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Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults (Review)

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[Intervention Review]

Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults

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ABSTRACT

Background

Community-acquired pneumonia (CAP) is caused by various pathogens, traditionally divided into 'typical' and 'atypical'. Initial antibiotic treatment of CAP is usually empirical, customarily covering both typical and atypical pathogens. To date, no sufficient evidence exists to support this broad coverage, while limiting coverage is bound to reduce toxicity, resistance and expense.

Objectives

The main objective was to estimate the mortality and proportion with treatment failure using regimens containing atypical antibiotic coverage compared to those that had typical coverage only. Secondary objectives included the assessment of adverse events.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2012 which includes the Acute Respiratory Infection Group's Specialized Register, MEDLINE (January 1966 to April week 1, 2012) and EMBASE (January 1980 to April 2012).

Selection criteria

Randomized controlled trials (RCTs) of adult patients hospitalized due to CAP, comparing antibiotic regimens with atypical coverage (quinolones, macrolides, tetracyclines, chloramphenicol, streptogramins or ketolides) to a regimen without atypical antibiotic coverage.

Data collection and analysis

Two review authors independently assessed the risk of bias and extracted data from included trials. We estimated risk ratios (RRs) with 95% confidence intervals (CIs). We assessed heterogeneity using a Chi^2 test.

Main results

We included 28 trials, encompassing 5939 randomized patients. The atypical antibiotic was administered as monotherapy in all but three studies. Only one study assessed a beta-lactam combined with a macrolide compared to the same beta-lactam. There was no difference in mortality between the atypical arm and the non-atypical arm (RR 1.14; 95% CI 0.84 to 1.55), RR < 1 favors the atypical arm. The atypical arm showed an insignificant trend toward clinical success and a significant advantage to bacteriological eradication, which disappeared when evaluating methodologically high quality studies alone. Clinical success for the atypical arm was significantly higher for *Legionella pneumophilae* (*L. pneumophilae*) and non-significantly lower for pneumococcal pneumonia. There was no significant difference between

the groups in the frequency of (total) adverse events, or those requiring discontinuation of treatment. However, gastrointestinal events were less common in the atypical arm (RR 0.70; 95% CI 0.53 to 0.92). Although the trials assessed different antibiotics, no significant heterogeneity was detected in the analyses.

Authors' conclusions

No benefit of survival or clinical efficacy was shown with empirical atypical coverage in hospitalized patients with CAP. This conclusion relates mostly to the comparison of quinolone monotherapy to beta-lactams. Further trials, comparing beta-lactam monotherapy to the same combined with a macrolide, should be performed.

PLAIN LANGUAGE SUMMARY

Initial antibiotic treatment for coverage of 'atypical' pathogens for community-acquired pneumonia in hospitalized adults

Pneumonia is a serious lung infection and is usually treated with antibiotics. Bacteria which cause community-acquired pneumonia (CAP, pneumonia contracted outside healthcare settings) are traditionally divided into 'typical' and 'atypical', each dictating a different antibiotic treatment. Atypical bacteria include, *Legionella pneumophila* (*L. pneumophila*), *Mycoplasma pneumoniae* (*M. pneumoniae*) and *Chlamydia pneumoniae* (*C. pneumoniae*). The main 'typical' agent causing CAP is *Streptococcus pneumoniae* (*S. pneumoniae*). It is usually not possible to determine which of the many potential agents is the cause of CAP, so that antibiotic treatment is empirical, customarily covering both typical and atypical bacteria. While typical coverage is essential, the necessity of the atypical coverage has not been proven. In the previous version of this review we showed that there was no advantage to the atypical arm. Given the persisting inconsistency between current guidelines for treatment of pneumonia and the available evidence, we undertook to update this systematic review.

This Cochrane review looked at trials comparing antibiotic regimens with atypical coverage to those without, limited to hospitalized adults with CAP. We included 28 trials, involving 5939 patients. For the regimens tested, no advantage was found for regimens covering atypical bacteria in the major outcomes tested - mortality and clinical efficacy. There was no significant difference between the groups in the frequency of total adverse events, or those requiring discontinuation of treatment. However, gastrointestinal events were less common in the atypical arm.

There are limitations to this review in that a single study compared the addition of the atypical antibiotic to a typical antibiotic, the major question in clinical practice; most compared a single atypical antibiotic to a single typical antibiotic. Seventeen of the 27 trials were open label, 21 of the 27 studies were sponsored by pharmaceutical companies of which all but one was conducted by the manufacturer of the atypical antibiotic.

BACKGROUND

Description of the condition

Community acquired pneumonia (CAP) is a common clinical disease with considerable mortality and overwhelming economic burden. The Pneumonia Patient Outcomes Research Team (PORT) has developed a prediction scheme utilizing clinical variables to stratify CAP patients into five mortality risk classes, by which 30-day mortality has been estimated up to 9.3% and 31.1% for patients stratified to risk class IV and V, respectively (Fine 1997). The CURB-65 score is based on five easily measurable factors (confusion, urea, respiratory rate, blood pressure and age), by which 30-day mortality has been estimated up to 17%, 41.5% and 57% for patients with three, four or five risk factors, respectively (Lim 2003). Although *Streptococcus pneumoniae* (*S. pneumoniae)* is the leading cause of CAP, frequency of other agents, especially those designated 'atypical pathogens' (*Legionella pneumophilae* (*L. pneumophilae), Mycoplasma pneumoniae (M. pneumoniae)* and *Chlamydia pneumoniae (C. pneumoniae*)), varies with geographical area, age groups and diagnostic means available. Distinctions between typical and atypical organisms is significant, as the latter share intracellularity and are treated with specific antibiotic drugs. The causing agent cannot be clearly sorted to either group by any clinical, radiological or laboratory parameter (Donowitz 2000; Levison 2001). As the microbiological diagnosis is often unknown, initial antibiotic treatment of CAP is largely empirical.

Description of the intervention

All major guidelines for treatment of CAP divide patients into three subgroups: outpatients, hospitalized patients on a general ward and hospitalized patients in intensive care units (ICUs). Major guidelines recommend in general, an antibiotic regimen covering both typical and atypical pathogens in hospitalized CAP patients (BTS 2001; Hedlund 2005; Lim 2009; Mandell 2000; Mandell 2007; Niederman 2001; Woodhead 2005; Woodhead 2011). Suggested regimens include extended spectrum cephalosporins, beta-lactams (BLs) or beta-lactam/beta-lactamase inhibitors (BL/BLIs), all combined with macrolides, or a single agent with broad coverage, i.e. fluoroquinolones. The British Thoracic Society (BTS) guidelines support this recommendation in view of a high percentage of atypical pathogens, particularly *L. pneumophilae,* in hospitalized patients in the UK (higher, incidentally, than in North America or Europe). The American Thoracic Society (ATS) reserves recommendation of atypical coverage to clinical circumstances, although conceding elsewhere that clinical presentation cannot establish etiology. All guidelines support extensive antibiotic coverage for ICU patients, noting the prevalence as well as high mortality rates of pneumonia caused by *L. pneumophilae* in that population. Admittedly, these guidelines are based on insufficient evidence, as there have been only few randomized controlled trials (RCTs) assessing CAP treatment protocols.

How the intervention might work

Most trials comparing different treatment arms were performed to evaluate a specific drug, frequently a macrolide or a fluoroquinolone. Several of these trials (incidentally) compared regimens with and without atypical antibiotic coverage and found results to be generally equal (Aubier 1998; Tremolieres 1998). A meta-analysis by Mills 2005 compared typical antibiotic coverage with BL to atypical coverage in non-severe pneumonia and found no advantage of antibiotics with atypical coverage over BLs (risk ratio (RR) 0.97; 95% CI 0.87 to 1.07), a lower failure rate in *L. pneumophilae* (RR 0.4; 0.19 to 0.85), and equivalence for *M. pneumoniae* and *C. pneumoniae*. Furthermore, a large percentage of atypical pneumonia cases have been shown to be dual infections, usually in combination with a typical pathogen (Donowitz 2000). In view of these data, one must wonder what the true role of atypical agents in the treatment of pneumonia really is. If patients improve regardless of atypical coverage, should this coverage be routinely included? Furthermore, a RCT by Malhotra-Kumar 2007 showed by obtaining pharyngeal swabs from patients before and after treatment with macrolides versus placebo, that macrolide use is the single most important driver of the emergence of macrolide resistance, and therefore the effect of prescribing macrolides is of ecological importance.

In the previous version of this systematic review (Robenshtok 2008), 25 RCTs were found comparing a treatment regimen with atypical antibiotic coverage to one without such coverage. No trials comparing an atypical antibiotic in combination with a non-atypical antibiotic (the regimen currently recommended in all guidelines) versus the non-atypical antibiotic alone were found. There was no difference in mortality between the atypical arm and the non-atypical arm. The atypical arm showed an insignificant trend toward clinical success and a significant advantage to bacteriological eradication, which disappeared when evaluating methodologically high quality studies alone. A large systematic review that included observational studies, evaluated the superiority of atypical coverage to non-atypical coverage regimens (Oosterheert 2003). Significant reduction in mortality with atypical coverage was found in six of the eight selected studies. However, these studies were non-experimental cohort studies and outcomes showed several inconsistencies. Using propensity analysis, we showed that the major pitfall of such observational studies is the marked difference between patients prescribed non-atypical coverage and those prescribed a regimen including atypical coverage, a difference that precludes the comparison of these treatment regimens in observational studies (Paul 2007). Expanding coverage to atypical pathogens is bound to increase toxicity, resistance and cost. Moreover, this broad coverage might be at the expense of efficacy of pneumococcal coverage (Johansen 2000).

Why it is important to do this review

Given the persisting inconsistency between current guidelines and the available evidence, we undertook to update this systematic review of hospitalized adults with CAP. The review encompassed all trials which compared treatment regimens with versus without atypical antibiotic coverage, in order to evaluate the efficacy and need of atypical coverage in this subset of patients.

OBJECTIVES

1. To evaluate mortality and proportion with treatment failure using regimens containing atypical antibiotic coverage compared to those without (typical coverage only).

Secondary objectives

1. To evaluate treatment failure with regimens containing atypical antibiotic coverage compared to those without (typical coverage only).

2. To evaluate the frequency of adverse effects associated with different types of antibiotic treatment.
3. To evaluate mortality and treatment failure of regimens containing atypical antibiotic coverage for patients with identified atypical pathogens.
4. To evaluate mortality and treatment failure of regimens containing atypical antibiotic coverage for patients with identified *S. pneumoniae*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) or quasi-RCTs. We excluded trials with a dropout rate of over 30%.

Types of participants

Adult patients hospitalized due to suspected CAP. We did not consider patients with major immunosuppressive state(s) (i.e. malignancy, cystic fibrosis, HIV) for inclusion on this review.

Types of interventions

Studies comparing antibiotic therapy with atypical coverage to antibiotic therapy without atypical coverage. Regimens containing the following drugs, were considered atypical coverage.

1. Macrolides: including erythromycin, roxithromycin, azithromycin and clarithromycin.
2. Fluoroquinolone: including ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, moxifloxacin and grepafloxacin.
3. Tetracyclines: including tetracycline, doxycycline, tigecycline and minocycline.
4. Chloramphenicol.
5. Streptogramins: including pristinamycin and quinupristin-dalfopristin.
6. Ketolides: including telithromycin (ketek, recently withdrawn from Food and Drug Administration (FDA) approval) (Ross 2007; Soreth 2007).

We included other drugs within the antibiotic classes listed above, if identified by our searches. We considered regimens lacking the above drugs as non-atypical coverage.
we reviewed both oral and intravenous (IV) therapies (whether comparing oral to oral, IV to oral or IV to IV).

Types of outcome measures

Primary outcomes

1. Overall mortality at the end of the study and up to 30 days following the end of treatment.

Secondary outcomes

1. Number of patients with treatment failure, as defined in the study.
2. Number of patients in whom bacteriological eradication was achieved.
3. Number of patients who needed mechanical ventilation during hospital stay.
4. Mean duration of hospital stay.
5. Number of patients excluded from outcome assessment after randomizations.
6. Number of patients who developed superinfection or resistance to the studied drug, defined as isolation of a pathogen or a colonizing micro-organism resistant to the study drug, during or after antibiotic treatment.
7. Mean duration to regaining previous functional capacity.

Adverse events

1. Any serious adverse events that were fatal, life-threatening, or requiring prolongation of existing hospitalization.
2. Any adverse events that required discontinuation of medication.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 3, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 16 April 2012), which includes the Acute Respiratory Infection Group's Specialized Register, MEDLINE (June 2007 to April Week 1, 2012) and EMBASE (June 2007 to April 2012).

We used the search strategy in Appendix 1 to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) Ovid format (Lefebvre 2011). We adapted the search for EMBASE (Appendix 2).

We inspected the references of all identified studies for more trials. In addition to this, we contacted the first or corresponding author of each included trial and researchers active in the field for information regarding unpublished trials or complementary information on their own trial. We imposed no language or publication restrictions.

See Appendix 3 for details of previous searches.

Searching other resources

In addition, we searched ClinicalTrials.gov (www.clinicaltrials.gov/) and FDA new drug approval documents for ongoing or unpublished trials (last searched 1 May, 2012).

Data collection and analysis

Selection of studies

Two review authors (DS, ER in the original review (Shefet 2005); ER, AG in the 2008 update (Robenshtok 2008); NER, ER in this current update) independently inspected each reference identified by the search and applied the inclusion criteria. For possible relevant articles, or in cases of disagreement between the two review authors, we obtained the full article and inspected it independently. A third review author (MP) checked the article in cases where resolving disagreement by discussion was not possible. When required, we contacted the trial authors of the study for clarification. We documented justifications for excluding studies from the review.

Data extraction and management

Two review authors (DS, ER in the original review (Shefet 2005); ER, AG in the 2008 update (Robenshtok 2008); NER, ER in this current update) independently extracted data from the included trials. A third review author (MP) extracted the data in case of disagreement between the two review authors. We discussed the data extraction, documented decisions and, where necessary, we contacted the trial authors for clarification.

We identified trials by the name of the first author and year in which the trial was first published and ordered chronologically. We extracted, checked and recorded the following data.

Trial characteristics

1. Year(s) and country/countries of study.
2. Trial sponsor.
3. Publication status: published in journal; abstract/proceeding; unpublished.
4. Intention-to-treat (ITT) analysis: performed; possible to extract; efficacy analysis.
5. Randomization methods: allocation generation; concealment; blinding.
6. Failure definition: including time of failure assessment.
7. Study follow-up duration.

Patient characteristics

8. Number of patients randomized and evaluated, per group.
9. Age: mean or median.

Infection characteristics

10. Number of patients with documented typical pathogen.
11. Number of patients with documented atypical pathogen.
12. Number of patients with infections caused by bacteria resistant to the administered antibiotic regimen.
13. Patients with *S. pneumococcus, L. pneumophilae* and *Mycoplasma* infections.
14. Severity of the disease (as classified by PORT).

Intervention characteristics

15. Antibiotics type, dose and route of administration.
16. Treatment duration.
17. Treatment modifications.

Measures of outcome, extracted as number of patients per group

18. Overall mortality at end of study follow-up.
19. Bacteriological eradication.
20. Treatment failure: as defined in study, with and without treatment modifications.
21. Mechanical ventilation.
22. Adverse events: life-threatening events, events necessitating specific medical treatment, events requiring cessation of treatment.

Assessment of risk of bias in included studies

Two review authors (DS, ER in the original review (Shefet 2005); ER, AG in the 2008 update (Robenshtok 2008); NER, ER in this current update) assessed the risk of bias in trials fulfilling the review inclusion criteria. We used the 'Risk of bias' tool (Higgins 2011) to assess methodological quality according to: sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting and free of other bias. A third review author (MP) was responsible for resolving disagreements.

We assessed risk of bias by allocation concealment (low risk of bias - adequate allocation concealment; unclear allocation concealment; high risk of bias - inadequate allocation concealment, i.e. quasi-randomized studies).
We graded randomization similarly (low risk - table of random numbers, computer generated or coin tossing; unclear; high risk - anything else) and did the same for blinding (low risk - triple-blinded or double-blinded; high risk - patient-blinded or no blinding; and unclear when there was not enough data).

Measures of treatment effect

We analyzed dichotomous data by calculating the RR for each trial with the uncertainty in each result being expressed using 95% CIs.

Unit of analysis issues

We analyzed studies with non-standard designs as follows.

1. Cluster-randomized trials: this design would not be appropriate to evaluate antibiotic treatment for CAP.
2. Cross-over trials: this design would not be appropriate to evaluate antibiotic treatment for CAP.
3. Studies with multiple treatment groups: we assessed intervention groups for relevance for our review. If more than two groups were relevant, we combined groups to create a single pair-wise comparison.

Dealing with missing data

We contacted the original trial authors for missing data and requested additional information. We assumed the data to be missing at random if additional data were unavailable. We noted missing data in the 'Risk of bias' table and performed a sensitivity analysis.

We did not include the data in the meta-analysis in cases of missing standard deviations.

Assessment of heterogeneity

We initially assessed heterogeneity in the results of the trials by inspection of graphical presentations and by calculating a test of heterogeneity (Chi^2 test). We had anticipated between-trial variation in estimation of morbidity and mortality for those patients who were hospitalized on a general ward or in ICU, if trials were performed in different geographical areas and among different age groups or if per different drug regimens were assessed. We performed subgroup analyses in order to assess the impact of these possible sources of heterogeneity on the main results.

Assessment of reporting biases

We examined a funnel plot estimating the precision of trials (plots of logarithm of the RR for efficacy against the sample size) in order to estimate potential asymmetry.

Data synthesis

We used a fixed-effect model throughout the review. We compared the fixed-effect model to a random-effects model when we

observed significant heterogeneity between the trials (P < 0.10). Continuous data were not available for analysis in this review.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis to assess the impact of the various treatment regimens, to analyze treatment effects on particular patient groups, and to investigate for heterogeneity. We planned to analyze mortality and clinical failure only on the following subgroups.

1. Type of antimicrobial agent in the atypical arm: quinolones, macrolides, combination of quinolones and macrolides, and others.
2. Age: under or over 65 years.
3. Geographical area: Europe, North America, and others.
4. Methodology: allocation generation, allocation concealment, blinding, and ITT analysis.
5. Type of bacteria: *S. pneumoniae,* atypical pathogens, and legionella.
6. Sponsoship: sponsored, non-sponsored, and unclear sponsorship.

Sensitivity analysis

We performed sensitivity analyses in order to assess the robustness of the findings to different aspects of the trials' methodology: allocation concealment (adequate or unclear), randomizations, blinding, exclusions after randomizations (reported or not reported), sample size (up to 100 or more than 100 patients), and length of follow-up (up to one month or one to 12 months).

RESULTS

Description of studies

Results of the search

In this 2012 update we retrieved 1301 records from the electronic database searches. The CENTRAL search identified 304 records, MEDLINE identified 594 records and the EMBASE search identified 823 records. We evaluated all records for this update. We did not evaluate further any studies in which the abstract suggested comparator antibiotic regimens incompatible with the inclusion criteria. We similarly excluded studies of outpatients, nosocomial (hospital-acquired) infections, respiratory tract infections other than pneumonia and non-randomized studies.

We retrieved 66 publications for full-text inspection, of which we excluded 38.

Included studies

Thirty publications fulfilled our inclusion criteria. Two were substudies of a parallel publication (Allegra 1995 of Rizzato 1997; Jardim 2003 of Petitpretz 2001). Thus, we included 28 trials in the review. We identified three new studies in the 2012 update (Hatipoglu 2010; Hong-yun 2007; Kohno 2011). Two were published as abstracts only. We requested additional information from nearly all the trial authors, seven of whom responded.

Study details can be found in the Characteristics of included studies table. The studies were performed between 1982 and 2011. Sixteen were multicentered. Fifteen were performed in Europe, three in North America and ten in other countries (Japan, Argentina and South Africa) or multicontinental. Twenty-one of the included trials were in English (including two abstracts, one of which was probably originally in Chinese), three in Japanese, two in French, one in Spanish and one in German. The studies encompassed 5939 randomized patients, of whom 5444 patients could be evaluated for our primary outcome analysis (overall mortality). The number of participants was 100 or lower in nine trials and over 100 in 19 trials (range 40 to 808 participants). All trials were restricted to adults (defined as aged above 18 years, and in one case above 16 years (Tremolieres 1998). The mean age in 14 studies was under 65 and in nine studies over 65, two of which were preformed in nursing homes (Hirata-Dulas 1991; Peterson 1988) and one was restricted per definition to patients over 70 (Romanelli 2002). Five studies did not report the mean age.

The inclusion criteria in most studies were adults hospitalized with CAP. Three trials included outpatients (Chuard 1989; Petitpretz 2001; Tremolieres 1998), who comprised less than 25% of patients. A fourth study (Lode 1995) stated that most patients were hospitalized, without further clarification. Nine of 24 studies included patients with either nosocomial pneumonia (three studies) or bronchitis (six studies), in addition to patients with CAP. In six studies (Carbon 1992; Feldman 2001; Hirata-Dulas 1991; Miki 1984; Norrby 1998; Peterson 1988), CAP patients consisted of over 60% (and in three of which, over 90%) of the patients. In two studies (Gleadhill 1986; Kobayashi 1984) results were given and analyzed separately for the CAP population. In the ninth study (Khan 1989), the distribution of nosocomial pneumonia versus CAP was unclear. However, the excellent results in a senior population suggest a low rate of nosocomial pneumonia. Two studies were carried out in nursing homes (Hirata-Dulas 1991; Peterson 1988).

Pneumonia was defined by a combination of clinical signs, chest X-ray (sole criteria in two studies - Bohte 1995; Vanderdonckt 1990 - and absent in five), laboratory (white blood count, 12 studies) and/or bacteriological evidence (six studies, in one as a necessary condition) (Zeluff 1988). The adjusted mean rate of bacteriological documentation was 47% in 20 studies that reported on the number of patients with bacteriological confirmation. Four studies were restricted to severe pneumonia (Fourrier 1986; Khan 1989; Rizzato 1997; Vanderdonckt 1990). In contrast, three studies excluded severe infections (Carbon 1992; Kalbermatter 2000; Lephonte 2004). Four studies included suspected pneumococcal infection (Bohte 1995; Lephonte 2004; Petitpretz 2001; Zeluff 1988), the latter was done exclusively in gold-miners and subsequently evaluated only the proven cases; a fifth study excluded suspected cases of atypical pneumonia (Tremolieres 1998). Eleven studies provided the percentage of patients with chronic obstructive pulmonary disease (COPD) (most others included the data in combination with other major co morbidities). In eight studies, up to a quarter of the patients were previously diagnosed with COPD. In three, the number of COPD patients exceeded 30% (up to 52.5%, Rizzato 1997). None of the studies included a comparison of COPD patients and/or smokers to non-COPD patients and/or non-smokers.

The specific antibiotic regimens used are detailed in the Characteristics of included studies table. The atypical arm consisted of a quinolone in 21 studies, a macrolide in five and pristinamycine in one study. In the remaining study, patients were randomized to one of three arms - quinolone, macrolide and a non-atypical regimen, and the two former arms were evaluated together (Lode 1995). In all but three studies, the atypical arm

was given as a monotherapy. In one case quinolone was combined with teicoplanin (Rizzato 1997) and in the second, macrolide was combined with either cephalosporin or an aminoglycoside (AG) (the two arms evaluated together, Romanelli 2002), the third is an abstract assessing the addition of an atypical antibiotic to a BL (Hatipoglu 2010). The drugs were administered orally in all but eight studies, of which most switched to oral administration within a few days.

The non-atypical arm consisted of BLs or cephalosporins: BL in nine cases, BL/BLI in three cases, cephalosporin in 11 cases, carbapenems in two cases and penicillin in one. One study had two non-atypical arms, cephalosporin or a BL/BLI, which were evaluated together (Kalbermatter 2000). Another study compared the atypical arm to 'customary antibiotic therapy', including BL, anti-staphylococcal drugs, cephalosporin and AG (Fourrier 1986). All BLs, one cephalosporin and two BL/BLI (12 studies) were administered orally, one cephalosporin was given intra-muscularly and the remaining drugs (15 studies) were administered intravenously.

Comparisons included: quinolone to BL (eight), BL/BLI (one), cephalosporin (nine, eight as quinolone monotherapy), carbapenem (one) or various non-atypical drugs (two); macrolide to penicillin (one), BL/BLI (one), cephalosporin (one) or to carbapenems (two, one as macrolide monotherapy); quinolone and macrolide to BL/BLI (one). One study compared pristinamycine with amoxycillin. One comparison of combination cephalosporin-macrolide to cephalosporin monotherapy was found.

The main outcome measure in all studies was clinical failure. Six studies mandated radiological resolution for success definition and one asked for bacteriological eradication. In four studies definition of success was unclear. None of the studies named mortality as a primary outcome.

Twenty-one trials assessed bacteriological failure, defined by eradication. Some reported results per patients, whereas others by pathogens (occasionally more than one pathogen per patient). Most took follow-up bacteriological specimens only from those patients found initially positive. Only 10 studies performed serology tests for atypical pathogens, one of which found all tests negative (Vogel 1991). Four studies were evaluated for atypical pathogens eradication rate while the other six did not fully report bacteriological success rates.

