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# Antibacterial class not obviously important in outpatient pneumonia: a meta-analysis

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**Short title:**
Antibacterial class in outpatient pneumonia

## ABSTRACT

**Purpose:** To systematically compare outcomes between antibiotic classes in treating outpatient community-acquired pneumonia, regarding antibacterials active against atypical organisms, or various antibacterial classes with similar atypical coverage.

**Methods:** Meta-analysis of randomized control trials of antibacterials for community-acquired pneumonia in outpatients at least 18 years old. Studies were independently reviewed two reviewers. We compared clinical success and mortality between different oral antibiotic classes and specifically compared antibacterials with atypical coverage (macrolides and fluoroquinolones) with others.

**Results:** Thirteen eligible studies involving 4,314 total patients were included. The quality of the studies was variable. Five studied macrolides and fluoroquinolones, three studied macrolides and beta-lactams, three studied fluoroquinolones and beta-lactams, and two studied cephalosporins versus beta lactams/ beta-lactamase inhibitors. There was no significant difference detected regarding clinical success or mortality regardless of atypical coverage, or between antibacterial classes with similar atypical coverage.

**Conclusions:** We could not demonstrate any advantage of specific antibacterials for mild community-acquired pneumonia in relatively healthy outpatients. The need for coverage of atypical pathogens in this setting is not apparent. In mild to moderate cases of outpatient-treated, community-acquired pneumonia, selecting antibacterials might be most appropriate according to side effects, patient preferences, availability, and cost.

**Key words:** Community-acquired pneumonia, Treatment, Antibiotic, Outpatient.

## INTRODUCTION

Community-acquired pneumonia (CAP) is common and associated with major morbidity, mortality and financial burden. The incidence of CAP is 1 to 5 per 1000, with mortality of 3%, and cost in the United States of 8.4 billion dollars annually.[1] It is the sixth leading cause of death, and the leading infectious cause of death.[2] It is likely that a minority of patients bear a majority of the morbidity, mortality and generate most of the treatment costs. More than 75% of patients are treated exclusively as outpatients, and typically those patients are younger than 65 years, have no significant co-morbidities, and have a mortality rate of less than 1%.[1] A traditional paradigm for the outpatient management of CAP presumes that the etiologic organism is usually not recognized, and uses empirical oral antibacterial treatment, to be directed toward the most likely causative pathogen. The clinician should also consider the severity of illness, patient age, clinical features, co-morbidities, concomitant medications, and the epidemiological setting. The group of most likely causative bacteria in outpatients includes *Streptococcus pneumoniae, Mycoplasma pneumoniae, Hemophilus influenzae*, and *Chlamydophila pneumoniae*.[2] *M. pneumoniae, C. pneumoniae* and *Legionella* species, sometimes grouped as "atypical organisms," are often given special consideration because of the high frequency of infection with organisms of this group, and the sensitivity to macrolides, ketolides and fluoroquinolones, with resistance to other antibacterial classes.[2]

Guidelines for the management of CAP vary in their antibacterial recommendations. The British Thoracic Society (BTS) recommends penicillin or amoxicillin, with erythromycin for atypical infections.[3] In contrast, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) recommend empiric macrolide or doxycycline therapy for most patients, or a fluoroquinolone or a beta-lactam plus a macrolide in the presence of comorbidities.[2] The Canadian Infectious Diseases Society (CIDS) and the Canadian Thoracic Society (CTS) recommend macrolide treatment for patients without modifiers such as aspiration or COPD.[4] The need for specific coverage for atypical organisms is a key difference between guidelines. Given the high reported incidence of atypical pneumonia in CAP, and the lack of in vitro activity of beta-lactams against *M pneumoniae* and *C pneumoniae,* the ability of beta-lactams to treat CAP has been questioned.[5] Two recent high-quality meta-analyses have addressed questions related to this issue. Bjerre *et al*. performed a meta-analysis of the efficacy of different antibacterials for outpatient-treated CAP (OCAP).[6] Although they found no evidence to support a particular drug class, the results are limited by a small number of studies included (three trials), with a total of 622 patients, all of whom received antibiotics with activity against atypical organisms. This meta-analysis therefore does not help address the question of whether atypical coverage is important in OCAP and provides no information

regarding antibacterials other than macrolides and one of the fluoroquinolones. In a second relevant meta-analysis, Mills *et al*. compared the efficacy of antibacterials with activity against atypical pathogens versus beta-lactams in non-severe CAP.[7] Their results are limited by the inclusion of studies containing only beta-lactams in the group without atypical coverage, and patients treated as in- and outpatients. Because the patients with inpatient-treated CAP likely differ significantly from patients with OCAP, and because the results for inpatients and outpatients were not presented separately in the Mills meta-analysis, the application to OCAP in general remains uncertain.

