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The treatment of community-acquired pneumonia in ambulatory patients

- A systematic review and meta-analysis -

(Behandlung der ambulant erworbenen Pneumonie bei ambulanten Patienten – eine systematische Übersicht und eine Meta-Analyse)

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Table of contents

1. Introduction

Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, a new infiltrate on chest x-ray or auscultatory findings such as altered breath sounds and/or localized rales in community-dwelling patients (Infectious Diseases Society of America 2000). It is a common condition that carries a high burden of mortality and morbidity, particularly in elderly populations. Although most patients recover without sequellae, CAP can take a very severe course, requiring admission to an intensive care unit (ICU) and even leading to death. According to US data, it is the most important cause of death from infectious causes and the sixth most important cause of death overall (Adams et al. 1996). Even though the mortality from pneumonia decreased rapidly in the 1940s after the introduction of antibiotic therapy, it has remained essentially unchanged since then or has even increased slightly (MMWR 1995).

Furthermore, significant costs are associated with the diagnosis and management of CAP. Between 22% and 42% of adults with CAP are admitted to hospital, and of those, 5% to 10% need to be admitted to an ICU (British Thoracic Society 2001). In the US, it is estimated that the total cost of treating an episode of CAP in hospital is about USD $ 7500, which is approximately 20 times more than the cost of treating a patient on an outpatient basis (Lave et al. 1999). CAP also contributes significantly to antibiotic use, which is associated with well-known problems of resistance.

In treating patients with CAP, the choice of antibiotic is a difficult one. Factors to be considered are the possible etiologic pathogen, the efficacy of the substance, potential side-effects, the treatment schedule and its effect on adherence to treat-

ment as well as the particular regional resistance profile of the causative organism and the co-morbidities that might influence the range of potential pathogens (such as in cystic fibrosis) or the dosage (as in the case of renal insufficiency). Although many studies have been published concerning CAP and its treatment, there is no concise summary of the available evidence and only few guidelines (British Thoracic Society 2001, American Thoracic Society 2001, Canadian Community-Acquired Pneumonia Working Group 2000, Infectious Diseases Society of America 2000) that can help clinicians in choosing the most appropriate antibiotic. The applicability of such guidelines is furthermore limited by wide variations in regional resistance profiles and by their focus on hospitalized patients.

1.1 Framework of the review: the Cochrane Collaboration

This review addresses the treatment of community-acquired pneumonia (CAP) in adolescent and adult outpatients. It was conducted within the framework of the Cochrane Collaboration, a worldwide network of researchers whose aim is to “prepare, maintain and promote the accessibility of systematic reviews of the effects of health care interventions” (see www.cochrane.org, www.cochrane.de) using the evidence available from randomized controlled trials (RCT). Reviews are initiated by researchers with an interest in a particular clinical question. A protocol in which the goals and methods of the review are described is then written and published in electronic form in the Cochrane Library (accessible for a fee at www.cochranelibrary.net). The review is then carried out independently by at least two reviewers who may be assisted by others, particularly when initially screening study reports for inclusion into the study. Having reached their own individual conclusions about which studies to

include in the review, the two reviewers compare their results and resolve any differences by discussion and consensus. One or both of the reviewers then proceeds to analysing the data of the selected studies and writing the final review. The review then undergoes peer review within the framework of the Cochrane Collaboration and is published as a citable peer-reviewed publication in the Cochrane Library of Systematic Reviews (accessible for a fee at www.cochranelibrary.net).

In order to disseminate the results of reviews more broadly and to circumvent the problems arising from the fact that the Cochrane Library is only accessible to paying subscribers, the Lancet has recently made a commitment to publishing Cochrane Reviews and has encouraged review authors to submit their reviews for publication in the Lancet (Clark and Horton 2001).

1.2 Statement of authorship

This review was initiated and published as a Cochrane protocol by Prof. Michael Kochen (MMK) in collaboration with other colleagues from the UK and the Netherlands, in particular Prof. Theo JM Verheij (TJMV) of Utrecht University (Verheij 2001). MMK co-wrote the protocol and screened abstracts and full articles for inclusion into the review. TJMV co-wrote the protocol, screened abstracts and full articles for inclusion into the study and decided, in agreement with me, which articles to include into the review.

As the main reviewer, I carried out a review of the background literature, screened abstracts and full articles for inclusion into the study, decided, in conjunction with TJMV, which articles to include, extracted the data from these articles, performed the quantitative analyses and wrote the text, tables and figures of the review.

The present dissertation is a report of the work that I carried out myself and is not the final text of the Cochrane review, which is less extensive in both scope and length. In particular, the literature review included in the present dissertation is much more extensive. Furthermore, the efficacy analyses as well as all the data pertaining to the open-label studies are unique to this dissertation. Except for discussions with TJMV concerning the choice of studies to be included into the review, I have carried out this study independently. As such, I take full responsibility for the contents of this study as well as for any shortcomings or errors that may remain.

2. Background and literature review

2.1 Community-acquired pneumonia

2.1.1 Incidence

In the industrialized world, the annual incidence of CAP in community-dwelling adults is estimated at 5 to 11 cases per 1000 adult population (British Thoracic Society 2001). The incidence is known to vary markedly with age, being higher in the very young and the elderly. In one Finnish study, the annual incidence for people aged 16-59 years was 6 cases per 1000 population, for those 60 years and older it was 20 per 1000, and for people aged 75 and over, 34 per 1000 (Jokinen et al. 1993). Annual incidences of 30-50 per 1000 population have been reported for infants below 1 year of age (Marrie 2001). Seasonal variations in incidence are also significant, with a peak in the winter months (Marrie 2001).

The annual incidence of CAP requiring hospitalisation has been estimated at 1 to 4 patients per 1000 population (Marrie 1990, Fine et al. 1996). The proportion of patients requiring hospitalisation varies from country to country and across studies and has been estimated as ranging anywhere between 15% and 56% (Foy et al. 1973, Minogue et al. 1998). Of those, 5% to 10% required admission to an intensive care unit (ICU) (British Thoracic Society Research Committee and Public Health Laboratory Service 1992, Torres et al. 1991). Conversely, about 8% to 10% of admissions to a medical ICU are due to severe CAP (Woodhead et al. 1985).

2.1.2 Etiology

More than 100 microorganisms have been identified so far as potential causative agents of CAP (Marrie 2001). They can be classified according to their biological characteristics as either bacteria, mycoplasma and other intracellular organisms, viruses, fungi and parasites. The most common causative agent of CAP is the bacterium *Streptococcus pneumoniae*, which is implicated in 20% to 75% of cases of CAP (Marrie 2001) and about 66% of bacteremic pneumonia (Infectious Diseases Society of America 2000). Another causative bacterium is *Haemophilus influenzae*. So-called “atypical” organisms have also been implicated as causal agents. These include *Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella pneumophila* (Marrie 2001).

Influenza is the most common serious viral pathogen causing airway infections in adults (Infectious Diseases Society of America 2000). Although it does not itself cause pneumonia, its most common serious complication is bacterial superinfection, usually due to *Streptococcus pneumoniae*. Affected patients are primarily older than 65 years and/or residents of chronic care facilities. Effective prevention is possible through yearly vaccination of populations at risk and should include vaccination of those who care for such patients (Potter et al. 1997).

The identification of the causal organism is a challenging task: since lung tissue cannot be routinely obtained, clinicians must rely on sputum samples – which can only be obtained successfully in about 33% of patients – or on blood cultures, that are positive in only 6% to 10% of patients with CAP (Canadian Community-Acquired Pneumonia Working Group 2000). Furthermore, it takes a minimum of 2 to 3 working days to obtain culture results, be it from sputum samples or blood. Consequently, it is often necessary to initiate therapy on empiric grounds alone. Further-

more, routine surveillance of samples sent to microbiology labs by primary care physicians does not provide an accurate picture of the actual situation in the community, as samples are often sent only when a first, empirical therapeutic attempt has failed.

2.1.3 Risk factors

A variety of risk factors predisposing a patient to CAP have been identified. These include host factors, such as chronic obstructive pulmonary disease (COPD), alcoholism or immune suppression, environmental factors, such as exposure to certain animals, for example parrots (*Chlamydia psittaci)*, parturient cats and sheep (*Coxiella burnetii)*, and rabbits (*Francisella tularensis)*, recent hotel stay (*Legionella pneumophila*), travel abroad or in endemic regions (*Coccidioides immitis, Histoplasma capsulatum*), and occupational factors, such as contact with body fluids containing infective agents (*Mycoplasma tuberculosis*) (Canadian Community-Acquired Pneumonia Working Group 2000). Smoking is also thought to be an important risk factor for acquiring CAP (Marrie 2001). As outlined above, a number of risk factors are related to particular causative organisms and enquiring about their presence may improve diagnostic accuracy with respect to the etiologic agent, however the British Thoracic Society (2001) cautions that due to the low frequency of some of these organisms in patients with CAP and the high frequency of the risk factors for exposure to these organisms in the population, routine questioning about such risk factors may be misleading.

2.1.4 Diagnosis

The diagnosis of CAP remains a challenge for clinicians. There is no single finding that is pathognomonic of CAP, and even the gold-standard chest x-ray may fail to provide the necessary information to make the correct diagnosis. However, there is good evidence supporting the view that the diagnosis of CAP is inaccurate without a chest x-ray (British Thoracic Society 2001).

It is important to differentiate between CAP and other lower respiratory tract infections, such as acute bronchitis, and to differentiate between these entities and other potential causes of similar symptom complexes, such as pulmonary neoplasia, congestive heart failure or pulmonary embolism, as the subsequent management of such patients differs greatly. Most cases of upper respiratory tract infections and acute bronchitis are caused by viruses, and therefore do not require antibiotic treatment (Infectious Diseases Society of America 2000). The use of antibiotics in such cases is inappropriate and should be avoided.

Despite the importance accorded to history, physical examination, chest x-rays and some laboratory investigations in the assessment of patients suspected of having CAP, only very few studies have attempted to assess the validity of such approaches (Canadian Community-Acquired Pneumonia Working Group 2000). Furthermore, none of these studies relied on autopsies as a diagnostic gold standard. Instead, they used chest x-rays or even clinical suspicion to decide whether pneumonia was present, thus making the validity of their conclusions highly questionable.

Another factor that further complicates the diagnosis of CAP are inter-observer variations in the identification of symptoms and signs in patients suspected of having CAP. The reliability of physical signs has been studied and found to be highly variable (Spiteri et al. 1988, Schilling et al. 1955). As for symptoms, inter-observer reli-

ability has not been studied, but it is known from studies of other respiratory conditions that there is significant variation between observers (Cochrane et al. 1951, Fletcher 1964).