Adverse events were addressed in all studies but the two abstracts. Two studies failed to report the number of events per treatment arm (Hirata-Dulas 1991; Lode 1995), the latter reporting the number of events in the comparator arms alone. Data relating specifically to antibiotic-associated diarrhoea were scarce and did not permit reliable evaluation.

Seven studies assessed duration of hospital stay, none reported standard deviations. Two of these studies reported mean deviations. Therefore, continuous data was not available for analysis in this review.

Excluded studies

We retrieved 66 publications for full-text inspection, of which we excluded 38 (Characteristics of excluded studies table). Reasons for exclusion (occasionally more than one per study) included: studies addressing outpatients (11), allowance of atypical antibiotics in the non-atypical arm (12), nosocomial infections (5), double publication or pooled data (5), studies addressing only patients with bronchitis (2) and a dropout rate of over 30% (1). Six excluded studies investigated general severe infections, including but not exclusively, pneumonia. The percentage of pneumonia cases was usually small, some may have been nosocomial and the data were not always given separately per site of infection. One was a retrospective observational cohort study.

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 1 and summarized in Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

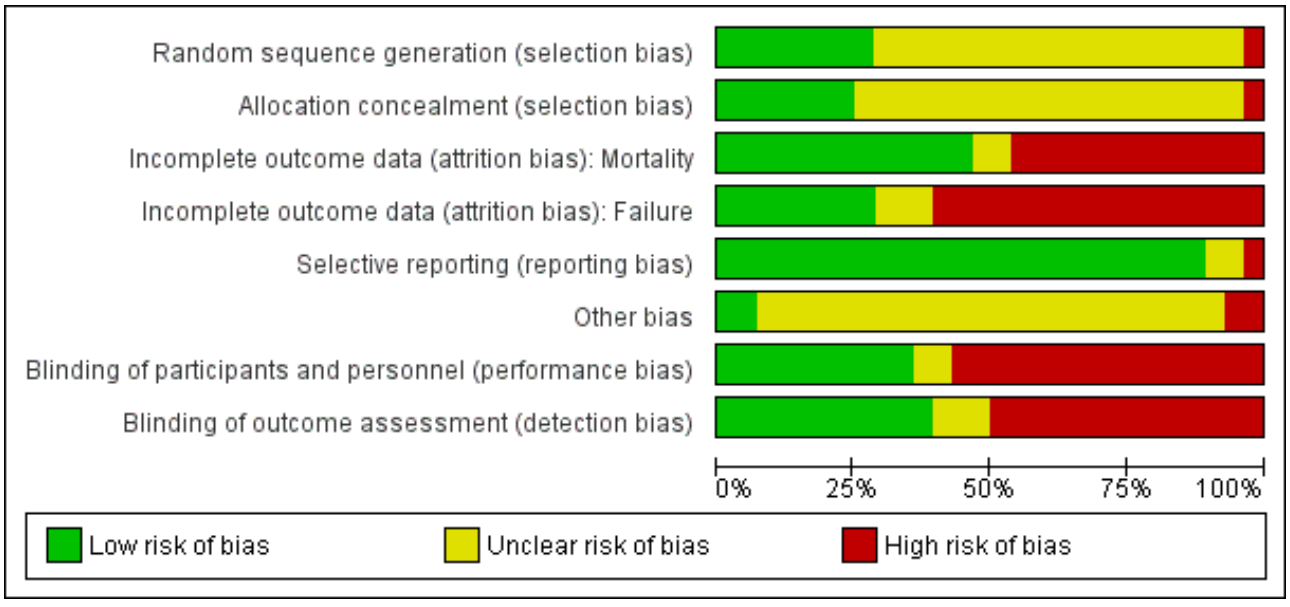


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

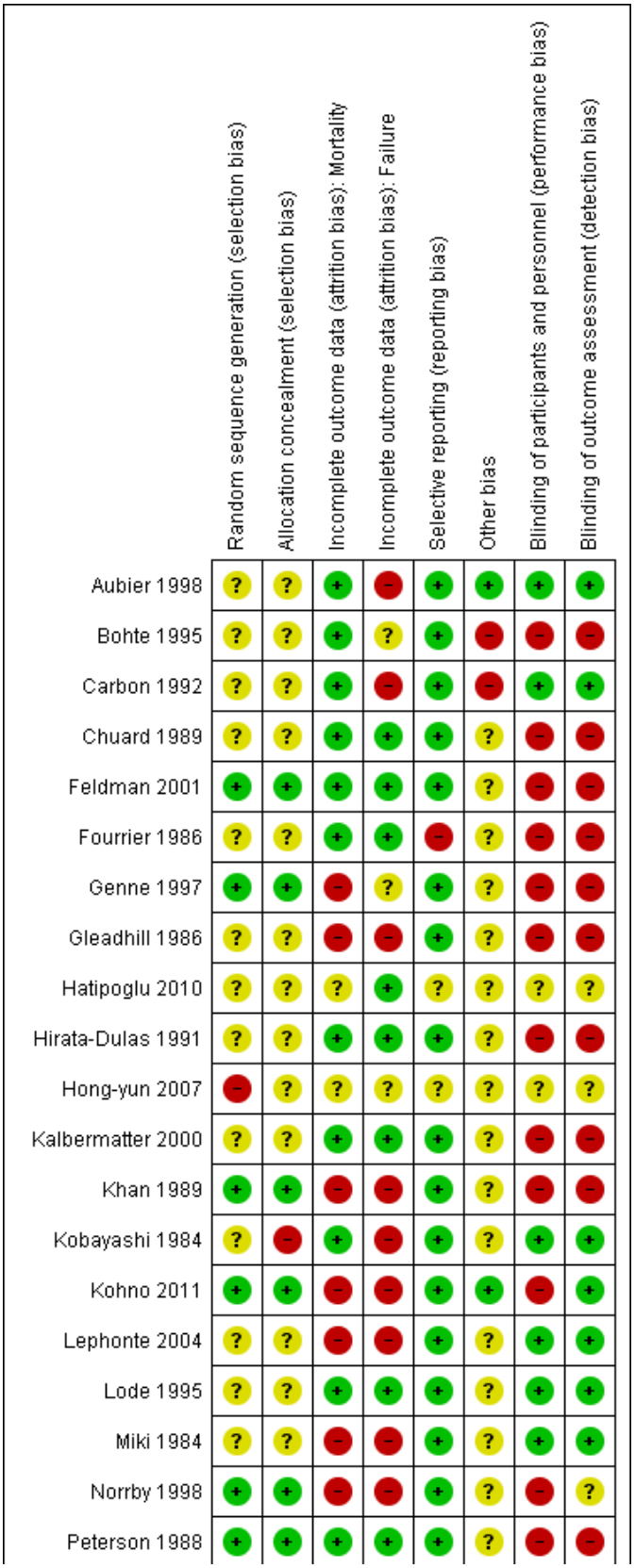
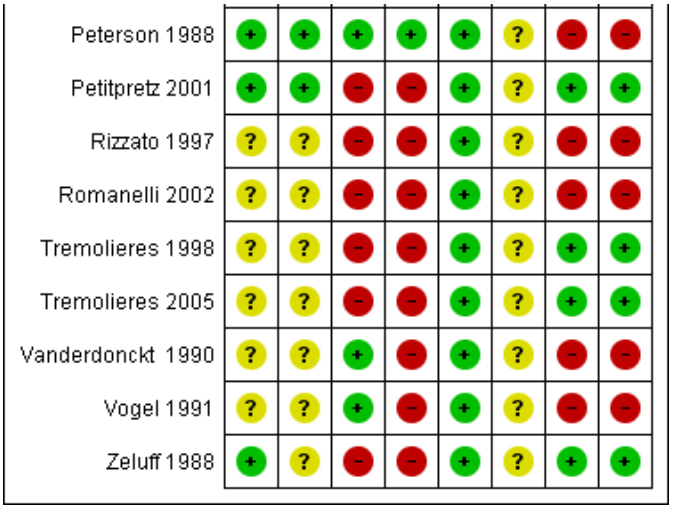


Figure 2. (Continued)



Allocation

Adequate allocation concealment was reported in 7 out of 28 studies. Insufficient information was available for the other studies. Allocation generation was adequate in 10 out of 28 studies. No information was available for 18 studies. All studies of adequate allocation concealment were also of adequate allocation generation.

Blinding

Ten studies were double-blind, one was single-blinded and the remaining (17 out of 28) were open label.

Incomplete outcome data

We separated between three levels of possible bias as follows.

1. Studies performed by ITT.
2. Per-protocol studies, in which the number of dropouts was given per study arm.
3. Per-protocol studies, in which the number of dropouts was reported or could be calculated but not given per study arm.

As mentioned above, the primary outcome in all studies was clinical success. Seven studies reported results by ITT (type 1). Fifteen additional studies reported the number of dropouts per study arm (type 2), permitting re-analysis by ITT assuming failure for all dropouts. Six studies did not refer to dropouts (type 3) and were analyzed by evaluated patients only in the sensitivity analysis. Mortality was not a primary outcome and was usually reported in the safety analysis. Thirteen studies recounted information regarding overall mortality by ITT (type 1), while 11 provided data per-protocol. One study does not specifically mention deaths (Kobayashi 1984), as is the case for the two abstracts (Hatipoglu 2010; Hong-yun 2007). Twenty-five of the 27 studies could be evaluated for mortality, encompassing 5444 of 5939 randomized patients (91.6%).

Twenty studies reported bacteriological eradication rates, encompassing 2310 patients/isolates. All but five trials reported on adverse events per treatment arm, including 4918 patients. None of the trials mentioned duration to regaining previous functional capacity, nor were there sufficient data regarding the number of patients who required mechanical ventilation.

Five studies assessed duration of hospital stay, two of these reported mean duration stay (Hirata-Dulas 1991; Rizzato 1997); one reported median duration (Norrby 1998); and the rest reported the total number of days in hospital (Chuard 1989; Romanelli 2002). Only one study (Rizzato 1997) reported standard deviation. Therefore, continuous data were not available for analysis in this review.

Follow-up duration was specified in 22 studies (81%), of which 16 studies (59%) defined a specific time for outcome measurement. Follow-up ranged from immediately after completion of treatment to three months after.

Selective reporting

We did not find any specific concerns over selective. All trials defined clinical success or failure as their primary outcome and reported on it. Mortality was not reported as a separate outcome in methods but was reported in results as a safety measure or otherwise. Specific data are reported for each study in the Characteristics of included studies tables.

Other potential sources of bias

At least 21 of the 27 studies were sponsored by pharmaceutical companies; all but one of these manufactured the atypical drug.

Two of the studies included in this review were abstracts, with data extracted only from the abstracts and no further data were available. Randomization and allocation concealment procedures in these trials are unknown. One of the abstracts was published in the Chinese journal *Chinese Journal of Antibiotics* (Hong-yun 2007) but we could not obtain its full-text. We failed to contact the authors of this abstract, and therefore we have no detailed information about randomizations and allocation concealment in this study.

Effects of interventions

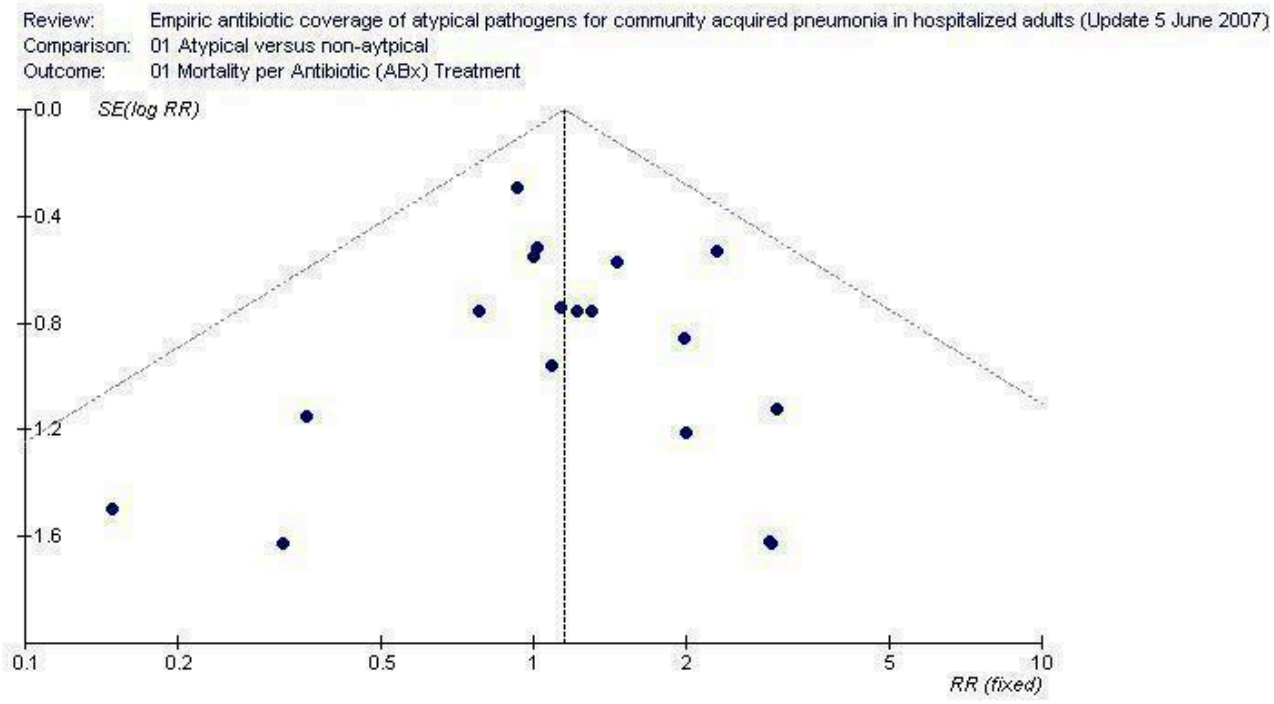
Overall mortality (Analyses 1.1 to 1.7)

Twenty-five of the 27 studies could be evaluated for mortality, encompassing 5444 of 5939 randomized patients (91.6%). Six studies reported no deaths, 12 reported a mortality rate between 0.4% to 5%, six reported a rate of 5% to 8%, and one study reported a 25% mortality rate (Fourrier 1986). In three studies, two of which were abstracts, mortality was not mentioned (Hatipoglu 2010; Hong-yun 2007; Kobayashi 1984). The adjusted mean mortality rate was 3.5%. None of the deaths according to the authors were related to the drug treatment.

There was no significant difference between the atypical arm and the non-atypical arm in the overall mortality rate (RR 1.14; 95% CI 0.84 to 1.55, Analysis 1.1). The difference remained non-significant when evaluating quinolone therapy (RR 0.98; 95% CI 0.69 to 1.39) and macrolide therapy (RR 1.25; 95% CI 0.52 to 3.01) alone. No heterogeneity was seen for the overall comparison (Chi^2 test = 8.34, df =17, P = 0.96, I^2 statistic = 0%).

Mortality was further analyzed by patient characteristics: age (mean age older or younger than 65 years); and geographical area (Europe, North America or other). Neither comparison disclosed a significant difference (Analysis 1.2 and Analysis 1.3, respectively). Overall mortality in both arms was similar when analyzing studies by randomizations generation, allocation concealment and blinding (Analysis 1.4, Analysis 1.5 and Analysis 1.6, respectively), as well as in the ITT analysis (Analysis 1.7). The effect of sponsorship by pharmaceutical companies could not be evaluated, as in the non-sponsored trials there was no mortality. In the funnel plot for overall mortality, which included 19 trials in which mortality was more than zero, results are symmetrically centered around the combined RR (Figure 3).

Figure 3.



Clinical failure (Analyses 1.8 to 1.18)

Clinical failure was the primary outcome in all 28 studies, comprising 5419 patients (of 5939 randomized). A non-significant trend toward an advantage to the atypical arm was observed combining all studies (RR 0.93; 95% CI 0.84 to 1.04) (Analysis 1.8). No heterogeneity for the total results was seen (Chi^2 test = 29.53, df = 24, P = 0.2, I^2 statistic = 18.7%). When evaluating the different atypical regimens, quinolone monotherapy showed non-significant advantage (RR 0.89; 95% CI 0.79 to 1.02) while macrolide monotherapy showed non-significant disadvantage (RR 1.11; 95% CI 0.76 to 1.62). The non-significant advantage of the atypical arm was seen in young patients (mean age < 65 years: RR 0.93; 95% CI 0.81 to 1.06) as well as older patients (mean age older than 65 years: RR 0.91; 95% CI 0.75 to 1.10) (Analysis 1.9). The advantage was statistically significant in the European studies (RR 0.85; 95% CI 0.74 to 0.98) but not in studies carried out elsewhere (Analysis 1.10).

There was no advantage to atypical treatment in studies of high methodological quality. There was no difference in clinical efficacy when combining studies that scored A in randomizations generation (RR 0.99; 95% CI 0.82 to 1.19) or allocation concealment (RR 0.99; 95% CI 0.82 to 1.19). Studies of B score accentuated an advantage toward the atypical arm (Analysis 1.11; Analysis 1.12). Rates of clinical failure were similar in trials sponsored by pharmaceutical companies (RR 0.97; 95% CI 0.86 to 1.08, 21 trials) and non-sponsored trials (RR 1.02; 95% CI 0.64 to 1.62, 3 trials) (Analysis 1.18).

We performed an ITT versus per-protocol design sensitivity analysis, counting all dropouts as failures in the ITT group (Analysis

1.14). No significant differences between type 1 (RR 0.92; 95% CI 0.76 to 1.12), type 2 (RR 0.94; 95% CI 0.84 to 1.05) or type 3 (RR 0.85; 95% CI 0.63 to 1.15) studies, although type 3 studies showed a higher effect estimate for atypical treatment.

Clinical failure with macrolide antibiotic treatment was the only comparison in which heterogeneity was detected (Chi^2 test = 6.68, df = 3, P = 0.08, I^2 statistic = 55.1%). Re-analysis done by the random-effects model did not alter results.

Clinical failure rates were evaluated per pathogens isolated. Of the 1021 pneumococcal pneumonia cases reported, there was a non-significant advantage to the non-atypical arm (RR 1.22; 95% CI 0.88 to 1.7, Analysis 1.15). Data were insufficient to distinctively analyze cases of pneumococcal bacteraemia. In contrast to *S. pneumoniae*, there was a non-significant advantage to the atypical arm in the treatment of atypical pathogens (RR 0.52; 95% CI 0.24 to 1.10, Analysis 1.16). Eradication of *L. pneumophilae* in particular was highly significant, with a RR of 0.17 and a narrow CI (0.05 to 0.63), although only 43 cases were available (Analysis 1.17).

Bacteriological failure (Analyses 1.19 to 1.20)

Twenty studies reported bacteriological eradication rates, encompassing 2310 patients/isolates (mixed results, as each study used different measures, see above). There was a statistically significant advantage to bacteriological eradication in the atypical treatment arm (RR 0.80; 95% CI 0.65 to 0.98, Analysis 1.19). No heterogeneity was seen (Chi^2 test = 12.4, df = 18, P = 0.0.83, I^2 statistic = 0%). When considering only the high quality studies ('A' score in allocation generation), no significant difference was detected in bacteriological eradication between the two treatment arms (RR 0.90; 95% CI 0.61 to 1.32, Analysis 1.20). Again, no heterogeneity was seen (Chi^2 test = 1.35, df = 6, P = 0.97, I^2 statistic = 0%). Only five studies reported super-infections, with numbers too small for statistical assessment.

Adverse events (Analyses 1.21 to 1.23)

All but five trials reported on adverse events per treatment arm, including 4918 patients. Total adverse events (Analysis 1.21) were similar in both treatment arms (RR 1.02; 95% CI 0.93 to 1.13). No heterogeneity was seen (Chi^2 test = 39.93, df = 21, P = 0.009, I^2 statistic = 29.8%). Gastrointestinal events (Analysis 1.22) were reported in 16 studies and were significantly less common in the atypical arm (RR 0.7; 95% CI 0.53 to 0.92). However, definition of gastrointestinal events differed, some including abdominal pain and some diarrhoea alone, thereby excluding an accurate comparison of the frequency of antibiotic-associated diarrhoea. Both arms were nearly equal with regard to adverse events requiring discontinuation (RR 1.01; 95% CI 0.72 to 1.41, Analysis 1.23).

Other outcomes

Treatment duration was conveyed in 14 studies and was almost uniformly 10 days, with no difference between the arms. None of the trials mentioned duration to regaining previous functional capacity, nor were there sufficient data regarding the number of patients who required mechanical ventilation.

DISCUSSION

Summary of main results

The primary outcome we assessed was overall mortality. There was no difference between the atypical arm and the non-atypical arm with respect to this outcome. This did not change when analyzing results per population characteristics or methodology. There was a non-significant trend toward clinical success in the atypical arm, accentuated with quinolone monotherapy. The advantage disappeared when evaluating high-quality methodological studies alone (i.e. studies that had a low risk of selection bias). A significant advantage in bacteriological eradication was detected in the atypical arm, especially in reference to *L. pneumophilae* eradication. This advantage was not demonstrated in an analysis restricted to studies with adequate allocation generation. There was no statistically significant difference in the frequency of total adverse events between the two groups, although less gastrointestinal events were noted in the atypical arm.

Failure was commonly defined as lack of clinical improvement, deterioration, relapse and/or modifications of the antibiotic treatment. These endpoints are subjective and should therefore be studied with care, especially as many are non-blinded. Although pharmaceutical companies producing the atypical antibiotic sponsored most studies, the point estimate for sponsored and non-sponsored trials for clinical failure is similar. The similar response of the young and old is somewhat surprising, as one might anticipate that younger people would benefit more from atypical coverage, given a higher prevalence of atypical pneumonia in this age group. Perhaps this prevalence diminishes in the hospitalized population. A higher *L. pneumophilae* prevalence in the elder population may also explain the similarity.

Overall completeness and applicability of evidence

Mortality data were obtained for 91.6% of randomized patients. The overall mortality in included studies (adjusted mean 3.5%) was lower than reported in the literature (MedisGroups overall mortality of 10.6% (Iezzoni 1988); PORT validation cohort inpatient mortality of 8.0% (Fine 1997)). This is surprising in view of the fact that 12 of the 27 studies target relatively severe pneumonia cases (two studies conducted in nursing homes, one excluding patients under 70 years of age, three including suspected or proven pneumococcal pneumonia (the fourth excluded severe cases), one excluding suspected atypical cases, four restricted to clinically severe pneumonia and one restricted to moderate-severe pneumonia (see above). The low mortality rate is not a result of under-reporting, as mortality data were almost complete. Mortality was not a primary outcome in any of the studies, although it is obviously the most significant outcome in a potentially lethal infectious episode.

Quality of the evidence

The atypical arm's advantage in bacteriological eradication could not be explained by the coverage of atypical pathogens alone: results of clinical success in those cases were equivocal and their proven share of events was small. As demonstrated above, its reliability is questionable, since it became insignificant in the evaluation of high quality studies. One should note that the atypical arm was usually a new drug (tested by the manufacturer) and therefore expected resistance rates were small, compared to the typical arm which comprised of BL or cephalosporins.

Furthermore, most publications date to the early 1990s, while new resistant trends have emerged since then (for example increasing pneumococcal resistance to quinolones). The clinical advantage of *L. pneumophilae* coverage is not surprising. It is interesting to note that cases of atypical pneumonia (including *L. pneumophilae*) often resolved even in the treatment arm lacking atypical coverage. Only a minority were co-infections with typical pathogens.

The total of adverse events did not differ significantly between treatment arms. Gastrointestinal side effects were studied separately in order to try and assess frequency of antibiotic-associated diarrhoea after BL or cephalosporin treatment and were found to be significantly more prevalent in the non-atypical arm. However, the trials differed in definition of events to a point that precludes this assessment.

We had set off to investigate the contribution of atypical coverage to empiric treatment of CAP in hospitalized patients. The most suitable study for our purpose is one comparing a BL or cephalosporin with the same BL or cephalosporin combined with a macrolide or a quinolone. The last update found no such trials. In this update we found only a single abstract assessing directly the addition of an atypical antibiotic to a BL, which found no positive effect on treatment success rates with the addition of atypical coverage (Hatipoglu 2010). The need to add a macrolide to a BL therapy is a common dilemma manifested within the guidelines themselves. Our meta-analysis is therefore chiefly based on comparison of BL or cephalosporin regimens to atypical monotherapy, mainly quinolone monotherapy. Regarding this comparison, we found no advantage to atypical coverage in terms of mortality or clinical success. The relatively low mortality rates in the existing hospitalized CAP trials included in the mortality analysis, further limits our conclusion.

Potential biases in the review process

Inclusion of abstracts and studies with missing data might have introduced bias.

Agreements and disagreements with other studies or reviews

The objective of our study was to assess the efficacy and need of adding antibiotic coverage for atypical pathogens in hospitalized patients with CAP, in terms of mortality and successful treatment.