We wondered whether the selection of antibacterial class for OCAP in adults changes outcome and whether the use of antibacterials effective against atypical organisms improves outcomes. We therefore performed meta-analyses of prospective comparative trials of different oral antibacterials for OCAP. The primary objective was to assess whether antibacterials with coverage for atypical organisms provide improved clinical outcomes in OCAP. The secondary objectives were to assess whether there were differences in outcomes between patients treated with other pairs of antibacterial drug classes, as long as both comparators provided similar coverage for atypical organisms.

## METHODS

### Identification of sources:

We identified studies of adult OCAP comparing different oral antibacterials by searching Medline (1966 - July 2007) and Embase (1980 – 7/2007) using the terms “pneumo” (truncated), “bronchopneumonia” or “lower respiratory tract infection,” combined with “outpatient”, (truncated), and “administration,” “oral administration” or “oral” and “randomized controlled trial,” “controlled clinical trial,” “randomized controlled trials,” “random allocation,” “double blind method” or “single blind method.” Terms were searched as subject headings or text words and the search was limited to English language, human and adult studies. In addition, evidence based medicine reviews including American College of Physicians Journal Club, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effectiveness were searched. Bibliographies of all retrieved studies, guidelines for the treatment of CAP and numerous pertinent review articles were also studied. When there were inadequate data to decide if a study was acceptable (e.g. did not clearly distinguish inpatients from outpatients), we requested additional information from the corresponding author or study sponsor.

Inclusion criteria were randomized double-blind trials comparing different antibacterial classes for OCAP. The primary outcome of interest was clinical cure or improvement, as defined by each study. We excluded open label, non-comparative, and non-randomized studies owing to potential important bias from the subjective nature of the primary outcome. We also excluded studies that combined in- and outpatients, unless data were available to analyze patient groups separately.

We organized studies into four groups. For the primary objective and meta-analysis we reviewed trials that compared patients who received an antibacterial with activity against atypical organisms against patients who received an antibacterial without activity against atypical organisms. For the secondary objectives and meta-analyses, we grouped studies that compared different antibacterial drug classes, as long as both comparators provided similar coverage for atypical organisms (for example, macrolides versus fluoroquinolones).

For the primary analysis we used the intention to treat or modified intention to treat populations (those with CAP who had received at least one dose of study drug). When the analysis was not clearly one of intention to treat, we reviewed and included the clinically evaluable, per protocol population. When both early and late end points were available, we used the earlier follow up time (following completion of therapy) as test of cure. We also reviewed all cause mortality, which would have included deaths until 28 days post treatment completion, since most studies followed patients until then. We had hoped to assess additional endpoints that may have been of greater relevance to studies of OCAP, including time to symptom improvement or resolution, time away from work or school, duration of therapy, need for hospitalization, and infective complications, but these data were rarely available. Selected studies were reviewed independently by two investigators to rate study quality and collect data on methods, patient characteristics and outcomes according to a pre-determined scheme adapted from Heintjes et al.,[8] detailed in the Appendix. Discrepancies were resolved through consensus.

We summarized the results for the dichotomous outcome of interest (clinical success, mortality) using risk ratios as estimates of relative risk, with 95% confidence intervals. Weightings and the summary estimates for each outcome were determined based on the DerSimonian and Laird random effects models. Heterogeneity was evaluated using the Mantel-Haenszel method and results were considered heterogeneous if the P value was less than 0.2. The $I^2$ statistic was used to assess the extent of inconsistency among results (how much of the total variation in apparent treatment effect was due to heterogeneity). The z-statistic was used to assess the overall effect, and a P value of 0.05 or less

considered significant. Calculations were performed using Review Manager (version 4.2, Cochrane Collaboration for Meta-analysis and Systematic Reviews).

