



Is Roxithromycin Better than Amoxicillin in the Treatment of Acute Lower Respiratory Tract Infections in Primary Care?

A Double-Blind Randomized Controlled Trial

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■ **OBJECTIVE** To assess the efficacy of roxithromycin relative to amoxicillin.

■ **STUDY DESIGN** We conducted a double-blind randomized controlled trial of oral 500 mg amoxicillin 3 times per day vs oral 300 mg roxithromycin once a day for 10 days.

■ **POPULATION** We included 196 adults who had presented to a general practitioner with lower respiratory tract infection (LRTI) and, in the physician's opinion, needed antibiotic treatment.

■ **OUTCOMES MEASURED** We measured clinical response after 10 and 28 days, defined in 4 ways: (1) decrease in LRTI symptoms; (2) complete absence of symptoms; (3) decrease in signs; and (4) complete absence of signs. Self-reported response included the decrease in symptoms and the time until resumption of impaired or abandoned daily activities on days 1 through 10, 21, and 27.

■ **RESULTS** Clinical cure rates after the completion of antibiotic treatment (10 days) were not significantly different for the 2 groups. After 28 days, the roxithromycin group showed no increase in cure rate as evidenced by the decrease in symptoms, indicating a significantly lower cure rate. However, this difference did not alter physicians' overall conclusion after complete follow-up that 90% of patients, regardless of age, had been effectively treated with either amoxicillin or roxithromycin.

■ **CONCLUSIONS** The surplus value of roxithromycin was not confirmed. Amoxicillin remains a reliable first-choice antibiotic in the treatment of LRTI in general practice.

■ **KEY WORDS** Respiratory tract infections; bronchitis; pneumonia; antibiotics; family practice. (*J Fam Pract* 2002; 51:329-336)

Acute community-acquired lower respiratory tract infections (LRTIs) in adults include acute bronchitis, pneumonia, and infectious episodes in patients with asthma or chronic obstructive pulmonary disease (COPD). In acute bronchitis and

KEY POINTS FOR CLINICIANS

- Amoxicillin and roxithromycin are equally effective in the treatment of patients presenting with lower respiratory tract infections and needing antibiotic treatment.
- Most patients remain symptomatic after 10 days of treatment with either drug.
- The low incidence of atypical pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae*) in the Netherlands minimizes the potentially greater surplus value of macrolide antibiotics over amoxicillin.

exacerbations of COPD, the value of antibiotic therapy is doubtful; in pneumonia, however, it is widely accepted. Because distinguishing between these disease entities on clinical grounds alone is often impossible, deciding which patients would benefit from antibiotic treatment remains difficult.¹⁶ In the Netherlands, as in the United States and Great Britain, antibiotics are prescribed for patients with acute bronchitis approximately 80% of the time.⁷⁻⁹

If a primary care physician (PCP) decides to treat LRTI with antibiotics, amoxicillin is the drug of first choice in the Netherlands.¹⁰⁻¹³ However, amoxicillin is not effective in infections caused by atypical organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, which are responsible for 1% to 50% of cases of LRTI.¹⁴⁻²⁰ Roxithromycin and the newer macrolide antibiotics are recommended as drugs of choice for the empirical treatment of com-

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munity-acquired pneumonia in low-risk patients in the United States and Canada²¹⁻²³ because those drugs cover both typical and atypical pathogens. Amoxicillin has long proved to be a reliable drug and one to which the resistance of common respiratory tract pathogens (*Streptococcus pneumoniae* and *Haemophilus influenzae*) in the Netherlands is low.²⁴⁻²⁹

Community-based studies that evaluate treatment for LRTI are lacking. Also lacking are independent randomized controlled studies comparing amoxicillin with roxithromycin or other new macrolides for LRTI. Our double-blind randomized trial attempted to determine whether the preference for amoxicillin in the Netherlands is well founded. In the trial, patients with LRTI who in their PCP's opinion needed antibiotic treatment were assigned to either amoxicillin or roxithromycin. We then compared the efficacy and safety of both drugs.