All major guidelines for treatment of CAP recommend in general, an antibiotic regimen covering both typical and atypical pathogens in hospitalized CAP patients (BTS 2001; Hedlund 2005; Lim 2009; Mandell 2000; Mandell 2007; Niederman 2001; Woodhead 2005). Admittedly, these guidelines are based on insufficient evidence, as there have been only few randomized controlled trials assessing CAP treatment protocols. Most trials comparing different treatment arms were performed to evaluate a specific drug, frequently a macrolide or a fluoroquinolone. Several of these trials (incidentally) compared regimens with and without atypical antibiotic coverage and found results to be generally equal (Aubier 1998; Tremolieres 1998).

A large systematic review that included observational studies, evaluated the superiority of atypical coverage to non-atypical coverage regimens (Oosterheert 2003). Significant reduction in mortality with atypical coverage was found in six of the eight selected studies. However, these studies were non-randomized cohort studies and outcomes showed several inconsistencies. Using propensity analysis, we showed that the major pitfall of such observational studies is the marked difference between patients prescribed non-atypical coverage and those prescribed a regimen including atypical coverage, a difference that precludes the comparison of these treatment regimens in observational studies (Paul 2007). Expanding coverage to atypical pathogens is bound to increase toxicity, resistance and cost. Moreover, this broad coverage might be at the expense of efficacy of pneumococcal coverage (Johansen 2000).

We conclude that no benefit of survival or clinical efficacy was shown to empirical atypical coverage in hospitalized patients with CAP. Further randomized controlled trials, comparing BL or cephalosporins therapy to BL or cephalosporins combined with a macrolide in this population, using mortality as its primary outcome, should be performed.

AUTHORS' CONCLUSIONS

Implications for practice

No benefit of survival or clinical efficacy was shown to empirical atypical coverage in hospitalized patients with CAP. This conclusion relates mostly to the comparison of quinolone monotherapy with BL monotherapy.

Implications for research

A RCT of a BL monotherapy compared to the same BL combined with a macrolide or a quinolone in hospitalized patients with CAP should be performed. Until then, the major regimen recommended in current guidelines remains unsubstantiated by evidence. The trial should have adequate randomizations generation and concealment and should report patient relevant outcomes (FDA 2009) and mortality. The trial should include patients with severe pneumonia, compatible (as regards severity) to those observed in sound observational studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aubier 1998

Methods	Randomized Multicenter
Participants	Adults (mean age: 42) Hospitalized CAP
Interventions	Atypical: PO sparfloxacin 400 mg X 1/d followed by 200 mg X 1/d Non-atypical: PO amoxacillin 1 G X /d
Outcomes	Success: resolution of signs and symptoms Modification = failure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	266/329 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Bohte 1995

Methods	Randomized Multicenter
Participants	Adults (18 to 75, age ˜ 53) CAP - clinically suspected pneumococcal pneumonia (suspected *Legionella pneumophilae* (*L. pneumophilae*) *Staphylococcus aureus (S. aureus)* and *Klebsiella pneumonia* (*K. pneumonia*) excluded) Hospitalized
Interventions	Atypical: PO azithromycin 500 mg X 2/d loading dose, followed by PO azithromycin 500 mg X 1/d Non-atypical: IV benzylpenicillin 1,000,000 IU X 4/d
Outcomes	Failure = clinical, radiological, change of antibiotics
Notes	Study included a second comparison between erythromycin and azithromycin, which was excluded from analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	Unclear risk	64/66 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	High risk	Not ITT (4/108 lost) Sponsored: grant from Pfizer Inc.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None (open label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Carbon 1992

Methods	Randomized Multicenter

Carbon 1992 *(Continued)*

Participants	Adults (mean age: 55) Hospitalized CAP (severe pneumonia excluded)
Interventions	Atypical: PO temafloxacin 600 mg X 2/d Non-atypical: PO amoxicillin 500 mg X 3/d
Outcomes	Failure = persistence of symptoms or signs, treatment modification Modification = failure
Notes	Severe pneumonia excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	243/246 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	High risk	Not ITT Sponsored
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Chuard 1989

Methods	Randomized Multicenter
Participants	Adults (mean ~ 66) 95% hospitalized 58% CAP (42% bronchitis or COPD exacerbation)
Interventions	Atypical: PO ofloxacin 200 mg X 2/d (several 400 mg X 2/d)

Chuard 1989 *(Continued)*

	Non-atypical: PO amoxicillin 750 mg X 3/d (several 375 mg X 4/d)
Outcomes	Clinical
Notes	Another trial reported in same study of non-randomized CAP suspected of atypical infection; relationship to this trial unclear Results given are for all patients, including non-pneumonia Study in German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None (open label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Feldman 2001

Methods	Randomized Multicentered
Participants	Adults 18 to 70 (mean age: 43) Hospitalized ˜ 90% CAP; ˜ 10% nosocomial
Interventions	Atypical: IV sitafloxacin 400 mg X 1/d Non-atypical: IV imipenem/cilastatin 500 mg X 3/d
Outcomes	Clinical success (as defined by investigator)
Notes	Phase II trial

Feldman 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization code designed to allocate equal numbers of patients to the 2 treatment groups using the method of random-permutated blocks of 4
Allocation concealment (selection bias)	Low risk	Sealed, serially-numbered envelopes, each containing details of the treatment allocation for a single patient
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None (open label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None (open label)

Fourrier 1986

Methods	Randomized Allocation A/B
Participants	Adults (no age mentioned) Hospitalized CAP; severe (per clinical)
Interventions	Atypical: PO pefloxacine 1200 mg/d Non-atypical: customary antibiotics: • beta lactam • cephalosporin - AG • anti-staphylococcal ABX
Outcomes	Failure = opposite of complete recovery
Notes	A lot of data missing (letter), even after correspondence with author Study in French

Fourrier 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	High risk	Number of patients with bacteriologically documented pathogen and pneumococcal pneumonia was lost (correspondence with author)
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	Maybe single-blinded - simple randomization
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Genne 1997

Methods	Randomized
Participants	Adults (mean age: 70) Hospitalized CAP
Interventions	Atypical: IV clarythromycin 500 mg X 2/d 3 to 5/d , followed by PO clarythromycin 500 mg X 2/d Non-atypical: IV amoxicillin-clavulanate 1.2 G X 4/d 3-5/d, followed by PO amoxicillin-clavulanate 625 mg X 3/d
Outcomes	Failure = change of ABX, persistence or progression of sx/radiological finding, death, s/e enabling completion of trial
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using sealed envelopes with random numbers

Genne 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes with numbers
Incomplete outcome data (attrition bias) Mortality	High risk	112/127 patients evaluated
Incomplete outcome data (attrition bias) Failure	Unclear risk	112/127 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Gleadhill 1986

Methods	Randomized
Participants	Adults (mean 71) 46% CAP; 50% COPD exacerbation; 4% acute bronchitis Hospitalized
Interventions	Atypical: PO ciprofloxacin 500 mg X 2/d Non-atypical: PO amoxicillin 250 mg X 3/d
Outcomes	Clinical and bacteriological: • complete success = clinical recovery, bacteriological eradication • partial success = clinical improvement, bacteriological reduction/indeterminate • unsuccessful = clinical failure, regardless of bacteriological response • undetermined (assessment impossible) • moderation = ?
Notes	Less than 50% CAP Data analyzed only for pneumonia patients (given separately)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

Gleadhill 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	High risk	48/52 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	48/52 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsor?
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Hatipoglu 2010

Methods	Randomized
Participants	Adults (no age mentioned) Hospitalized CAP, moderately-severe
Interventions	Atypical: ceftriaxone + clarithromycin Non-atypical: ceftriaxone
Outcomes	Success rate Incremental cost-effectiveness analysis
Notes	Data extracted from abstract, no correspondence

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Unclear risk	Not described

Hatipoglu 2010 *(Continued)*

Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not enough data
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough data
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough data

Hirata-Dulas 1991

Methods	Randomized
Participants	Adults (mean age: 79) Nursing home residents Hospitalized Nursing home-acquired lower respiratory tract infection (54 pneumonia, 6 acute bronchitis)
Interventions	Atypical: IV ciprofloxacin 200 mg/400 mg* X 2/d, followed by PO ciprofloxacin 750 mg X 2/d (* protocol changed from 200 mg to 400 mg on 4/1989, 5/24 P in new protocol) Non-atypical: IV ceftriaxone 2 G X 1/d, followed by IM ceftriaxone 1 G X 1/d
Outcomes	Success = resolution or marked improvement in clinical signs and symptoms of lower RTI and completion of 14 d treatment course Failure = all cause death, early termination due to lack of improvement, adverse event or superinfection Indeterminate = withdrawal due to protocol specification or to other factors unrelated to study drug administration Moderation = failure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated

Hirata-Dulas 1991 *(Continued)*

Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None (unknown)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None (unknown)

Hong-yun 2007

Methods	Randomized
Participants	Adults (no age mentioned) Hospitalized CAP
Interventions	Atypical: iv gatifloxacin (400 mg) Non-atypical: iv cefuroxime (2 G)
Outcomes	Success: clinical and bacteriological Adverse reactions
Notes	Data extracted from abstract, no correspondence

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Unclear risk	Not described
Incomplete outcome data (attrition bias) Failure	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described

Hong-yun 2007 *(Continued)*

Other bias	Unclear risk	Not enough data
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough data
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough data

Kalbermatter 2000

Methods	Randomized
Participants	Adults (mean age: 69 years) Hospitalized CAP; severe pneumonia was excluded
Interventions	Atypical: PO levofloxacin 500 mg X 2/d Non-atypical: IV amoxicillin/clavulanate 1 G X 3/d IV ceftriaxone 1 G X 2/d
Outcomes	Success = clinical and radiological Modification = failure
Notes	3 arms, amoxicillin/clavulanate and ceftriaxone calculated together as non-atypical arm Study in Spanish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Not identified
Blinding of participants and personnel (performance bias)	High risk	None

Kalbermatter 2000 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Khan 1989

Methods	Randomized
Participants	Adults (mean age: 58) Severe bacterial respiratory tract infection (34/122 presumed bacterial, no isolation) CAP + nursing home-acquired + nosocomial
Interventions	Atypical: IV ciprofloxacin 200 mg X 2/d (5 patients received 300 mg X 2/d) Non-atypical: IV ceftazidime 1 to 2 G X 2/d to 3/d
Outcomes	Failure = continuation/worsening of signs and symptoms
Notes	Distribution of nosocomial pneumonia versus CAP unclear; good results suggest low rate of nosocomial pneumonia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Antibiotics were administered with a computer-generated, randomized code
Allocation concealment (selection bias)	Low risk	Antibiotics were administered in a sequential manner
Incomplete outcome data (attrition bias) Mortality	High risk	122/140 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	122/140 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Manufacturer/Pharmaceutical company sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Kobayashi 1984

Methods	Randomized
Participants	Adults CAP + COPD (results given separately)
Interventions	Atypical: PO levofloxacin 200 mg X 3/d Non-atypical: PO amoxicillin 250 mg X 4/d
Outcomes	
Notes	Study in Japanese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	Inadequate
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	74/76 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Kohno 2011

Methods	Randomized, open-label, non-inferiority study Multicenter
Participants	Adults (mean age: 58.5) CAP mild to severe (70% moderate)
Interventions	Atypical: IV levofloxacin 500 mg X 1/d for 7 to 14 days

Kohno 2011 *(Continued)*

	Non-atypical: IV ceftriaxone 1 G X 2/d for 7 to 14 days
Outcomes	Success: clinical, radiological and laboratory
Notes	Study in Japanese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central, registration control system
Allocation concealment (selection bias)	Low risk	Evaluator center, randomly allocated patients
Incomplete outcome data (attrition bias) Mortality	High risk	200/260 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	200/260 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Low risk	Not identified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A separate party committee evaluated the effects of the drugs, not knowing which drug had been used

Lephonte 2004

Methods	Randomized Multicenter
Participants	Adults (mean age: 54) CAP Suspected pneumococcal pneumonia > 90% hospitalized
Interventions	Atypical: PO gemifloxacin 320 mg X 1/d for 1 week Non-atypical: amoxicillin/clavulanate 1 G/125 mg X 3/d for 10 days
Outcomes	Failure = clinical, bacteriological and radiological
Notes	Phase III Suspected pneumococcal pneumonia

Lephonte 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	High risk	249/324 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	249/324 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Manufacturer/Pharmaceutical company sponsored No ITT analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Lode 1995

Methods	Randomized Multicenter
Participants	Adults (mean age: 54) Hospitalized and outpatients CAP
Interventions	Atypical: PO sparfloxacin 400 mg loading dose, followed by PO sparfloxacin 200 mg X 1/d PO erythromycin 1 G X 2/d Non-atypical: PO amoxicillin-clavulanic acid 500/125 mg X 3/d
Outcomes	Failure = clinical, radiological, change of antibiotics Modification = failure
Notes	3 arms in 2:1:1 randomizations (sparfloxacin: amoxicillin-clavulanic acid: erythromycin); the two atypical arms were calculated as one, in comparison to the non-atypical arm Note: also outpatients - no further data, short of stating the majority of patients were hospitalized

Risk of bias

Lode 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	Low risk	All patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Miki 1984

Methods	Randomized
Participants	Adults Hospitalized Suspected bacterial pneumonia (CAP), small percentage of upper RTI
Interventions	Atypical: PO enoxacin 600 mg/d Non-atypical: PO amoxicillin 1 G/d
Outcomes	
Notes	Study in Japanese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Miki 1984 *(Continued)*

Incomplete outcome data (attrition bias) Mortality	High risk	145\147 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	139/147 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Norrby 1998

Methods	Randomized Multicenter
Participants	Adults (mean 65) Hospitalized Pneumonia (CAP 94%; nosocomial 6%)
Interventions	Atypical: IV levofloxacin 500 mg X 2/d, followed by PO levofloxacin 500 mg X 2/d Non-atypical: IV ceftriaxone 4 G X 1/d
Outcomes	Cure = all infection related signs and symptoms disappeared or returned to pre-infection state and chest X-ray findings at least improved Failure = all infection related signs and symptoms unchanged or worsened; patients developed new clinical findings consistent with active infection; patient died due to the infection; drug study discontinued; one or more antibiotics added to drug due to treatment failure
Notes	CAP and nosocomial infection

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central, computerized telephone system
Allocation concealment (selection bias)	Low risk	Evaluator-blinded for selected patients
Incomplete outcome data (attrition bias)	High risk	619/625 patients evaluated

Norrby 1998 *(Continued)*

Mortality		
Incomplete outcome data (attrition bias) Failure	High risk	619/625 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored No ITT
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Three types of assessments were performed according to the study protocol: protocol, conducted by computer; investigator, conducted by the investigator and evaluator-blinded, conducted by an external evaluator for selected patients using blinded data

Peterson 1988

Methods	Randomized
Participants	Adults > 60 years old (mean: 81 years) Nursing home residents Hospitalized CAP/RTI
Interventions	Atypical: PO ciprofloxacin 750 mg X 2/d Non-atypical: IM cefamandole 1 G X 4/d
Outcomes	Success = improvement in signs and symptoms and patient not given another course of drug treatment for RTI within 6 weeks of discharge
Notes	2/3 CAP, 1/3 RTI, most data combined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random assignment code
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias)	Low risk	All patients evaluated

Peterson 1988 *(Continued)*

Failure		
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Petitpretz 2001

Methods	Randomized Multinational, multicenter
Participants	Adults (mean age: 51) CAP: suspected pneumococcal pneumonia 79% hospitalized
Interventions	Atypical: PO moxifloxacin 400 mg X 1/d Non-atypical: PO Amoxicillin 1 G X 3/d Both for 10 days
Outcomes	Clinical response Failure = insufficient resolution of symptoms/death
Notes	Presumed pneumococcal pneumonia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Author confirmed in correspondence adequate methods
Allocation concealment (selection bias)	Low risk	Author confirmed in correspondence adequate methods
Incomplete outcome data (attrition bias) Mortality	High risk	408/411 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	408/411 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored

Petitpretz 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Rizzato 1997

Methods	Randomized Multicenter
Participants	Age > 65 or 18 to 65 years + comorbidities (mean age: 68.5) Severe CAP: exclusion: "risk of death within 48h of study start" Hospitalized
Interventions	Atypical: IV teicoplanin 400 mg LD, followed by 400/200 mg X 1/d (per investigator's discretion) + PO ciprofloxacin 500 mg X 2/d Non-atypical: IV ceftriaxone 2 G X 1/d
Outcomes	Clinical response: success (cure, improvement), failure and data could not be evaluated
Notes	Severe CAP; elderly or comorbidities Allegra 1995 is a double publication of this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	High risk	225/240 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	225/240 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None

Rizzato 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Romanelli 2002

Methods	Randomized Multicenter
Participants	Elderly > 70 (mean age: 76) CAP Hospitalized
Interventions	Atypical: IV clarythromycin 500 mg + IV ceftriaxone 1 G X 2/d IV clarythromycin 500 mg + IV amikacin 250 mg X 2/d versus Non-atypical: IV meropenem 500 mg X 3/d IV imipenem/cilastatin 500 mg X 3/d
Outcomes	Clinical response Failure = no improvement or deterioration of signs and symptoms OR relapse
Notes	Elderly

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	High risk	204/226 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	204/226 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Tremolieres 1998

Methods	Randomized Multicenter
Participants	Adults > 16 years old (mean age: 52) 75% hospitalized CAP: exclusion: high probability of atypical pneumonia
Interventions	Atypical: PO trovafloxacin 200 mg X 1/d Non-atypical: PO amoxicillin 1 G X 3/d
Outcomes	Primary = clinical response; Secondary = bacteriological response Failure = lack of resolution of signs and symptoms/radiological failure/additional ABX given to patient
Notes	Adult defined as age > 16 years old (rather than 18 years old, as in other studies) Only 75% hospitalized

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) Mortality	High risk	335/344 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	285/344 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Tremolieres 2005

Methods	Randomized Multicenter
Participants	Adults > 18 years old (mean age: 48)

Tremolieres 2005 *(Continued)*

	CAP
Interventions	Atypical: PO pristinamycin 1 G x 3 Non-atypical: amoxacillin 1 G x 3
Outcomes	Clinical failure, bacteriological failure, pneumococcal treatment failure, mortality, s/e
Notes	20% with COPD; 6.5% asthma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not identified
Allocation concealment (selection bias)	Unclear risk	Not identified
Incomplete outcome data (attrition bias) Mortality	High risk	285/342 patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	285/342 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	sponsored by Pfizer Center Research
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Vanderdonckt 1990

Methods	Randomized Multicentre
Participants	Adults (mean 60) Severe bronchopulmonary infections Hospitalized
Interventions	Atypical: PO pefloxacin 400 mg X 2/d Non-atypical: IV ceftazidime 2 G X 2/d
Outcomes	Success not defined in study Bacteriological outcome

Vanderdonckt 1990 *(Continued)*

Notes	Severe infection = failure on previous treatment, multi-resistant pathogens, severe underlying disease, poor general condition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not identified
Allocation concealment (selection bias)	Unclear risk	Not identified
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	156/170 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Unknown sponsorship
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Vogel 1991

Methods	Randomized Multicenter
Participants	Adults (mean age: 62) Hospitalized CAP
Interventions	Atypical: PO temafloxacin 600 mg X 2/d Non-atypical: IV cefotaxime 2 G X 3/d
Outcomes	Cure: all signs and symptoms resolved Improvement: reduction of severity or numbers of signs and symptoms Failure: evidence of fever or worsening of signs, symptoms or chest X-ray after 3 treatment days Modification = ?
Notes	

Risk of bias

Vogel 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not identified
Allocation concealment (selection bias)	Unclear risk	Not identified
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients evaluated
Incomplete outcome data (attrition bias) Failure	High risk	75/100 patients evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	Sponsored
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Zeluff 1988

Methods	Randomized
Participants	Adults (mean age: 31; all South-African black gold miners) Hospitalized Pneumococcal pneumonia per chest X-ray and sputum (analyzed only culture positive)
Interventions	Atypical: PO roxithromycin 150 mg X 2/d Non-atypical: PO cephradine 1 G X 2/d
Outcomes	Clinical response (= improvement of signs and symptoms and resolution of lung infiltrate)
Notes	Pneumococcal pneumonia in a young homogenous group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An allocation schedule of random numbers
Allocation concealment (selection bias)	Unclear risk	Not identified

Zeluff 1988 *(Continued)*

Incomplete outcome data (attrition bias) Mortality	High risk	158/160 participants evaluated
Incomplete outcome data (attrition bias) Failure	High risk	90/160 participants evaluated
Selective reporting (reporting bias)	Low risk	Not identified
Other bias	Unclear risk	? sponsored
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

ABX: antibiotics
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease
IM: intramuscular
ITT: intention-to-treat
IV: intravenous
LD: loading dose
PO: per oral
RTI: respiratory tract infection
s/e: side effects
1/d: once a day
2/d: two times a day
3/d: three times a day
4/d: four times a day

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ailani 1999	Doxycycline versus standard therapy - latter arm not differentiated to regimens with atypical coverage and those without such coverage
Aubier 1996	Pooled analysis of 2 studies (1 = this paper) Sparfloxacin versus comparator arm, including erythromycin The results of studies are combined, thus no differentiation between atypical and non-atypical coverage Note: very large study (N = 1137
Chokshi 2007	Retrospective observational cohort study
Donowitz 1997	Outpatients
Fass 1989	Study of general serious infections Of 98 participants, 29 were non-randomized but included with randomized participants in the analysis

Study	Reason for exclusion
	Only 21/98 participants with pneumonia, some may be nosocomial
File 1997	Atypical coverage (macrolide or doxycycline) could be added to non-atypical arm at investigator's discretion (if atypical pathogens were suspected or proven)
Fink 1994	Of 402 participants randomized, 78% were diagnosed with nosocomial pneumonia
Fong 1995	Outpatients
Geijo Martinez 2002	Non-atypical group were given a macrolide optionally
Hagberg 2002	Outpatients
Hoepelman 1993	1. Most probably outpatients. The data is consistent with outpatients (rather than hospitalized patients), both in antibiotic regimen, follow-up setting and results; however, not stated specifically in the text. Trial author did not reply to further enquires. After consulting with the third review author (MP), we had decided it was most probably outpatients and therefore excluded it 2. 9 of 99 patients with pneumonia; data not given separately
Katz 2004	In the typical arm, patients could receive azithromycin or/and flagyl
Khajotia 1990	Over 80% lower respiratory tract infection without parenchymal involvement per chest X-ray. No separate information given for the (15 + 7) patients with CAP
Kinasewitz 1991	Outpatients
Krumpe 1999	Study of treatment of severe infections: of 540 patients enrolled, 310 were diagnosed with pneumonia, of whom more than 50% (57% of original patients) were diagnosed with nosocomial pneumonia
Kuzman 2005	In the typical arm 30% received doxycycline
Leophonte 1999	Meta-analysis of 5 trials, out of which 2 are included and 2 are excluded in this study; the fifth is yet to be located
Levine 1989	> 30% dropout rate (45/113 patients)
Lode 1987	Study of general severe clinical infections. Pneumonia patients 25/66, some may be nosocomial (no response from trial author)
Lode 1990	Reports 4 trials. The first is included in our study and the second compares two quinolones. The third and the forth have insufficient data regarding the study populations and outcomes. Not published elsewhere
Lode 1998	Retroactive analysis of 4 randomized clinical trials, concentrating on CAP patients with pneumococcal bacteraemia. Relevant studies were extracted and analyzed separately
Lode 2004	Both ambulatory and hospitalized patients could be included in the study but that information was not recorded. Therefore, the proportion of hospitalized patients is unknown
Mendoca 2004	In the typical arm 11% received a macrolide antibiotic
Mouton 1991	Non-atypical group were given amoxicillin and/or erythromycin
O'Doherty 1997	Outpatients

Study	Reason for exclusion
Ott 2008	Study of aspiration pneumonia and lung abscess
Peacock 1987	Study of general serious infections. Small number of pneumonia patients (7 and 4)
Plouffe 1996	Ofloxacin versus standard therapy - latter arm not differentiated to regimens with atypical coverage and those without such coverage
Rahav 2004	Outpatients
Siami 1995	Of 54 randomized patients, 89% were diagnosed with nosocomial pneumonia and only 11% diagnosed with CAP
Sifuentes 1989	Study of general severe infections. Small number of pneumonia patients. Data of mortality not given separately
Snydman 1995	Previously published (Fink 1994, excluded due to a high percentage of nosocomial pneumonia in enrolled patients)
Stocks 1989	Outpatients
Sujata 2008	In the typical arm, patients could receive macrolide
Torres 2003	Outpatients
Trenholme 1989	1. Over 50% of treated patients (27/44) were diagnosed with nosocomial pneumonia 2. Ciprofloxacin versus ceftazidime - when feasible, patients in latter group were switched to ANY alternative oral therapy
Welte 2005	In the typical arm, patients could receive erythromycin
Wollschlager 1987	1. Outpatients 2. Bacterial bronchitis