## RESULTS

From over 2,300 hits, we retrieved 103 potentially eligible citations (93 from the literature review and 10 from reference lists), whose abstracts were reviewed. Ninety articles were excluded: 22 because inpatients and outpatients could not be discerned, 20 because comparator antibacterials were of the same drug class, 16 because they included only inpatients, 10 because they were reviews, seven because they were uncontrolled, six because they included acute exacerbations of chronic bronchitis, and nine for other reasons. We contacted the author or study sponsor for additional information regarding 22 articles. Two contacts indicated that additional data were unavailable, two contacts confirmed that their studies included only outpatients and thus eligible, and one author provided data to calculate outcomes in the outpatients and permit inclusion in our analysis. We therefore included 13 studies (Table 1).[9,10,11,12,13,14,15,16,17,18,19,20,21] The two reviewers had initial agreement on 340/416 (82%) entries regarding study methods and results, and 115/130 (88%) entries regarding study quality rating. All discrepancies were resolved by discussion. The 13 trials were performed in 36 countries between 1988 and 2002. Included were 4,314 total patients, and 3,402 analyzable patients (patients without protocol violations and not lost to follow-up). For the primary objective and meta-analysis (atypical versus no atypical coverage), there were six eligible studies - three regarding macrolides versus beta-lactams,[15,16,17] and three of fluoroquinolones versus beta-lactams[11,13,14] – with a total of 1,193 patients. For the secondary objective and meta-analyses, there were seven eligible studies - five regarding macrolides versus fluoroquinolones,[9,12,18,19,20] and two of cephalosporins versus beta lactams/ beta-lactamase inhibitors[10,21] – with a total of 2,209 patients.

All study drugs were given orally. All studies generally excluded patients with severe illness, usually defined by the need for hospitalization and parenteral therapy. Other exclusion criteria were major cardiac, pulmonary, hepatic or renal dysfunction and immunocompromised states. The inclusions and exclusions resulted in participants who were younger and with generally favorable prognosis compared to most inpatient CAP cohorts. Pharmaceutical companies sponsored 12 of the 13 studies. Five trials provided data on the intention to treat population. Three studies reported only on the clinically evaluable population, with an overall dropout rate of less than 20%. As all studies were blinded, we did not consider the lack of intention to treat data in some studies as critical and we therefore included the data. None of the included

studies clearly reported exclusively “on-treatment” results. Table 1 presents the design and Table 2 presents the outcomes of the included studies.

The average age of patients was 49 years. Men comprised 53% (1803/3402) of patients. Although none of the studies provided information regarding pneumonia severity index (PSI) scores, all studies were designed to evaluate outpatient populations likely in PSI risk class 1 or 2.[22] The time of assessment varied between studies. Patients were assessed during treatment in ten studies, and at the end of therapy in seven studies. In all studies evaluation for cure occurred within 10 days of treatment completion. Study quality was moderate, with a median (range) score of 6.9 (6.0-8.2) out of a possible 10 (Appendix 1). The most common deficiencies were in the descriptions of whether overall care was comparable between groups, whether groups were similar, and whether randomization was sound. In addition, most trials did not clearly present an intention to treat analysis.

The overall rate of clinical cure or improvement was 90%, and was reported in all trials. We found no significant difference between treatments in any study or significant heterogeneity between studies. There was moderate, but not statistically significant, heterogeneity between studies for the primary analysis - atypical coverage versus no atypical coverage. The $I^2$ statistic suggested that nearly 50% of the moderate heterogeneity observed for the primary analysis was due to heterogeneity (Figure 1(a)). This appears to be due to somewhat broader exclusion criteria and somewhat more rigorous outcome assessment criteria in three of the seven studies included in the primary analysis.[11,14,17] Regarding the primary objective, we found no evidence that antibacterials active against atypical pathogens, were superior to other antibacterials ($Z=1.27$, $p=0.2$, Figure 1(a)). Similarly, for the secondary objective, we found no evidence to support differences in rates of cure or improvement when comparing other antibacterials, including fluoroquinolones and macrolides ($Z=0.19$, $p=0.85$, Figure 1(b)), or cephalosporins versus beta-lactam/ beta-lactamase inhibitors ($Z = 0.46$, $P = 0.65$, Figure 1(c)).

There were 24 deaths reported in five studies (mortality 0.7%). This low mortality is in keeping with mild to moderate (non-severe) community acquired pneumonia. There was no significant heterogeneity in either the primary analysis (atypical coverage versus no atypical coverage) or the secondary analysis (differences between drug classes with similar atypical coverage – macrolides versus fluoroquinolones). Regarding the primary objective, we observed no differences in mortality between patients who received coverage for atypical agents (fluoroquinolones or macrolides) versus other drugs ($Z=0.95$, $p=0.34$, Figure 2(a)). Similarly, for the secondary objective, no differences in mortality were observed between macrolides and fluoroquinolones ($Z = 0.39$, $P = 0.70$, Figure 2(b)).

