

Impact of antimicrobial resistance on health outcomes in the out-patient treatment of adult community-acquired pneumonia: a probability model

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Out-patient treatment of community-acquired pneumonia (CAP) is a major challenge in an era of increasing prevalence of antimicrobial resistance. However, data describing the clinical impact of such resistance are scarce. A probability model was developed to estimate the impact of antimicrobial resistance on clinical outcomes for adults with CAP, eligible for out-patient care. The model assumed patients would be evaluated at 48–72 h, with those failing to improve being either hospitalized or switched to a different antibiotic. Two strategies were considered: amoxicillin followed by erythromycin (amoxicillin/erythromycin) and erythromycin followed by levofloxacin (erythromycin/levofloxacin). Analyses were conducted based on susceptibility of the major pathogens in France and the UK. Primary model-generated outcome measures were the proportion of patients successfully treated with first-line therapy and the proportion of patients subsequently hospitalized. The model estimated that in France, the amoxicillin/erythromycin strategy would lead to 67.8% improving within 48–72 h and 12.7% subsequently being hospitalized, compared with 48.6% and 13.7% for erythromycin/levofloxacin. For the UK, first-line success and hospitalization rates were, respectively, 71.7% and 8.1% for amoxicillin/erythromycin, and 65.3% and 9.3% for erythromycin/levofloxacin. The model estimated that antimicrobial resistance was responsible for >40% of hospitalizations in France and 15% in the UK. These data suggest that in areas with substantially reduced levels of susceptibility, antimicrobial resistance may be a significant contributor to subsequent hospitalization in adults initially treated as out-patients for CAP. Choice of out-patient treatment strategy should consider local resistance rates in order to maximize the likelihood of early cure, thereby minimizing hospitalizations.

Keywords: community-acquired pneumonia, antimicrobial resistance, patient outcomes, *Streptococcus pneumoniae*, *Haemophilus influenzae*

Introduction

Community-acquired pneumonia (CAP) remains a common and potentially life-threatening disease. In the early 1990s, for

example, an annual incidence for CAP of one to three cases per 1000 population was reported in the UK,¹ while a recent Spanish study showed an annual incidence of 4.7 cases per 1000 adults.² In the USA, there are 2–3 million cases of CAP

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each year,³ accounting for 500 000 hospitalizations that are not only costly,⁴ but are also associated with significant mortality.^{5,6} Such trends show no signs of slowing, despite many advances in the development of antimicrobial agents.

Streptococcus pneumoniae is the most common bacterial cause of CAP, being identified in 20–75% of cases.^{7,8} Initial treatment, however, is generally empirical, as the causative pathogen is unknown in most cases. This approach dictates the use of antimicrobials that provide good coverage of all key respiratory pathogens likely to be encountered, although in recent years a marked increase in resistance among such pathogens has begun to restrict the usefulness of the available armamentarium for the treatment of CAP. For example, resistance in respiratory pathogens, particularly *S. pneumoniae* and *Haemophilus influenzae*, is now a major problem worldwide.^{9–11} Although macrolides were a useful alternative to penicillin, resistance to these agents is now also becoming established, particularly among *S. pneumoniae*, and in some areas is more prevalent than penicillin resistance.⁹ Moreover, resistant pathogens frequently show cross-resistance to other related and non-related antimicrobials, adding to the complexity of selecting appropriate empirical therapy. The limitations that increasing resistance continues to place on the usefulness of available antimicrobials for the treatment of CAP highlight the need for new broad-spectrum agents that retain activity against strains resistant to existing antimicrobials and have a low potential to select for, or induce, resistance.

Previous studies have demonstrated that antimicrobial resistance has a marked effect on clinical outcomes in patients with meningitis^{12,13} and otitis media.^{14,15} The clinical impact of resistance is less clear in CAP,^{16–18} where studies have found conflicting results.^{19–23} Unquestionably, however, the risk of mortality increases for those hospitalized patients infected with strains that are highly resistant to penicillin.^{24,25} A potential limitation of these studies was that they were conducted in patients who had already been admitted to hospital; as such, the authors could not address whether patients with resistant strains were more likely to require hospitalization in the first instance. Using a probability modelling approach, the present study was therefore conducted to investigate the potential impact of antimicrobial resistance on clinical outcomes in the out-patient treatment of patients with CAP.