METHODS

Eligibility Criteria and Baseline Characteristics

Eligible study subjects were patients in the southern part of the Netherlands who presented with signs and symptoms of LRTI that their PCPs believed warranted antibiotic therapy. Table 1 lists the inclusion and exclusion criteria.

Baseline data (at day 1) were obtained to evaluate the comparability of prognostic factors between the intervention groups. The PCP performed an extensive medical history and physical examination. In addition, a sputum sample, oral washing, and nasopharyngeal swab were taken for bacteriologic examination. Venous blood samples were taken for blood chemistry, hematology, and serology (initial titers of the viral pathogens *M pneumoniae* and *L pneumophila*).

Interventions

Once the samples had been collected, patients were randomly assigned to oral treatment with either 500 mg amoxicillin 3 times daily for 10 days or 300 mg roxithromycin once daily for 10 days. A computer program using random permuted blocks of 6 prepared a randomization list for each participating center. Batches of drug packages, each provided with a

TABLE 1

CHECKLIST FOR PATIENT ELIGIBILITY

Inclusion Criteria	Exclusion Criteria
<p>A: Age 18 years or older</p> <p>AND</p> <p>B: New* or increasing cough</p> <p>AND</p> <p>C: At least 1 of the following:</p> <ol style="list-style-type: none"> 1) Shortness of breath 2) Wheezing 3) Chest pain 4) Auscultation abnormalities <p>AND</p> <p>D: At least 1 of the following:</p> <ol style="list-style-type: none"> 1) Fever ($\geq 38^{\circ}\text{C}$) 2) Perspiring 3) Headache 4) Myalgia <p>AND</p> <p>E: Diagnosis of LRTI according to PCP and</p> <p>F: Antibiotics required (in PCP's opinion)</p>	<ul style="list-style-type: none"> • Pregnant or present wish to become pregnant • Breastfeeding • Terminal disease • Drug or alcohol abuse • History of hypersensitivity to penicillins or macrolides • Hospital stay in previous 4 weeks for respiratory complaints • Treatment with antibiotics within preceding 14 days • Treatment with any other investigational drug within 4 weeks before entry into the trial • History of severely impaired hepatic or renal function • Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study or evidence of uncooperative attitude • Inability to attend follow-up visits • Immunocompromised status • Required admission to hospital • Concomitant treatment with ergot alkaloids or terfenadine during the study period
<p>* Onset within the previous 29 days. LRTI denotes lower respiratory tract infection; PCP, primary care physician.</p>	

unique trial code, had been sent in advance to the participating general practices. A double-dummy technique achieved blinding of patients, treating physicians, and investigators to the assigned medication. This was necessary because amoxicillin and roxithromycin have different dosing schedules (3 times a day versus once daily) and are not identical in appearance (capsule versus tablet). All capsules and tablets had identical appearance and taste. All patients received both forms of their assigned medication. Compliance with medication regimens was measured by Medical Event Monitoring Systems (MEMS), an electronic recording system that compiles the dosing history of ambulatory patients taking oral medication.³⁰