Recently, a urine test for rapid detection of *Streptococcus pneumoniae* has been approved by the American Food and Drug Administration (FDA) (Henney 1999). The test can be carried out in the physician's office or in the emergency room, requires only 5 ml of urine and results are available within 15 minutes. The test is reported to have a sensitivity of 86% to 90% and a specificity of 71% to 94%. It is intended as an adjunct to the usual clinical, laboratory and radiological investigations for suspected CAP. Whether it will become part of the diagnostic armamentarium in actual practice remains to be seen.

Consequently, the diagnosis of CAP should be made based on a combination of physical, laboratory, microbiologic and radiographic findings, keeping in mind that none of them is perfectly reliable for diagnosis (Canadian Community-Acquired Pneumonia Working Group 2000).

2.1.5 Treatment

Since the majority of cases CAP are caused by organisms amenable to treatment with an antibiotic drug, rapid initiation of antibiotic treatment is indicated in the vast majority of cases. Difficulties arise when a clinician is confronted with the need to choose an antibiotic drug for a particular patient. The appropriate choice of antibiotic for the ambulatory treatment of CAP in adults and adolescents is the focus of the present study and I will attempt to provide an answer to this question on the basis of the currently available evidence.

2.1.5.1 Antibiotic resistance

The problem of antibiotic resistance has received increasing attention in recent years. The problem is not confined to community-acquired pneumonia, however, since CAP can take a very severe course even leading to death, it is a condition for which the issue of antibiotic resistance takes on even greater importance.

Traditionally, the preferred antimicrobial agent for the treatment of *Streptococcus pneumoniae* was penicillin G (Infectious Diseases Society of America 2000). However, widespread penicillin use for a variety of infectious conditions has lead to the emergence and rise of penicillin resistance. Recent studies estimate the proportion of penicillin resistant *Streptococcus pneumoniae* at around 25% (Marrie 2001). Similarly, the use of other antibiotics has led to the emergence of resistance against these agents in a variety of microorganisms. For example, it is estimated that approximately 30% of Haemophilus influenzae isolates are resistant to amoxicillin (Marrie 2001).

Furthermore, the phenomenon of antibiotic resistance is subject to wide regional and international variations, as access to and patterns of use of antibiotics vary widely.

As is the case with the identification of pathogens, it is also difficult to estimate the exact prevalence of antibiotic resistance in a particular area by simple surveillance of specimen sent to microbiology laboratories because these come from preselected patients, some them having already failed a first empirical treatment and therefore being more likely to carry a resistant pathogen.

For this reason, some practice guidelines emphasize the importance of obtaining baseline microbiologic specimen – the minimum being a Gram stain, with or with-

out culture – before initiation of empiric therapy (Infectious Diseases Society of America 2000).

2.1.6 Prognosis

The prognosis of CAP ranges from full recovery without sequellae to death on an intensive care unit within a few days of disease onset. Because of this broad and dramatic spectrum, prognostic factors for the identification of high-risk patients have been the subject of much research.

The Pneumonia Patient Outcome Research Team (Pneumonia PORT) has developed a clinical prediction rule to identify patients at risk of short-term mortality from CAP that is intended as a tool to assist clinicians in making decisions about the initial location and intensity of treatment (Fine et al. 1997). This prediction rule has gained wide acceptance and has been included into recent clinical practice guidelines (Infectious Diseases Society of America 2000, Canadian Community-Acquired Pneumonia Working Group 2000).

In ambulatory patients, the mortality rate from pneumonia is low, probably below 1% (British Thoracic Society 2001), but some estimates go as high as 5% (American Thoracic Society 2001). In hospitalized patients, it hovers around 12%, increasing to close to 40% (American Thoracic Society 2001) or even 50% (British Thoracic Society 2001) in patients requiring admission to an ICU.

2.2 Practice guidelines for the treatment of community-acquired pneumonia

In recent years, there has been an explosion in the number of clinical practice guidelines being produced and published. The field of infectious diseases is no ex-

ception, and a few guidelines for the diagnosis and treatment of community-acquired pneumonia have been published over the past decade. Most recently, four major professional societies have updated the guidelines they had published in the early 1990s. These guidelines are based on a combination of literature review and expert opinions. As such, they represent an attempt at synthesizing the available evidence and aim at providing clinicians with diagnosis and treatment strategies that are based as much as possible on the current state of knowledge. In the following sections, these guidelines will be examined in further detail in an attempt to get an overall view of the current state of knowledge with respect to CAP.

These guidelines were identified in the course of searching the literature for studies and reviews concerned with community-acquired pneumonia. This was done using the search strategy reported in section 4.2. No language restrictions were applied. In an effort to broaden the search, the Internet was searched for websites listing guidelines about the treatment of CAP. This search was conducted both in English and in German. No German-language guidelines could be identified using this search strategy. A few German language review articles dealing with CAP were identified (Dusch and Täuber 2001, Gillissen and Ewig 2000 a, Gillissen and Ewig 2000 b, Rosseau and Suttorp 2000, Ruef 2001), however these were all “secondary literature” article summarizing evidence from other studies and guidelines in a non-systematic way and intended for a general medical readership.

2.2.1 American Thoracic Society (2001)

In 2001, the American Thoracic Society published an update of its original 1993 statement on community-acquired pneumonia (American Thoracic Society 2001). These guidelines were developed by a committee composed of pulmonary,

critical care, infectious disease and general internal medicine specialists. Ambulatory care physicians, general practitioners in particular, appear to have been left out. This raises concerns that the ambulatory care perspective may have been neglected.

The guidelines development strategy is described in detail, however there is no detailed account of how the literature was searched.

The American Thoracic Society claims that its guidelines are evidence-based and reports using a classification system based on the system used by the Canadian Infectious Diseases Society and Canadian Thoracic Society in their CAP guidelines update (Canadian Community-Acquired Pneumonia Working Group 2000), however, they do not state the level of evidence for each of their therapeutic recommendations, nor do they give any specific references supporting those recommendations. Finally, the committee reports that they focused on "studies that included an extensive diagnostic approach to define the etiologic pathogen" and that "most [studies] involved hospitalized patients" (American Thoracic Society 2001, p. 1733). This raises concerns that the evidence-base on which the recommendations for outpatients were made may have been insufficient.

The new statement includes a summary of the available literature as well as "evidence-based recommendations for patient management" (American Thoracic Society 2001, p. 1730). The guidelines recommend that all patients with suspected CAP should have a chest radiograph to confirm the diagnosis, yet they recognize that this may not be feasible in some ambulatory settings. Sputum Gram stain and culture are recommended only if drug-resistant bacteria or an organism not covered by the usual empiric therapy are suspected.

As for therapy and management, the Society advocates an empiric approach based on likely pathogens. Patients are to be classified into one of four groups de-

pending on factors thought to influence the spectrum of potential pathogens, namely: 1) the place of therapy (outpatient, inpatient regular ward, inpatient ICU), 2) the presence of cardiopulmonary disease (COPD, heart failure), and 3) the presence of modifying factors, which include risk factors for drug-resistant *Streptococcus pneumoniae* (DRSP), enteric gram-negatives (nursing home residence) and *Pseudomonas aeruginosa*. Using these factors, the guidelines define four patient groups: 1) outpatients with no history of cardiopulmonary disease and no modifying factors, 2) outpatients with cardiopulmonary disease and/or other modifying factor, 3) inpatients not admitted to the ICU; this group is further subdivided into those with and without cardiopulmonary disease and/or other modifying factors, and 4) ICU-admitted patients, who are further subdivided into those with or without risk factors for *Pseudomonas aeruginosa*.

For each group, the available evidence was reportedly combined to identify the most likely pathogens, and recommendations for empiric therapy were made on this basis. For group 1 (outpatients without additional risk factors), the recommended therapy is an advanced generation macrolide, such as azithromycin or clarithromycin, or doxycycline. The advanced generation macrolides were recommended on the grounds that erythromycin does not cover *Haemophilus influenzae* and is not tolerated as well. In group two (outpatients with cardiopulmonary disease and/or other modifying factors), a combination of a beta-lactam with either one of the above-mentioned macrolides or doxycycline is recommended. The beta-lactams mentioned include cefpodoxine, high-dose amoxicillin and amoxi/clavulanate. The combination treatment is advocated because amoxicillin does not offer adequate coverage for *H. influenzae.* Furthermore, it is recommended that all patients, regardless of what group they belong to, should be treated for “atypical” organisms (*Chlamydia pneu-*

moniae, Mycoplasma pneumoniae, Legionella species). This is usually done by including a macrolide antibiotic in the recommended treatment plan.

2.2.2 British Thoracic Society (2001)

The British Thoracic Society also recently updated its 1993 guidelines for the treatment of CAP in adults admitted to hospital to include patients treated in an ambulatory setting (British Thoracic Society 2001). The British Thoracic Society guidelines committee was composed of 12 members, of which 6 were general practitioners, four of them with a special interest in respiratory medicine and an "active research interest" in respiratory infectious diseases. The other members of the committee were a clinical microbiologist, two infectious disease specialists, a registrar in respiratory medicine, a clinical epidemiologist and a medical librarian. The search and study selection strategy employed is described in details, and a level of evidence is explicitly given for every recommendation made by the committee.

The guidelines do not advocate the routine use of chest radiographs or sputum culture for the majority of patients with CAP who are managed on an outpatient basis. The diagnosis of CAP is to be made on clinical grounds, and severity assessment is emphasized as the key to appropriate management, whether the patients are to be treated in the community or in hospital. The choice of antibiotic treatment for outpatients is empiric and the main target organism remains *S. pneumoniae*.

The authors emphasize the fact that their literature search for the period 1981-99 yielded only 16 articles judged relevant to the antibiotic treatment of CAP and that few of these studies were conducted within a setting comparable to those of UK practices. Nonetheless, and despite explicitly acknowledging that the currently available

evidence forms an “unsatisfactory basis” for making solid evidence-based recommendations, the British Thoracic Society continues to recommend amoxicillin as the preferred agent on the grounds of cost, current practice, “wide experience”, safety and drug tolerance, but recommends a higher dose (500 mg to 1000 mg po tid) than used commonly in practice. The fact that clinical treatment failures have rarely been documented when penicillin-resistant strains are treated with higher doses of amoxicillin and that penicillin resistant pneumococci are still relatively rare in the UK is given as the rationale for recommending higher doses of amoxicillin. Erythromycin (500 mg po qid) is recommended as the alternative treatment for patients who do not tolerate amoxicillin. Clarithromycin (500 mg po bid) is suggested as the alternative agent for the sub-group of these patients who do not tolerate erythromycin, usually due to gastrointestinal side-effects.

Interestingly, the guidelines committee considered tetracyclines (doxycycline) as an agent of first choice because resistance rates for pneumococci are lower that for penicillins or erythromycin and it is also active against “atypical” agents, however they refrained from making it a first choice recommendation in their guidelines due to a presumed reluctance of physicians to change their current practice that would “limit compliance with recommendations”. This is an interesting example of how perceived inertia on the part of practitioners (whether real or only imagined by the guidelines committee) can significantly influence the content of practice recommendations (Keeley 2002).