Materials and methods

A probability model was developed to represent the out-patient treatment of adult CAP. Probability models have been used to predict outcomes in acute sinusitis and acute otitis media.^{26,27} For this study, the model was developed based on a population of adults with a confirmed diagnosis of CAP and eligible for out-patient care based on presentation, age and

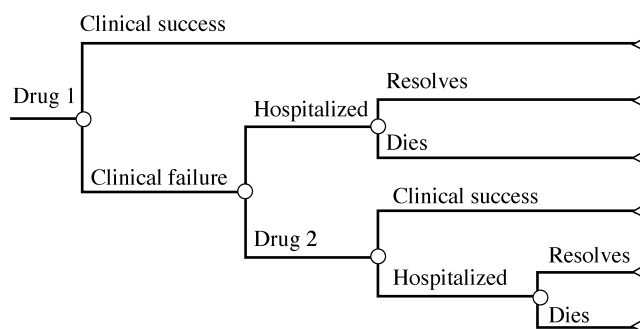


Figure 1. Diagrammatic representation (simplified) of the probability model for out-patient treatment of adults with CAP.

consideration of co-morbid conditions. The model (Figure 1) was also based on the following assumptions: (i) initial treatment in the out-patient setting would consist of a first-line oral antimicrobial ('drug 1'); (ii) if the patient had not responded to first-line therapy after 48–72 h, then he/she would either be admitted to hospital or given a second course of oral antimicrobial therapy with a different agent ('drug 2'); (iii) all patients who failed the second course of out-patient treatment would be hospitalized.

A formal decision analysis for the purpose of selecting optimal treatment strategy would have to consider a larger number of candidate strategies and the model would have to be customized for distinct patient subgroups, such as the young, the elderly and those with co-morbid illness. Since, however, the goal of this study was to examine in aggregate the impact of antibiotic resistance on outcomes and not to recommend specific strategies for particular subgroups of patients, we chose two common strategies for demonstration purposes. We included a β -lactam, a macrolide and a fluoroquinolone in order to represent important classes of antimicrobials, and we identified specific drugs for the strategies, since the analyses were based on drug-specific surveillance data. Two two-step strategies were considered, each consisting of a first-line treatment and a second-line treatment. (i) Amoxicillin/erythromycin: initial treatment with amoxicillin 500 mg three times a day; second-line treatment with erythromycin 500 mg four times a day. (ii) Erythromycin/levofloxacin: initial treatment with erythromycin 500 mg four times a day; second-line treatment with levofloxacin 500 mg once a day.

Analyses were conducted from the French and UK perspectives, where antimicrobial resistance is high and low, respectively.

Two primary outcome measures were evaluated: the proportion of patients successfully treated with first-line therapy, and the total proportion of patients hospitalized after first- or second-line therapy. These measures were calculated overall and on a per-country and per-pathogen (*S. pneumoniae* and *H. influenzae*) basis. The baseline ('real') scenario incor-

