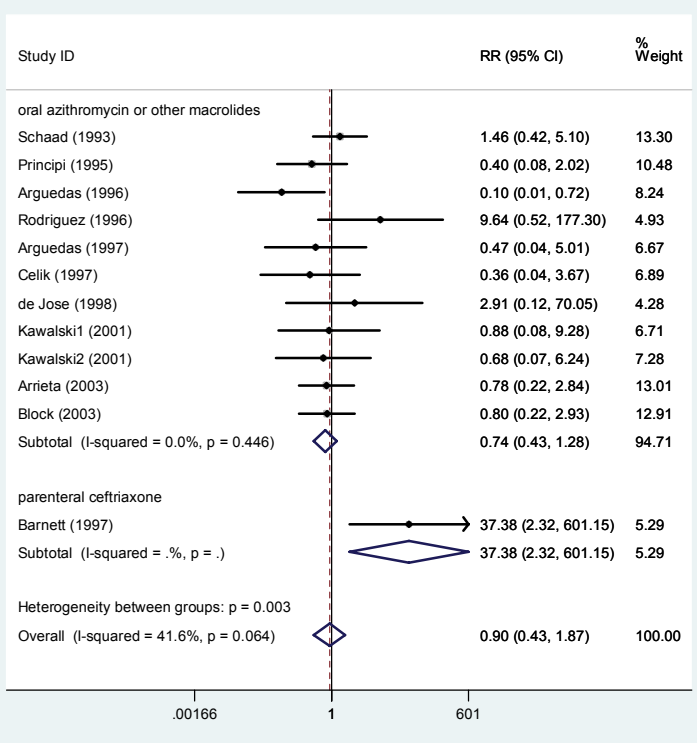

Fig. 55: Forest plot for other adverse effects by random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short arm (analytic components =12)

Overall, there was no evidence of an increased risk of *laboratory abnormalities* in the short course as compared to the long course (RR=0.90, 95% CI 0.59 to 1.38, P=0.631; test for heterogeneity: Cochran Q=6.75, I^2=0 %, P=0.563) (Table 12 and Fig. 56). There was no evidence of significant heterogeneity in the two subgroups (P=0.430).

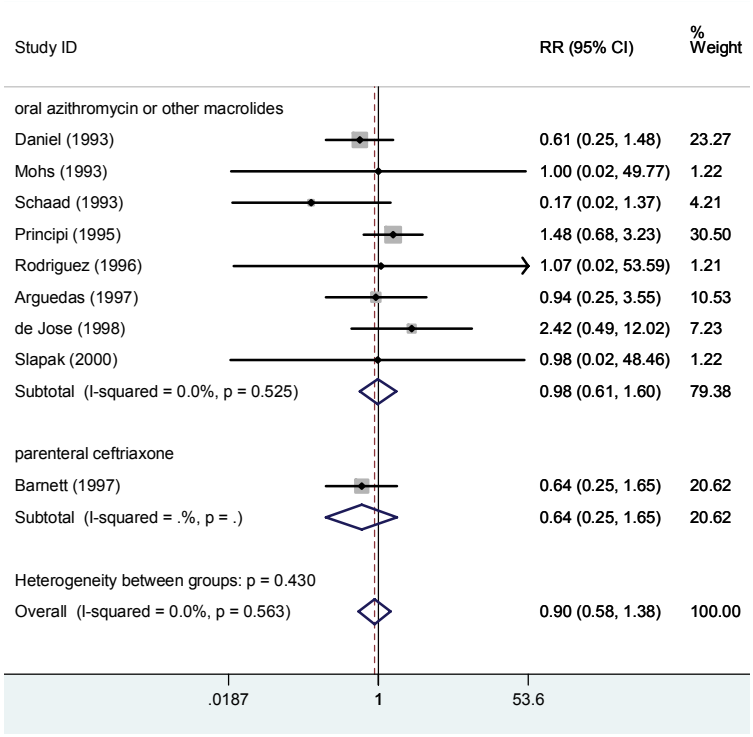

Fig. 56: Forest plot for laboratory abnormalities by random effects model for short course *versus* long course in relation to pharmacokinetics of antibiotic in short arm (analytic components =9)

In summary, available data indicates that the possibility of adverse effects is lower with the short course. There is a suggestion that among the antibiotics used in the short course arm, oral azithromycin may result in decreased risk of diarrhoea and rash whereas parenteral ceftriaxone may be associated with decreased risk of vomiting but an increased risk of injection site pain.