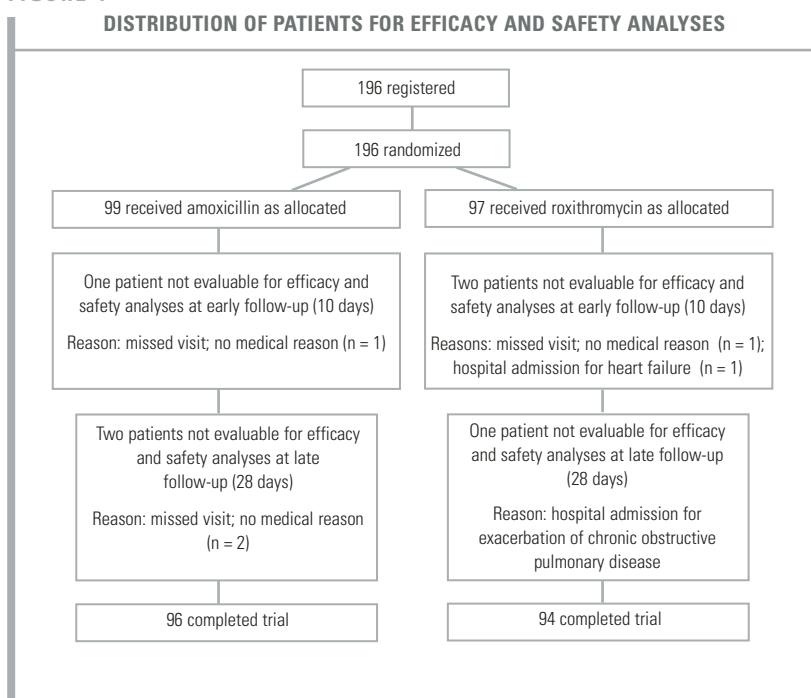
Chest X-Rays

Every patient underwent chest x-ray. The radiographs were reassessed for the presence or absence of infiltrate by a blinded independent senior radiologist. If the first and second radiologist disagreed, a third senior radiologist made a final assessment.

Follow-Up

Follow-up consultations similar to the examination on day 1 took place on days 10 and 28. During treatment (days 1 through 10) and on days 21 and 27, follow-up was supplemented by a short diary in which patients recorded their symptoms and the times at which they resumed daily activities that they had abandoned or that had been impaired.

FIGURE 1



Outcomes Measured

Efficacy was assessed by comparing the groups' clinical response on day 10 (the primary outcome measure) and day 28 and their bacteriologic response on day 10. Satisfactory clinical response was defined in 4 ways: (1) decrease in symptoms of LRTI; (2) absence of symptoms of LRTI; (3) decrease in signs of LRTI; and (4) absence of signs of LRTI. All other outcomes were regarded as unsatisfactory responses.

Self-reported symptoms and time to resolution were compared between the 2 groups on days 1 through 10, 21, and 27. The percentage of patients who had abandoned daily activities or whose participation in daily activities had been impaired by illness was followed over time. Bacteriologic cure was defined as the absence of growth of a predominant bacterial pathogen (cultured at baseline) in a sputum sample taken on day 10.

We recorded patients' compliance rates, frequency of adverse events, and acquired bacterial resistance. Compliance was defined as the number of doses taken divided by the number of doses prescribed.

Statistical Analyses

The efficacy of amoxicillin and roxithromycin was evaluated using an intention-to-treat analysis. Differences were tested using a 2-sided chi-square test ($\alpha = 0.05$). Multiple logistic regression analysis was performed to analyze the effect of differences in

baseline characteristics between the randomized groups. Differences in symptoms, time to resolution of symptoms, and time to resumption of abandoned and impaired daily activities were tested in life table analyses using the Gehan test. All statistical analyses were performed with Statistical Package for the Social Sciences software, version 8.0.

RESULTS

Patient Population

From January 1998 to April 1999, 25 PCPs from 15 practices recruited 196 patients aged 18 years to 89 years. Of these patients, 99 received amoxicillin and 97 received roxithromycin (Figure 1). The 2 groups' demographic data, signs and symptoms, comorbidities, identified

pathogens, and radiographic abnormalities were similar (Table 2). Multiple logistic regression analysis showed that none of the covariables altered the effects of the study medication.

Clinical Cure

Early Follow-Up. The rate of clinical cure, defined as the decrease in symptoms and signs at 10 days after randomization, was high and not significantly different between both groups. Using the stricter definition of clinical cure as the complete absence of symptoms and signs led to the same conclusion. Absolute cure rates using this strict definition were low (Table 3).