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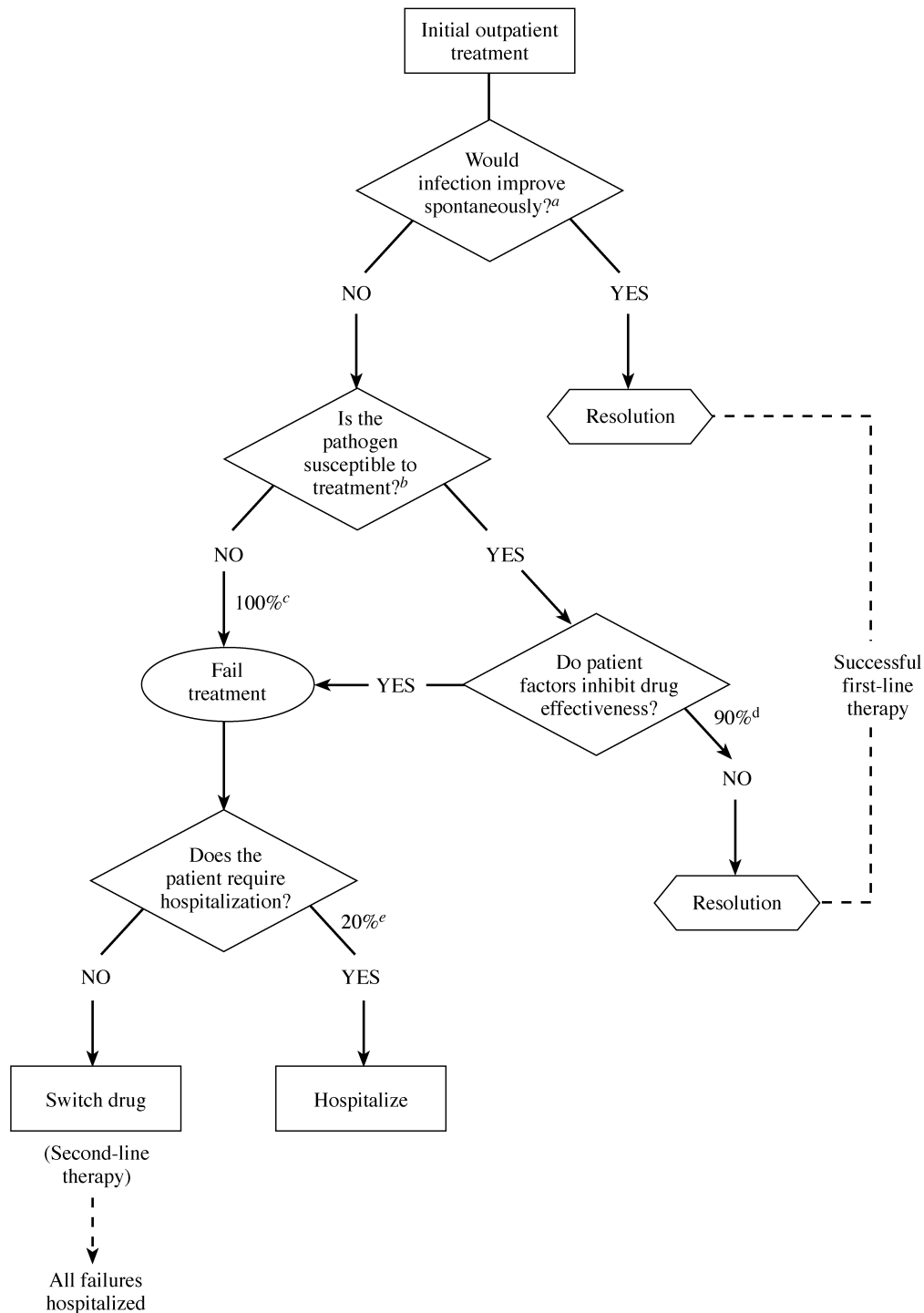


Figure 2. Flow chart presenting an overview of the model. ^aAssumptions made according to the pathogen (see Table 1). ^bBy-country rates from recent surveillance data (sensitivity analysis allows for two-fold shift in breakpoints). ^cIn sensitivity analysis it is assumed that 50% will behave as though susceptible. ^dFor example, discontinuation of treatment due to side-effects, poor compliance, patient host factors; assumption that 90% of susceptible infections will respond to treatment (80% in sensitivity analysis). ^eTen to 30% in sensitivity analysis.

porated actual resistance and cross-resistance rates derived from the latest surveillance data in the two countries. For *S. pneumoniae* and *H. influenzae*, we also considered the hypothetical scenario in which there was no resistance. This scenario was based strictly on a drug's baseline coverage before the

development of resistance in these organisms, and was used as a comparison with the 'real' scenario in order to estimate the impact of current levels of resistance on health outcomes.

A flow chart, showing factors that are built into the model is depicted in Figure 2.

Aetiology of CAP

For the purposes of the present model, the aetiology of out-patient CAP was based primarily on a meta-analysis of 16 CAP studies, each involving >100 patients, by Fang *et al.*²⁸ In this analysis the authors noted that *S. pneumoniae* was identified as the most common cause of CAP (12–76% of cases) in 14/16 studies ('aspiration' was identified as the main cause of CAP in the remaining two studies, *S. pneumoniae* being ranked in second place). *H. influenzae* was the second most common cause of CAP in 6/16 studies, followed by *Legionella pneumophila* and *Mycoplasma pneumoniae*, which were each identified as the second most common cause in 2/16 studies.