Discussion

Overall, this systematic review did not document an increased risk of treatment failure until one month with a short (≤ 3 days) course of antibiotics (RR=1.06, 95% CI 0.95 to 1.17, P=0.298; I^2=0.1%, P=0.468). However, on sensitivity, subgroup and metaregression analyses, azithromycin use in the short course arm and compliance monitoring emerged as significant predictors of heterogeneity, which were associated with a lower risk of treatment failure. When treatment failure was redefined to include subjects showing improvement, the risk of this outcome was significantly lower with the short course (RR=0.83, 95% CI 0.70 to 0.98, P=0.024; I^2=46.5%, P=0.004). Limited data did *not* suggest that a short course of antibiotics resulted in an increased risk of: (i) treatment failure in culture-positive cases or in high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media, and specific bacterial pathogens); (ii) bacteriologic failure; (iii) relapse; (iv) recurrence; or (v) persistent middle ear effusion. At an earlier evaluation point (10-14 days), there was no evidence of an increased risk of treatment failure, or of persistent middle ear effusion (data from six studies only). Limited data (three studies) evaluating outcomes between 1-3 months also did not suggest an increased risk of treatment failure, relapse, recurrence or persistent middle ear effusion with a shorter course of antibiotics. The risk of individuals reporting adverse effects was significantly lower in the short course (RR=0.58, 95% CI 0.48 to 0.70, P<0.001; I^2=0.0%, P=0.821). There was a suggestion that among the antibiotics used in the short course arm, oral azithromycin resulted in decreased risk of diarrhoea and rash whereas parenteral ceftriaxone might be associated with decreased risk of vomiting but an increased risk of injection site pain.

Strengths and limitations of analyses

This is an updated systematic review on the subject with pre-specified inclusion and exclusion criteria, which also incorporates relevant sensitivity, subgroup and metaregression analyses. Diligent efforts were made to include relevant non-English publications and the analyzed data did not reveal any evidence of publication bias. The main conclusion regarding the primary outcome (treatment failure at an evaluation point until one month after initiation of therapy) remained stable over a large spectrum of sensitivity and subgroup analyses performed and evidence of heterogeneity was unusual. Influence analysis, namely the effect of omitting one study at a time, did not reveal an overwhelming effect of any single trial. Bacteriologic failure was also analyzed to factor in the possibility of the "Pollyanna phenomenon" (14-16). Furthermore, on sensitivity, subgroup and metaregression analyses, significant predictors of heterogeneity were identified (azithromycin use in the short course arm and compliance monitoring).

It would be prudent to consider the following limitations of the systematic review before drawing any inferences for revising clinical practice and policy. First, there were only four trials (37, 38, 39, 54) that involved a head-to-head comparison of different durations of the same antibiotic. Of these, only two trials had used an antibiotic currently recommended by WHO for otitis media, namely amoxicillin (13). The results of the vast majority of individual trials may therefore reflect differences in pharmacokinetic and pharmacodynamic properties of the antibiotics used in the short and long course arms rather than the duration of drug use. Second, interpretation was confounded by the wide variation in diagnostic and outcome criteria. Acute otitis media has been defined as an infection of the middle ear with acute onset, presence of middle ear effusion, and signs of middle ear inflammation (72). Presence of all these criteria was considered essential to diagnose acute otitis media (72). However, these diagnostic criteria were not used in all the trials, which could have resulted in treatment of children without acute otitis media. Uniform outcome criteria were also not employed by the included studies. Differences in outcome may be imperceptible if assessed too early or too late. The "test of cure" end point, defined as clinical outcome 28-30 days after initiation of antimicrobial therapy, is the recommended criteria by the Food and Drug Administration (FDA) for acute otitis media trials (73). In most of the trials clinical outcome was measured at less than 14 days alone and no further follow-up was available. Third, in only three analytic components both bacteriologic diagnosis and outcome measures were available for all subjects. In the remaining trials diagnosis and outcome were either assessed by clinical criteria only or diagnosis was based on bacteriologic culture but outcome was assessed clinically (five analytic components). This could minimize the true differences between the bacteriologic efficacies of two treatment courses because of the high spontaneous cure rate in cases of clinically diagnosed acute otitis media (15). Fourth, there were only a few studies providing information on high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media and specific bacterial pathogens), which limited the statistical power to detect differences in treatment failure in such subjects. Fifth, the majority of the trials (28 or 74% of analytic components) were conducted in developed countries, which could have a bearing on applying these findings to developing countries. However, trial site was not a significant predictor of risk of treatment failure, and thus extrapolation to developing-country settings may be appropriate. Finally, multiple subgroup and metaregression analyses were done for important pre-specified variables, which increased the possibility of false positive results. The identified significant predictors of treatment failure should therefore be considered as tentative in nature, rather than definitive.