Physicians discontinued treatment with the study medication in 2 cases (1 amoxicillin and 1 roxithromycin) because of unsatisfactory clinical response. Both patients recovered rapidly after alternative antibiotic treatment. In one case, the patient discontinued amoxicillin after 8 days because of rash and urticaria and recovered quickly without further treatment.

Late Follow-Up. According to the physicians' final assessments, the rate of clinical cure at 28 days was not significantly different between the 2 groups, although the percentage of patients who showed a decrease in symptoms was significantly higher in the amoxicillin group than in the roxithromycin group (Table 3). Again, cure rates were much lower when the strict definition of cure was used. Eleven patients in the amoxicillin group and 8 in the roxithromycin group were not clinically cured after 28 days. Of

TABLE 2

FINDINGS ON PRESENTATION		
Finding	Amoxicillin Group No. (%)	Roxithromycin Group No. (%)
Number of Patients	99 (51)	97 (49)
Demographic Data		
Ratio of men to women	46/53	53/44
Mean age in years (SD)	55 (15)	50 (16)
Symptoms		
Recent cough in number of days		
1-7	34 (36)	41 (43)
8-14	31 (33)	25 (26)
15-28	22 (23)	23 (24)
No recent cough	8 (8)	6 (6)
Productive cough	77 (78)	84 (88)
Dyspnea	78 (79)	76 (79)
Wheezing	68 (69)	61 (64)
Risk Factors		
Cigarette smoking	36 (36)	29 (31)
Comorbidity		
None	55 (56)	48 (52)
Asthma	19 (19)	20 (22)
COPD	17 (17)	11 (12)
Heart failure	3 (3)	4 (4)
Diabetes mellitus	2 (2)	3 (3)
Other	23 (24)	21 (23)
Asthma medication prescribed at start of study	16 (16)	13 (14)
Signs		
Auscultation abnormalities	93 (94)	87 (91)
Body temperature $\geq 38.0^{\circ}\text{C}$	25 (26)	22 (24)
Infection		
Mild/moderate	91 (93)	89 (93)
Severe	7 (7)	7 (7)
Laboratory Tests		
CRP, median (range)	23 (2-228)	26 (2-312)
ESR, median (range)	21 (1-104)	19 (1-121)
Leukocytes, median (range)	8.3 (3.9-19.7)	8.4 (4.3-15.4)
Patients with pathogens	45 (45)	46 (47)
Chest X-Ray		
Infiltrate on chest x-ray	14 (14)	13 (14)

NOTE: Values are numbers (percentages) unless otherwise stated. Percentages are based on number of patients for each variable.
COPD denotes chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation.

these patients, 10 (5 in each group) recovered shortly thereafter or did not consult their physician again for persisting symptoms of LRTI. Nine patients (6 in the amoxicillin group, 3 in the roxithromycin group) with exacerbation of COPD slowly returned to their baseline clinical situation. Four patients (3 in the amoxicillin group, 1 in the roxithromycin group) were found to have concomitant pulmonary cancer. Curative bilobectomy was performed in one of the patients. The others received palliative treatment.

Self-Reported Response Over Time

The time before resolution of symptoms according to the patients' diaries was similar for patients treated with amoxicillin and those treated with roxithromycin (Figures 2A and 2B). The percentage of patients who had abandoned daily activities was followed over time. At baseline, more than half of the patients in the

amoxicillin group and fewer than 40% in the roxithromycin group reported that they had abandoned daily activities. At day 10, this percentage had fallen to less than 20% in both groups and to less than 10% in both groups at day 28. Differences between the amoxicillin and roxithromycin groups were not significant.

Furthermore, the patients' diaries revealed information about the time of impaired daily activities. The percentage of patients with impaired daily activities gradually decreased in both treatment groups from approximately 75% at baseline to 30% at day 10 and 20% at day 28.