2.2.3 Canadian Infectious Diseases Society / Canadian Thoracic Society (2000)

In 2000, the Canadian Infectious Diseases Society and the Canadian Thoracic Society updated their 1993 guidelines for the treatment of CAP (Canadian Community-Acquired Pneumonia Working Group 2000). Members of the guidelines committee are listed at the end of the report, however there is no mention of the members' area of specialty, so it is unclear whether physicians primarily involved in the care of ambulatory patients were involved in the guidelines formulation process.

The literature search strategy is described in reasonable detail and a hierarchical evaluation of the strength of evidence was carried out. Accordingly, a level of evidence is explicitly given for each recommendation made by the committee, unfortunately these are included only in the text of the guidelines and not in the tables where the recommendations are also summarized.

The committee bases its recommendations on a classification of patients according to the place of treatment (outpatient, inpatient, nursing home). The guidelines also provide a scoring system that uses objective criteria to assist physicians in deciding whether a patient should be hospitalized or not.

With respect to chest radiography, the committee points out that a number of infectious and non-infectious conditions may present a radiographic picture that is indistinguishable from that of pneumonia and that only one small study has assessed the ability of chest radiography to detect pulmonary infiltrates in patients suspected of having CAP (the gold standard used was high resolution CT scanning). They also point out that expert opinions are divided concerning the necessity of performing routine chest x-rays in patients suspect of having CAP. Nonetheless, the committee recommends that chest x-rays be performed routinely "under most circumstances" in

such patients because the diagnosis of pneumonia is strengthened (although not confirmed) by the presence of an infiltrate.

As for microbiological studies, no specific investigations are recommended for the majority of patients treated on an outpatient basis.

For outpatients without modifying risk factors, the treatment of choice is a macrolide (erythromycin, azithromycin or clarithromycin), the second choice treatment being doxycycline. Outpatients with modifying factors are further subdivided into three groups: those with chronic obstructive pulmonary disease (COPD) who did not receive antibiotics or steroids within the past 3 months, COPD patients who did get antibiotics or steroids within the past three months, and patients in whom macroaspiration is suspected (alcoholics, patients with impaired consciousness, impaired gag reflex or other deglutitional dysfunction).

In the first group (COPD, no antibiotics or steroids in past 3 months), the first choice is a so-called “newer” macrolide, namely azithromycin or clarithromycin, the second choice being doxycycline. In patients with COPD who received an antibiotic or steroids in the past three months, a “respiratory” quinolone (levofloxacin, gatifloxacin or moxifloxacin) is recommended, the second line choice being amoxicillin-clavulanate plus a macrolide, or alternatively a second-generation cephalosporin plus a macrolide. In cases of suspected macroaspiration, the first choice recommendation is amoxicillin-clavulanate plus a macrolide, the second choice being levofloxacin plus either clindamycin or metronidazole.

2.2.4 Infectious Diseases Society of America (2000)

In 2000, the Infectious Diseases Society of America (IDSA) updated their 1998 guidelines for the treatment of CAP in adults (Infectious Diseases Society of America

2000). Members of the guidelines committee are listed as co-authors of the report together with their affiliated institution, however there is no mention of the members' area of specialty, so it is unclear whether primary care physicians were involved in the guidelines formulation process.

The literature search strategy is not described, however, the committee used a grading system to assess the quality of the evidence provided by the research studies that they reviewed, as well as another grading system to classify the strength of the recommendations they made. The grades for quality of evidence and strength of recommendation are explicitly stated with each recommendation presented in the guidelines.

The IDSA guidelines emphasize the clinical importance of the decision to hospitalize a patient or to treat on an outpatient basis. They recommend the use of the clinical prediction rule for short-term mortality developed and validated by the Pneumonia Patient Outcome Research Team (Pneumonia PORT) (Fine et al. 1997) as a basis for deciding whether or not to hospitalize a patient.

The IDSA guidelines state that the diagnosis of CAP is based on a combination of clinical and laboratory data, adding that a chest x-ray is usually necessary to establish the diagnosis. The guidelines recommend that posteroanterior and lateral chest radiography be part of the routine workup of patient in whom CAP is considered a likely diagnosis and they discourage the initiation of empiric therapy without radiographic confirmation, although they acknowledge that obtaining chest x-rays "may not always be practical" (Infectious Diseases Society of America 2000, p. 370).

For outpatients, sputum collection for Gram stain and culture are deemed optional, however the IDSA panel makes a strong case in favour of establishing an etio-

logic diagnosis for all patients. For outpatients, the guidelines state that it is desirable to perform at least a Gram stain, with or without culture.

Treatment recommendations emphasize a pathogen-directed antimicrobial therapy and prompt antimicrobial treatment. Treatment recommendations are made based on suspected pathogens. Recommendations for empiric antibiotic selection in the absence of an etiologic diagnosis, i.e. when Gram stain and culture are not diagnostic, are also made. Drugs of first choice are recommended in “no particular order” and include doxycycline, a macrolide (erythromycin, clarithromycin or azithromycin) or a fluoroquinolone (levofloxacin, moxifloxacin or gatifloxacin). For older patients or patients with co-morbidities, a fluoroquinolone is to be preferred. When S. pneumoniae or H. influenzae are the suspected etiologic agents, amoxicillin-clavulanate or some second-generation cephalosporins (cefuroxime, cefpodoxime and cefprozil) are considered appropriate alternatives.

2.3 Current best evidence in the treatment of community-acquired pneumonia

The guidelines reviewed above differ in many respects: in the composition of the guidelines committees, in the extent of reporting about the literature review and guidelines formulation process, in the use of classification systems to assess evidence and rank recommendations, and in the content of the recommendations, be it in terms of diagnosis or treatment. Table 1 summarizes the main features of the guidelines.

A few common points also emerge from the above guideline review process: firstly, the importance of assessing the severity of disease and of the resulting decision to hospitalize was emphasized in all guidelines. Furthermore, all guidelines ac-

knowledge – with varying degrees of openness - that there is little evidence on which to base treatment recommendations, particularly concerning ambulatory patients. However, in the end, in most cases it remains unclear on what basis the specific treatment recommendations were made and exactly what evidence was used to substantiate these recommendations.

Consequently, the current project aims at identifying, evaluating and summarizing the evidence available from RCT with respect to the treatment of CAP in adult and adolescent outpatients.

Table 1: Characteristics and recommendations of clinical practice guidelines for the treatment of CAP

Guideline	Guideline formulation process			Routine diagnostic studies recommended			Treatment of outpatients	
	Primary care physician on guidelines committee	Search strategy reported in detail	Level of evidence stated for each recommendation	Chest x-ray	Gram stain	Sputum culture	Without modifying risk factors	With modifying risk factors
American Thoracic Society (2001)	no	no	no	yes	no	no	macrolide (azi, clari) or doxycycline	beta-lactam **plus** macrolide (azi, clari) or doxycycline
British Thoracic Society (2001)	yes	yes	yes	no	no	no	high-dose amoxicillin (500-1000mg po tid) 2nd choice: ery or clari	no separate recommendation
Canadian Community-Acquired Pneumonia Working Group (2000)	?	yes	yes	yes	no	no	macrolide (ery, azi, clari) 2nd choice: doxycycline	newer macrolide (azi, clari) or "respiratory" quinolone (see section 2.2.3 for details) 2nd choice: doxycycline
Infectious Diseases Society of America (2000)	?	no	yes	yes	yes	optional	"in no particular order": macrolide (ery, azi, clari), doxycycline, fluoroquinolone (levo, moxi, gati)	fluoroquinolones (levo, moxi, gati)

Abbreviations: azi=azithromycin, clari=clarithromycin, ery=erythromycin, gati=gatifloxacin, levo=levofloxacin, moxi=moxifloxacin

3. Objectives

The objectives of this review are:

1. To assess and compare the efficacy of individual antimicrobial therapies with respect to clinical, radiological and bacteriological outcomes in adult outpatients with CAP;

2. To assess and compare the efficacy of drugs across drug groups;

3. To make evidence-based practice recommendations if possible.

4. To assess the effect of drug schedule on adherence to treatment by carrying out an effectiveness analysis with open-label studies using different drug administration regimen.

4. Methods

Randomized controlled trials (RCT) are considered the gold standard in clinical research when it comes to establishing the efficacy of a treatment. This favoured status is attributable to the fact that RCT most closely mirror a scientific experiment in the classical sense and are least susceptible to bias. When properly conducted, they can lead to clear-cut conclusions about the relative efficacy of two treatments in a defined group of patients. Consequently, we chose to focus our review exclusively on RCT.

The following criteria were applied in selecting studies for inclusion into this review. The rationale underlying the decision to use each criterion is detailed in the following sections.

4.1 Study selection criteria

4.1.1 Types of studies

All randomized trials of antibiotics in adolescent and adult outpatients with CAP reporting on clinical parameters, cure rates or mortality were considered for inclusion.

4.1.2 Types of participants

Trials that included outpatients of either gender over 12 years of age in which pre-defined criteria for CAP were met as defined by the British Thoracic Society (2001) were included in this review.

4.1.3 Clinical Signs and Symptoms

CAP in outpatients is defined as follows by the British Thoracic Society (2001):

- Clinical definition, in the absence of a chest X-ray:

  - Symptoms of an acute lower respiratory tract (LRT) infection (cough and at least one other LRT symptom);
  - New focal chest signs on physical examination;
  - at least one systemic feature (either a symptom complex of sweating, fevers, shivers, aches and pains and/or temperature >38.0°C).
  - No other explanation for the illness, which is treated as pneumonia with antibiotics.

- Definition when a chest X-ray is available:

  - Symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation (e.g. not pulmonary oedema or infarction)
  - The illness is the primary clinical problem and is managed as pneumonia

4.1.4 Types of interventions

All double-blind randomized controlled comparisons of at least two antibiotics (or one antibiotic and a placebo) used to treat community-acquired pneumonia were included. Trials comparing two doses of the same drug were not included.

The perceived efficacy of antibiotics in pneumonia means that most of the available research deals with comparisons of two antibiotics. Comparisons involving intravenous drugs are usually carried out in a hospital setting. However, as this might occasionally be performed in an ambulatory setting, we did not a priori exclude studies dealing with intravenous drug applications.

Trials allowing concurrent use of other medications such as antitussives, antipyretics, bronchodilators, or mucolytics were included if they allowed equal access to such medications for patients in both arms of the trial.

4.1.5 Types of outcome measures

When available, the following outcomes measures were documented in each of the selected studies:

1. Clinical response: improvement of signs and symptoms. Where possible, duration of clinical signs and symptoms were used as outcome measures. We used a clinical definition of cure as the primary outcome since radiographic resolution lags behind clinical improvement (Macfarlane et al. 1984).
2. Radiologic response: resolution or improvement of a new finding on chest x-ray after antibiotic therapy
3. Bacteriologic response: negative sputum culture in patients previously found to have causative pathogens in their sputum.
4. Frequency of hospitalization.
5. Mortality.