## DISCUSSION

We could not demonstrate a difference between antibacterials, regardless of coverage of atypical organisms, in mortality or success, in treating outpatients with CAP. Regarding the primary objective, there was no evidence to support that antibacterials active against atypicals (fluoroquinolones and macrolides) were superior to beta-lactams in a variety of forms (cephalosporins, narrow spectrum penicillins, and beta-lactam/ beta-lactamase inhibitors), which all lack activity against atypical pathogens. These data do not support the need for antibacterials that possess specific activity against atypical pathogens in OCAP and we could also not identify differences in outcome regardless of antibacterial class. Further, regarding our secondary objective, we could also not demonstrate any differences in outcomes between drug classes with similar atypical coverage (including macrolides versus fluoroquinolones, and cephalosporins versus beta-lactam/beta-lactamase inhibitor combinations).

Previous meta-analyses, although of high quality, have addressed somewhat different questions, using different inclusion criteria.[6,7] Bjerre *et al*., although limiting their analysis to studies of outpatients, included studies where all participants received therapy with atypical activity, making it impossible to address whether atypical coverage is helpful.[6] Two of the three studies included compared two macrolides (clarithromycin versus erythromycin) and one of the studies (also included in our analysis) compared a macrolide to a fluoroquinolone. To the Bjerre meta-analysis, our study therefore adds an analysis of nearly 1,200 patients to assess whether atypical therapy is useful in OCAP, an analysis of an additional 1,200 patients comparing macrolide versus fluoroquinolone therapy, and analyses comparing other drug classes. Mills *et al*. apparently included both in- and outpatient studies in their meta-analysis and focused exclusively on whether atypical coverage is beneficial.[7] Our study adds to the Mills study in several ways. First, we focused on exclusively outpatients, a group that is likely different than patients admitted with CAP. Intuitively, one might assume that since inpatient-treated CAP has a higher mortality, it should be easier to detect a difference in outcomes with inpatients, so studying cohorts with inpatients might improve the sensitivity of interventional trials in CAP. However, it is not clear to us that this can be stated with certainty. Outpatients and inpatients are assessed in different ways and clinical trials comparing these groups may be designed differently. In addition, it may be difficult to design appropriate clinical endpoints for both inpatients and outpatients in a single trial. For example, if one chooses the resolution of symptoms as the definition of clinical cure, it may be that very few inpatients reach this

endpoint within a reasonable follow-up period, while complete resolution is likely more common in outpatients. Using the endpoint of "resolution of symptoms" in a study of outpatients might therefore contain more patients reaching the endpoint, and therefore allow a more useful analysis. We therefore believe there is merit in doing a meta-analysis focusing on outpatients. Second, our analysis of atypical coverage included two additional studies with a total of 486 patients not included in the Mills paper.[17,15] Third, we also assessed for differences between other classes of antibacterials in OCAP, to maximize guidance to clinicians. Our study adds significantly to previous meta-analyses, and our results are in general consistent with both previous meta-analyses.

Although our confidence intervals for differences in effect were wide, we do not believe that lack of power necessarily explains our results. There are several alternative explanations for our findings. First, there may be a high incidence of self-limiting viral infections as a cause of mild CAP. Second, the natural history of atypical bacterial mild CAP in most cases is one of resolution with or without therapy, and antibiotic intervention may simply hasten resolution – an important outcome, but one which we could not adequately study due to incomplete data availability. Third, atypical bacterial CAP may be an asymptomatic co-infection, along with a clinically important pathogen that succumbs to beta lactams.[5] In OCAP, the possibility that the role of self-limiting viral infections is often underestimated, and the role of atypical bacterial pathogens is often overestimated, is consistent with a recent study by Creer *et al*. In this study, viral infections were highly prominent causes of lower respiratory tract infections and the most prevalent bacterial pathogen was *S. Pneumoniae*.[23]

It is possible that undetected bias played a role in obscuring a positive outcome from atypical coverage. Based on this possibility, we calculated the sample sizes required to detect minimal clinically important differences in clinical success and mortality in OCAP, using the method of two proportions.[24] For clinical success, assuming a 90% success rate in controls, to detect a two percent benefit (92% clinical success) with the intervention, using a two-sided alpha of 0.05 and 80% power, over 3,200 patients per group would be required. If the minimal clinically important difference is 1%, the required sample size increases to over 13,000 patients per group. For mortality, based on a 0.7% baseline mortality, to detect a decrease to 0.35% (a 50% relative reduction and 0.35% absolute reduction), using similar parameters, more than 6,700 patients per group would be required. These estimates suggest that much more data than are currently available are required to confidently address the outcomes we sought to study. If the total number of patients in the studies was too small to detect an important difference in outcomes that was actually present, our negative results would represent a type 2 error. Because, the outcomes are generally

good in uncomplicated patients with mild OCAP, and the observed point estimates did not favor the intervention (atypical coverage), we think that it is unlikely, that larger studies could have demonstrated a large effect on clinical success and mortality. Questions regarding time to resolution of symptoms however remain more uncertain. Although heterogeneity between studies may call the results of a meta-analysis into question, we are confident that we have accurately interpreted the available data. We found no statistically significant advantage or disadvantage with any oral treatment, the majority of studies found similar outcomes in both groups, and there were no sources of heterogeneity between the studies. For these reasons, we doubt that there is an important difference that was missed based on the available data.