Subgroup Analyses

The above analyses were repeated for a group of patients aged less than 65 years and a group aged 65 years and older. The trend in cure rates was the same. No differences were found between these age groups regarding the percentage of patients with satisfactory clinical response. Furthermore, the same analyses were performed for each of the clinical diagnoses made by the PCPs at baseline (ie, pneumonia, acute bronchitis, exacerbation of asthma or COPD, and unclassified LRTI). Overall, no significant differences were found between the amoxicillin and roxithromycin groups.

Bacteriologic Evaluation

Pathogens were identified in 91 patients (46%). Viruses were most frequent, followed by *H (Para) influenzae*, *S pneumoniae*, and *Moraxella catarrhalis* (Table 4). Bacteriologic cure was achieved in 21 of the 23 patients (91%) in the amoxicillin group and in 23 of the 27 patients (85%) in the roxithromycin group (NS, Fisher's exact test). In 9 patients of the amoxicillin group and 8 patients of the roxithromycin group, only the sample obtained after 10 days showed the growth of a predominant bacterial pathogen (superinfection).

Safety and Compliance

Thirty possible or probable adverse events were reported in 19 of 99 patients (19%) treated with amoxicillin: diarrhea (13), stomach ache (3), headache (3), and 11 other side effects, including nausea, vomiting, and rash, once each. In the roxithromycin group, 24 events were reported in 16 patients (16%): nausea (5), diarrhea (4), vomiting (4),

rash (2), headache (2), and 7 others, including pruritus ani, dizziness, and mild bradycardia, once each.

Compliance with the medication regimen was high. Data from electronic monitoring were available for 160 patients (78 in the amoxicillin group, 82 in the roxithromycin group). The overall compliance rate for patients in both groups (ie, the number of doses taken divided by the number of doses prescribed) was 98%. In the amoxicillin group, the numbers of patients with less than 90% compliance in taking the tablets and capsules were 7 and 4, respectively. In the roxithromycin group, compliance in taking the tablets was at least 90% in all patients but compliance in taking the capsules was less than 90% in 6 patients.

DISCUSSION

This community-based study shows that amoxicillin and roxithromycin are equally effective in the treatment of LRTI in the Netherlands. Clinical cure rates after 10 days of antibiotic treatment were approxi-

mately 90% in both study groups, although complete absence of symptoms was achieved in only a minority of cases. After 28 days of follow-up, cure rates remained high. The amoxicillin group had a significantly higher cure rate than the roxithromycin group as evidenced by the decrease in symptoms. However, this significant difference in favor of the amoxicillin group did not alter the PCPs' overall conclusion after complete follow-up: that 90% of patients who received either drug had been effectively treated. Patients' diary entries agreed with that impression.

The time to resolution of symptoms, the cumulative cure rate per day, and the influence of the illness on daily activities were not significantly different between patients treated with amoxicillin versus those given roxithromycin. Adverse events were mild and were divided evenly over both groups with the exception of diarrhea, which occurred more often in those taking amoxicillin.

In our study, complete absence of symptoms and signs after 28 days, as assessed by both physicians and patients, was achieved in only approximately half the patients. Complete remission of LRTI often takes more than 4 weeks.

Although LRTI is often managed in primary care, diagnostic and therapeutic decisions are usually based on the experiences of hospital-based specialists and on the results of trials conducted in hospital settings. Generalizing these results to primary care is of limited value, since disease in patients recruited