CAP: community-acquired pneumonia

DATA AND ANALYSES

Comparison 1. Atypical versus non-aytpical

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality per antibiotic (ABX) treatment	25	5444	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.55]
1.1 Quinolone (atypical arm)	19	3698	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.69, 1.39]
1.2 Macrolide (atypical arm)	4	540	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.52, 3.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Combined quinolone and macrolide (atypical arm)	1	808	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [0.81, 6.44]
1.4 Pristinamycine (atypical arm)	1	398	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.37, 10.69]
2 Mortality per age	25	5444	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.55]
2.1 Mean age under 65 years old	15	3820	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.75, 1.94]
2.2 Mean age over 65 years old	8	1439	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.69]
2.3 Data unavailable	2	185	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.34, 2.93]
3 Mortality - per geographical area	25	5444	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.55]
3.1 Europe	14	3209	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.79, 1.89]
3.2 North America	3	232	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.52, 3.86]
3.3 Other	8	2003	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.62, 1.60]
4 Mortality per allocation generation	25	5444	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.55]
4.1 A	10	1953	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.68, 1.68]
4.2 B	15	3491	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.79, 1.81]
4.3 C	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Mortality per allocation concealment	25	5444	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.55]
5.1 A	7	1590	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.66, 1.65]
5.2 B	18	3854	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.81, 1.83]
5.3 C	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Mortality per blinding	25	5444	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.55]
6.1 Non-blinded	16	2290	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.72, 1.50]
6.2 Single-blind	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Double or triple-blind	9	3154	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.79, 2.38]
7 Mortality - ITT analysis	12	2143	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.70, 2.15]

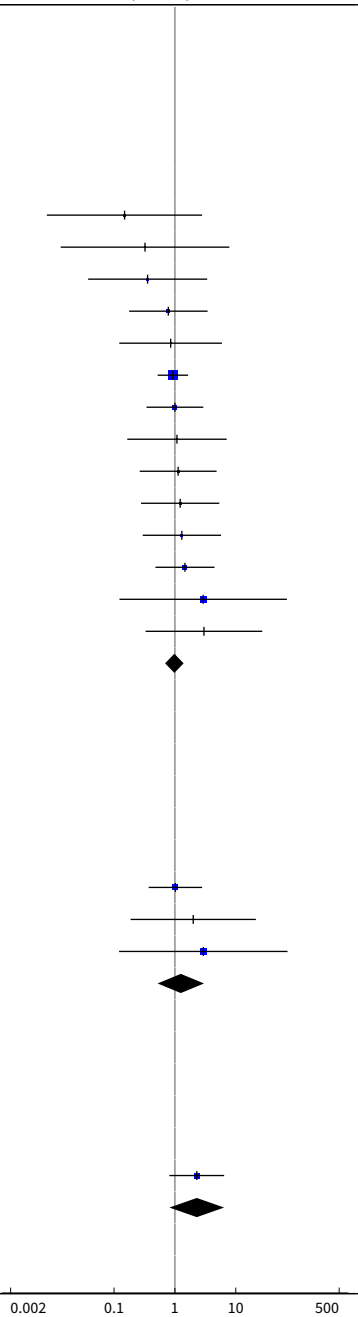
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 ITT (type 1)	12	2143	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.70, 2.15]
8 Clinical failure per antibiotic (ABx) treatment	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
8.1 Quinolone (atypical arm)	21	3704	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.79, 1.02]
8.2 Macrolide (atypical arm)	5	536	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.76, 1.62]
8.3 Combined quinolone and macrolide (atypical arm)	1	808	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.75, 1.17]
8.4 Pristinamycine (atypical arm)	1	371	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.77, 1.81]
9 Clinical failure per age	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
9.1 Mean age under 65 years old	15	3554	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.81, 1.06]
9.2 Mean age over 65 years old	8	1439	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.10]
9.3 Data unavailable	5	426	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.77, 1.50]
10 Clinical failure per geographical area	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
10.1 Europe	15	3084	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.98]
10.2 North America	3	232	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.59, 1.45]
10.3 Other	10	2103	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.24]
11 Clinical failure per allocation generation	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
11.1 A	10	1878	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.19]
11.2 B	17	3467	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.02]
11.3 C	1	74	Risk Ratio (M-H, Fixed, 95% CI)	7.29 [0.41, 130.64]
12 Clinical failure per allocation concealment	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
12.1 A	7	1583	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.19]
12.2 B	20	3762	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.80, 1.02]
12.3 C	1	74	Risk Ratio (M-H, Fixed, 95% CI)	7.29 [0.41, 130.64]

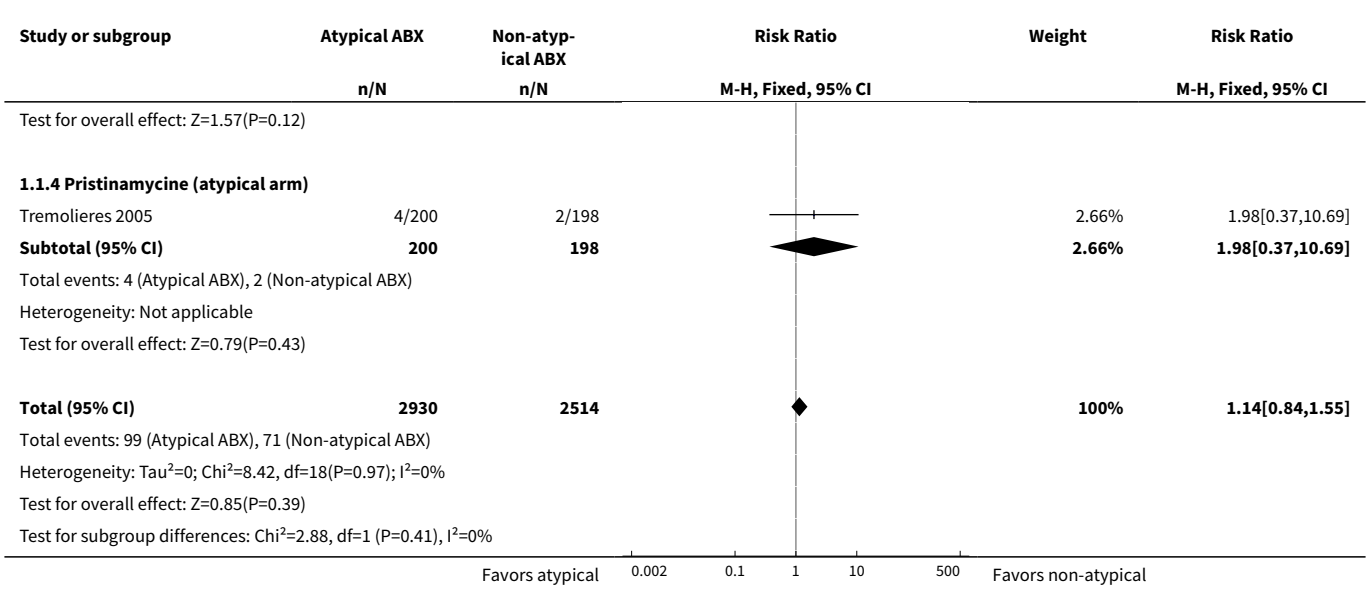
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Clinical failure per blinding	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
13.1 Non-blinded	18	2415	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
13.2 Single-blind	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Double or triple-blind	10	3004	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.11]
14 Clinical failure - ITT analysis	28	5682	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.85, 1.02]
14.1 ITT studies (type 1)	7	1232	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.76, 1.12]
14.2 Dropouts assumed as failure (type 2)	15	3849	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.84, 1.05]
14.3 Non-ITT, dropouts cannot be calculated (type 3)	6	601	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.15]
15 Clinical failure - pneumococcal pneumonia	18	1021	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.88, 1.70]
16 Clinical failure - atypical pathogens	4	158	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.24, 1.10]
17 Clinical failure - Legionella pneumophilae	5	43	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.63]
18 Clinical failure per sponsorship	28	5419	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
18.1 Sponsored trials	21	4540	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.08]
18.2 Non-sponsored trials	3	288	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.64, 1.62]
18.3 Unclear sponsorship	4	591	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.49, 0.93]
19 Bacteriological failure	21	2310	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.98]
19.1 Overall	21	2310	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.98]
20 Bacteriological failure per allocation generation	21	2310	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.98]
20.1 A	8	708	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.61, 1.32]
20.2 B	13	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.59, 0.96]
21 Adverse events - total	24	4918	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.13]
22 Adverse events - gastrointestinal events	16	4129	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.53, 0.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Adverse events - requiring discontinuation of treatment	12	3806	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.72, 1.41]

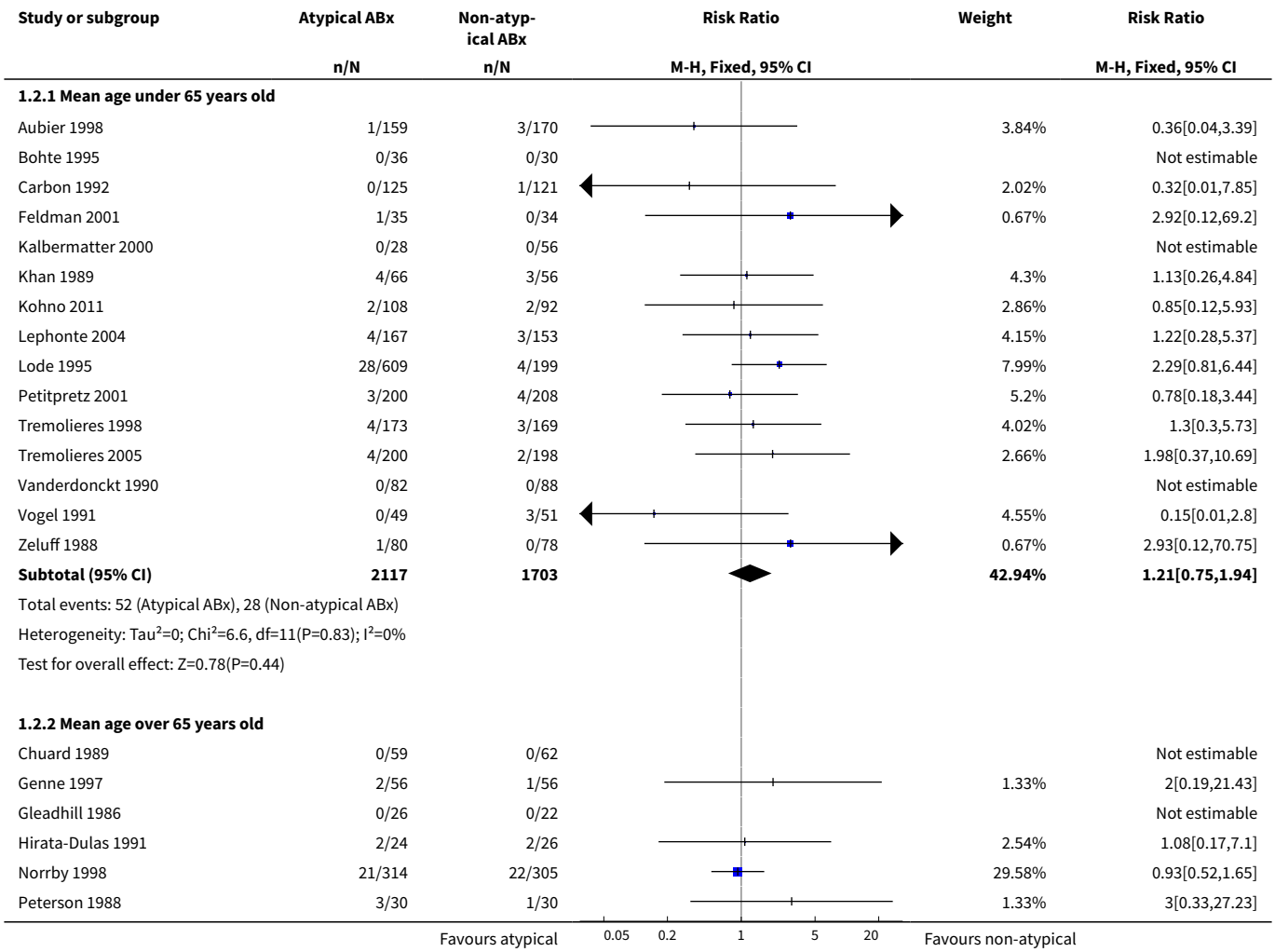
Analysis 1.1. Comparison 1 Atypical versus non-aytpical, Outcome 1 Mortality per antibiotic (ABX) treatment.

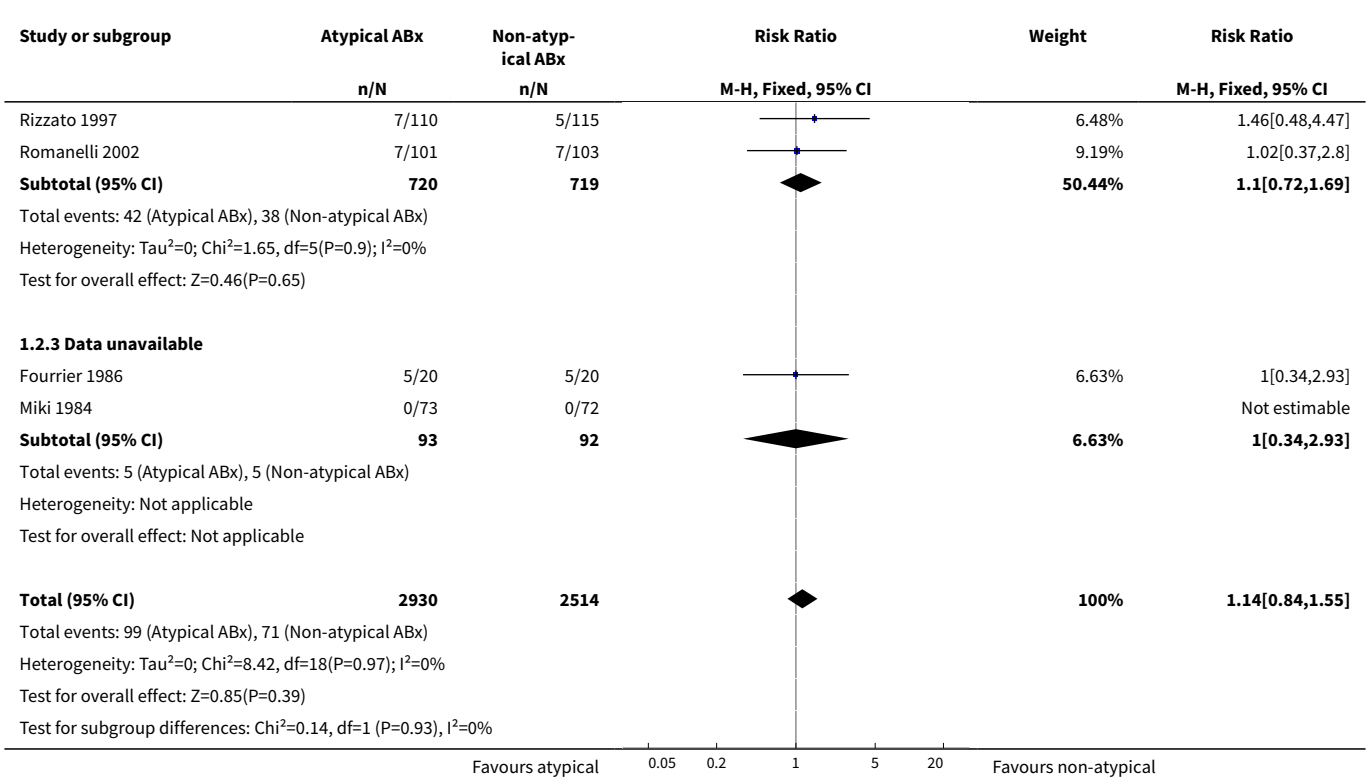
Study or subgroup	Atypical ABX n/N	Non-atypical ABX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Quinolone (atypical arm)					
Vanderdonckt 1990	0/82	0/88			Not estimable
Gleadhill 1986	0/26	0/22			Not estimable
Miki 1984	0/73	0/72			Not estimable
Kalbermatter 2000	0/28	0/56			Not estimable
Chuard 1989	0/59	0/62			Not estimable
Vogel 1991	0/49	3/51		4.55%	0.15[0.01,2.8]
Carbon 1992	0/125	1/121		2.02%	0.32[0.01,7.85]
Aubier 1998	1/159	3/170		3.84%	0.36[0.04,3.39]
Petitpretz 2001	3/200	4/208		5.2%	0.78[0.18,3.44]
Kohno 2011	2/108	2/92		2.86%	0.85[0.12,5.93]
Norrby 1998	21/314	22/305		29.58%	0.93[0.52,1.65]
Fourrier 1986	5/20	5/20		6.63%	1[0.34,2.93]
Hirata-Dulas 1991	2/24	2/26		2.54%	1.08[0.17,7.1]
Khan 1989	4/66	3/56		4.3%	1.13[0.26,4.84]
Lephonte 2004	4/167	3/153		4.15%	1.22[0.28,5.37]
Tremolieres 1998	4/173	3/169		4.02%	1.3[0.3,5.73]
Rizzato 1997	7/110	5/115		6.48%	1.46[0.48,4.47]
Feldman 2001	1/35	0/34		0.67%	2.92[0.12,69.2]
Peterson 1988	3/30	1/30		1.33%	3[0.33,27.23]
Subtotal (95% CI)	**1848**	**1850**		**78.16%**	**0.98[0.69,1.39]**
Total events: 57 (Atypical ABX), 57 (Non-atypical ABX)					
Heterogeneity: Tau^2=0; Chi^2=5.19, df=13(P=0.97); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
1.1.2 Macrolide (atypical arm)					
Bohte 1995	0/36	0/30			Not estimable
Romanelli 2002	7/101	7/103		9.19%	1.02[0.37,2.8]
Genne 1997	2/56	1/56		1.33%	2[0.19,21.43]
Zeluff 1988	1/80	0/78		0.67%	2.93[0.12,70.75]
Subtotal (95% CI)	**273**	**267**		**11.18%**	**1.25[0.52,3.01]**
Total events: 10 (Atypical ABX), 8 (Non-atypical ABX)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					
1.1.3 Combined quinolone and macrolide (atypical arm)					
Lode 1995	28/609	4/199		7.99%	2.29[0.81,6.44]
Subtotal (95% CI)	**609**	**199**		**7.99%**	**2.29[0.81,6.44]**
Total events: 28 (Atypical ABX), 4 (Non-atypical ABX)					
Heterogeneity: Not applicable					



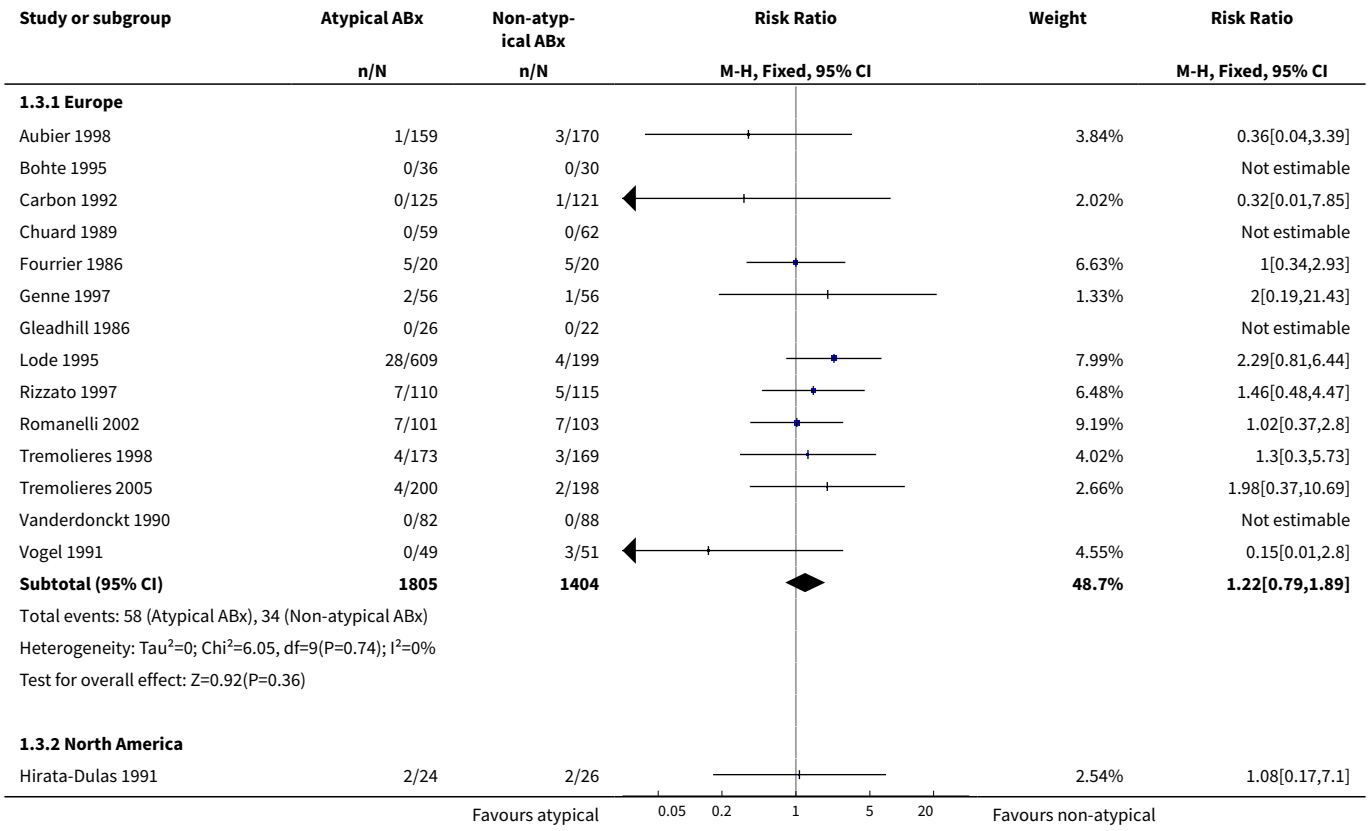


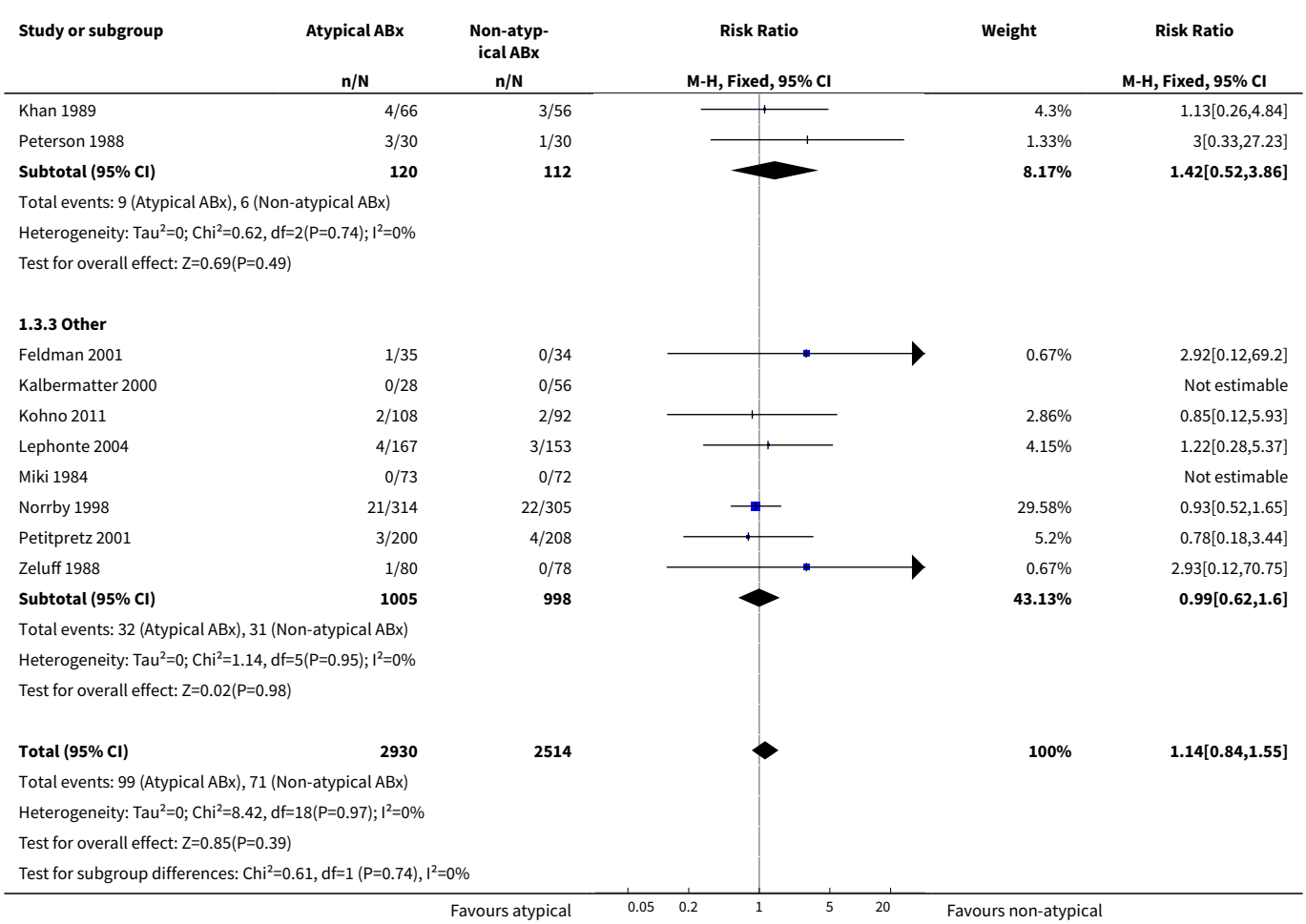
Analysis 1.2. Comparison 1 Atypical versus non-aytpical, Outcome 2 Mortality per age.