A major strength of our study is the inclusion of only randomized prospective double-blinded studies using only oral therapy in exclusively outpatients. The multinational origin of the studies, done in 35 different countries, also increases the generalizability. Our results must however be interpreted in light of these same factors. The inclusions resulted in patients with mild pneumonia, reflected in the low mortality. We are therefore not able to provide any guidance for the management of severe CAP, where the standard of care is hospitalization and intravenous antibacterials. Therefore, our results are only applicable to the subset of patients with mild CAP. Nevertheless, this subset makes up a major proportion of patients with pneumonia. Another factor to consider regarding generalizability stems from the paucity of information that was available regarding the referral source of the patients (primary care versus specialty practices versus urgent care centers). Even within the population of outpatients, there is an important spectrum of patients that could be better understood if this information was provided. However, focusing our analyses to studies that contained only outpatients, aims to minimize this type of limitation.

A limitation of our work is that we were unable to address whether there is a difference in recovery time between antibacterials. Comparing time to recovery is important in this setting, where the majority of patients experience mild, often self-limiting disease, and the rationale for treatment is to prevent complications and shorten illness duration. Unfortunately, data regarding time to clinical success or symptom improvement were not available. Data regarding need for hospitalization and infective complications were also not systematically reported. The lack of adequate information regarding these very important outcomes is a critical limitation of the currently available controlled trials in OCAP. An additional limitation is that we could review only initial antibacterial therapy due to the availability of clinical trials. We emphasize that antibacterial treatment should always be reassessed in a patient who shows signs of deterioration or failure to improve.

Our findings are at conflict with the ATS and IDSA guidelines, which state that all populations with CAP, should be treated for possible infection with atypical pathogens.[2] Our findings tend to support the BTS guidelines,[3] which consider *S pneumoniae* the most important target of initial antibacterials. The BTS guidelines state that a policy aiming to always cover the atypical pathogens is inappropriate. Additionally our findings are consistent with the recent study by Creer et al., demonstrating the importance of viral infections, and among bacteria, a predominance of pneumococcus, as a cause of lower respiratory tract infection.[23] Our conclusions likely apply most closely to those patients referred to by the ATS and IDSA guidelines as outpatients who are previously healthy and without risk factors for drug-resistant *S. pneumoniae*. Generalizing to patients with comorbidity or recent antibiotic use, even though some patients with these characteristics were included in the studies is probably inappropriate.

Our results provide the best level of evidence currently available addressing the selection of initial antibacterials for relatively healthy outpatients with mild CAP. It appears that the outcome of OCAP is generally good regardless of whether there is coverage for atypical agents, as long as there is coverage for *S. pneumoniae*. We speculate that these results may be due to the fact that many cases of OCAP are due to viral or other self-limiting pathogens. Thus the selection of antibacterials in this context should likely be based upon side effect profile, price, physician and patient preferences, and resistance-induction considerations.

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**Tables**

**Table 1 – Characteristics included studies of outpatient treated community-acquired pneumonia**

| Reference | Country, number of sites, study years | Intervention | Participants at randomization | Outcome assessments post starting therapy (days) |
|---|---|---|---|---|
| Fogarty, 1999[18] | US, 51 centres, 1996-8 | 10 days of Moxifloxacin 400mg qd or Clarithromycin 500mg bid | Quinolones - 194<br>Macrolides - 188 | 16, 24-45 |
| Sokol, 2002[20] | US, 35 centres, 1998-9 | 7 days of Trovafloxacin 200mg qd or Clarithromycin 1000mg ER qd | Quinolones - 66<br>Macrolides - 85 | 2-3, 7-10, 21-28 |
| Ramirez 1999[19] | US, 54 centres, 1996 | 10 days of Sparfloxacin 200mg qd or Clarithromycin 250mg bid | Quinolones - 167<br>Macrolides - 175 | 4, 20, 38 |
| Hoeffken, 2001[12] | Multinational, 50 centres, 1996-8 | 10 days of Moxifloxacin 400mg or 200mg qd or Clarithromycin 500mg bid | Quinolones - 357<br>Macrolides - 174 | 3-5, 13-15, 21-28 |
| Gotfried, 2002[9] | US and Canada, 51 centres, 1999-2000 | 7 days of Levofloxacin 500mg qd or Clarithromycin 1000mg qd | Quinolones - 124<br>Macrolides - 128 | 2-3, 6-8, 10, 21-28 |
| Kinasewitz, 1991[16] | US, 28 centres, 1996 | 5 days of Azithromycin 500mg qd or 10 days of Cefaclor 500mg tid | Cephalosporins - 39<br>Macrolides - 32 | 6, 11, 18, 30 |
| Salvarezza, 1998[15] | Argentina, 3 centres | 10 days of Roxithromycin 300mg qd or Cefixime 400mg qd | Cephalosporins - 30<br>Macrolides - 30 | 3-4, 10, 30 |
| Macfarlane, 1996[17] | England, 14 centres, 1993-4 | 7 days of Amoxycillin 250mg tid or Clarithromycin 250mg bid | Penicillins - 212<br>Macrolides - 214 | 8, 15 |