We needed to take into account, however, that most studies involved hospitalized patients where a causative pathogen was only identified in about half of all cases, that many patients had completed an initial course of treatment (thereby introducing a selection bias) and that studies were performed >10 years ago, when there was little resistance and initial treatment was likely to have provided adequate coverage for *S. pneumoniae*, but varying coverage for other pathogens. Moreover, we had to consider potential underestimation of the frequency of atypical/intracellular pathogens, because older studies were not designed to detect them. In order to address the issue of prior antimicrobial use, we took into account the aetiological findings of two community-based studies with low rates of prior antimicrobial treatment.^{29,30} In the first study, Woodhead *et al.*²⁹ found *S. pneumoniae* in 36% of cases and *H. influenzae* in 10%, with no causative pathogen identified in 45% of cases; only 17% of patients had recently taken an antimicrobial prior to entering the study. Macfarlane *et al.*,³⁰ in a study of adult lower respiratory tract infections, found that *S. pneumoniae* was the cause in 30% of cases and *H. influenzae* in 8%, with 56% of cases of unknown aetiology (patients with recent prior use of an antimicrobial were excluded from this study). Recent evidence suggests that a significant proportion of cases of CAP that are reported to be of 'unknown aetiology' may actually be caused by pathogens such as *S. pneumoniae* and *H. influenzae*.³¹ If we apply such results then *S. pneumoniae* would be the causative pathogen in 45% of cases in the Woodhead study and 42% in the Macfarlane study. Similarly, *H. influenzae* would be implicated in 12% of cases in the Woodhead study and 11% in the Macfarlane study.

Together with the findings of Fang *et al.*²⁸ noted above, we used the following distribution of pathogens in out-patient CAP in our model: 44% for *S. pneumoniae*, 14.3% for *H. influenzae*, 15.6% for atypical/intracellular species, 13.5% for other bacterial pathogens and 12.6% for infections of viral origin (Table 1).

Table 1. Values for distribution of pathogens and rates of spontaneous resolution in patients with CAP used in the model

Causative pathogen	Frequency (% of patients)	Spontaneous resolution (% of patients)
<i>S. pneumoniae</i>	44.0	10
<i>H. influenzae</i>	14.3	40
Atypical/intracellular	15.6	95
Other bacteria	13.5	20
Viral	12.6	95

Table 2. Susceptibility rates (%)^a among respiratory pathogens isolated during 1999–2000 in the PROTEKT study

	<i>S. pneumoniae</i>		<i>H. influenzae</i>	
	France (n = 184)	UK (n = 91)	France (n = 193)	UK (n = 96)
Amoxicillin				
all isolates	94.57	100	67.88	85.42
Erythromycin				
all isolates	41.85	86.81	1.55	0
AMX susceptible	44.25	86.81	1.53	0
AMX resistant	0	– ^b	1.61	0
Levofloxacin				
all isolates	100	100	100	100
ERY susceptible	100	100	100	100
ERY resistant	100	100	100	100

AMX, amoxicillin; ERY, erythromycin.

^aPharmacokinetic/pharmacodynamic breakpoints for susceptibility: amoxicillin, ≤ 2 mg/L; erythromycin, ≤ 0.25 mg/L; levofloxacin, ≤ 2 mg/L.

^bNot applicable as there were no amoxicillin-resistant isolates of *S. pneumoniae* in the UK.

Antimicrobial susceptibility of pathogens

We used 1999–2000 data from a longitudinal antimicrobial resistance surveillance study, Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT; www.protekt.org) to estimate rates of antimicrobial susceptibility among *S. pneumoniae* and *H. influenzae* (Table 2). Susceptibility of both pathogens was defined using pharmacokinetic/pharmacodynamic breakpoints: for amoxicillin, MIC ≤ 2 mg/L susceptible, MIC >2 mg/L resistant; for erythromycin, MIC ≤ 0.25 mg/L susceptible, MIC >0.25 mg/L resistant; and for levofloxacin, MIC ≤ 2 mg/L susceptible, MIC >2 mg/L resistant.^{32,33} All drugs were considered to have full coverage for *S. pneumoniae*, meaning there would be 100% susceptibility in the absence of resistance. Similarly, levofloxacin was considered to have full

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coverage against *H. influenzae*, but not amoxicillin or erythromycin, for which we estimated that *H. influenzae* would be 97% susceptible to amoxicillin and 3% susceptible to erythromycin in the absence of resistance. These estimates were based on observed susceptibility levels in surveillance studies in times and places preceding onset of resistance.