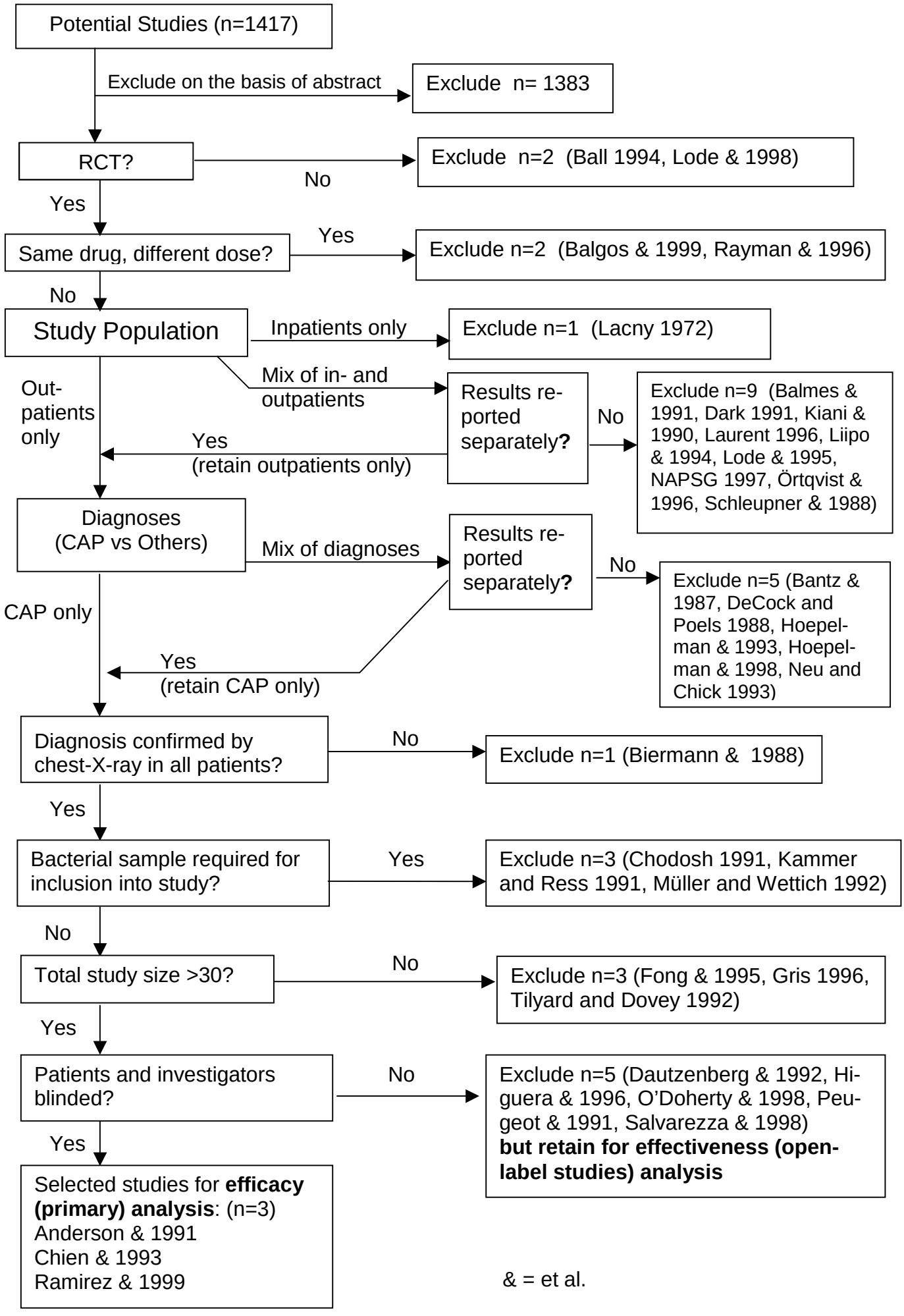
4.2 Search strategy for identification of studies

The Cochrane Acute Respiratory Infections Group's trial register, The Cochrane Library, EMBASE and MEDLINE (1966-December 31st 2001) were searched using the following terms: COMMUNITY-ACQUIRED INFECTION, PNEUMONIA, RESPIRATORY TRACT INFECTION, ANTIBIOTICS. Studies were also identified by checking the bibliographies of studies and review articles retrieved, and if necessary by contacting the first or corresponding authors of included studies. This search strategy yielded a total of 1417 references, some of which were double entries, due to the overlapping content of databases.

4.3 Selection process

Titles and abstracts of the identified citations were screened to exclude trials that clearly did not meet the inclusion criteria of the review. If it was felt that a trial might possibly meet the inclusion criteria, the full paper was obtained for further study. The most common reason for exclusion was that studies were conducted exclusively in hospitalized patients. Articles having passed this initial screen (34) were then reviewed independently by two reviewers (myself (LMB) and TJMV) to determine whether they met the inclusion criteria of the review. The selection process is shown graphically in Fig. 1.

Figure 1: Study selection process



& = et al.

Studies could be excluded for any one of the following reasons: if they were not truly randomized, if they only compared two doses of the same substance, if the results were not reported separately for inpatients and outpatients, or if the indication for treatment consisted of a mix of diagnoses (most commonly: acute bronchitis, exacerbation of chronic bronchitis, and pneumonia) and the results were not reported separately for each diagnostic group. Studies including only bacteriologically evaluable patients were excluded, because these patients are not necessarily typical of the spectrum encountered in primary practice. In order to avoid that patients with bronchitis or other non-pneumonia lower respiratory tract infections be included, we excluded studies that did not confirm the diagnosis of CAP by chest x-ray. Finally, studies were excluded if the total number of patients was less than 30, because below this limit, the estimate of a binomial parameter (in this case, the proportion of patients cured or improved) becomes unstable (Armitage and Berry 1994). Furthermore, when randomized controlled trials are too small, one can no longer safely assume that all potential confounders (both documented and undocumented) have been controlled for by being distributed equally between the two treatment groups (Rothman and Greenland 1998). For the primary analysis, we included only blinded RCT conducted in outpatients with CAP. Trials in which allocation to treatment or control group was not concealed (open-label studies) that otherwise fulfilled all other inclusion and exclusion criteria were retained for a sub-group analysis concerning the effect of drug schedule on compliance (effectiveness analysis) (see Fig.2 and Section 5.2.2).

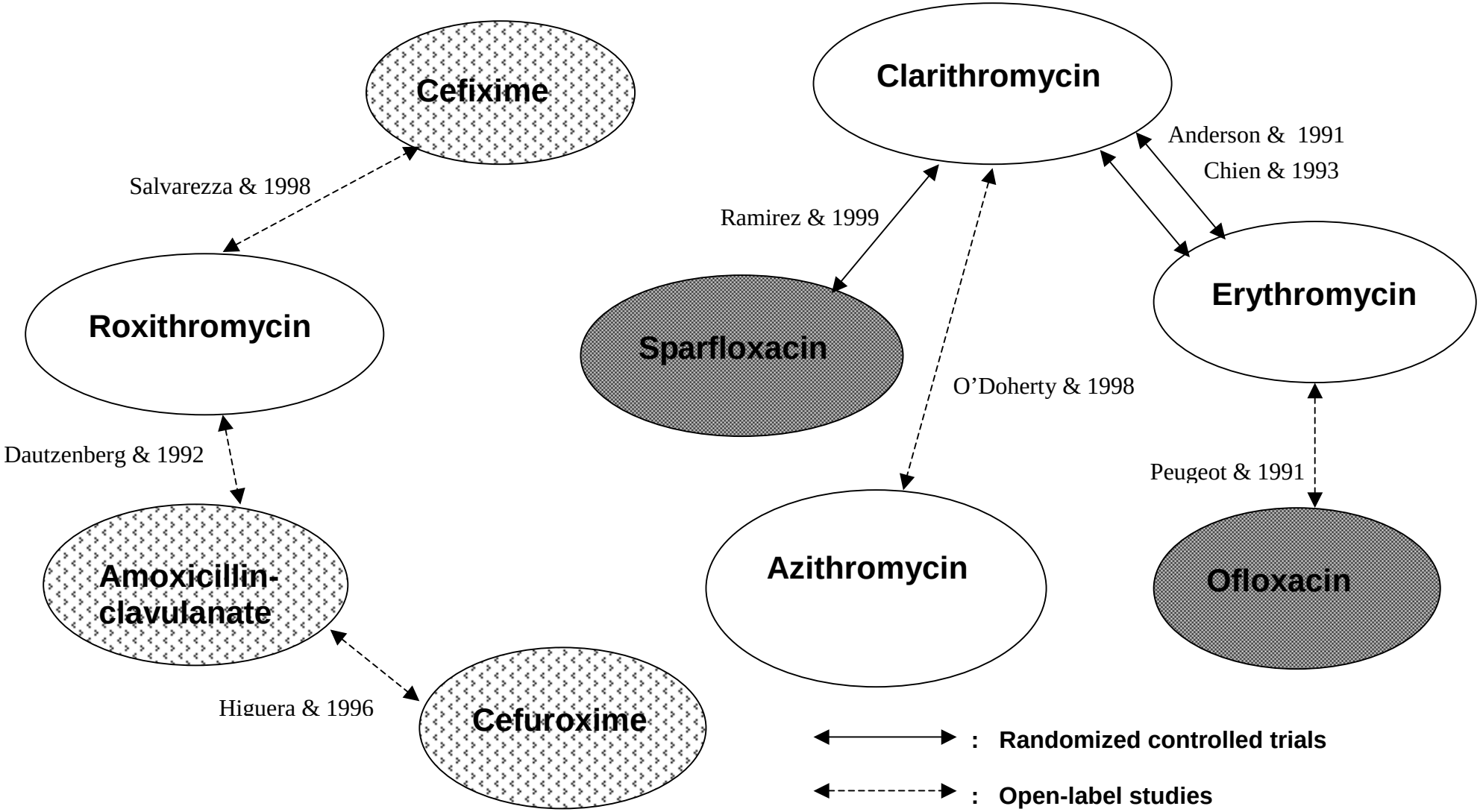


Figure 2: Antibiotic comparisons

4.4 Data extraction

The following data were extracted from each study whenever possible:

- description of participants (outpatients over 12 years)
- description of pathogens identified and their anti-microbial resistance profiles
- description of intervention
- description of control therapy
- total number of participants in each arm of the trial
- study setting
- mean duration of symptoms in each arm of the trial
- clinical, radiographic and bacteriologic cure rates in each arm of the trial
- proportion of patients admitted to hospital in each arm of the trial
- mortality rates in each arm of the trial
- study sponsor

The studies were assessed independently by 2 reviewers (LMB and TJMV) and disagreements were resolved by discussion and consensus. There were no irreconcilable disagreements. Reviewers were not blinded to the identity and affiliation of the study authors.