TABLE 3
CLINICAL CURE RATE AT EARLY (10-DAY) AND LATE (28-DAY) FOLLOW-UP

Characteristic	Amoxicillin No. (%)	Roxithromycin No. (%)	Relative Risk* (CI)
Decrease in Symptoms and Signs			
<i>Day 10</i>			
Symptoms	84/96 (88)	90/95 (95)	2.38 (0.87-6.48)
Signs (physical examination)	85/98 (87)	89/95 (94)	2.10 (0.83-5.30)
<i>Day 28</i>			
Symptoms	91/95 (96)	79/93 (85)	0.28 (0.10-0.82)†
Signs (physical examination)	90/96 (94)	87/94 (93)	0.74 (0.29-2.41)
Absence of Symptoms and Signs			
<i>Day 10</i>			
Symptoms	18/96 (19)	22/95 (23)	2.38 (0.87-6.48)
Signs (physical examination)	68/98 (69)	76/95 (80)	1.53 (0.93-2.53)
<i>Day 28</i>			
Symptoms	59/95 (62)	50/93 (54)	0.82 (0.58-1.15)
Signs (physical examination)	82/96 (85)	80/94 (85)	0.98 (0.49-1.94)
Fever (≥38°C) gone, day 10	21/25 (84)	16/22 (73)	1.37 (0.25-7.41)
Cure, final conclusion by physician, day 28	84/95 (88)	86/94 (91)	1.36 (0.57-3.23)

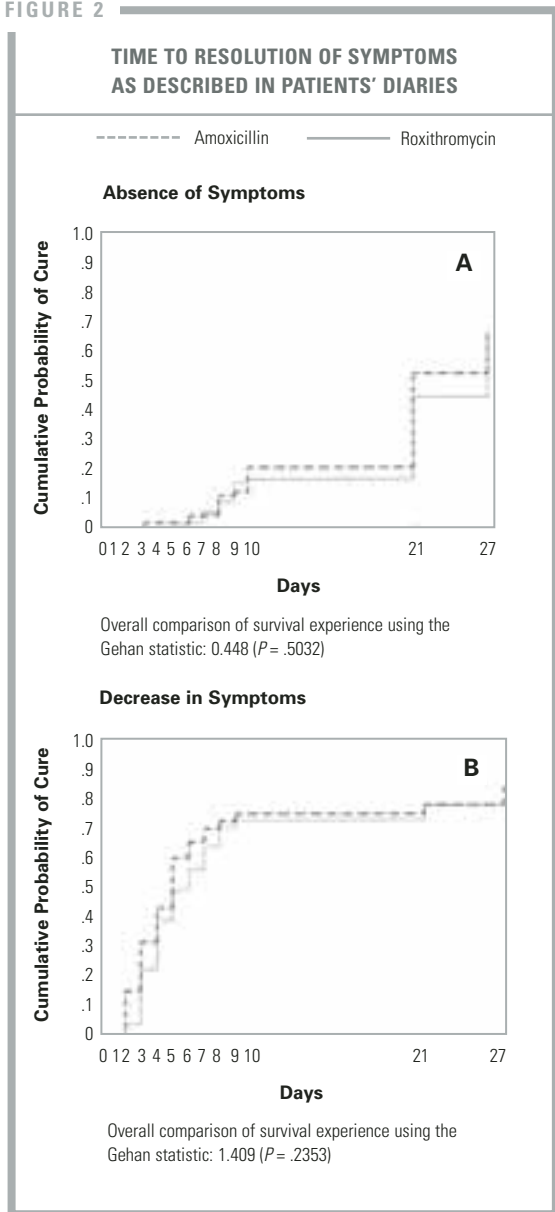
NOTE: Percentages are based on number of patients for each variable.
*Risk of no cure with amoxicillin vs roxithromycin.
† P < .05.

TABLE 4
RESPIRATORY TRACT PATHOGENS ISOLATED

Microorganism	No. (%)
Typical Bacterial Pathogens	
<i>Haemophilus (Para) influenzae</i>	34 (17)
<i>Streptococcus pneumoniae</i>	12 (6)
<i>Moraxella catarrhalis</i>	6 (3)
Other*	5 (3)
Atypical Pathogens	
<i>Mycoplasma pneumoniae</i>	2 (1)
<i>Legionella pneumophila</i>	1 (0.5)
Viruses	
Influenza A	29 (16)
Influenza B	7 (4)
Parainfluenzae 1, 2, 3	7 (4)
Adenovirus	5 (3)
Respiratory syncytial virus	5 (3)
No organism (number of patients)	122 (49)

* Enterobacteriaceae (n = 2), *Staphylococcus aureus* (n = 1), *Streptococcus viridans* (n = 1), *Neisseria meningitidis* (n = 1).