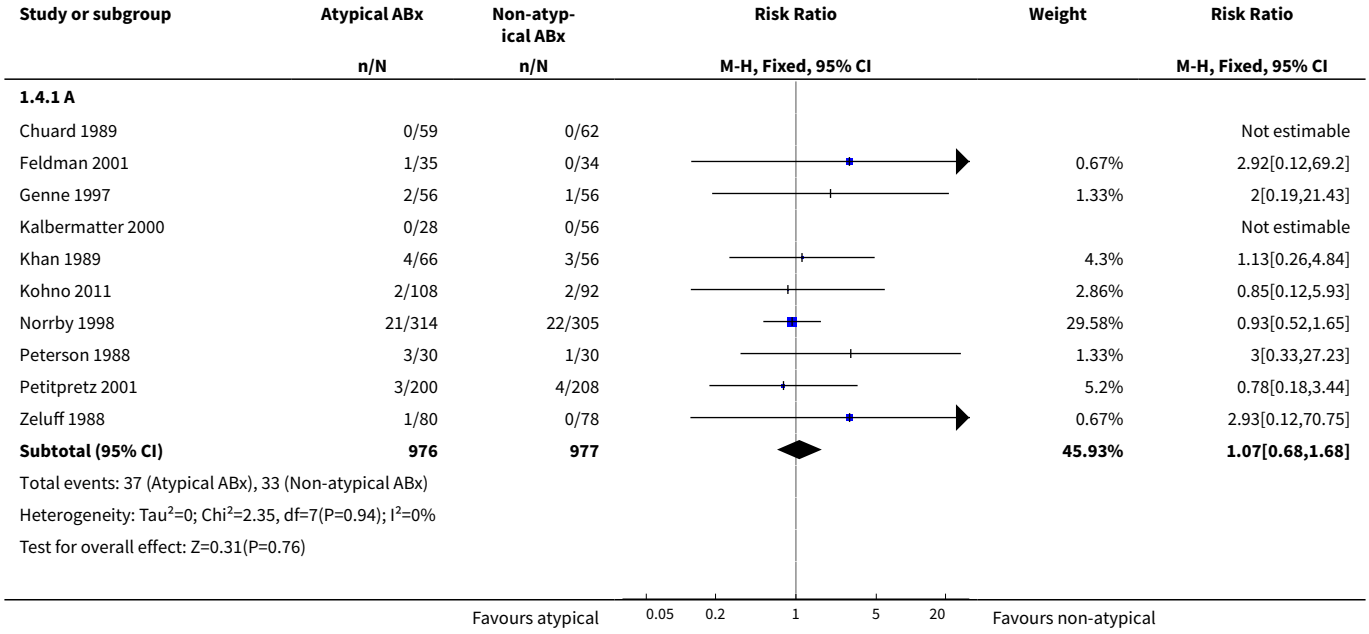


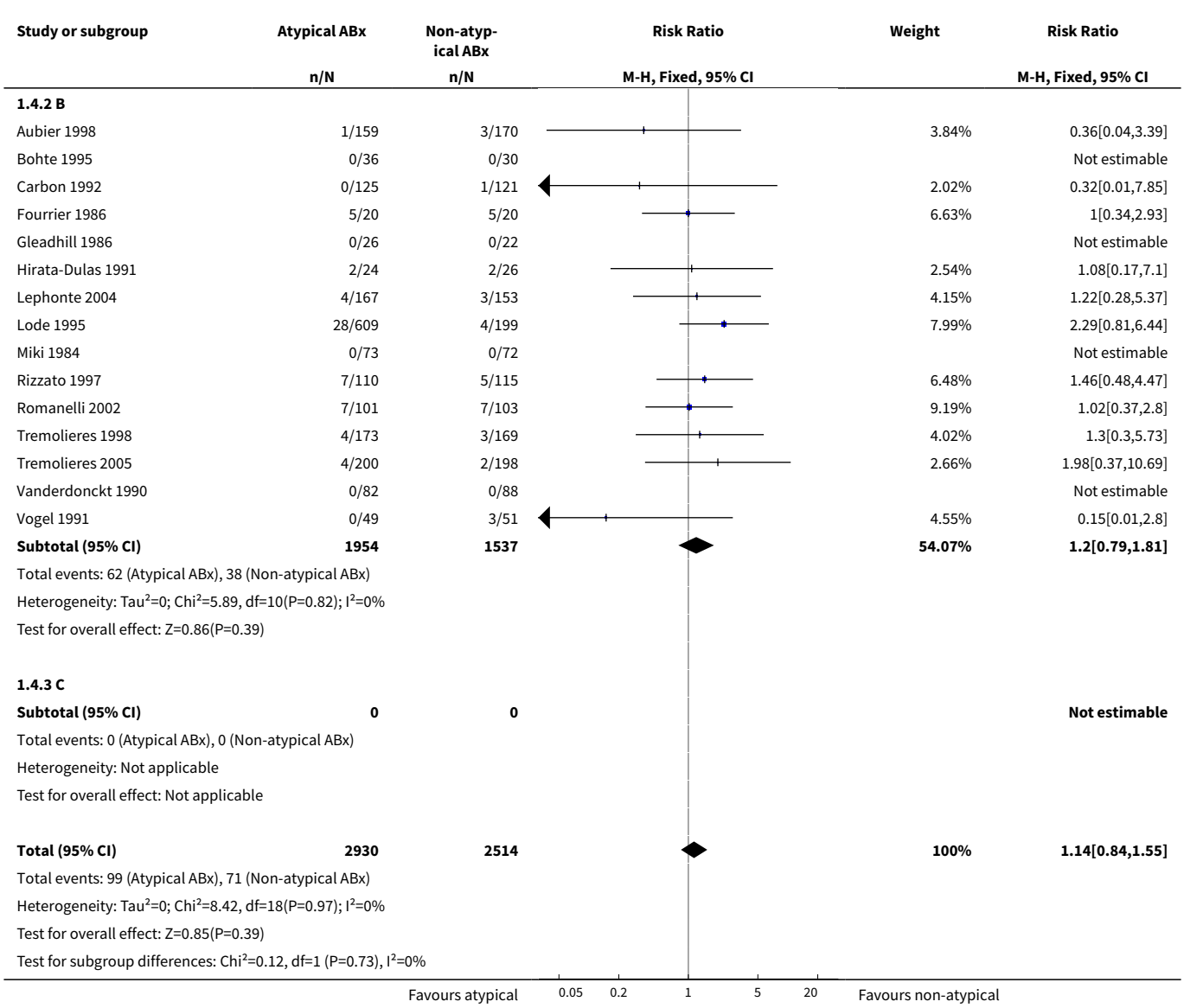
Analysis 1.3. Comparison 1 Atypical versus non-aytpical, Outcome 3 Mortality - per geographical area.



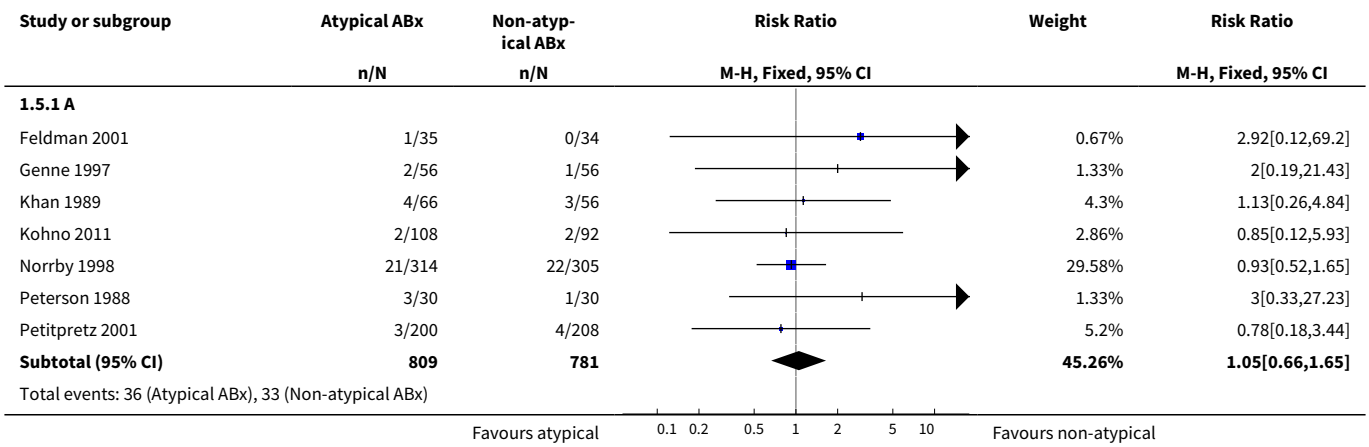


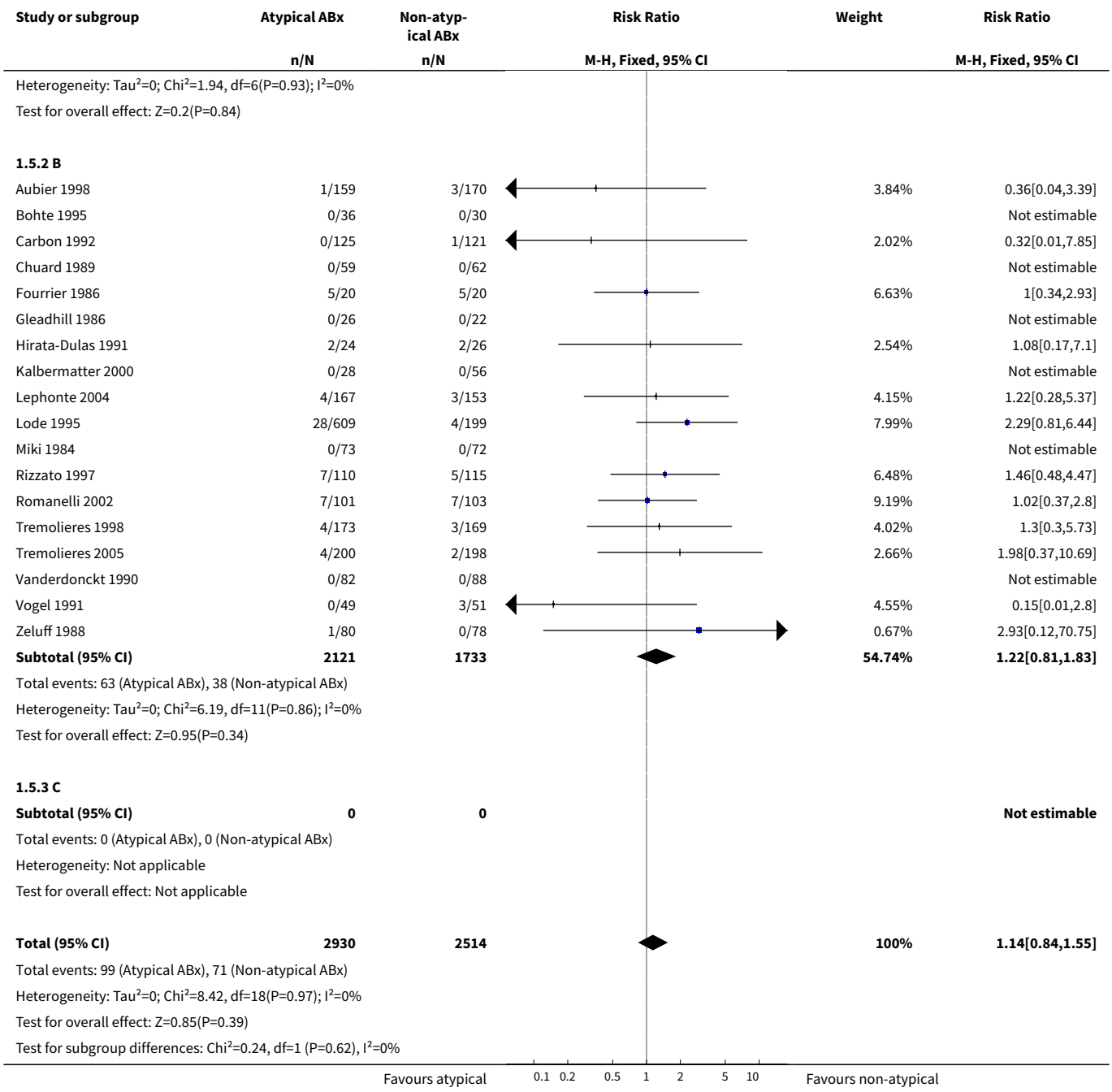
Analysis 1.4. Comparison 1 Atypical versus non-aytpical, Outcome 4 Mortality per allocation generation.



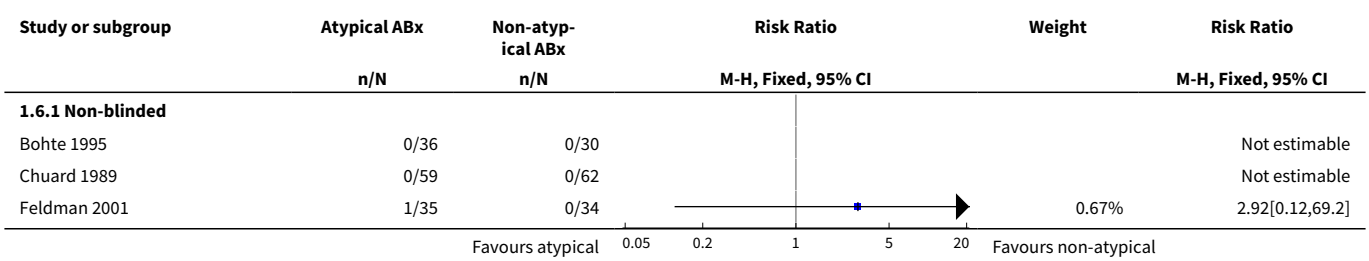


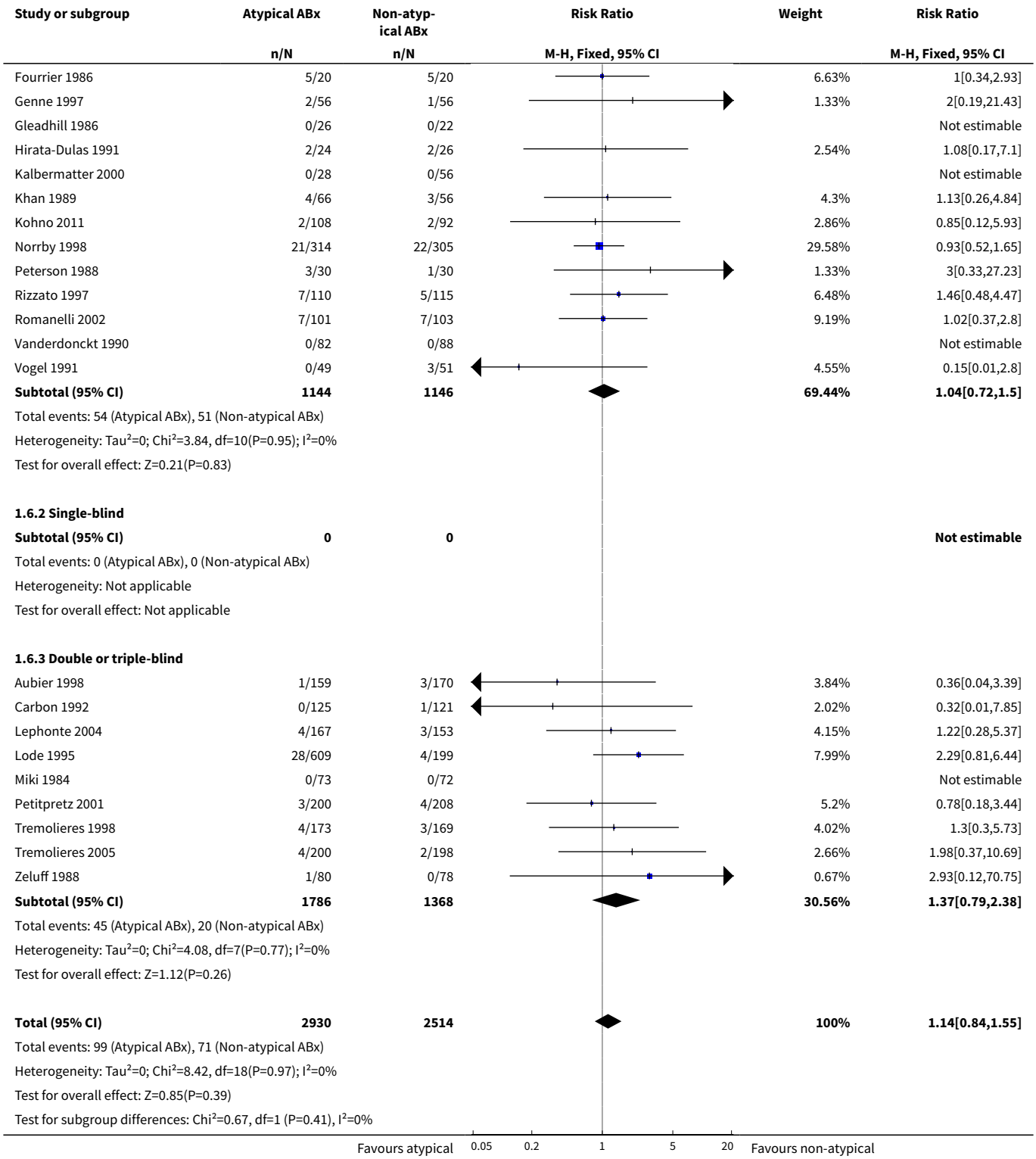
Analysis 1.5. Comparison 1 Atypical versus non-aytpical, Outcome 5 Mortality per allocation concealment.





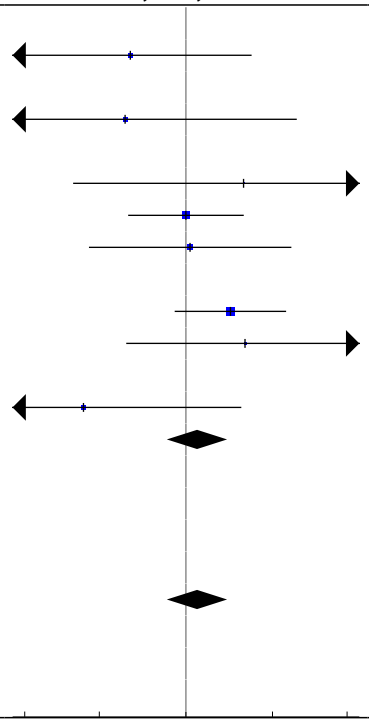
Analysis 1.6. Comparison 1 Atypical versus non-aytpical, Outcome 6 Mortality per blinding.





Analysis 1.7. Comparison 1 Atypical versus non-aytpical, Outcome 7 Mortality - ITT analysis.

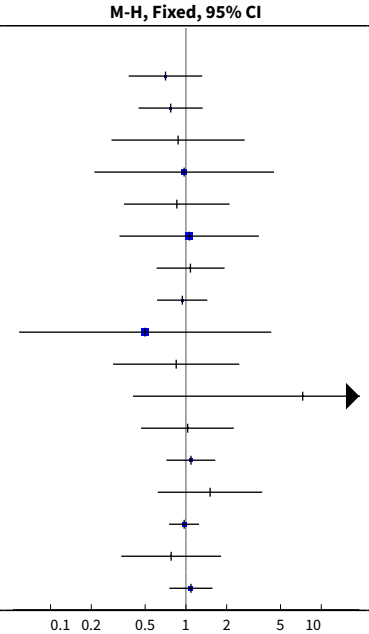
Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 ITT (type 1)					
Aubier 1998	1/159	3/170		13%	0.36[0.04,3.39]
Bohte 1995	0/36	0/30			Not estimable
Carbon 1992	0/125	1/121		6.83%	0.32[0.01,7.85]
Chuard 1989	0/59	0/62			Not estimable
Feldman 2001	1/35	0/34		2.27%	2.92[0.12,69.2]
Fourrier 1986	5/20	5/20		22.41%	1[0.34,2.93]
Hirata-Dulas 1991	2/24	2/26		8.61%	1.08[0.17,7.1]
Kalbermatter 2000	0/28	0/56			Not estimable
Lode 1995	28/609	4/199		27.02%	2.29[0.81,6.44]
Peterson 1988	3/30	1/30		4.48%	3[0.33,27.23]
Vanderdonckt 1990	0/82	0/88			Not estimable
Vogel 1991	0/49	3/51		15.38%	0.15[0.01,2.8]
Subtotal (95% CI)	**1256**	**887**		**100%**	**1.23[0.7,2.15]**
Total events: 40 (Atypical ABx), 19 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=6.28, df=7(P=0.51); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
Total (95% CI)	**1256**	**887**		**100%**	**1.23[0.7,2.15]**
Total events: 40 (Atypical ABx), 19 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=6.28, df=7(P=0.51); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					



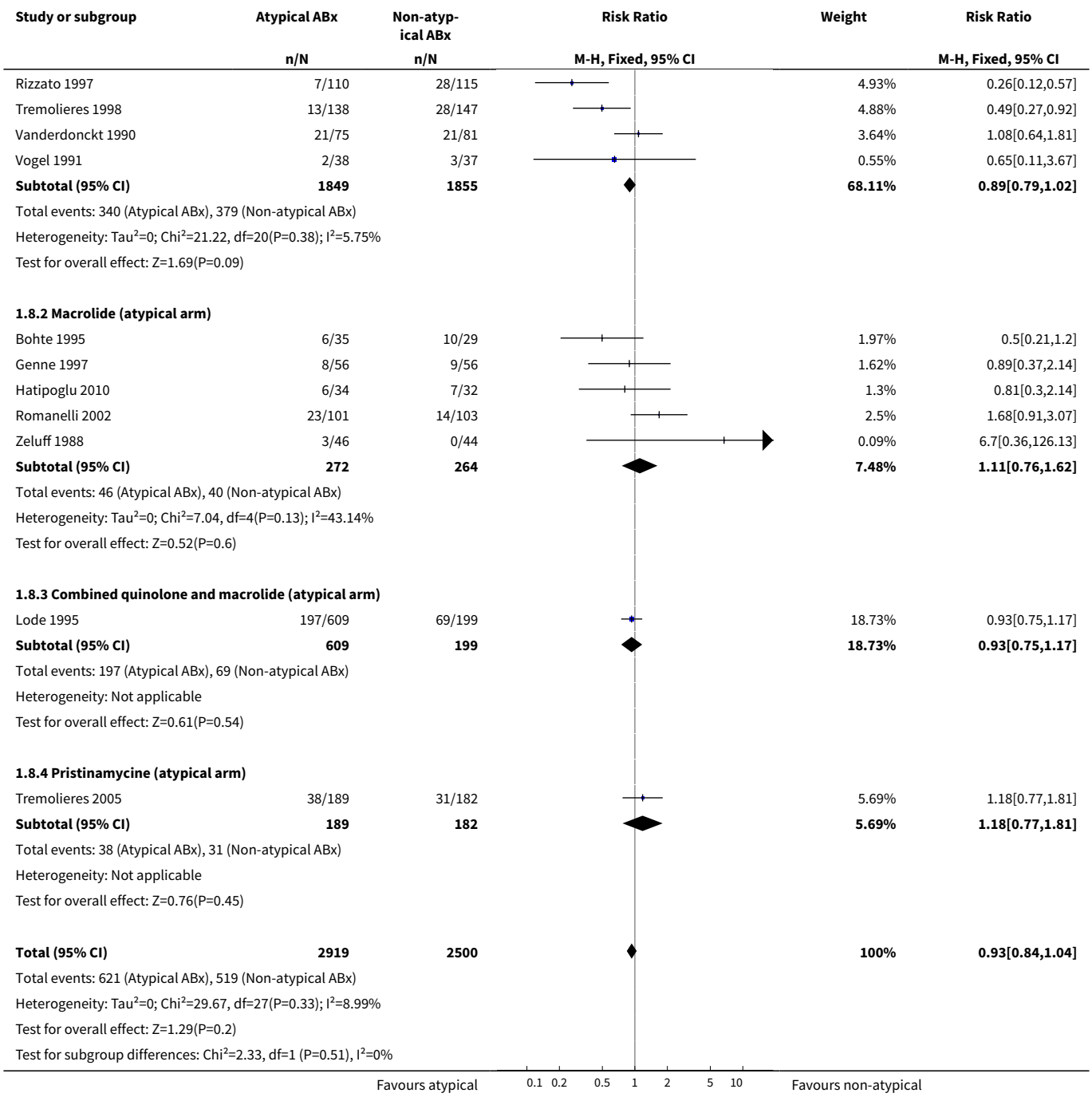
Favours atypical — Favours non-atypical

Analysis 1.8. Comparison 1 Atypical versus non-aytpical, Outcome 8 Clinical failure per antibiotic (ABx) treatment.

Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Quinolone (atypical arm)					
Aubier 1998	14/126	22/140		3.75%	0.71[0.38,1.32]
Carbon 1992	19/123	24/120		4.37%	0.77[0.45,1.33]
Chuard 1989	5/59	6/62		1.05%	0.88[0.28,2.72]
Feldman 2001	3/35	3/34		0.55%	0.97[0.21,4.48]
Fourrier 1986	6/20	7/20		1.26%	0.86[0.35,2.1]
Gleadhill 1986	5/26	4/22		0.78%	1.06[0.32,3.46]
Hirata-Dulas 1991	12/24	12/26		2.07%	1.08[0.61,1.93]
Hong-yun 2007	23/54	24/53		4.36%	0.94[0.61,1.44]
Kalbermatter 2000	1/28	4/56		0.48%	0.5[0.06,4.27]
Khan 1989	6/66	6/56		1.17%	0.85[0.29,2.48]
Kobayashi 1984	4/41	0/33		0.1%	7.29[0.41,130.64]
Kohno 2011	12/104	10/89		1.94%	1.03[0.47,2.26]
Lephonte 2004	38/167	32/153		6.01%	1.09[0.72,1.65]
Miki 1984	11/71	7/68		1.29%	1.51[0.62,3.66]
Norrby 1998	85/314	85/305		15.53%	0.97[0.75,1.25]
Peterson 1988	7/30	9/30		1.62%	0.78[0.33,1.82]
Petitpretz 2001	46/200	44/208		7.77%	1.09[0.75,1.57]

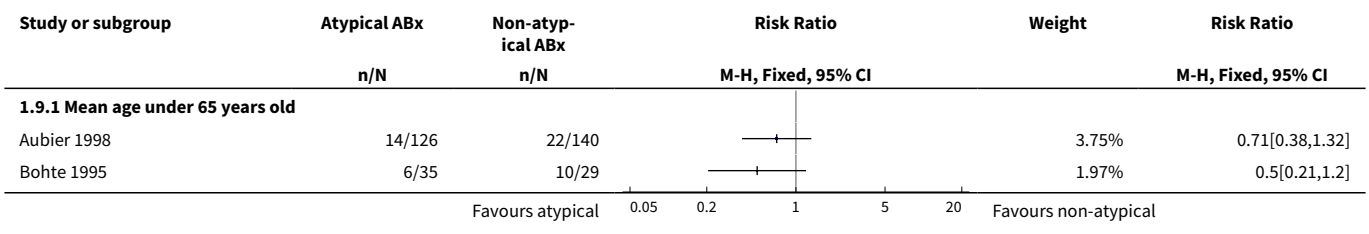


Favours atypical — Favours non-atypical

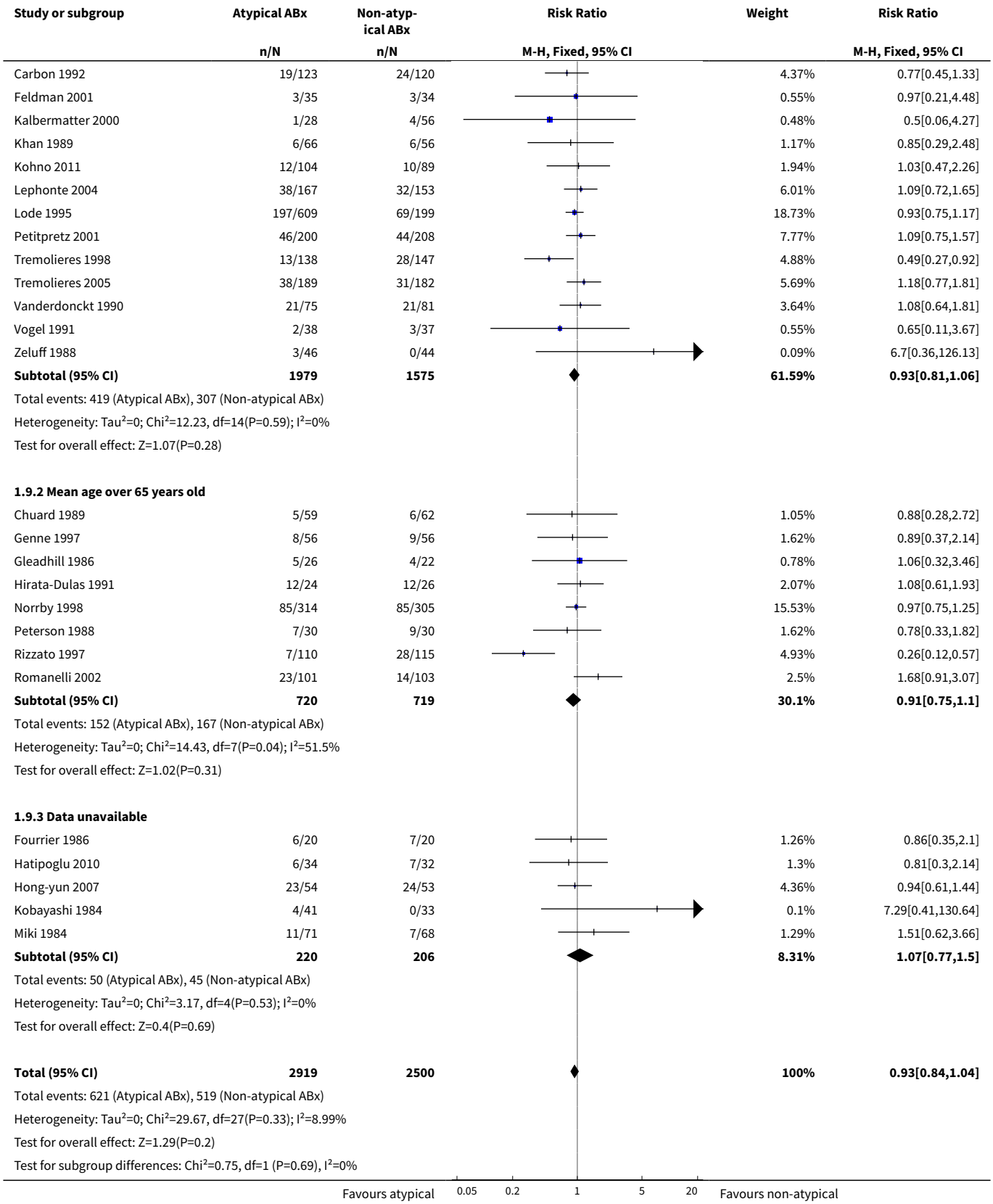


Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rizzato 1997	7/110	28/115		4.93%	0.26[0.12,0.57]
Tremolieres 1998	13/138	28/147		4.88%	0.49[0.27,0.92]
Vanderdonckt 1990	21/75	21/81		3.64%	1.08[0.64,1.81]
Vogel 1991	2/38	3/37		0.55%	0.65[0.11,3.67]
Subtotal (95% CI)	**1849**	**1855**		**68.11%**	**0.89[0.79,1.02]**
Total events: 340 (Atypical ABx), 379 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=21.22, df=20(P=0.38); I^2=5.75%					
Test for overall effect: Z=1.69(P=0.09)					
1.8.2 Macrolide (atypical arm)					
Bohte 1995	6/35	10/29		1.97%	0.5[0.21,1.2]
Genne 1997	8/56	9/56		1.62%	0.89[0.37,2.14]
Hatipoglu 2010	6/34	7/32		1.3%	0.81[0.3,2.14]
Romanelli 2002	23/101	14/103		2.5%	1.68[0.91,3.07]
Zeluff 1988	3/46	0/44		0.09%	6.7[0.36,126.13]
Subtotal (95% CI)	**272**	**264**		**7.48%**	**1.11[0.76,1.62]**
Total events: 46 (Atypical ABx), 40 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=7.04, df=4(P=0.13); I^2=43.14%					
Test for overall effect: Z=0.52(P=0.6)					
1.8.3 Combined quinolone and macrolide (atypical arm)					
Lode 1995	197/609	69/199		18.73%	0.93[0.75,1.17]
Subtotal (95% CI)	**609**	**199**		**18.73%**	**0.93[0.75,1.17]**
Total events: 197 (Atypical ABx), 69 (Non-atypical ABx)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
1.8.4 Pristinamycine (atypical arm)					
Tremolieres 2005	38/189	31/182		5.69%	1.18[0.77,1.81]
Subtotal (95% CI)	**189**	**182**		**5.69%**	**1.18[0.77,1.81]**
Total events: 38 (Atypical ABx), 31 (Non-atypical ABx)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					
Total (95% CI)	**2919**	**2500**		**100%**	**0.93[0.84,1.04]**
Total events: 621 (Atypical ABx), 519 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=29.67, df=27(P=0.33); I^2=8.99%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi^2=2.33, df=1 (P=0.51), I^2=0%					

Analysis 1.9. Comparison 1 Atypical versus non-aytpical, Outcome 9 Clinical failure per age.

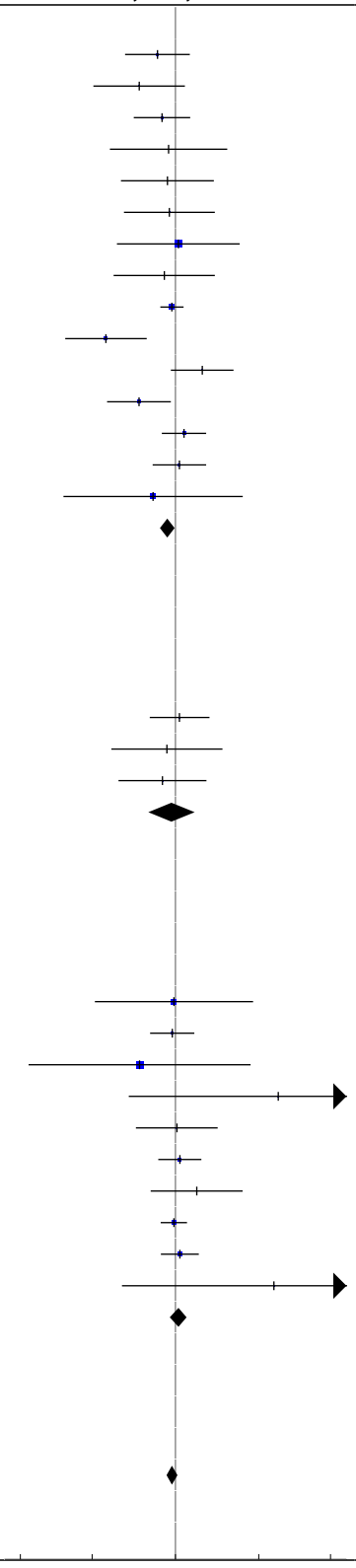


Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Mean age under 65 years old					
Aubier 1998	14/126	22/140		3.75%	0.71[0.38,1.32]
Bohte 1995	6/35	10/29		1.97%	0.5[0.21,1.2]



Analysis 1.10. Comparison 1 Atypical versus non-aytpical, Outcome 10 Clinical failure per geographical area.

Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Europe					
Aubier 1998	14/126	22/140		3.75%	0.71[0.38,1.32]
Bohte 1995	6/35	10/29		1.97%	0.5[0.21,1.2]
Carbon 1992	19/123	24/120		4.37%	0.77[0.45,1.33]
Chuard 1989	5/59	6/62		1.05%	0.88[0.28,2.72]
Fourrier 1986	6/20	7/20		1.26%	0.86[0.35,2.1]
Genne 1997	8/56	9/56		1.62%	0.89[0.37,2.14]
Gleadhill 1986	5/26	4/22		0.78%	1.06[0.32,3.46]
Hatipoglu 2010	6/34	7/32		1.3%	0.81[0.3,2.14]
Lode 1995	197/609	69/199		18.73%	0.93[0.75,1.17]
Rizzato 1997	7/110	28/115		4.93%	0.26[0.12,0.57]
Romanelli 2002	23/101	14/103		2.5%	1.68[0.91,3.07]
Tremolieres 1998	13/138	28/147		4.88%	0.49[0.27,0.92]
Tremolieres 2005	38/189	31/182		5.69%	1.18[0.77,1.81]
Vanderdonckt 1990	21/75	21/81		3.64%	1.08[0.64,1.81]
Vogel 1991	2/38	3/37		0.55%	0.65[0.11,3.67]
Subtotal (95% CI)	**1739**	**1345**		**57.02%**	**0.85[0.74,0.98]**
Total events: 370 (Atypical ABx), 283 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=22.27, df=14(P=0.07); I^2=37.13%					
Test for overall effect: Z=2.18(P=0.03)					
1.10.2 North America					
Hirata-Dulas 1991	12/24	12/26		2.07%	1.08[0.61,1.93]
Khan 1989	6/66	6/56		1.17%	0.85[0.29,2.48]
Peterson 1988	7/30	9/30		1.62%	0.78[0.33,1.82]
Subtotal (95% CI)	**120**	**112**		**4.86%**	**0.93[0.59,1.45]**
Total events: 25 (Atypical ABx), 27 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					
1.10.3 Other					
Feldman 2001	3/35	3/34		0.55%	0.97[0.21,4.48]
Hong-yun 2007	23/54	24/53		4.36%	0.94[0.61,1.44]
Kalbermatter 2000	1/28	4/56		0.48%	0.5[0.06,4.27]
Kobayashi 1984	4/41	0/33		0.1%	7.29[0.41,130.64]
Kohno 2011	12/104	10/89		1.94%	1.03[0.47,2.26]
Lephonte 2004	38/167	32/153		6.01%	1.09[0.72,1.65]
Miki 1984	11/71	7/68		1.29%	1.51[0.62,3.66]
Norrby 1998	85/314	85/305		15.53%	0.97[0.75,1.25]
Petitpretz 2001	46/200	44/208		7.77%	1.09[0.75,1.57]
Zeluff 1988	3/46	0/44		0.09%	6.7[0.36,126.13]
Subtotal (95% CI)	**1060**	**1043**		**38.12%**	**1.06[0.9,1.24]**
Total events: 226 (Atypical ABx), 209 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=5.07, df=9(P=0.83); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					
Total (95% CI)	**2919**	**2500**		**100%**	**0.93[0.84,1.04]**
Total events: 621 (Atypical ABx), 519 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=29.67, df=27(P=0.33); I^2=8.99%					



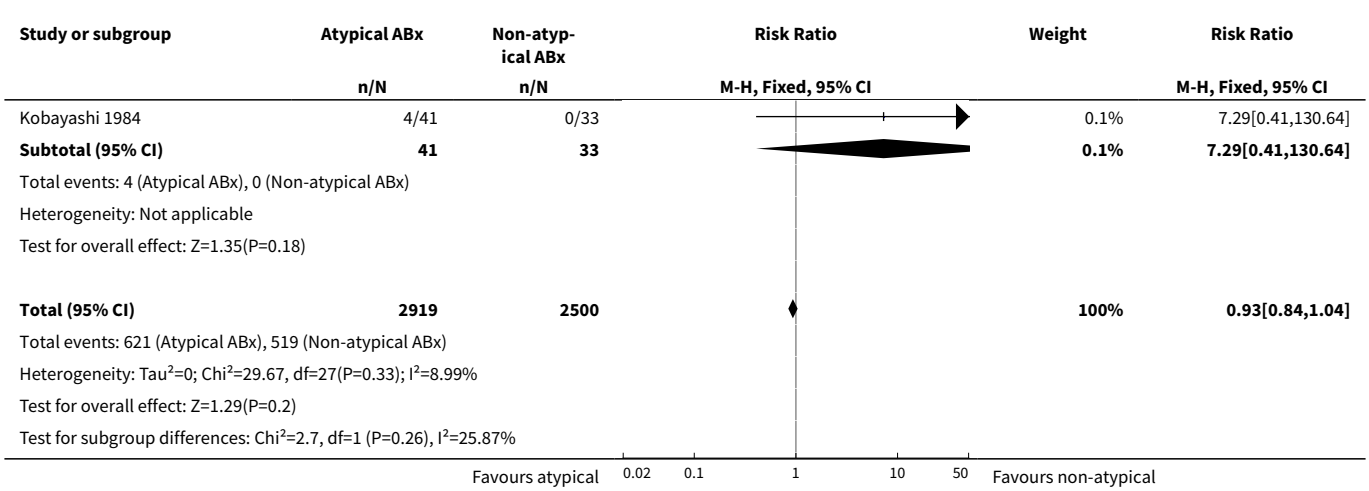
Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi^2=3.68, df=1 (P=0.16), I^2=45.63%					

Favours atypical 0.05 0.2 1 5 20 Favours non-atypical

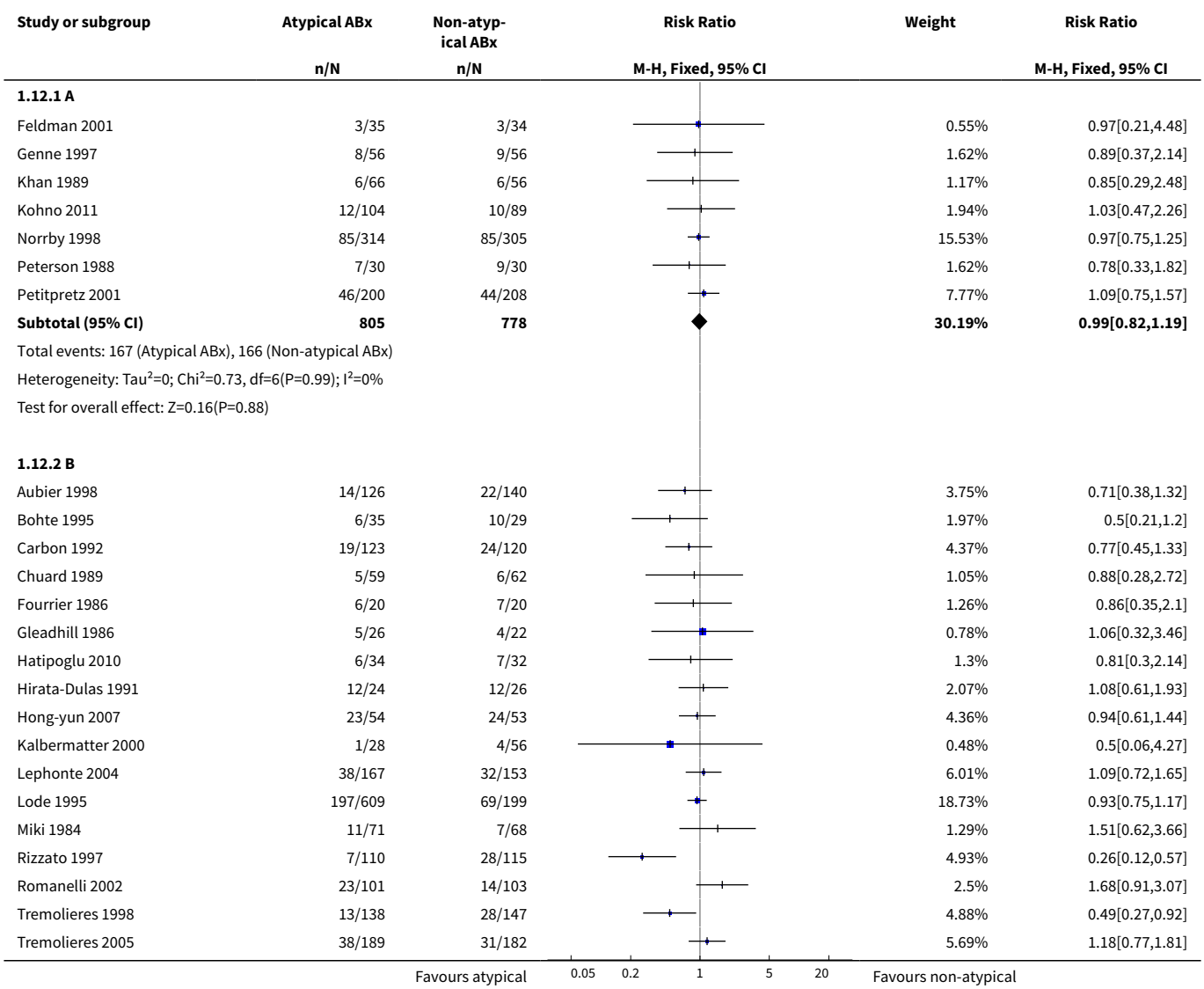
Analysis 1.11. Comparison 1 Atypical versus non-aytpical, Outcome 11 Clinical failure per allocation generation.

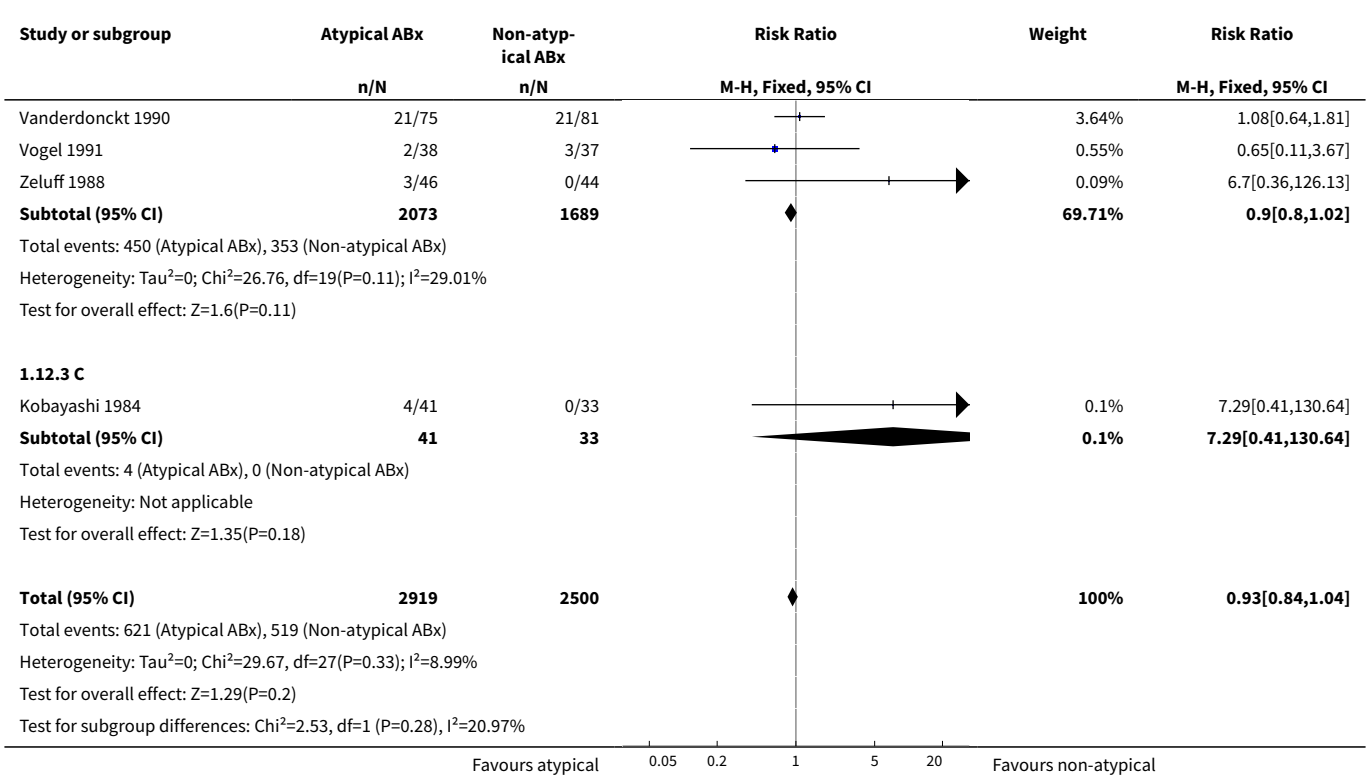
Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
1.11.1 A					
Chuard 1989	5/59	6/62		1.05%	0.88[0.28,2.72]
Feldman 2001	3/35	3/34		0.55%	0.97[0.21,4.48]
Genne 1997	8/56	9/56		1.62%	0.89[0.37,2.14]
Kalbermatter 2000	1/28	4/56		0.48%	0.5[0.06,4.27]
Khan 1989	6/66	6/56		1.17%	0.85[0.29,2.48]
Kohno 2011	12/104	10/89		1.94%	1.03[0.47,2.26]
Norrby 1998	85/314	85/305		15.53%	0.97[0.75,1.25]
Peterson 1988	7/30	9/30		1.62%	0.78[0.33,1.82]
Petitpretz 2001	46/200	44/208		7.77%	1.09[0.75,1.57]
Zeluff 1988	3/46	0/44		0.09%	6.7[0.36,126.13]
Subtotal (95% CI)	**938**	**940**		**31.82%**	**0.99[0.82,1.19]**
Total events: 176 (Atypical ABx), 176 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=2.8, df=9(P=0.97); I^2=0%					
Test for overall effect: Z=0.1(P=0.92)					
1.11.2 B					
Aubier 1998	14/126	22/140		3.75%	0.71[0.38,1.32]
Bohte 1995	6/35	10/29		1.97%	0.5[0.21,1.2]
Carbon 1992	19/123	24/120		4.37%	0.77[0.45,1.33]
Fourrier 1986	6/20	7/20		1.26%	0.86[0.35,2.1]
Gleadhill 1986	5/26	4/22		0.78%	1.06[0.32,3.46]
Hatipoglu 2010	6/34	7/32		1.3%	0.81[0.3,2.14]
Hirata-Dulas 1991	12/24	12/26		2.07%	1.08[0.61,1.93]
Hong-yun 2007	23/54	24/53		4.36%	0.94[0.61,1.44]
Lephonte 2004	38/167	32/153		6.01%	1.09[0.72,1.65]
Lode 1995	197/609	69/199		18.73%	0.93[0.75,1.17]
Miki 1984	11/71	7/68		1.29%	1.51[0.62,3.66]
Rizzato 1997	7/110	28/115		4.93%	0.26[0.12,0.57]
Romanelli 2002	23/101	14/103		2.5%	1.68[0.91,3.07]
Tremolieres 1998	13/138	28/147		4.88%	0.49[0.27,0.92]
Tremolieres 2005	38/189	31/182		5.69%	1.18[0.77,1.81]
Vanderdonckt 1990	21/75	21/81		3.64%	1.08[0.64,1.81]
Vogel 1991	2/38	3/37		0.55%	0.65[0.11,3.67]
Subtotal (95% CI)	**1940**	**1527**		**68.08%**	**0.9[0.79,1.02]**
Total events: 441 (Atypical ABx), 343 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=24.73, df=16(P=0.07); I^2=35.31%					
Test for overall effect: Z=1.66(P=0.1)					
1.11.3 C					