4.5 Analyses

For dichotomous outcome data, an estimate of the relative risk with approximate 95% confidence intervals was calculated. This was done using the Cochrane Collaboration's Review Manager software, version 4.1.

5. Results

5.1 Description of studies

The characteristics of the studies included in the primary analysis as well as in the effectiveness analysis are shown in Table 2. All studies except one (Peugeot et al. 1991) acknowledged the sponsorship of a corporate sponsor. Two of the open-label studies (Dautzenberg et al. 1992, Peugeot et al. 1991) included multiple diagnoses but provided separate data for CAP patients, so it was possible to include these studies into the review. Remarkably, four of the five open-label studies used different administration schedules for the drugs being tested within each study – for example, twice daily compared to four times daily. The effect of these differences on compliance will be examined (see Section 5.2.2).

Table 2: Drug administration schedules and other study characteristics

Study	Drug	Regimen			Sponsor	Multiple Diagnoses
		Dose	Frequency	Duration		
Double-blind studies						
Anderson & 1991	Clarithromycin	250 mg	bid	14 d		
	Erythromycin	500 mg	qid	14 d	Abbott	no
Chien & 1993	Clarithromycin	250 mg	bid	7-14 d		
	Erythromycin	500 mg	qid	7-14 d	Abbott	no
Ramirez & 1999	Clarithromycin	250 mg	bid	10 d		
	Sparfloxacin	200 mg*	qd	10 d	Rhône-Poulenc Rorer	no
Open-label studies						
Dautzenberg & 1992	Amoxi-Clav	500 mg + 125 mg	tid	14 d		
	Roxithromycin	150 mg	bid	14 d	Roussel	yes
Higuera & 1996 §	Amoxi-Clav	500 mg + 125 mg	tid	10 d		
	Cefuroxime	500 mg	bid	10 d	Glaxo Wellcome	no
O'Doherty & 1998	Azithromycin	500 mg	qd	3 d		
	Clarithromycin	250 mg	bid	10 d	Pfizer	no
Peugeot & 1991	Erythromycin	400 mg	qid	10 d		
	Ofloxacin	400 mg	bid	10 d	none declared	yes
Salvarezza & 1998	Cefixime	400 mg	qd	8-10 d		
	Roxithromycin	300 mg	qd	8-10 d	Hoechst Marion Roussel	no

* except Day 1: 400 mg loading dose

§ Investigators blinded to administration schedules, patients not blinded & = et al.

Abbreviations:

qd = once daily bid = twice daily tid = three times a day qid = four times a day

5.1.1 Number of trials and trial size

Three randomized controlled trials involving a total of 622 patients aged 12 years and older diagnosed with community-acquired pneumonia were included in the primary analysis (Anderson et al. 1991, Chien et al. 1993, Ramirez et al. 1999). Five open-label randomized, but unblinded trials including a total of 405 patients and meeting all other inclusion/exclusion criteria were retained for sub-group analyses of effectiveness and compliance (Dautzenberg et al. 1992, Higuera et al. 1996, O'Doherty et al. 1998, Peugeot et al. 1991, Salvarezza et al. 1998). The trials in the primary analysis included varying numbers of patients, the largest having 342 patients (Ramirez et al. 1999), the smallest 107 (Anderson et al. 1991). The median trial size in the primary analysis was 173 patients, the mean size 207; in the effectiveness analysis, the median size was 60 and the mean size 81.

5.1.2 Diagnoses

All three trials in the primary analysis exclusively enrolled patients with community-acquired pneumonia. Two of the open-label trials (Dautzenberg et al. 1992, Peugeot et al. 1991) also included patients with other diagnoses, usually acute bronchitis or acute exacerbation of chronic bronchitis, but reported results separately for each diagnostic group, so that it was possible to extract data separately for pneumonia patients.

5.1.3 Diagnostic criteria

In all trials, the diagnosis of community-acquired pneumonia was based on clinical signs and symptoms as well as confirmation by radiographic findings in all patients. The signs and symptoms used as diagnostic criteria included combinations of the following: fever, chills, recent onset of productive cough, pleuritic chest pain, dyspnoea, pyrexia, tachypnoea, dullness to percussion, egophony, rales, localized reduced breath sounds and bronchial breath sounds.

5.1.4 Out- vs Inpatients

In all trials, patients were treated exclusively as outpatients.

5.1.5 Patient inclusion and exclusion criteria

Two trials (Anderson et al. 1991, Ramirez et al. 1999) in the primary analysis included only adult patients, one (Chien et al. 1993) also included adolescents (12 years of age and older). In the open-label trials, two trials reported including patients 12 years of age and older (Higuera et al. 1996, O'Doherty et al. 1998) and one trial (Dautzenberg et al. 1992), patients as old as 90. Only one of the studies used older age (>75 years) as an exclusion criterion (O'Doherty et al. 1998). Overall, the trials excluded patients with conditions that could have affected the treatment or interfered with follow-up. Exclusion criteria were reported in more or less detail in the various study reports. The most common criteria reported were: pregnancy and lactation, women not using adequate contraception (usually oral contraceptives or a barrier method), history of allergic reaction to the study drugs, recent treatment with or con-

comitant use of an antimicrobial agent, concurrent medication with ergotamine, cyclosporin, antacids (except H2-antagonists) or digitalis, conditions affecting GI absorption, severe renal or hepatic impairment, terminal illness or conditions precluding study completion, infectious mononucleosis, HIV/AIDS, and prior participation in the study.

5.1.6 Antibiotics

The trials varied with respect to the antibiotics studied (see Fig. 2). Two trials in the primary analysis (Anderson et al. 1991, Chien et al. 1993) studied the same antibiotic pair (clarithromycin and erythromycin). The other trial (Ramirez et al. 1999) studied a different antibiotic pair, namely clarithromycin and sparfloxacin. Antibiotic pairs studied in open-label trials were: Dautzenberg et al. 1992: amoxiclav vs roxithromycin; Higuera et al. 1996: amoxiclav vs cefuroxime; O'Doherty et al. 1998: azithromycin vs clarithromycin; Peugeot et al. 1991: erythromycin vs ofloxacin; Salvarezza et al. 1998: cefixime vs roxithromycin (see Fig. 2).

5.1.7 Methodological quality of included studies

All three trials included in the primary analysis were randomized, double-blind studies comparing two antibiotics. The extent of reporting was variable between studies. None of the studies clearly stated the randomization method used. None of the articles reported any test of effectiveness of the blinding procedures used. Compliance with treatment was assessed by pill count in two studies (Anderson et al. 1991, Chien et al. 1993); neither reported any difference in the number of pills re-

maining between the two groups, however in the Chien et al. (1993) study, forty patients were excluded because they received "less than the minimum therapy" (7 days) and these patients were distributed unevenly across the two groups (10 in the clarithromycin group and 30 in the erythromycin group). The third study (Ramirez et al. 1999) reports having assessed patient compliance but does not state how. Regarding co-interventions with other medications, most studies excluded patients whose co-medication included certain drugs such as other antibiotics, chemotherapeutics or antiretrovirals. Only one study (Chien et al. 1993) reported how many patients were excluded because of forbidden co-medication. Withdrawals were reported by all studies with varying degree of detail as to the reasons for withdrawal. The number of patients lost to follow-up was reported in all three studies. Losses to follow-up appeared to be minor, amounting to a maximum of 10% of the initially randomized patients.

5.2 Study results

5.2.1 Efficacy analysis (“primary analysis”)

The success rates for each of the treatment arms of the three trials are shown in Table 3. "Success" was defined as cure or improvement, be it clinical, bacteriological or radiological, as assessed at a predefined follow-up visit that took place between 7 and 14 days after initiation of therapy. None of the clinical, bacterial or radiological success rates differed significantly among treatment arms within each of the studies, nor did they achieve clinical significance when the results of the two studies comparing clarythromycin with erythromycin (Anderson et al. 1991 and Chien et al. 1993) were pooled together.

To assess this, we pooled the outcomes of the two studies (Anderson et al. 1991 and Chien et al. 1993) and calculated relative “risks” (RR) of success, be it clinical, bacteriological or radiological. These analyses were performed using the Cochrane collaboration’s Review Manager Software Version 4.1, and illustrated graphically using the MetaView software, a subset of the Review Manager package (see Fig. 3, 4 and 5).

Table 3: Clinical, bacteriological and radiological cure rates

Study	Drug	Clinical success		Bacteriological success		Radiological success	
		%	n cured / N total	%	n cured / N isolated	%	n cured / N x-rayed
Double-blind studies							
Anderson & 1991	Clarithromycin	98%	63/64	89%	8/9	90%	55/61
	Erythromycin	91%	39/43	100%	5/5	90%	38/42
Chien & 1993	Clarithromycin	97%	89/92	88%	23/26	96%	88/92
	Erythromycin	96%	78/81	100%	17/17	96%	78/81
Ramirez & 1999	Clarithromycin	83%	145/175	91%	74/81	Not reported separately	
	Sparfloxacin	80%	133/167	97%	64/66		
Open-label studies							
Dautzenberg & 1992	Amoxi-Clav	63%	10/16	No specimen taken		Not reported separately	
	Roxithromycin	93%	14/15				
Higuera & 1996	Amoxi-Clav	100%	55/55	93%	37/40	Not reported separately	
	Cefuroxime	96%	49/51	94%	32/34		
O'Doherty & 1998	Azithromycin	94%	83/88	97%	31/32	Not reported separately	
	Clarithromycin	95%	84/88	91%	32/35		
Peugeot & 1991	Erythromycin	100%	13/13	Not reported separately		92%	12/13*
	Ofloxacin	100%	19/19			94%	18/19*
Salvarezza & 1998	Cefixime	94%	28/30	95%	20/21	97%	28/29
	Roxithromycin	100%	30/30	100%	19/19	90%	27/30

* one patient per group not followed up by x-ray

Definitions of success:

clinical success = cure or improvement
radiological success = resolution or improvement
bacteriological success = eradication of a previously identified pathological strain

& = et al.