There is a paucity of similar earlier analyses for direct comparison. A systematic review of randomized controlled trials, based on a search conducted in March 1998, compared the effectiveness of short and long courses of antibiotic therapy; however, the definitions of short and long course antibiotic therapy varied from this review (less than seven days *versus* seven days or greater) (11,12). The authors concluded that five days of short-acting antibiotic was an effective treatment for uncomplicated ear infections in children. On a subgroup analysis, the summary odds ratio for failure at one month or less in trials that compared less than 48 hours of short-acting antibiotic treatment with at least seven days was 2.99 (95% CI: 1.04 – 8.54). In three trials comparing ceftriaxone with a longer course of oral antibiotics, the summary odds ratio for failure at one month or less was 1.25 (95% CI 0.90-1.72). In a comparison of three days of azithromycin with 10 days of another antibiotic, the summary odds ratio for failure at one month or less was 1.02 (95% CI 0.78-1.34). These subgroup analyses may not be directly comparable with the current review because of variation in the duration of antibiotic therapy. In another later systematic review (3), risk differences instead of relative risks were used to compare outcomes for different antibiotic durations among various subgroups of antibiotics. In three trials comparing ceftriaxone with 7-10 days of amoxicillin, the combined failure rate difference was 3.4% (95% CI-1.6 to 8.5). In a comparison of <5 days of azithromycin with 7-10 days of amoxicillin-clavunate, the pooled failure rate difference was 2.1% (95% CI 0.6 to 4.8), which was reported as not significant.

The observed comparability between short and long courses of antibiotics is biologically plausible, on the basis of (11, 12): (i) spontaneous resolution of untreated otitis media; (ii) early eradication of pathogens after three to five days of treatment (74); (iii) poorer penetration of antibiotic into the ear with continued administration as inflammation decreases (75); and (iv) treatment of children without acute otitis media because of diagnostic uncertainty. Furthermore, pharmacokinetic and pharmacodynamic properties offer a plausible explanation for comparable treatment failure with the short course and a lower treatment failure with azithromycin in comparison to other antibiotics in the short course arm. Azithromycin has a high tissue to serum ratio, elevated concentration in the middle ear (76), and prolonged elimination half-life. In marked contrast to low concentration in serum, azithromycin reaches higher concentration in many tissues, which has a bactericidal effect. The concentration of azithromycin in tissues 12-48 hours after a single dose is significantly above concurrent serum levels and greater than that observed for either erythromycin (77) or roxithromycin (78). As a result of slow depletion of azithromycin from tissues, the drug concentration remains above the minimal inhibitory concentration (MIC) for most clinically important pathogens for several days. Recent preclinical infection models suggest that the plasma half-life of azithromycin is 68 hours and because clearance of a drug or a decrease in concentration to below the MIC takes between five and seven half-lives, azithromycin might persist *in vivo* for at least 3–4 weeks after treatment (79). The total administered dose of azithromycin is thus most likely to correlate with the clinical outcome rather than the duration of therapy (80). Ceftriaxone is a broad-spectrum, parenterally administered third generation cephalosporin characterized by good antibacterial activity against most pathogens causing acute otitis media (81). It is absorbed rapidly following intramuscular administration and achieves high peak serum levels two hours after administration (82). Because of its prolonged half-life, the drug is ideally suited to a single dose therapy. On the other hand drugs such as penicillins and cephalosporins display minimal concentration-dependent bactericidal activity (80). Although enhanced killing is seen as the concentration is increased from one to four times the MIC, no further enhancement is seen at higher concentrations. The extent of bactericidal activity for this group is largely dependent on the length of exposure. For time-dependent agents, maintaining drug concentrations above the MIC for at least 40% of the dosing interval is the best predictor of efficacy, and the goal of dosing is to optimize the duration of therapy (80, 83). This may explain the pooled high risk of treatment failure with the short course in the three analytic components, which had compared different durations of amoxicillin or penicillin therapy.