Favours atypical 0.02 0.1 1 10 50 Favours non-atypical

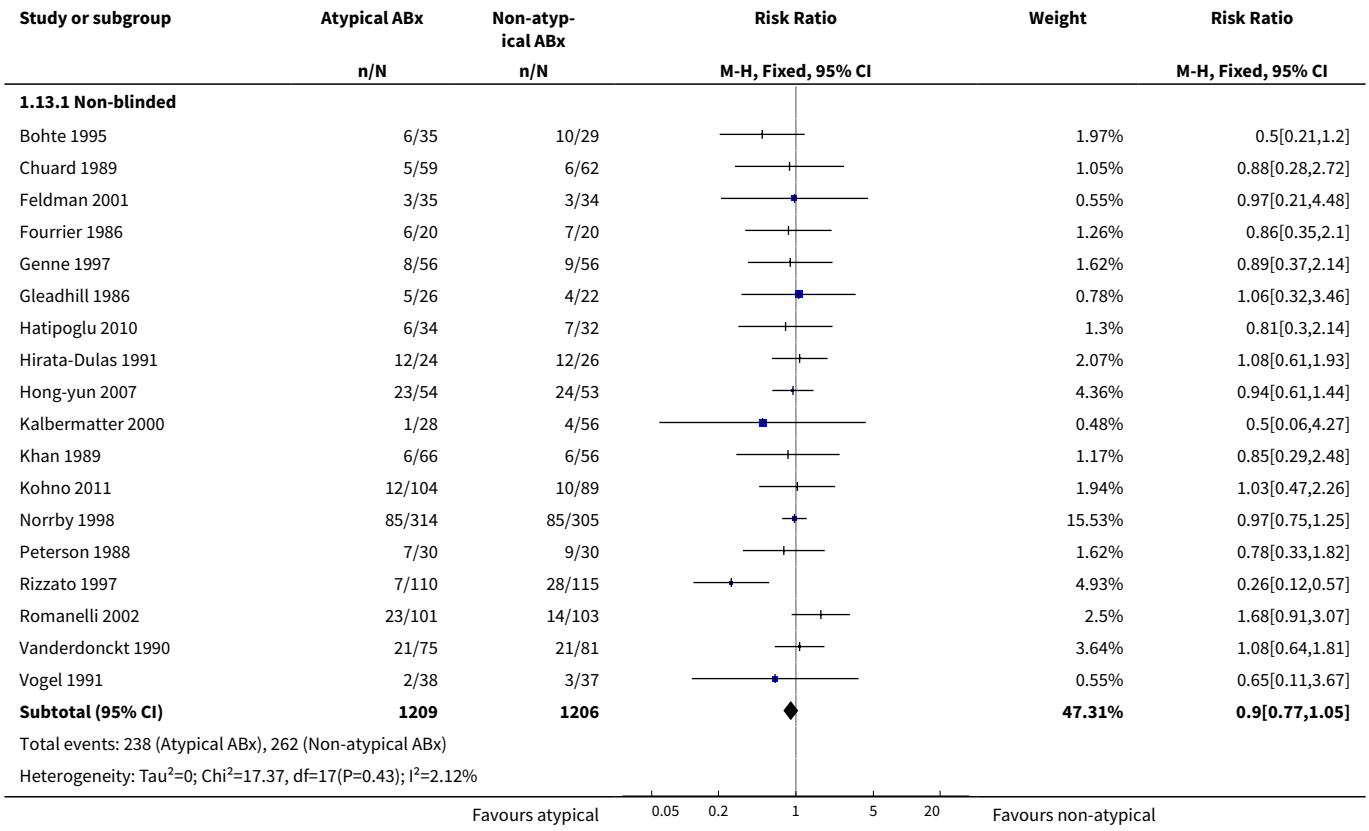


Analysis 1.12. Comparison 1 Atypical versus non-aytpical, Outcome 12 Clinical failure per allocation concealment.





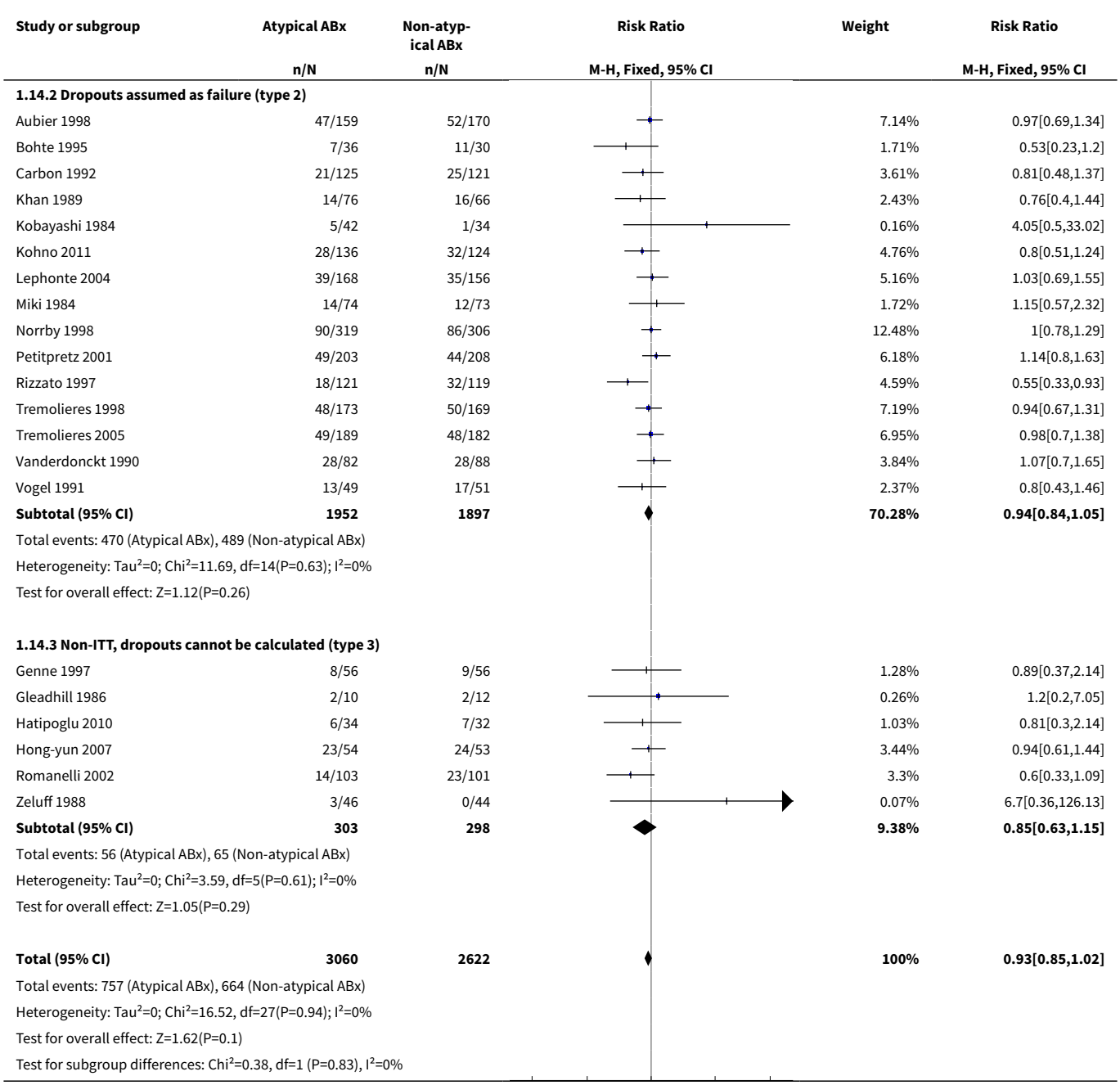
Analysis 1.13. Comparison 1 Atypical versus non-aytpical, Outcome 13 Clinical failure per blinding.



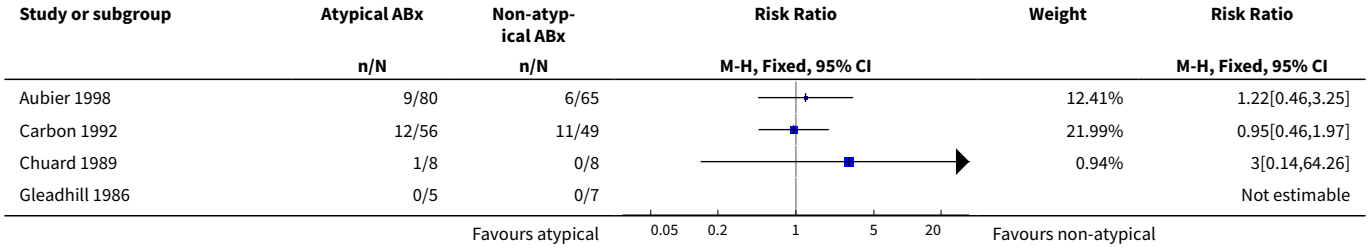
Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.38(P=0.17)					
1.13.2 Single-blind					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Atypical ABx), 0 (Non-atypical ABx)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.13.3 Double or triple-blind					
Aubier 1998	14/126	22/140		3.75%	0.71[0.38,1.32]
Carbon 1992	19/123	24/120		4.37%	0.77[0.45,1.33]
Kobayashi 1984	4/41	0/33		0.1%	7.29[0.41,130.64]
Lephonte 2004	38/167	32/153		6.01%	1.09[0.72,1.65]
Lode 1995	197/609	69/199		18.73%	0.93[0.75,1.17]
Miki 1984	11/71	7/68		1.29%	1.51[0.62,3.66]
Petitpretz 2001	46/200	44/208		7.77%	1.09[0.75,1.57]
Tremolieres 1998	13/138	28/147		4.88%	0.49[0.27,0.92]
Tremolieres 2005	38/189	31/182		5.69%	1.18[0.77,1.81]
Zeluff 1988	3/46	0/44		0.09%	6.7[0.36,126.13]
Subtotal (95% CI)	**1710**	**1294**		**52.69%**	**0.97[0.84,1.11]**
Total events: 383 (Atypical ABx), 257 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=12.31, df=9(P=0.2); I^2=26.91%					
Test for overall effect: Z=0.47(P=0.64)					
Total (95% CI)	**2919**	**2500**		**100%**	**0.93[0.84,1.04]**
Total events: 621 (Atypical ABx), 519 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=29.67, df=27(P=0.33); I^2=8.99%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi^2=0.47, df=1 (P=0.49), I^2=0%					

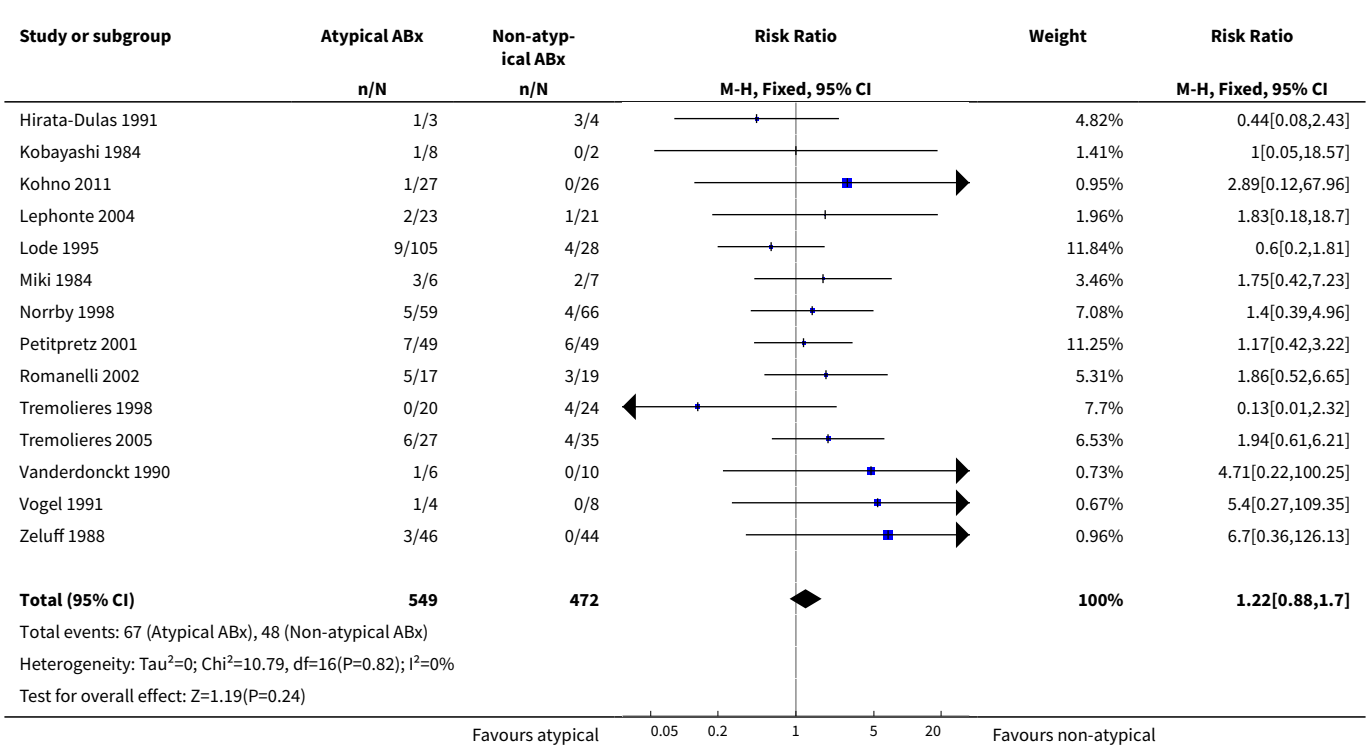
Analysis 1.14. Comparison 1 Atypical versus non-aytpical, Outcome 14 Clinical failure - ITT analysis.

Study or subgroup	Atypical ABx n/N	Non-atypical ABx n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 ITT studies (type 1)					
Chuard 1989	5/59	6/62		0.83%	0.88[0.28,2.72]
Feldman 2001	3/35	3/34		0.43%	0.97[0.21,4.48]
Fourrier 1986	6/20	7/20		0.99%	0.86[0.35,2.1]
Hirata-Dulas 1991	12/24	12/26		1.64%	1.08[0.61,1.93]
Kalbermatter 2000	1/28	4/56		0.38%	0.5[0.06,4.27]
Lode 1995	197/609	69/199		14.78%	0.93[0.75,1.17]
Peterson 1988	7/30	9/30		1.28%	0.78[0.33,1.82]
Subtotal (95% CI)	**805**	**427**		**20.34%**	**0.92[0.76,1.12]**
Total events: 231 (Atypical ABx), 110 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=0.82, df=6(P=0.99); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					

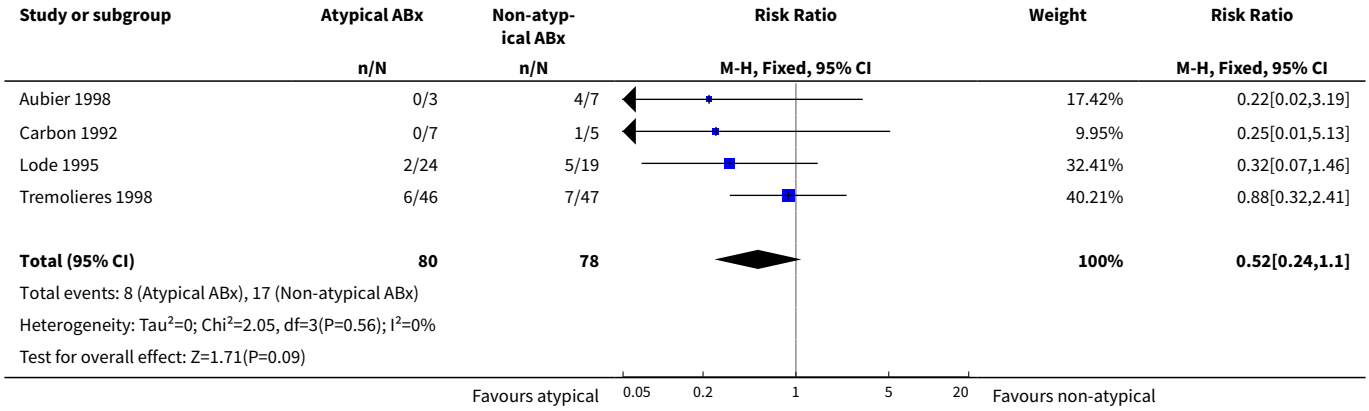


Analysis 1.15. Comparison 1 Atypical versus non-aytpical, Outcome 15 Clinical failure - pneumococcal pneumonia.

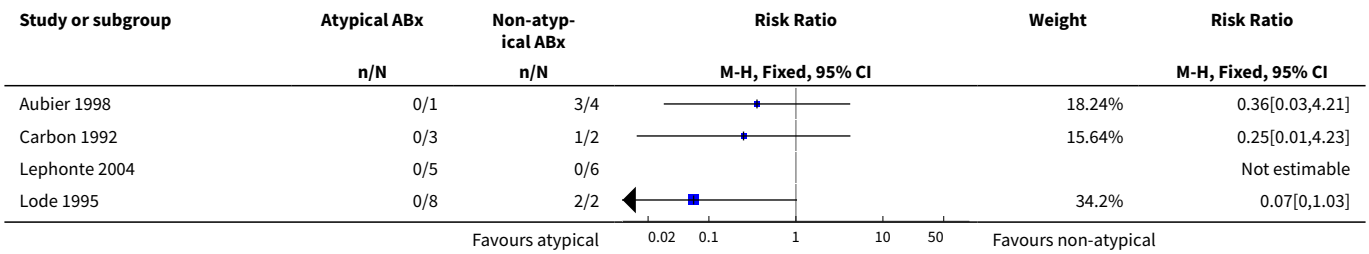


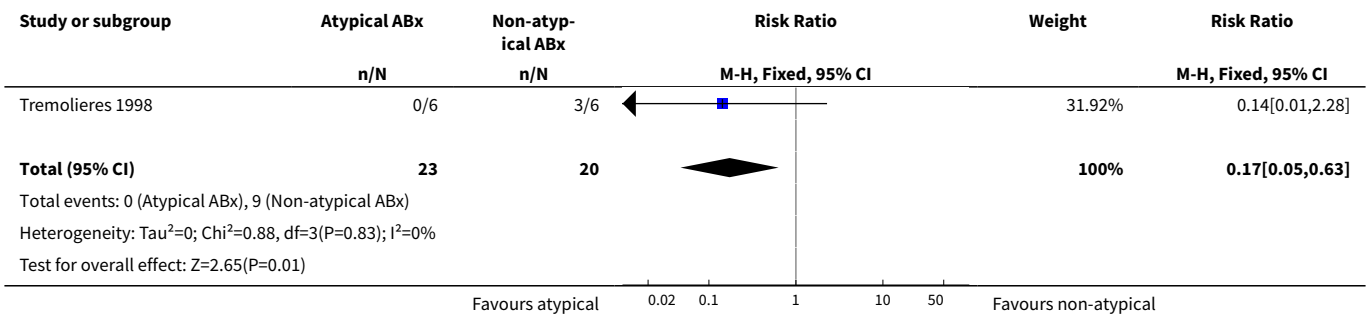


Analysis 1.16. Comparison 1 Atypical versus non-aytpical, Outcome 16 Clinical failure - atypical pathogens.

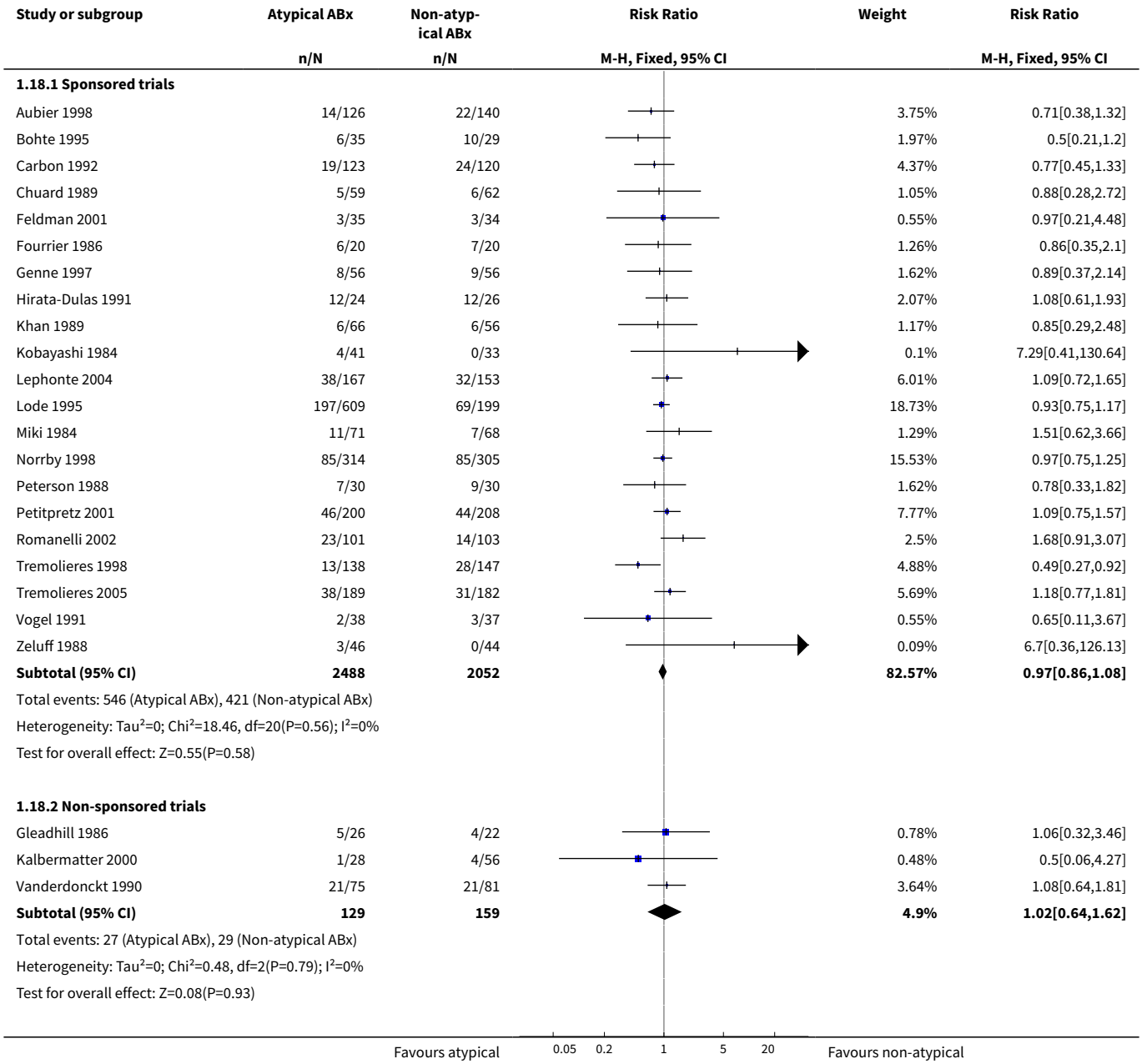


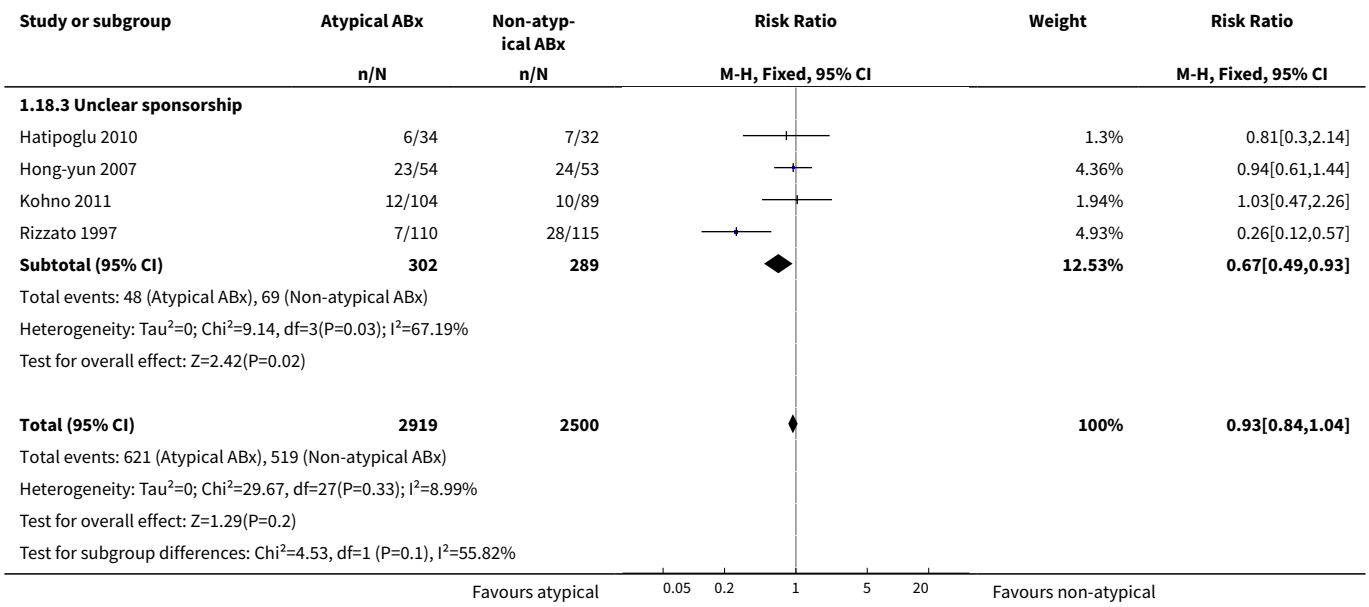
Analysis 1.17. Comparison 1 Atypical versus non-aytpical, Outcome 17 Clinical failure - Legionella pneumophilae.