Figure 3: Clinical success (pooled results)

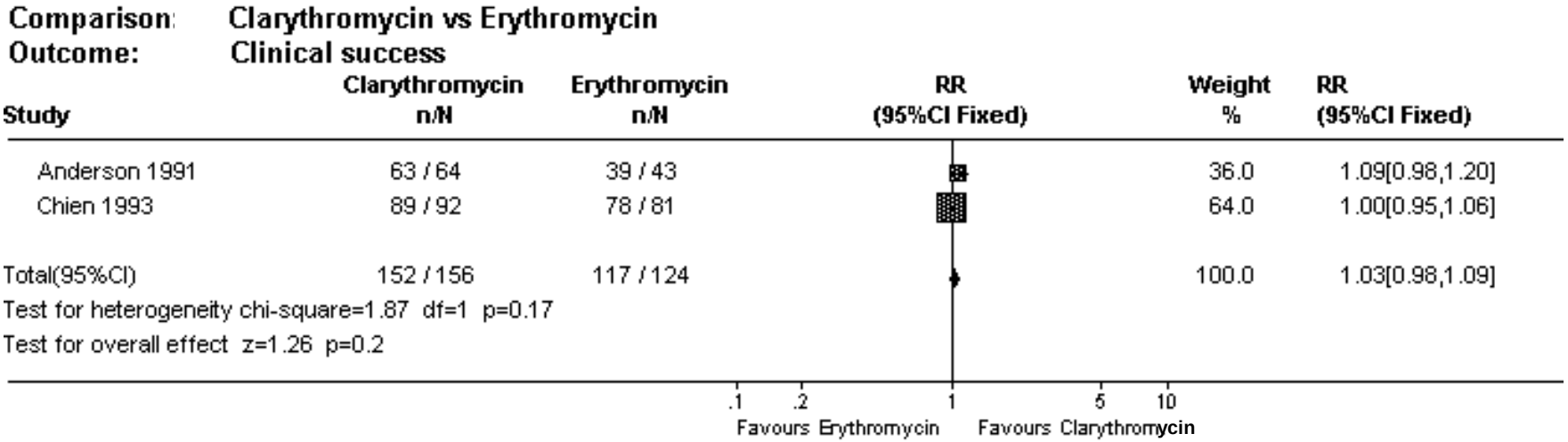


Figure 4: Bacteriological success (pooled results)

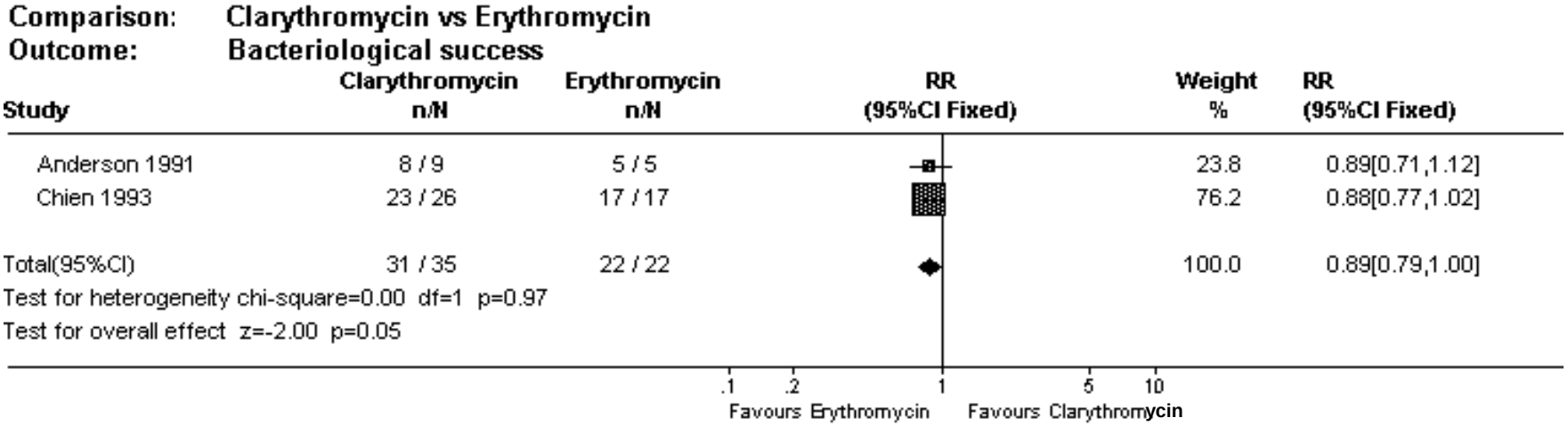
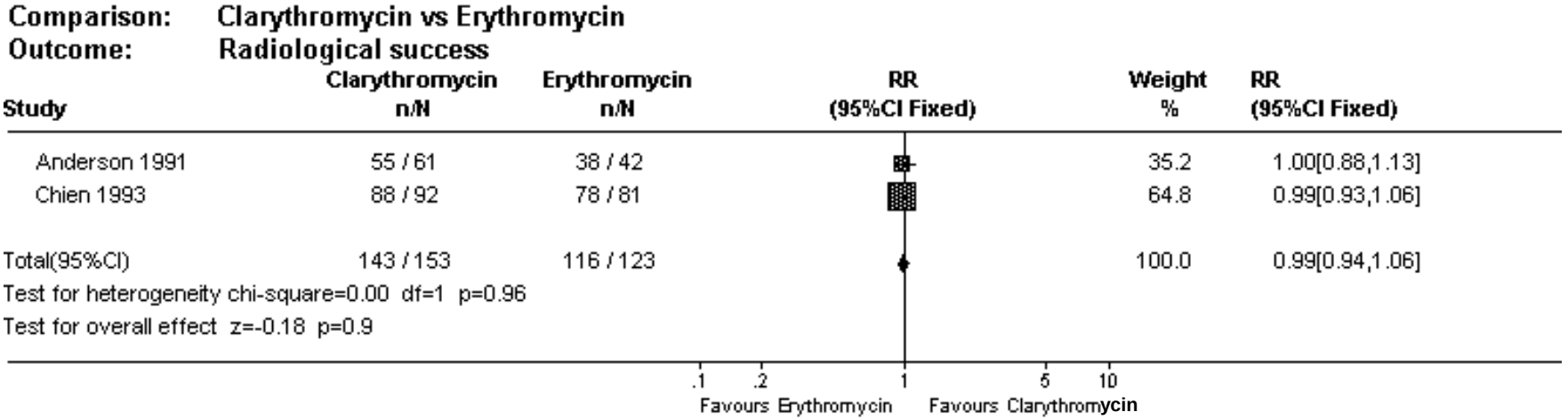


Figure 5: Radiological success (pooled results)



It can be seen in figures 3 to 5 that all RR are close to the null value of 1, and all confidence intervals include or abut on 1, thereby indicating no significant difference in the respective success rates of treatment with clarythromycin and erythromycin. In the case of bacteriological success, there appears to be a tendency favouring erythromycin, however this does not achieve statistical significance.

5.2.1.1 Comparisons across antibiotic groups

The only comparison across antibiotic groups is provided by the study by Ramirez et al. (1999), whereby a macrolide (clarithromycin) and a quinolone (sparfloxacin) were compared. Again, there was no significant difference in clinical or bacteriological success (see Table 3); radiological outcomes were not reported separately for the two treatment arms.

5.2.1.2 Side-effects

There were, however, significant differences in the occurrence of side-effects attributed to the study drug in the two studies comparing clarithromycin with erythromycin (Anderson et al. 1991 and Chien et al. 1993) (Table 4). In both cases, there were significantly more side-effects in the erythromycin group, the majority being gastrointestinal side-effects. This was not, however, reflected in the rate of side-effects leading to withdrawal from the study, which was not significantly different across treatment arms.

Table 4: Reasons for exclusion from efficacy analyses and drug-related side-effects

Study	Drug	Regimen			Reasons for exclusion from efficacy analyses				Adverse events			
					Less than minimum therapy		Loss to follow-up		Total (drug-related)		Leading to withdrawals	
		Dose	Frequency	Duration	N / total N excluded	%	N / total N excluded	%	N / total N enrolled	%	N / total N enrolled	%
Double-blind studies												
Anderson & 1991	Clarithromycin	250 mg	bid	14 d	4/32	13%	0/32	0%	15/96*	16%	4/96	4%
	Erythromycin	500 mg	qid	14 d	16/68	24%	1/68	1%	37/112*	33%	21/112	19%
Chien & 1993	Clarithromycin	250 mg	bid	7-14 d	20/41	49%	6/41	15%	34/133*	26%	6/133	5%
	Erythromycin	500 mg	qid	7-14 d	43/54	80%	5/54	9%	76/135*	56%	37/135	27%
Ramirez & 1999	Clarithromycin	250 mg	bid	10 d	10/48 $	21%	7/48	15%	47/175	27%	10/175	6%
	Sparfloxacin	200 mg*	qd	10 d	10/42 $	24%	6/42	14%	42/167	25%	14/167	8%
Open-label studies												
Dautzenberg & 1992 !	Amoxi-Clav	500 mg + 125 mg	tid	14 d	Not reported		13/477 3% (both groups combined)		67/242*	28%	21/242	9%
	Roxithromycin	150 mg	bid	14 d	Not reported				21/235*	9%	3/235	1%
Higuera & 1996 §	Amoxi-Clav	500 mg + 125 mg	tid	10 d	56#/162 35% (both groups combined)		Not reported		6/78	8%	Not reported	
	Cefuroxime	500 mg	bid	10 d			Not reported		3/84	4%	Not reported	
O'Doherty & 1998	Azithromycin	500 mg	qd	3 d	1/101	1%	Not reported		14/101	14%	0/101	0%
	Clarithromycin	250 mg	bid	10 d	4/102	4%	Not reported		13/102	13%	2/102	2%
Peugeot & 1991 !	Erythromycin	400 mg	qid	10 d	Not reported		Not reported		4/28	14%	0/28	0%
	Ofloxacin	400 mg	bid	10 d	Not reported		Not reported		8/28	29%	2/28	7%
Salvarezza & 1998	Cefixime	400 mg	qd	8-10 d	Not reported		Not reported		0/30	0%	0/30	0%
	Roxithromycin	300 mg	qd	8-10 d	Not reported		Not reported		0/30	0%	0/30	0%

Footnotes:

* = significant difference between treatment groups of a given study
! = results are for all patients in study (all diagnoses combined), results for pneumonia were not reported separately
§ = investigators blinded, patients not blinded
$ = includes "protocol deviations" (not further specified)
# = "clinically unevaluable" (less than 3 days of therapy, resistant pathogen in pre-treatment culture, other protocol deviation)

& = et al.

5.2.1.3 Bacterial pathogens

Various bacterial pathogens were identified with varying frequency across studies (see Table 5). The proportion of samples yielding an identifiable pathogen ranged from 19% (Anderson et al. 1991) to 43% (Ramirez et al. 1999). Anderson et al. (1991) reported on a majority of cases being positive for Haemophilus influenzae (62% of positive cultures) with *S. pneumoniae* (18%) being second most common, whereas Chien et al. (1993) predominantly identified *Streptococcus pneumoniae* as the causative organism in 56% of cultures, with *H. influenzae* taking second place at 40%. On the contrary, *Haemophilus parainfluenza*e (31%) was the most commonly identified pathogen in the study by Ramirez et al. (1999), with *H. influenzae* (23%) in second place.