It is difficult to explain the observation that compliance monitoring was associated with a lower risk of treatment failure in the short course arm. This may represent a false positive result due to multiple testing. However, it is possible that compliance monitoring was selectively more important for the short course arm, particularly for azithromycin.

A sensitivity and subgroup analysis of the treatment failure definition did not alter the main finding. Conversely, when treatment failure was redefined to include subjects showing improvement, the overall risk of this outcome was significantly lower with the short course in the studies that provided relevant information. It is possible that this may be a reflection of better antibiotic (azithromycin and ceftriaxone) efficacy in eradicating the bacteria in the short course arm, as an overwhelming majority of trials had compared different antibacterial agents in the short and long course arms. It is also reassuring that results of other analyses (secondary outcomes, sensitivity, subgroup and metaregression) are in consonance with the main conclusion. These analyses include treatment failure between 10-14 days and between 1-3 months, treatment failure in culture positive cases or in high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media, and specific bacterial pathogens), bacteriologic failure, relapse, recurrence, and persistent middle ear effusion. However, it would be prudent to caution that some of these conclusions are based on only a few trials.

The available limited data did not document an increased risk of treatment failure with the short course in otitis media due to *S. pneumoniae* or *H. influenzae.* Amoxicillin was used in only one (39) of these trials in the short-course arm. In rest of the trials azithromycin was used in the short-course arm and amoxicillin (70), amoxicillin-clavulanate (48, 63, 64, 71), or cefaclor (61) were used in the long-course arm. In only one trial clarithromycin (63) was used in the long course arm. As azithromycin is a relatively newer antibiotic, resistance is likely to be lower than earlier antibiotics such as penicillin and cephalosporin.

Adverse effects are a common reason for poor patient compliance. A shorter course of therapy is likely to reduce the adverse effects associated with antibiotic use. This review documented a lower risk for individuals reporting adverse effects when using short course antibiotics (RR=0.58, 95% CI 0.48 to 0.70, P<0.001). The risk of developing diarrhoea and rash was lower with azithromycin use in the short course arm. Similar results have been reported earlier (84, 85), resulting in better compliance with azithromycin. As ceftriaxone is administered intramuscularly, food and drug interactions are of less concern than with other orally administered antibiotics; however, injection site reactions may occur. Pain at injection site was reported to be a common adverse effect in a single trial with relevant data (52). Vomiting was significantly lower when ceftriaxone was used.

It is important to address the concern that the pooled results are biased due to pharmaceutical industry support in several trials. On a *post hoc* analysis of stated sources of financial support, among the 38 analytic components, two (5.3%) were funded by non-pharmaceutical sources, 13 (34.2%) by pharmaceutical industry and in 23 (60.5%) the source of funding was not stated, which precludes a robust examination of the above hypothesis. Nevertheless, for the purpose of further analyses, we compared support by the pharmaceutical industry with others (not stated and non-pharmaceutical sources). Industry-supported trials are generally viewed with suspicion as bias can occur due to non-publication of negative studies, and a poor design and quality of trials yielding a favourable result for the manufactured product. In this review, formal tests did not suggest any evidence of publication bias or differences in trial quality in relation to industry support (adequate allocation concealment 2/13 *vs.* 2/25, P=0.91; attrition below 10% 7/13 *vs.* 16/23, P=0.58; and double blinding 5/13 *vs.* 4/25, P=0.26). Stratified analysis indicated significant (P=0.010) heterogeneity for relative risk of treatment failure until one month between the two groups of industry-supported trials (RR 0.98, 95% CI 0.87 to 1.10, P=0.717) and other studies (RR 1.34, 95% CI 1.09 to 1.64, P=0.006). However, there was no evidence of heterogeneity when a similar analysis was done separately for trials using azithromycin or ceftriaxone in the short course arm. On univariable metaregression for the entire data set, industry support emerged as a significant predictor of lower risk (0.73, 95% CI 0.57, 0.94, P=0.015); however, with adjustment for other variables it did not remain a significant predictor (0.73, 95%CI 0.35, 1.52, P=0.384). There is thus no concrete evidence on a *post hoc* analysis that the industry-supported trials have biased the pooled results; however, this possibility cannot be totally excluded. It would be prudent to remember that drug comparison trials, especially for newer drugs, are invariably conducted with industrial support. Publication of such data in peer reviewed journals provides some confidence about the quality of trial. Adopting a radical posture by ignoring all such evidence on the basis of unsubstantiated suspicion will create biased systematic reviews. It may be more appropriate to tread a middle path by exploring potential sources of bias for such trials and being extremely cautious in drawing inferences or formulating recommendations from industry-supported data.