| | | | | |
|---|---|---|---|---|
| Fogarty, 2002[10] | US, 83 centres 1998-2001 | 14 days of Ceftidoren 200mg or 400mg bid or Amoxicillin/clavulanate 875/125mg bid | Penicillins - 144<br>Cephalosporins - 301 | 3-5, 7-10, 16, 21-28 |
| Higuera, 1996[21] | Multinational, 31 centres, 1988-1991 | 10 days of Cefuroxime 500mg bid or Amoxicillin/clavulanate 500/125mg tid | Penicillins - 51<br>Cephalosporins – 55 | 3-5, 11-13, 24 |
| Donowitz, 1997[11] | US, 74 centres 1992-1995 | 10 days of Sparfloxacin 200mg qd or Cefaclor 500mg tid | Quinolones - 168<br>Cephalosporins - 162 | 3-5, 17-23, 31-45 |
| O'Doherty, 1997[14] | UK and US, 43 centres, 1992-1993 | 7-10 days of Grepafloxacin 600mg qd or Amoxycillin 500mg tid | Quinolones – 114<br>Penicillins - 111 | During, at the end, and at follow-up |
| Petitpretz, 2001[13] | Multinational, 82 centres, 1997-1998 | 10 days of Moxifloxacin 400mg qd or Amoxycillin 1000mg tid | Quinolones – 41<br>Penicillins – 40 | 3-5, 13-15, 31-38 |

**Table 2 – Outcome in outpatient community-acquired pneumonia by antibacterial classes**

| Antibacterial class | Total | Adverse events – number (%)* | Clinical success – number (%)* | Hospitalization – number* | Mortality – number (%)* |
|---|---|---|---|---|---|
| Quinolones | 1231 | 58 (4.7%) | 1071 (87%) | 4 | 13 (1%) |
| Macrolides | 1026 | 50 (4.9%) | 908 (88.5%) | 7 | 6 (0.6%) |
| Penicillins | 558 | 21 (3.8%) | 521 (93.4%) | NR | 2 (0.4%) |
| Cephalosporins | 587 | 30 (5.1%) | 553 (94.2%) | NR | 3 (0.5%) |

***Total number of patients for who this variable was available**

## Figure Legends

**Figure 1: Clinical success in studies of outpatient-treated community-acquired pneumonia according to empiric antibacterial therapy**