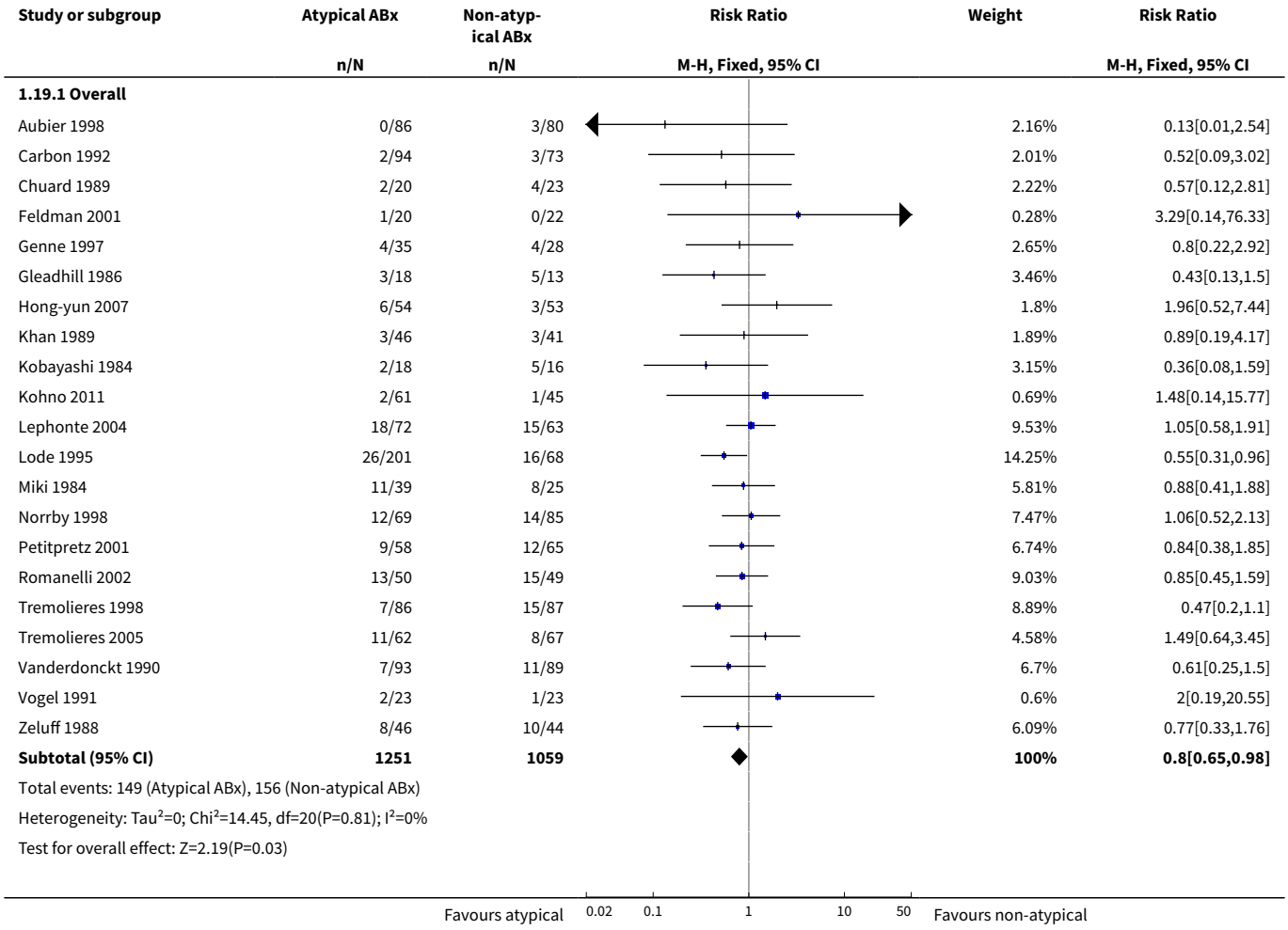


Analysis 1.18. Comparison 1 Atypical versus non-aytpical, Outcome 18 Clinical failure per sponsorship.





Analysis 1.19. Comparison 1 Atypical versus non-aytpical, Outcome 19 Bacteriological failure.



Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Total (95% CI)	**1251**	**1059**		**100%**	**0.8[0.65,0.98]**
Total events: 149 (Atypical ABx), 156 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=14.45, df=20(P=0.81); I^2=0%					
Test for overall effect: Z=2.19(P=0.03)					

Analysis 1.20. Comparison 1 Atypical versus non-aytpical, Outcome 20 Bacteriological failure per allocation generation.

Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
1.20.1 A					
Chuard 1989	2/20	4/23		2.22%	0.57[0.12,2.81]
Feldman 2001	1/20	0/22		0.28%	3.29[0.14,76.33]
Genne 1997	4/35	4/28		2.65%	0.8[0.22,2.92]
Khan 1989	3/46	3/41		1.89%	0.89[0.19,4.17]
Kohno 2011	2/61	1/45		0.69%	1.48[0.14,15.77]
Norrby 1998	12/69	14/85		7.47%	1.06[0.52,2.13]
Petitpretz 2001	9/58	12/65		6.74%	0.84[0.38,1.85]
Zeluff 1988	8/46	10/44		6.09%	0.77[0.33,1.76]
Subtotal (95% CI)	**355**	**353**		**28.03%**	**0.9[0.61,1.32]**
Total events: 41 (Atypical ABx), 48 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=1.53, df=7(P=0.98); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
1.20.2 B					
Aubier 1998	0/86	3/80		2.16%	0.13[0.01,2.54]
Carbon 1992	2/94	3/73		2.01%	0.52[0.09,3.02]
Gleadhill 1986	3/18	5/13		3.46%	0.43[0.13,1.5]
Hong-yun 2007	6/54	3/53		1.8%	1.96[0.52,7.44]
Kobayashi 1984	2/18	5/16		3.15%	0.36[0.08,1.59]
Lephonte 2004	18/72	15/63		9.53%	1.05[0.58,1.91]
Lode 1995	26/201	16/68		14.25%	0.55[0.31,0.96]
Miki 1984	11/39	8/25		5.81%	0.88[0.41,1.88]
Romanelli 2002	13/50	15/49		9.03%	0.85[0.45,1.59]
Tremolieres 1998	7/86	15/87		8.89%	0.47[0.2,1.1]
Tremolieres 2005	11/62	8/67		4.58%	1.49[0.64,3.45]
Vanderdonckt 1990	7/93	11/89		6.7%	0.61[0.25,1.5]
Vogel 1991	2/23	1/23		0.6%	2[0.19,20.55]
Subtotal (95% CI)	**896**	**706**		**71.97%**	**0.76[0.59,0.96]**
Total events: 108 (Atypical ABx), 108 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=12.49, df=12(P=0.41); I^2=3.88%					
Test for overall effect: Z=2.28(P=0.02)					
Total (95% CI)	**1251**	**1059**		**100%**	**0.8[0.65,0.98]**
Total events: 149 (Atypical ABx), 156 (Non-atypical ABx)					
Heterogeneity: Tau^2=0; Chi^2=14.45, df=20(P=0.81); I^2=0%					
Test for overall effect: Z=2.19(P=0.03)					

Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=0.58, df=1 (P=0.45), I²=0%					

Favours atypical 0.05 0.2 1 5 20 Favours non-atypical

Analysis 1.21. Comparison 1 Atypical versus non-aytpical, Outcome 21 Adverse events - total.

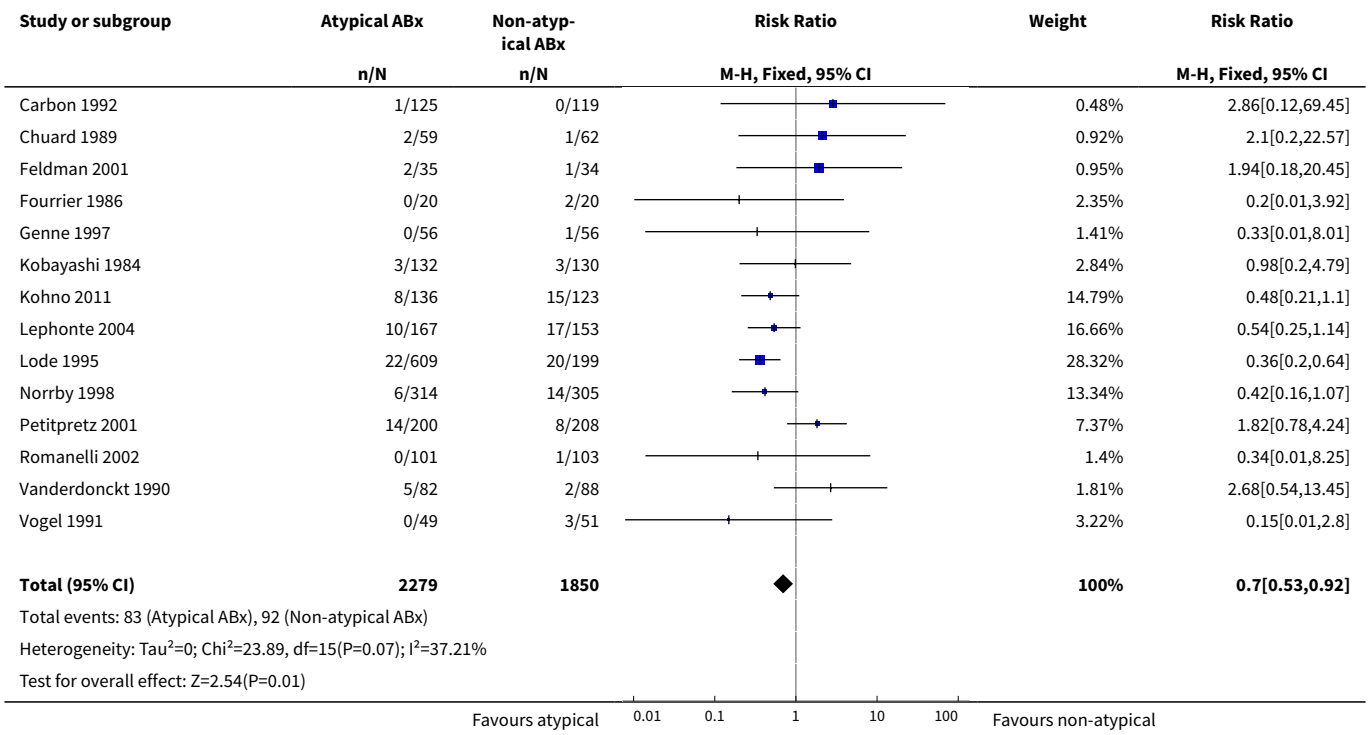
Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Aubier 1998	20/159	27/170		4.8%	0.79[0.46,1.35]
Bohte 1995	7/35	0/29		0.1%	12.5[0.74,210.01]
Carbon 1992	30/125	19/119		3.58%	1.5[0.9,2.52]
Chuard 1989	4/59	3/62		0.54%	1.4[0.33,6]
Feldman 2001	15/35	14/34		2.61%	1.04[0.6,1.81]
Fourrier 1986	0/20	3/20		0.64%	0.14[0.01,2.6]
Genne 1997	19/56	12/56		2.21%	1.58[0.85,2.94]
Gleadhill 1986	2/26	3/22		0.6%	0.56[0.1,3.08]
Kalbermatter 2000	0/28	0/56			Not estimable
Khan 1989	6/66	3/56		0.6%	1.7[0.44,6.48]
Kobayashi 1984	8/132	10/130		1.85%	0.79[0.32,1.93]
Kohno 2011	73/136	70/123		13.51%	0.94[0.76,1.17]
Lephonte 2004	31/167	42/153		8.06%	0.68[0.45,1.02]
Miki 1984	4/73	3/72		0.56%	1.32[0.31,5.67]
Norrby 1998	169/314	165/305		30.77%	0.99[0.86,1.15]
Peterson 1988	4/30	6/30		1.1%	0.67[0.21,2.13]
Petitpretz 2001	56/200	42/208		7.57%	1.39[0.98,1.97]
Rizzato 1997	8/121	7/119		1.3%	1.12[0.42,3]
Romanelli 2002	7/101	6/103		1.09%	1.19[0.41,3.42]
Tremolieres 1998	29/173	18/169		3.35%	1.57[0.91,2.72]
Tremolieres 2005	41/200	31/198		5.73%	1.31[0.86,2]
Vanderdonckt 1990	13/82	18/88		3.19%	0.78[0.41,1.48]
Vogel 1991	9/49	14/51		2.52%	0.67[0.32,1.4]
Zeluff 1988	9/80	20/78		3.72%	0.44[0.21,0.9]
Total (95% CI)	**2467**	**2451**		**100%**	**1.02[0.93,1.13]**
Total events: 564 (Atypical ABx), 536 (Non-atypical ABx)					
Heterogeneity: Tau²=0; Chi²=30.43, df=22(P=0.11); I²=27.69%					
Test for overall effect: Z=0.48(P=0.63)					

Favours atypical 0.05 0.2 1 5 20 Favours non-atypical

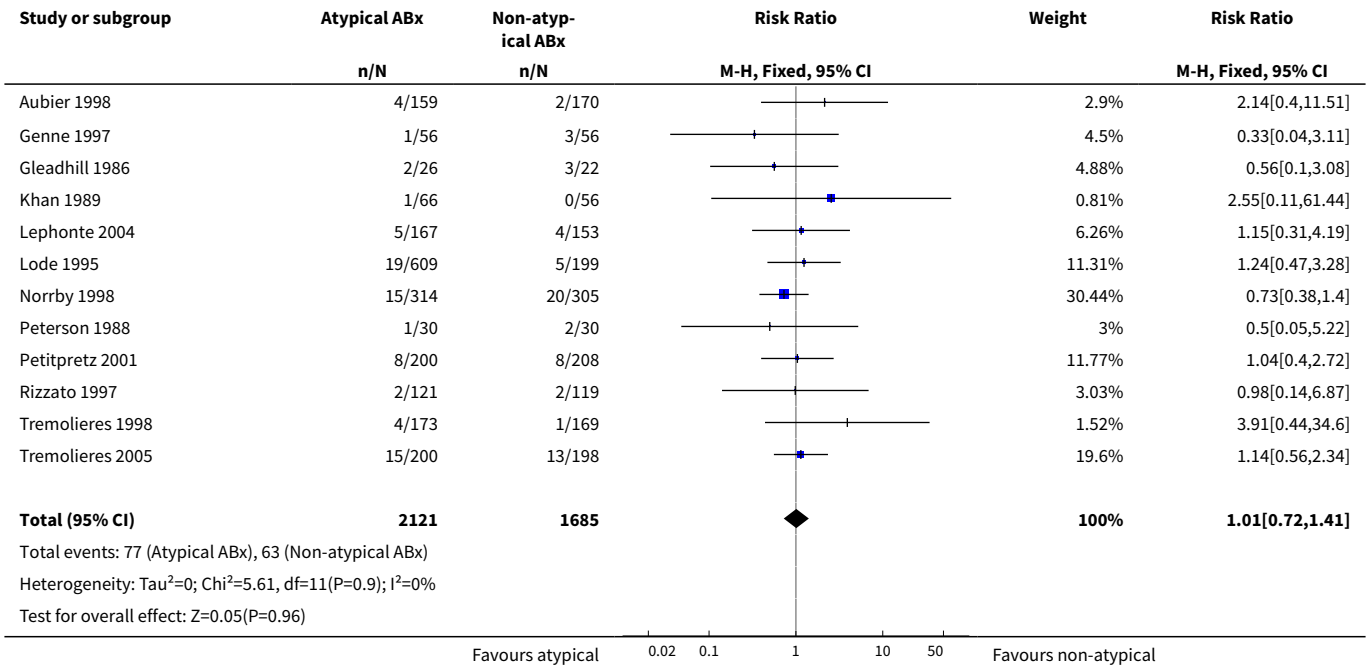
Analysis 1.22. Comparison 1 Atypical versus non-aytpical, Outcome 22 Adverse events - gastrointestinal events.

Study or subgroup	Atypical ABx	Non-atypical ABx	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Aubier 1998	6/159	4/170		3.63%	1.6[0.46,5.58]
Bohte 1995	4/35	0/29		0.51%	7.5[0.42,133.78]

Favours atypical 0.01 0.1 1 10 100 Favours non-atypical



Analysis 1.23. Comparison 1 Atypical versus non-aytpical, Outcome 23 Adverse events - requiring discontinuation of treatment.



APPENDICES

Appendix 1. CENTRAL and MEDLINE search strategy

MEDLINE (PUBMED)
1 exp Pneumonia/
2 (pneumon* or cap).tw.
3 1 or 2
4 exp Anti-Bacterial Agents/
5 antibiotic*.tw.
6 exp Quinolones/
7 exp Macrolides/
8 exp Tetracyclines/
9 exp Chloramphenicol/
10 exp Streptogramins/
11 Ketolides/
12 (quinolon* or fluoroquinolon* or macrolid* or doxycyclin* or tetracyclin* or chloramphenicol* or streptogramin* or ketolid* or erythromycin* or roxithromycin* or azithromycin* or clarithromycin* or ciprofloxacin* or ofloxacin* or levofloxacin* or trovafloxacin* or moxifloxacin* or grepafloxacin* or tigecyclin* or minocyclin* or pristinamycin* or quinupristin* or telithromycin*).tw,nm.
13 or/4-12
14 3 and 13

Appendix 2. EMBASE search strategy

#13. #9 AND #12 3,993 1 Jun 2011
#12. #10 OR #11 866,353 1 Jun 2011
#11. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti AND [embase]/lim 826,523 1 Jun 2011
#10. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 242,926 1 Jun 2011
#9. #3 AND #8 54,097 1 Jun 2011
#8. #4 OR #5 OR #6 OR #7 788,217 1 Jun 2011
#7. quinolon*:ab,ti OR fluoroquinolon*:ab,ti OR macrolid*:ab,ti OR doxycyclin*:ab,ti OR tetracyclin*:ab,ti OR chloramphenicol*:ab,ti OR streptogramin*:ab,ti OR ketolid*:ab,ti OR erythromycin*:ab,ti OR roxithromycin*:ab,ti OR azithromycin*:ab,ti OR clarithromycin*:ab,ti OR ciprofloxacin*:ab,ti OR ofloxacin*:ab,ti OR levofloxacin*:ab,ti OR trovafloxacin*:ab,ti OR moxifloxacin*:ab,ti OR grepafloxacin*:ab,ti OR tigecyclin*:ab,ti OR minocyclin*:ab,ti OR pristinamycin*:ab,ti OR quinupristin*:ab,ti OR telithromycin*:ab,ti AND [embase]/lim 95,680 1 Jun 2011
#6. 'quinolone derivative'/exp OR 'macrolide'/exp OR 'tetracycline derivative'/exp OR 'chloramphenicol'/exp OR 'streptogramin derivative'/exp OR 'ketolide'/exp AND [embase]/lim 230,698 1 Jun 2011
#5. antibiotic*:ab,ti AND [embase]/lim 176,808 1 Jun 2011
#4. 'antibiotic agent'/exp AND [embase]/lim 706,809 1 Jun 2011
#3. #1 OR #2 169,385 1 Jun 2011
#2. pneumon*:ab,ti OR cap:ab,ti AND [embase]/lim 122,834 1 Jun 2011
#1. 'pneumonia'/de OR 'infectious pneumonia'/exp AND [embase]/lim 92,744 1 Jun 2011

Appendix 3. Previous search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 2) which includes the Acute Respiratory Infection Group's specialized register, MEDLINE (January 1966 to June 2007), and EMBASE (January 1980 to June 2007).

We ran the following search strategy over MEDLINE and CENTRAL and adapted it for EMBASE.

MEDLINE (PUBMED)
1 exp Anti-Bacterial Agents/
2 exp Quinolones/
3 exp Fluoroquinolones/
4 exp Macrolides/
5 exp Doxycycline/
6 exp Tetracycline/
7 exp Chloramphenicol/
8 exp Streptogramins/
9 exp Ketolides/
10 (Quinolon$ or Fluoroquinolon$ or Macrolide$ or Doxycycline$ or Tetracycline$ or Chloramphenicol$).ti,ab.
11 empirical antibiotic$.ti,ab.

12 empiric antibiotic$.ti,ab.
13 or/1-12
14 exp Community-Acquired Infections/
15 exp Pneumonia/
16 and/14-15
17 (community acquired pneumonia or CAP).mp.
18 16 or 17
19 exp Inpatients/
20 inpatient$.ti,ab.
21 exp Hospitalization/
22 ((hospitaliz$ or hospitalis$) adj patient$).mp.
23 or/17-20
24 13 and 18 and 23

We inspected the references of all identified studies for more trials. In addition to this, we contacted the first or corresponding author of each included trial and researchers active in the field for information regarding unpublished trials or complementary information on their own trial. We imposed no language or publication restrictions.

WHAT'S NEW

Date	Event	Description
16 April 2012	New search has been performed	Searches updated. Three new trials were included (Hatipoglu 2010; Hong-yun 2007; Kohno 2011) and three new trials were excluded (Chokshi 2007; Ott 2008; Sujata 2008). After integrating the data from the new included studies, no significant changes were noted in any of the comparisons evaluated. Our conclusions and recommendations for further research remain unchanged
14 September 2011	New citation required but conclusions have not changed	A new author joined the team to lead the update of this review

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 2, 2005

Date	Event	Description
22 June 2008	Amended	Converted to new review format.
12 November 2007	New search has been performed	In the 2007 update, one new study was included and six new studies were excluded. After integrating the data from the new included study, no significant changes were noted in all comparisons evaluated. Our conclusions and recommendations for further research remain unchanged.
20 January 2005	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Noa Eliakim Raz (NER) co-ordinated this updated review, guided by Leonard Leibovic (LL).
NER and Eyal Robenshtok (ER) were responsible for data collection, writing to trial authors for additional information and organizing retrieval of papers.

NER and ER were responsible for undertaking searches.
NER, ER, Daphna Shefet (DS), Anat Gafter-Gvili (AG) and Mical Paul (MP) were responsible for screening search results, abstracting data from papers, screening retrieved papers against inclusion criteria and appraising quality of papers (the latter review author was in-charge in case of disagreement).
NER was responsible for entering data into Review Manager 5 (RevMan).
All review authors participated in analysis and interpretation of data.
NER and ER were responsible for writing the review.

DECLARATIONS OF INTEREST

None known.

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- The Rothschild-Caesarea Foundation “Optimal antibiotic treatment of moderate to severe infections: Integration of PCR technology and medical informatics/artificial intelligence”, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; *Hospitalization; Anti-Bacterial Agents [*therapeutic use]; Community-Acquired Infections [drug therapy] [microbiology] [mortality]; Drug Therapy, Combination; Pneumonia [*drug therapy] [microbiology] [mortality]; Randomized Controlled Trials as Topic; Treatment Failure

MeSH check words

Adult; Humans