Implications for practice and policy

A reduction in the World Health Organization's currently advocated oral antibiotic (co-trimoxazole or amoxicillin) therapy from five to three days *cannot* be proposed because of the possibility of an increased risk of treatment failure with a reduced course of short-acting oral antibiotics.

The slightly increased risk of treatment failure with parenteral ceftriaxone (1.13, 95% CI 0.99 – 1.30) was not statistically significant; however, as the lower confidence interval was close to 1, the possibility of higher treatment failure rates cannot be confidently excluded. Administration of a parenteral drug in the prevailing public health infrastructure of developing countries also raises logistic challenges including training of paramedical personnel and availability of single use needles and syringes. A study published in 1993 documented a higher cost of single dose intramuscular ceftriaxone in comparison to 10 days of oral amoxicillin (43), which highlights the need for detailed comparative cost-effectiveness analysis with the current five-day recommendation. Further, the concern about indiscriminate use of broad-spectrum antibiotics causing enhanced bacterial resistance needs to be addressed. The comparative safety profile of parenteral ceftriaxone provides a mixed picture; it may be associated with decreased risk of vomiting but an increased risk of injection site pain. However, consumers preferred parenteral ceftriaxone in clinic settings (43, 49, 59, 69) and its compliance is likely to be better. On the basis of the above deliberations, it would be difficult to propose consideration of parenteral ceftriaxone as an alternative to the current WHO recommendation.

There was no evidence of an increased risk of treatment failure with short course oral azithromycin while adverse effects were significantly lower, especially diarrhoea and rash. Earlier studies had documented that consumers

preferred shorter treatment courses (86), which resulted in better compliance. A methodologically weak study (63) suggests that azithromycin may be a cheaper choice than clarithromycin or amoxicillin-clavulanic acid for treatment of acute otitis media; but in order to draw a robust inference, a detailed cost-effectiveness analysis is essential in the context of the current WHO recommendation. The possible disadvantages of recommending short course azithromycin also need detailed consideration. First, what are the logistic implications for public health programmes of recommending two separate antibiotics (co-trimoxazole or amoxicillin, and azithromycin) for different respiratory tract infections, namely, pneumonia and otitis media? Second, the concern about indiscriminate use of broad-spectrum antibiotics causing enhanced bacterial resistance needs to be adequately addressed. Theoretically, shorter drug exposures decrease the chance of developing resistance, whereas higher tissue persistence and slowly receding azithromycin concentrations increase the chance of development of drug-resistant organisms (87). Some ecological studies have identified a strong relation between azithromycin use and macrolide resistance (88), whereas others did not find a correlation (89). A recent randomized, double blind placebo-controlled trial demonstrated that azithromycin use caused emergence of macrolide resistance to the oral streptococcal flora of healthy volunteers (87). However, a recent observational cohort study indicated that amoxicillin use also caused transient resistance among respiratory pathogens (*Haemophilus* species) in individuals, which may be sufficient to sustain a high level of antibiotic resistance in the population (90). Similarly, prescribing co-trimoxazole resulted in an increased resistance to co-trimoxazole in gram-negative bacilli in urine samples (91). On the basis of above considerations, a thorough decision tree analysis should be initiated to explore the possibility of recommending short course azithromycin for routine treatment of otitis media in children in individual practice and in public health settings.

Implications for research

The important researchable areas, which have implications for guiding future practice and policy include the following: (i) data in high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media, and in relation to specific bacterial pathogens); (ii) trials involving outcome analysis for longer periods, preferably at one month of intervention and beyond, if feasible; (iii) comparison of different treatment durations of the same antibiotic, particularly those currently recommended by WHO, and of antibiotics with a similar pharmacokinetic profile to segregate confidently the effects of therapy duration from antibiotic profile; (iv) data on bacteriologic failure and success rates; and (v) development of antibiotic resistance during follow-up.