**(a) Atypical coverage (treatment) versus no atypical coverage (control)**

**(b) Macrolides (treatment) versus fluoroquinolones (control)**

**(c) Cephalosporins (treatment) versus beta-lactams / beta-lactamase inhibitors (control)**

**Figure 1(a)**

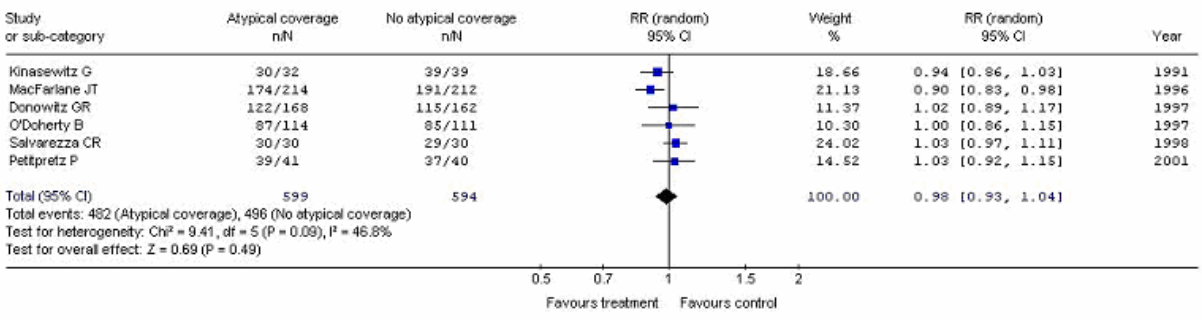



**Figure 1(b)**

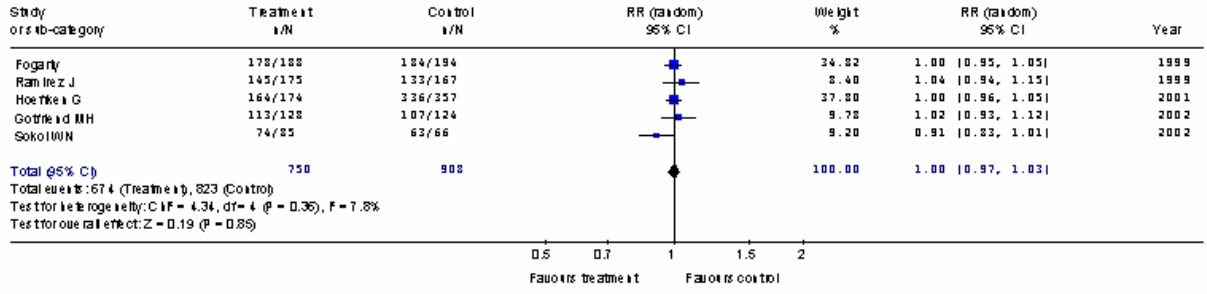



**Figure 1(c)**

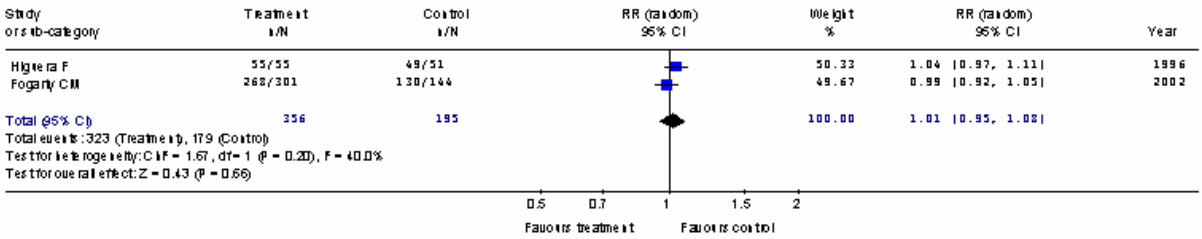
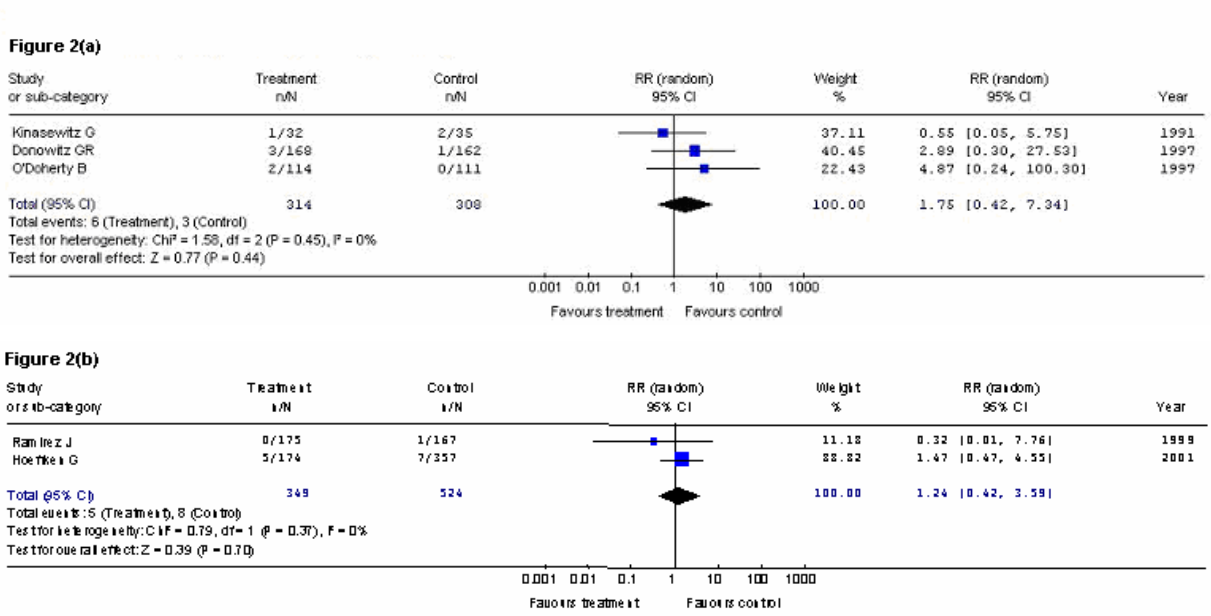