This model is heavily dependent on resistance rates as determined by applying pharmacokinetic/pharmacodynamic breakpoints to surveillance data. Therefore, we also analysed the data allowing for a two-fold dilution shift of breakpoints in either direction. This also simulates the effect of measurement error.

Atypical/intracellular organisms were regarded as susceptible to macrolides and fluoroquinolones, but resistant to β -lactams. Infections designated as 'other bacterial' were considered to be 50% susceptible to all antimicrobials.

Response to treatment

Patients improve because of a response to treatment, spontaneous resolution due to host defences or resolution of a preceding viral infection. If a particular organism is susceptible to the administered drug *in vitro* then there is a high probability that the infection will resolve. However, *in vitro* susceptibility does not necessarily guarantee clinical success, because factors such as patient non-compliance, discontinuation of treatment as a result of adverse events or host factors inhibiting clinical efficacy can all lead to treatment failure. We estimated that clinical success would be achieved in 90% of cases in which the pathogen was susceptible. This was based on a meta-analysis of clinical trials of macrolides, in which clinical success rates for erythromycin, clarithromycin and azithromycin were 85.5%, 93.4% and 93.9%, respectively.³⁴ A lower rate of 80% was also considered in sensitivity analysis (see 'Model validation' below).

When an infection is treated with an antimicrobial that lacks coverage for that pathogen, the infection may still resolve because some infections are inherently non-persisting and will eventually resolve regardless of treatment. For ease of exposition, the term 'spontaneous resolution' will be used for any case where the infection resolves in the absence of effective treatment. It is further assumed that these inherently non-persisting infections do not result in hospitalizations. The rate of spontaneous resolution varies according to the causative pathogen, but is difficult to estimate since placebo-controlled trials for CAP are considered unethical. In order to calculate rates of spontaneous resolution of CAP, we therefore considered findings from the treatment of sinusitis and otitis media. In patients with bacteriologically confirmed acute otitis media, for example, bacteriological 'efficacy' of 27% was predicted for patients who received no antimicrobial therapy.²⁷ In untreated children with acute bacterial rhinosinusitis, however, it has been estimated that spontaneous resolution would occur in 50% of cases.²⁶ For our model

we assumed that CAP would have lower rates of spontaneous resolution than otitis media, based on the significant mortality and morbidity associated with CAP. We therefore estimated that 10% of infections caused by *S. pneumoniae*, 40% caused by *H. influenzae*, 95% caused by atypical/intracellular pathogens, 20% caused by other bacterial pathogens and 95% caused by viruses would resolve spontaneously (Table 1). The rate for atypical/intracellular pathogens was based on the extremely high rates of clinical resolution reported in patients with such infections despite treatment with antimicrobials without coverage for these pathogens.^{35–37} For example, in a study reported by Donowitz *et al.*,³⁷ eradication or presumed eradication of *Mycoplasma* and *Chlamydomphila* (*Chlamydia*) species was achieved in 33/37 cases treated with cefaclor, an agent that has no proven efficacy against these pathogens. In another study, 22 patients hospitalized with CAP due to atypical/intracellular pathogens were given treatment that lacked coverage for these pathogens, with no mortality.³⁸

Time to resolution of infection was also considered in our model. In particular, patients who respond to antimicrobial treatment were presumed to show improvement within 48–72 h. For patients whose infections resolve spontaneously, it was estimated that in half of these cases the infection would show improvement within 48–72 h, while the remainder of the patients would appear to be non-responders to treatment, be prescribed new antimicrobials and then show improvement within 48–72 h of starting second-line therapy.