FIGURE 2



for these studies is often at a later stage and more serious. In our trial, patients were recruited, diagnosed, and treated by PCPs in their natural setting, maintaining regular care as much as possible.

Nevertheless, generalization of our findings to everyday care may not be valid. To explore the degree of selection in our recruited patients, we compared the actual numbers of cases of LRTI in 3 practices (with a total of 9 PCPs and a total population of 13,269) with the numbers included in the present trial during 1 year of the inclusion period. Of the 463 presumably eligible patients, only 43 (9%) were actually included. This proportion is similar to that in a recent study of randomized controlled trials in primary care in which less than 10% of the eligi-

ble population were recruited for the trial.³¹ Included patients did not differ from other eligible patients with regard to age, clinical diagnosis, severity of illness, and need for antibiotic treatment (according to the PCPs).

Clinical studies, mostly in inpatient settings, on community-acquired pneumonia have identified causative pathogens in 50% to 69% of patients.^{14-17,21,23,32,33} Outpatient studies of acute bronchitis and LRTI have generally reported considerably lower percentages (16% to 44%).^{19,20,34-36} In our study, pathogens that presumably caused LRTI were found in 46% of patients.

Because atypical pathogens were the presumptive causative agent in only 3 cases (2 *M pneumoniae*, 1 *L pneumophila*), the potential advantage of macrolide antibiotics over amoxicillin is minimal. Furthermore, bacterial resistance to macrolide antibiotics is believed to be considerable.^{37,38} In Finland, bacterial resistance to erythromycin has been shown to rise quickly after an increase in the consumption of macrolide antibiotics.³⁹ In contrast to alarming reports in the literature,^{14,17,22,40,41} the low incidence of *M pneumoniae* and *L pneumophila* found in the current study supports the conservative approach (ie, amoxicillin or doxycycline) to treating community-acquired LRTI in the Netherlands.

M pneumoniae occurs at high rates in 4-year to 5-year cycles.⁴² This timing implies that the frequency of *M pneumoniae* might be higher if the same study were performed 1 year later. Because most *M pneumoniae* infections are self-limiting and clinical cure rates of macrolide antibiotics compared with those of placebo are the same,^{43,44} however, this epidemiologic observation does not change the conclusions of the present study.

Compliance with medication was reliably measured and quantified by Medical Event Monitoring Systems. For both ethical and practical reasons, patients were informed about the monitoring mechanism. Their knowledge about the monitoring may have slightly increased compliance as compared with daily practice, although this assumption has not been confirmed in other studies.^{45,46} Furthermore, compliance with antibiotic regimens is known to be greater than compliance with chronic medication regimens.^{47,48}

CONCLUSIONS

General practitioners frequently diagnose LRTI in general or pneumonia and acute bronchitis in particular, including infectious episodes in patients with asthma or COPD. In many cases, treatment with antibiotics follows. The results of our randomized

controlled trial did not confirm the potentially greater value of roxithromycin, which is often recommended as the drug of choice for empirical treatment of community-acquired pneumonia, over amoxicillin. Because amoxicillin was as effective as roxithromycin, it remains a reliable first-choice antibiotic in the treatment of community-acquired LRTI.

JFP

ACKNOWLEDGMENTS

The authors wish to thank the patients, general practitioners, and physicians' assistants who participated in this study. They also thank Hans Verloop, director of the Vandra paper factory, Meer-Hoogstraten, Belgium, for donating cardboard boxes and Alexander Thissen, Josephine Asberg, and Ramon Ottenbeijm for their assistance with the logistics of the study. The study was supported by a grant from the Research Institute for Extramural and Transmural Health Care, Maastricht.

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