**Figure 2: Mortality, in studies of outpatient-treated community-acquired pneumonia according to empiric antibacterial therapy**

**(a) Atypical coverage (treatment) versus no atypical coverage (control)**

**(b) Macrolides (treatment) versus fluoroquinolones (control)**



**Appendix 1: Methodologic quality rating scales for trials of different antibacterials in outpatient-treated community-acquired pneumonia**

| Study | Rating scale (see notes below) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Inclusions, exclusions | Truly randomized | Groups comparable | Intervention clear | Comparable care | Blinding | Outcomes clear | Outcomes appropriate | Follow-up appropriate | Intention to treat | Total (max 10) |
| Fogarty 1999[18] | 1 | 0.5 | 0.5 | 1 | 0 | 1 | 1 | 0.33 | 1 | 0 | 6.33 |
| Sokol 2002[20] | 1 | 0.5 | 0.5 | 1 | 0 | 1 | 1 | 0.67 | 1 | 0 | 6.67 |
| Ramirez 1999[19] | 1 | 1 | 0.5 | 1 | 0 | 1 | 1 | 0.67 | 1 | 1 | 8.17 |
| Hoeffken 2001[12] | 1 | 0.5 | 0.5 | 1 | 0 | 1 | 1 | 0.67 | 1 | 0 | 6.67 |
| Gotfried 2002[9] | 1 | 0.5 | 0.5 | 1 | 0 | 0.67 | 1 | 0.67 | 1 | 0 | 6.34 |
| Kinasewitz 1991[16] | 1 | 0.5 | 0 | 1 | 0 | 1 | 1 | 0.67 | 1 | 0.5 | 6.67 |
| Salvarezza 1998[15] | 0.5 | 1 | 0.5 | 1 | 0 | 0 | 1 | 0.33 | 1 | 1 | 6.33 |
| MacFarlane 1996[17] | 1 | 0.5 | 1 | 1 | 0 | 0.67 | 0.5 | 0.33 | 1 | 0 | 6 |
| Fogarty 2002[10] | 1 | 1 | 0.5 | 1 | 0 | 0.67 | 1 | 0.67 | 1 | 0 | 6.84 |
| Higuera 1996[21] | 1 | 0.5 | 0.5 | 1 | 0 | 0.67 | 1 | 0.33 | 1 | 0 | 6 |
| Donowitz 1997[11] | 1 | 0.5 | 1 | 1 | 0 | 1 | 1 | 0.67 | 1 | 1 | 8.17 |
| O'Doherty 1997[14] | 1 | 0.5 | 0.5 | 1 | 0 | 1 | 1 | 0.67 | 1 | 1 | 7.67 |
| Petitpretz 2001[13] | 1 | 0.5 | 0.5 | 1 | 0 | 1 | 1 | 0.33 | 1 | 1 | 7.33 |

Inclusion and exclusion criteria clearly defined: 1 = Yes; 0.5 = Inadequately defined; 0 = Not defined

Truly randomized: 1 = Yes, clearly described (including concealed potential allocation); 0.5 = Unclear; 0 = No

Groups comparable at entry: 1=Yes; 0.5=Inadequately described; 0 = Obvious differences

Interventions clearly defined and applied via standardized protocol: 1 = Yes; 0 = Intervention poorly or not defined

Care programs, other than trial options, identical: 1 = Yes; 0.5 = Clear but trivial differences; 0 = Not mentioned or important differences

Patients, treatment providers and outcome assessors blinded to treatment group: 1 = Yes; 2/3 = Two of three blinded; 1/3 = One of three blinded; 0 = No blinding or not mentioned

Outcomes clearly defined: 1 = Yes; 0.5 = Inadequately defined; 0 = Not defined

Outcomes include clinical success, mortality and LOS: 1 = Yes; 2/3 = Any two; 1/3 = Any one; 0 = None

Follow-up active and of appropriate duration (>3 weeks): 1 = Yes; 0.5 = Active, inadequate duration; 0 = Not active or not defined

Outcomes of patients who withdrew described and included in intention to treat analysis: 1 = Yes; 0.5 = Inadequately described; 0 = No mention or obvious differences