Clinical significance of resistant organisms

As discussed earlier, the impact of *in vitro* resistance on clinical outcomes has been well established in some indications,^{12–15} but not in CAP.^{16–18} In *S. pneumoniae*, intermediate-level penicillin resistance has been defined as a penicillin MIC of 0.12–1 mg/L, with fully resistant isolates having penicillin MICs of ≥ 2 mg/L. However, based on the pharmacokinetic/pharmacodynamic properties of β -lactams, pathogens with an MIC ≤ 2 mg/L would be considered susceptible to appropriate dosing regimens of parenteral penicillin and other β -lactams. Thus, it is not surprising that earlier studies, which were based primarily on pathogens with intermediate-level penicillin resistance, did not find resistance to be correlated with outcomes. The impact of high-level penicillin resistance on clinical outcomes in pneumococcal disease, however, is better established. One study found that after excluding mortality in the first 2 days, which would precede any potential benefit from antibiotic treatment, there was a large mortality effect associated with penicillin MICs ≥ 4 mg/L (odds ratio 5.5).²⁴ The results are even stronger considering that this study was not able to link susceptibility to actual use of specific agents, so that some of the patients with strains considered to be resistant may have been treated with an agent to which the organism was actually susceptible. Turett *et al.*²⁵ studied the effect of penicillin resistance in

pneumococcal bacteraemia. After adjusting for severity of illness and other factors, high-level penicillin resistance was associated with a statistically significant increase in mortality (odds ratio 6.0). Because of the relationship with clinical outcomes, the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group recommended a change in the NCCLS susceptible range for penicillin to ≤ 4 mg/L for pneumonia.³⁹ The relationship between macrolide resistance and treatment failure has recently been demonstrated in a case-control study of 86 cases with macrolide-resistant strains and 141 controls with macrolide-susceptible strains, all with pneumococcal bacteraemia. Nineteen of the 86 cases were being treated with macrolides at the time of presentation, compared with none of the 141 controls.⁴⁰ The results were the same for high-level resistance as for the low-level resistant M phenotype. For the purposes of our baseline analysis, therefore, we assumed that patients infected with organisms deemed resistant according to pharmacokinetic/pharmacodynamic breakpoints for the antibiotic received could only achieve clinical success due to spontaneous resolution. However, in sensitivity analysis we considered the more conservative assumption that 50% of organisms found to be resistant *in vitro* behave as though susceptible.

Outcomes

We focused our analysis on two health outcomes: the proportion of patients expected to achieve clinical success with first-line therapy and the overall rate of hospitalization. We employed an earlier estimate⁴¹ that 20% of patients failing first-line therapy are hospitalized. To corroborate this estimate, we analysed medical claims from 1999–2001 for 12 managed care organizations in the USA using a database from Pharmetrics, Inc. Among the non-elderly, otherwise healthy adults failing initial out-patient therapy, 98/879 (11%) of those aged 18–44 years and 143/807 (18%) of those aged 45–64 years were hospitalized. These numbers underestimate the rate required for our model, which includes the elderly and those with co-morbidities. Thus, a baseline rate of 20% for all patients appears reasonable. A range of 10–30% was further explored in sensitivity analysis (see ‘Model validation’ below). In our model, non-hospitalized patients would be given a second course of antimicrobial treatment, and anyone failing second-line therapy would then be hospitalized. Overall hospitalization rates therefore included those hospitalized following failure of initial treatment as well those who failed second-line out-patient therapy.

Model validation

As in any model, we had to make some simplifying assumptions and resort to expert opinion where data were lacking. The potential impact of uncertainty regarding parameter values was estimated through sensitivity analysis, in which

we varied parameter values to see how the results might change if any of our parameters were poorly estimated in the baseline analysis. The overall model and its assumptions were tested through validation against published data from prospective studies.^{29,42} Model-generated rates of first-line treatment success and hospitalization rates were compared with those reported in the literature. In order to facilitate comparison, we employed treatment strategies that reflected practice in the given study, and applied pharmacokinetic/pharmacodynamic breakpoints to Alexander Project surveillance data (www.Alexander-Network.com) to estimate susceptibility rates in the country concerned for the time period covered by the study.⁴³

Results

Baseline model results

Baseline results generated by the model showed that, overall (i.e. across all pathogens), amoxicillin produced similar first-line therapy clinical success rates (67.8% and 71.7%) in the two countries studied (Table 3). The clinical success rate of erythromycin as first-line therapy was more variable (48.6% in France and 65.3% in the UK). By way of comparison, the model showed that a ‘perfect’ antimicrobial (i.e. a drug to which all bacterial pathogens are 100% susceptible) would achieve initial success in 86% of cases, while a placebo would attain initial success in 19.8% of cases.