Table 5: Eradication rates and proportional importance of bacterial pathogens

Study	Bacterial isolates: n isolated/Total N sampled		Pathogens as % of all isolates											
			Gram-negative aerobes								Gram-positive aerobes			
			H. influenzae		*H. parainfluenzae*		*H. parahaemolyticus*		*M. catarrhalis*		*S. Pneumoniae*		*Staph. Aureus*	
Double-blind studies														
Anderson &1991	39/208	19%	24/39	62%	5/39	13%	******	******	3/39	8%	7/39	18%	******	******
Chien & 1993	43/173	25%	17/43	40%	2/43	5%	******	******	******	******	24/43	56%	******	******
Ramirez & 1999	147/342	43%	34/147	23%	45/147	31%	8/147	5%	******	******	18/147	12%	5/147	3%
Open-label studies														
Dautzenberg & 1992	***** **Not tested** ******													
Higuera & 1996 §	97/162	60%	17/97	18%	*******		*******		*******		37/97	38%	*******	
O'Doherty & 1998	66/203	33%	34/67	51%	*******		*******		9/67	13%	6/67	9%	2/67	3%
Peugeot & 1991	6/32	19%	3/6	50%	*******		*******		*******		3/6	50%	*******	
Salvarezza & 1998	37/58	64%	3/37	8%	*******		*******		3/37	8%	26/37	70%	*******	

§ = investigators blinded, patients not blinded
& = et al.

5.2.1.4 Serologically identified pathogens

Only two of the three studies carried out serologic tests to identify putative pathogens (Anderson et al. 1991 and Chien et al. 1993; see Table 6). In both these studies, the most frequently identified pathogen was *Mycoplasma pneumoniae*, which represented 69% (Anderson et al. 1991) and 74% (Chien et al. 1993) of positive serology results. *Chlamydia pneumoniae* accounted for the remainder with 38% (Anderson et al. 1991) and 26% (Chien et al. 1993) respectively. There were no samples positive for *Legionella pneumoniae* or for *Chlamydia psittaci* in either study.

Table 6: Proportional importance of serologically identified pathogens

Study	**Serology: positive serologic tests**				
	n positive / total N tested	*Mycoplasma pneumoniae*	*Chlamydia pneumoniae*	*Legionella pneumoniae*	*Chlamydia psittaci*
Double-blind studies					
Anderson & 1991	16/208° 8%	11/16 69%	6/16 38%	*******	*******
Chien & 1993	27/173 16%	20/27 74%	7/27 26%	*******	*******
Ramirez & 1999		*****	**Not tested**	******	
Open-label studies					
Dautzenberg & 1992		*****	**Not tested**	******	
Higuera & 1996		*****	**Not tested**	******	
O'Doherty & 1998	7/203 3%	4/7 57%	1/7 14%	2/7 29%	*******
Peugeot & 1991	2/32 6%	*******	2/2 100%	*******	*******
Salvarezza & 1998	10/60 17%	5/10 50%	*******	*******	5/10 50%

° = one patient was positive for both *M. pneumoniae* and *C. pneumoniae*
& = et al.

5.2.2 Effectiveness analysis (open-label studies)

All of the trials in the effectiveness analysis were randomized open-label or single-blind studies comparing two antibiotics. In one of the studies (Higuera et al. 1996), the investigator were blinded to the treatment insofar as the drugs were dispensed by a pharmacist or study coordinator and the patients were instructed not to discuss the frequency of dosing with the investigator. All studies except one (Salvarezza et al. 1998) compared different dosage regimen (see Table 2), whereby one drug was given at a higher frequency (twice vs four times daily; Peugeot et al. 1991); in some cases, one of the drugs was also given over a longer time period (ten vs three days; O'Doherty et al. 1998). Only two of the studies (Salvarezza et al. 1998, Higuera et al. 1996) clearly stated the randomization method used. Compliance with treatment was assessed by pill count as well as urine testing in one of the studies (Higuera et al. 1996). Most studies excluded patients who received co-medication with certain drugs, such as other antibiotics, chemotherapeutics or anti-retrovirals. Only one study (O'Doherty et al. 1998) reported how many patients were excluded because of forbidden co-medication. One other study (Higuera et al. 1996) reported that patients were excluded on these grounds but did not report how many patients were thereby excluded. None of the studies reported losses to follow-up; therefore, it is not possible to quantify the extent of the problem. In most studies, withdrawals were reported along with the reasons for withdrawal.

5.2.2.1 Effect of administration schedule on adherence to treatment

It would be reasonable to assume that a higher frequency and longer duration of drug administration would impose a burden on patients that could result in de-

creased compliance. In order to test this hypothesis, I extracted data on losses to follow-up and patients receiving “less than minimum therapy” for all open-label studies (see Table 4). Unfortunately, four studies (Higuera et al. 1996, O’Doherty et al. 1998, Peugeot et al. 1991, Salvarezza et al. 1998) did not report on losses to follow-up and the only study that did (Dautzenberg et al. 1992) pooled the results of both treatment groups together, making it impossible to determine whether there was any differential loss to follow-up across treatment groups. Likewise, three studies (Dautzenberg et al. 1992, Peugeot et al. 1991, Salvarezza et al. 1998) did not report how many patients received “less than minimum therapy”. One of the studies that did (Higuera et al. 1996) reported combined results for both treatment groups. Finally, O’Doherty et al. (1998) reported results separately for both treatment groups, and these were not significantly different from each other.

Therefore, due to inadequate reporting, it was not possible to draw any conclusions about the effect of administration schedules on compliance.

6. Discussion

6.1 Evidence

The overwhelming feature of this systematic review is the utter paucity of relevant studies that could be identified and included in the review. Given this current state of affairs, it is not possible to make solid evidence-based recommendations for the treatment of community-acquired pneumonia in ambulatory outpatients. One important reason for this lack of evidence is that a large number of the trials originally identified were conducted in hospitalized patients and were therefore excluded because they were not directly relevant to the treatment of ambulatory patients.

Another remarkable feature of the collected studies is the incompleteness of the reporting. This further complicated matters by making it difficult or impossible to compare and combine the available results in a meaningful way. Finally, the heterogeneity of the antibiotic pairs studied precludes pooling study results quantitatively.

6.2 Methods

It could be argued that the inclusion/exclusion criteria for this review were too strict and that this is the reason why so few studies were retained. I do, however, believe that the criteria I applied were necessary in order to validly address the question of the efficacy of treatment of CAP in ambulatory patients. In particular, it could be argued that the decision to exclude studies based on size is not desirable, since one aim of the review is to pool results and that each study therefore would contribute some information. I felt, however, that this criterion was necessary to exclude studies where the number of patients with pneumonia was so small that randomiza-

tion could no longer be expected to achieve a balanced distribution of confounders, both known and unknown, across study groups. Finally, arguing retrospectively, it can be seen that dropping size as an exclusion criteria would not have made much difference to the results obtained, as the three excluded studies would have contributed a total of 23 (Fong et al. 1995), 6 (Gris 1996) and 8 (Tilyard and Dovey 1992) patients respectively, thereby only increasing the size of the primary analysis group by 5.9 % (from 622 to 659). Furthermore, the study by Fong et al. (1995) being an open-label study, it would only have been included in the effectiveness analysis.

As for the requirement that the diagnosis of CAP be confirmed by a chest radiograph, I felt that this was necessary to avoid diagnostic misclassification, which could have led to inclusion of patients with bronchitis into the review.

6.3 Implications for practice

Currently available evidence from RCT is insufficient to make truly evidence-based recommendations for the treatment of community-acquired pneumonia. Individual study results do not reveal significant differences in efficacy between various antibiotics and antibiotic groups. Until better evidence becomes available, practitioners should favour shorter course therapies with lower drug costs whenever possible as a means of enhancing compliance and reducing expenses, while still taking into account the regional resistance profiles prevalent in their area of practice as well as the characteristics of each patient.

National guidelines may provide additional decision-making support, but clinicians should keep in mind that current guideline recommendations for the treatment of CAP in ambulatory patients are based on very scanty evidence.

6.4 Implications for research

Multi-drug, multi-drug-group double-blind comparisons using similar administration schedules and carried out in the ambulatory setting are needed to provide the evidence necessary for practice recommendations if these are to be applicable to outpatient treatment. Study conditions should ensure that diagnosis and management of patients with community-acquired pneumonia are as similar as possible to real practice, while still ensuring that the study question is addressed in a valid way. Whether a study of this extent and character would find the necessary funding is, however, doubtful.

7. Summary

BACKGROUND

Community-acquired pneumonia (CAP) is a common condition representing a significant disease burden for the community, particularly for the elderly. It also contributes significantly to health care expenditures and antibiotic use, which is associated with well-known problems of resistance. Although many studies have been published concerning CAP and its treatment, there is no concise summary of the available evidence and only few guidelines that can help clinicians in choosing the most appropriate antibiotic

OBJECTIVES

The goal of this study was to summarize the evidence currently available from randomized controlled trials (RCT) concerning the efficacy of antiobiotic treatment of CAP in ambulatory adolescent and adult patients and to formulate evidence-based practice recommendations.

SEARCH STRATEGY

The Cochrane Acute Respiratory Infections Group's trial register, The Cochrane Library, MEDLINE and EMBASE were searched using the following terms: COMMUNITY-ACQUIRED INFECTION, PNEUMONIA, RESPIRATORY TRACT INFECTION, and ANTIBIOTICS up to and including December 31st 2001. Studies were also identified by checking the bibliographies of the articles retrieved.

SELECTION CRITERIA

All randomized controlled trials in which one or more antibiotics were tested for the treatment of CAP in ambulatory adolescent or adult patients were considered for inclusion. Studies testing one or more antibiotics and reporting the diagnostic criteria used in selecting patients as well as the clinical outcomes achieved were included. No language restrictions were applied.

DATA COLLECTION & ANALYSIS

Study reports were assessed and data extracted using predefined criteria. Authors of studies were contacted as needed to resolve any ambiguities in the study reports. The data were analyzed using the Cochrane Collaboration's Review Manager 4.1 Software.

MAIN RESULTS

Three randomized controlled trials involving a total of 622 patients aged 12 years and older diagnosed with community-acquired pneumonia were included. The quality of the studies and of the reporting was variable. A variety of clinical, radiological and bacteriological diagnostic criteria and outcomes were reported. Overall there was no significant difference in the efficacy or effectiveness of the various antibiotics under study. However, the available evidence is too incomplete to form a solid basis for making evidence-based recommendations.

Five open-label studies were retained in order to carry out an effectiveness analysis to assess the impact of different drug regimen on patient compliance. Unfor-

tunately, the reporting of losses to follow-up was so incomplete that it precluded drawing any conclusions about this question.

CONCLUSIONS

Currently available evidence from randomized controlled trials is insufficient to make evidence-based recommendations for the treatment of community-acquired pneumonia. Pooling of study data was limited by the very low number of studies, by their heterogeneity and by incomplete reporting of study results. Individual study results do not reveal significant differences in efficacy between various antibiotics and antibiotic groups. Multi-drug comparisons using similar administration schedules are needed to provide the evidence necessary for practice recommendations. Until better evidence becomes available, practitioners should favour shorter course therapies with lower drug costs whenever possible as a means of enhancing compliance and reducing expenses, while still taking into account the regional resistance profiles prevalent in their area of practice as well as the clinical course of each patient.