Conclusions

Overall, there is no evidence of an increased risk of treatment failure until one month with a short (≤ 3 days) course of antibiotics for treating acute otitis media in children. However, in the short course arm, azithromycin use was associated with a lower risk of treatment failure while short-acting oral antibiotics and possibly parenteral ceftriaxone may be associated with a higher risk of treatment failure. Overall, adverse effects were significantly lower with the short course; oral azithromycin resulted in a decreased risk of diarrhoea and rash whereas parenteral ceftriaxone was associated with a decreased risk of vomiting but an increased risk of injection site pain. Adequately designed trials need to be conducted, funded by sources other than the pharmaceutical industry, to confirm unequivocally the above findings in relation to a shortened course of azithromycin. A thorough decision tree analysis should also simultaneously explore the possibility of recommending short course azithromycin for treatment of uncomplicated acute otitis media in children in individual practice and in public health settings in the event that clinicians or other prescribers or parents decide to use antibiotics.

Potential conflict of interest

None

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Annexes

Annex 1: Data Abstraction Form

ID Number	
First author's name	
Journal's name	
Year of publication	
Year end of study	
Country	
Continent	
Country development status	
Setting (Health facility/Community/not mentioned)	
Catchment area 1. Urban 2. Urban slums 3. Semi-rural 4. Rural 5. Not specified	

Participants

Inclusion criteria

Exclusion criteria

Clinical diagnostic criteria for acute otitis media

Broad Categorization of Subjects

Age Group

1. Age <2 years
2. Age >2 years
3. Both

Age range lower (mo)	Age range upper (mo)	Mean age (mo)	Age SD (mo)

Eardrum perforation

1. Only children with perforated eardrum
2. Only children with non-perforated eardrum
3. Children with both of the above
4. Not mentioned

Recurrent otitis media

1. Only children with recurrent otitis media
2. Only children without recurrent otitis media
3. Children with both of the above
4. Not mentioned

Methodological Quality
Method of randomization
Cluster randomization (Y/N) If yes, analysis cluster adjusted (Y/N)
Allocation concealment
A. Adequate
B. Unclear
C. Inadequate
D. Not used
Placebo controlled
A. Yes
B. No
Blinding
A. Double blinding
B. Single blinding
C. No blinding
D. Unclear
Loss to follow-up
A. < 3%
B. 3 – 9.9%
C. 10 –19.9%
D. 20% or more

Intention to treat analysis	Used	Not used	Unclear
Compliance checked	Yes	No	Not mentioned
Method of checking compliance	1. Checking empty bottles 2. Urine assay for presence of study drug 3. Medicine given under supervision 4. Serum assay for presence of study drug 5. Maintaining diaries 6. Others _____		

Grouping of antibiotic use in short treatment arm

(i) Short-acting oral antibiotic (Penicillin, Amoxicillin, Cefaclor, Cefuroxime, *etc.)*
(ii) Oral Azithromycin or other macrolides
(iii) Parenteral Ceftriaxone

Antibiotic	**Short course**	**Long course**
Name		
Dose given/day		
Frequency/day		
No. of days		
Route (oral/parenteral)		

Cointerventions			
Analgesic	yes	no	not mentioned
Decongestant	yes	no	not mentioned
Surgical	yes	no	not mentioned

Baseline Characteristics

Characteristic	Short course	Long course
Age in mo (mean ± SD)		
No. enrolled		
No. followed up at primary outcome assessment		
Loss to follow-up (%)		
Girls (%)		
No. with perforated eardrum		
No. with recurrent otitis		
No. with bilateral disease		
No. attending day care		
No. with elder siblings		
No. with age < 6 months at first AOM episode		
No. with household smoke exposure		
No. with pacifier use		
No. received conjugate pneumococcal vaccine		
Culture positive cases		
Total culture positive		
S. pneumoniae		
H. influenzae		
M. catarrhalis		
S. pyogenes		
Staph. aureus		
Other pathogens		
Multiple pathogens		

Antibiotic sensitivity of isolates

Bacteria isolated	*No. of isolates*	*No. sensitive to*								
		AZT	AMC	AMS	CEF	CHLO	CRO	CXM	P	TMX
S. pneumoniae										
H. influenzae										
M. catarrhalis										
S. pyogenes										
Staph. aureus										

AMC: amoxicillin-clavulanate, AMS: amoxicillin, AZT: azithromycin, CEF: cefaclor, CHLO: chloramphenicol, CRO: ceftriaxone, CXM: cefuroxime, P: penicillin, TMX: trimethoprim/sulphamethoxazole

Outcomes

Study definition of clinical failure:

Study definition of relapse:

Study definition of recurrence:

Outcome within 10 to 14 days
1. Clinical failure a. Non-resolution of clinical symptoms b. Persistent eardrum changes
Bacteriologic failure
Middle ear effusion
Outcome between 14 days and 1 month (31 days) Days of outcome assessment ___ to ____ days
1. Clinical failure a. Non-resolution of clinical symptoms b. Persistent eardrum changes
Clinical treatment failure in culture positive cases
Bacteriologic failure in culture positive cases
Relapse
Recurrence
Middle ear effusion
Treatment failure (redefining subjects showing improvement as failure)
Treatment failure (children < 2 years)
Treatment failure (children > 2 years)
Treatment failure (children with recurrent otitis media)
Treatment failure (children without recurrent otitis media)
Treatment failure (children with perforated eardrum)
Treatment failure (children without perforated eardrum)
Treatment failure (children with *S. pneumoniae or H. influenzae* on tympanocentesis)
Treatment failure (children with pathogens other than *S. pneumoniae or H. influenzae* on tympanocentesis)
Outcome between 1 to 3 months Day of outcome assessment ___ to ____ days
1. Clinical failure a. Non-resolution of clinical symptoms b. Persistent eardrum changes
Bacteriologic failure
Relapse
Recurrence
Middle ear effusion
Other outcomes at last follow-up Time of last follow-up (weeks)
Middle ear effusion
Hearing problems
Mastoiditis
Abnormal tympanometry
Contralateral otitis media
Perforation
Other complications (Y/N) If yes, nature of complication
Mean (SD) duration of analgesic use (days)

Mean (SD) duration of decongestant use (days)

Adverse drug effects (no.)
Diarrhoea
Rash
Vomiting
Abdominal pain
Derangement of lab parameters
Others

Investigators contacted for further information (if required)	
Name:	
Postal address:	
Email:	
Data requested:	Status:

General

- For assessment of outcomes until one month, wherever information was not available at one month, outcomes mentioned at a time period closest to one month (at or after 10-14 days visit) were considered for analysis.
- Where necessary and possible, an intention to treat analysis was reconstructed from the available data. Subjects who had been excluded as failure at an earlier evaluation point were included in follow-up at a later time point as failure.
- Wherever subjects were excluded because of lack of compliance, these were considered as failure.
- If a follow-up visit was optional, such data was not used for analysis to prevent bias.
- If information for middle ear effusion was given only in cured patients, it was not considered.

Specific

- *Meistrup-Larsen, 1983 (38)*
  Clinical failure was not defined. Use of another antibiotic was presumed to be treatment failure.
- *Daniel, 1993 (42) and Schaad, 1993 (45)*
  In the methods section, age group was mentioned as more than two years but in the results section, there were children less than two years of age also. Therefore both these studies were presumed to have included children below two years of age.
- *Mohs, 1993 (44)*
  This was presumed to be a randomized trial, primarily because baseline characteristics in the two treatment courses were similar.
- *Chamberlain, 1994 (46)*
  The outcome evaluation done between 7 and 10 days for the purpose of our analysis was combined with data from other studies at 10-14 days. Follow-up was done up to 90 days but the primary outcome was given as failure in number of ears rather than failure in individuals. Thus the data up to 90 days could not be analyzed.
- *Arguedas, 1996 (48) and Arguedas, 1997 (51)*
  The outcome evaluation done between 28 and 32 days post-therapy for the purpose of our analysis was combined with data from other studies until one month. Follow-up was done till 55-60 days post-therapy. This data was not considered for analysis as the follow-up was for only those cases that had persistent middle ear effusion or recurrence.
- *Bauchner, 1996 (49)*
  Only the dose of amoxicillin was mentioned. We calculated the total dose of amoxicillin-clavulanate considering a ratio of amoxicillin:clavulanate as 4:1.
- *Celik, 1997 (53) and Kawalsaki, 2001 (63)*
  When improved symptoms were redefined as failure, this information was not available at one month. Thus the relevant data available at 14 days was analyzed even though the follow-up for all cases was done till one month.
- *Ficnar, 1997 (54)*
  The clinical response end point was not specifically mentioned. However, this was presumed to be equivalent to the last follow-up visit, namely three weeks.
- *Varsano, 1997 (55)*
  Loss to follow-up in children with recurrent otitis media was not given separately. It was presumed to be nil as the number of cases with recurrent otitis media were very few as compared to cases with non-recurrent otitis media

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