8. Zusammenfassung (Summary in German)

EINLEITUNG

Die ambulant erworbene Pneumonie (AEP) ist eine häufige, oft schwere Erkrankung von großer Bedeutung für die Bevölkerung, die insbesondere für ältere Patienten kompliziert verlaufen kann. Die übliche Behandlung der AEP besteht in der Gabe von Antibiotika. Dies trägt u.a. zur Zunahme von Antibiotikaresistenzen bei. Obwohl bereits viele Studien zur Behandlung der AEP veröffentlicht wurden, gibt es keine aktuelle Zusammenfassung der vorhandenen Evidenz und nur einzelne Leitlinien, die den behandelnden Arzt bei der Wahl eines Antibiotikums unterstützen.

ZIEL

Ziel dieser Studie war es, die vorhandene Evidenz randomisierter, kontrollierter Studien (RCT) bzgl. der AEP Behandlung bei ambulanten Patienten zusammenzufassen und ggf. eine evidenz-basierte Leitlinie/Therapieempfehlung zu formulieren.

METHODEN

Eine umfassende elektronische und manuelle Literatursuche wurde durchgeführt mit dem Ziel, alle RCT zu identifizieren, in denen zwei oder mehr Antibiotika für die Behandlung der AEP geprüft wurden. Die Cochrane Library, MEDLINE und EMBASE (bis einschließlich 31.12.2001) wurden mit folgenden Suchbegriffen durchsucht: COMMUNITY-ACQUIRED INFECTION, PNEUMONIA, RESPIRATORY TRACT INFECTION und ANTIBIOTICS. Die Literaturverzeichnisse der ausgewählten Studien wurden auf weitere relevante Artikel durchsucht. Alle RCT, die ein oder mehrere Antibiotika prüften und deren diagnostische Kriterien und Outcomes dargestellt

waren, wurden eingeschlossen. Es wurden keine Spracheinschränkungen verwendet. Die jeweiligen Artikel wurden begutachtet und deren Inhalt mit der Software „Review Manager“ (Version 4.1) in standardisierter Form extrahiert.

ERGEBNISSE

Es wurden drei Studien gefunden, die die Einschlusskriterien erfüllen. Die Studien umfassten insgesamt 612 Patienten mit einer ambulant erworbenen Pneumonie. Verschiedene klinische, bakteriologische und radiologische Endpunkte wurden berichtet. Die vorhandene Evidenz wurde zusammengefasst und beurteilt. Insgesamt gab es keinen wesentlichen Unterschied zwischen den verschiedenen Präparaten bezogen auf die Wirksamkeit oder damit verbundene unerwünschte Arzneimittelwirkungen. Jedoch ist die vorhandene Evidenz zu unvollständig, um eine einheitliche evidenz-basierte Leitlinie oder Therapieempfehlungen formulieren zu können.

Fünf randomisierte Studien ohne Verblindung wurden in einer Effektivitätsanalyse beurteilt, um den Einfluss verschiedener Therapiepläne auf die Patientencompliance zu evaluieren. Leider wurden Therapieabbrüche so unvollständig berichtet, dass es unmöglich war, Schlussfolgerungen aus diesen Daten zu ziehen.

SCHLUSSFOLGERUNGEN

Die zur Zeit vorhandene Evidenz von randomisierten kontrollierten Studien ambulanter Patienten reicht nicht aus, um evidenz-basierte Therapieempfehlungen zu formulieren. Die Zusammenfassung der Studienergebnisse wurde durch die niedrige Studienzahl, die Heterogenität der Studien und die Unvollständigkeit der Studienberichte stark eingeschränkt. Einzelne Studienergebnisse zeigen keinen signifikan-

ten Unterschied in der Wirksamkeit der verschiedenen Antibiotika. Randomisierte kontrollierte Blindstudien, in denen mehrere Antibiotika aus verschiedenen Gruppen miteinander verglichen werden, sind erforderlich, um evidenz-basierte Therapieempfehlungen formulieren zu können. Bis solche Evidenz zur Verfügung steht, sollten behandelnde Ärzte kurze Therapien mit geringen Kosten bevorzugen. Dabei sollten die Charakteristika der einzelnen Patienten und, soweit vorhanden, regionale Resistenzprofile berücksichtigt werden.

9. Appendices

9.1 List of abbreviations

CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
DRSP	Drug-resistant *Streptococcus pneumoniae*
ICU	Intensive care unit
LRT	Lower respiratory tract
RCT	Randomized controlled trial
RR	Relative risk

qd	once daily
bid	twice daily
tid	three times a day
qid	four times a day
po	by mouth
iv	intravenous

MMK	Prof. Michael M. Kochen
TJMV	Prof. Theo V.M. Verheij
LMB	Lise M. Bjerre

9.2 List of figures

9.3 List of tables

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Finally, I also wish to extend my thanks to all my colleagues in the Department of Family Medicine here at Göttingen University for stimulating discussions, helpful suggestions, good company and strong support throughout.

Curriculum Vitae

I, Lise Marie Bjerre, was born on May 23rd, 1969 in Montreal, Quebec, Canada, the first-born child of Poul Bjerre, MSEng, MBA, electrical engineer, and of Dr. Carmen Couillard Bjerre, BA, MSW, PhD, social worker.

From 1975 to 1981, I attended grade school in my home-town of Brossard, a suburb of Montreal, and, from 1981 to 1986, Jean-de-la-Mennais high school in the nearby town of LaPrairie, from which I graduated in June of 1986 with a Diploma of Secondary Studies (Diplôme d'études secondaires; DÉS). I attended Champlain College (St-Lambert Campus) from 1986 to 1989, obtaining a Diploma of Collegial Studies in Pure and Applied Sciences (Diplôme d'études collégiales; DÉC).

In 1989, I was admitted to Concordia University (Montreal), where I obtained a Bachelor of Science with Honours in Biology (BSc Hon.). In addition, I completed the Science College Program, a multidisciplinary program for gifted science students. After graduating from Concordia University in 1993, I pursued a Master of Science in Epidemiology (MSc) at McGill University (Montreal) under the supervision of Prof. Olli S. Miettinen, which I obtained in 1995. From 1995 to 1999, I attended McGill University Medical school (Montreal), from which I graduated with the degree of Doctor of Medicine, Master of Surgery (MDCM) in May of 1999.

In the fall of 1999, I got married and moved to my husband's native Germany. Since the 15th of November 1999, I have been working as a research fellow and family medicine resident in the Department of Family Medicine of Göttingen University. I completed my training as a resident intern ("Arzt im Praktikum"), obtaining the Ger-

man certification as a physician (“Approbation”) on April 20th 2001. I continued my clinical training as a resident until the 31st of December 2001. Since then I have taken a one-and-a-half year leave of absence from clinical work in order to complete a research project (PhD thesis, Department of Epidemiology and Biostatistics, McGill University) in collaboration with Prof. Jacques LeLorier (Université de Montréal) and Prof. Michal Abrahamowicz (McGill University), for which we successfully obtained funding. I also continue to work on a part-time basis in the Department of Family Medicine. I plan on completing my residency training in Family Medicine starting in July 2003, after finishing the PhD research project.

Göttingen, November 2002

Lebenslauf

Ich, Lise Marie Bjerre, wurde am 23. Mai 1969 als erstes Kind des Diplomingenieurs Poul Bjerre und seiner Ehefrau, der Sozialarbeiterin Dr. Carmen Couillard Bjerre, in Montreal (Kanada) geboren.

Von 1975 bis 1981 besuchte ich die Grundschule in meiner Heimatstadt Brossard, einem Vorort von Montreal. Nach dem Wechsel auf die Jean-de-la-Mennais-Hochschule in der Nachbarstadt LaPrairie konnte ich 1986 die Abiturprüfung ablegen (Diplôme d'études secondaires; DÉS). Von 1986 bis 1989 lernte ich am Champlain College (St Lambert Campus), an dem ich das Kollegdiplom in Natur- und angewandten Wissenschaften erlangte (Diplôme d'études collégiales en sciences pures et appliquées; DÉC).

Von 1989 bis zum erfolgreichen Abschluss des „Bachelor of Science with Honours in Biology" (BSc Hon.) im Jahr 1993 studierte ich an der Universität Concordia (Montreal). Parallel dazu habe ich den Studiengang des "Science College Program", einem multidisziplinären Programm für begabte Studenten der Naturwissenschaften, erfolgreich absolviert. Anschließend absolvierte ich von 1993 bis 1995 ein Aufbaustudium im Bereich Epidemiologie an der McGill University (Montreal) unter Betreuung von Prof. Olli S. Miettinen; den Abschluss „Master of Science in Epidemiology" (MSc) erlangte ich 1995. Von 1995 bis 1999 studierte ich an der medizinischen Hochschule der McGill Universität (Montreal) und beendete erfolgreich das Medizinstudium mit der Erlangung des Titels „Doctor of Medicine, Master of Surgery**"** (MDCM) im Mai 1999.

Im Herbst 1999 heiratete ich und emigrierte mit meinem deutschen Mann, Dr. rer. nat. Christoph Läer, Dipl. Epid., MRPharmS, in die Bundesrepublik Deutschland. Seit dem 15. November 1999 bin ich als Ärztin im Praktikum (ÄiP) und anschließend dazu als wissenschaftliche Mitarbeiterin und Weiterbildungsassistentin an der Universität Göttingen, Abteilung für Allgemeinmedizin, tätig. Ab 1.1.2001 habe ich parallel dazu als ÄiP und danach als Assistenzärztin im St. Martini Krankenhaus, Abteilung Innere Medizin (Duderstadt), meine Weiterbildung fortgesetzt. Die deutsche Approbation als Ärztin erhielt ich am 20.4.2001.

Meine Tätigkeit als Assistenzärztin setzte ich bis zum 31. Dezember 2001 fort. Seitdem habe ich meine Weiterbildung für anderthalb Jahre vorübergehend unterbrochen, um mich mit einem Forschungsvorhaben zu beschäftigen (PhD thesis, Department of Epidemiology and Biostatistics, McGill University), das ich in Zusammenarbeit mit Prof. Jacques LeLorier (Université de Montréal) und Prof. Michal Abrahamowicz (McGill University) erfolgreich beantragt habe. Weiterhin setze ich meine Forschungstätigkeit in der hiesigen Abteilung für Allgemeinmedizin auf Teilzeitbasis fort. Ich habe vor, meine Facharztausbildung im Bereich Allgemeinmedizin nach dem Abschluss des PhD-Projekts (etwa Mitte 2003) abzuschließen.

Göttingen, im November 2002