The results for individual pathogens varied greatly. In France, the clinical success rate of initial treatment with amoxicillin was 85.9% for *S. pneumoniae* and 68.9% for *H. influenzae*, compared with 90.5% and 81.5%, respectively, in the UK. However, first-line clinical success rates with erythromycin against *S. pneumoniae* varied more dramatically, at 40.8% in France and 79.2% in the UK. For *H. influenzae*, clinical success rates for initial therapy with erythromycin were only ~20%. Initial treatment with placebo would be successful in just 5% of cases caused by *S. pneumoniae* and 20% of cases caused by *H. influenzae*, while rates would be 90.5% and 92%, respectively, for a ‘perfect’ drug.

Stratified analysis of other aetiologies of CAP was not based on surveillance data and was therefore not country specific. Initial clinical success rate predicted against atypical/intracellular pathogens was 47.5% for amoxicillin and 94.8% for erythromycin (Table 4). Both amoxicillin and erythromycin were assumed to be equally efficacious against other bacterial pathogens with an initial success rate of 50.1%. Although antimicrobials are ineffective against viruses, early spontaneous resolution would appear as initial treatment success and this was apparent in 47.5% of cases in CAP of viral origin.

Rates of hospitalization varied according to strategy and country (Table 3). In France, hospitalization rates ranged from 12.7% for amoxicillin/erythromycin to 13.7% for

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Table 3. Model outcomes (% of patients) for CAP in France and the UK, overall and by pathogen (*S. pneumoniae* and *H. influenzae*), based on current resistance rates and assuming a hypothetical zero rate of resistance

Pathogen/strategy	Incorporating resistance					
	France		UK		No resistance	
	Rx 1 success ^a	hospitalized	Rx 1 success ^a	hospitalized	Rx 1 success ^a	hospitalized
Overall						
AMX/ERY	67.8	12.7	71.7	8.1	72.9	6.9
ERY/LEV	48.6	13.7	65.3	9.3	70.6	7.9
placebo	19.8	60.4	19.8	60.4	19.8	60.4
perfect Rx ^b	86.0	2.3	86.0	2.3	86.0	2.3
<i>S. pneumoniae</i>						
AMX/ERY	85.9	10.7	90.5	3.4	90.5	2.5
ERY/LEV	40.8	15.7	79.2	5.5	90.5	2.5
placebo	5.0	90.0	5.0	90.0	5.0	90.0
perfect Rx ^b	90.5	2.5	90.5	2.5	90.5	2.5
<i>H. influenzae</i>						
AMX/ERY	68.9	23.1	81.5	13.9	89.8	7.6
ERY/LEV	21.1	16.6	20.0	16.8	22.2	16.4
placebo	20.0	60.0	20.0	60.0	20.0	60.0
perfect Rx ^b	92.0	1.7	92.0	1.7	92.0	1.7

AMX, amoxicillin; ERY, erythromycin; LEV, levofloxacin; Rx, treatment.

^aRate of clinical success with first-line therapy.

^bThe 'perfect' antimicrobial, i.e. a drug to which all bacterial pathogens are susceptible.

erythromycin/levofloxacin. Rates were lower in the UK—under 10% for both strategies. For CAP caused by *S. pneumoniae*, the hospitalization rate for erythromycin/levofloxacin in France (15.7%), where macrolide resistance is high, was much higher than for amoxicillin/erythromycin (10.7%). For *H. influenzae*, where macrolides have poorer coverage, the hospitalization rates for erythromycin/levofloxacin and amoxicillin/erythromycin were higher in both countries: 16.6% (France) and 16.8% (UK) for erythromycin/levofloxacin compared with 23.1% and 13.9%, respectively, for amoxicillin/erythromycin.

Impact of resistance

As stated in Materials and methods, the model also analysed the hypothetical scenario in which no resistance was present. The results of these analyses, compared with the baseline scenario, are shown in Table 3. By calculating the difference between hospitalization rates in these scenarios it was possible to separate the proportion of hospitalizations attributable to the recent development of resistance and the treatment strategy itself (Figure 3).

In the absence of any resistance, the hospitalization rate predicted by the model was 6.9% for amoxicillin/erythromycin.

In comparison, the actual predicted rate of hospitalization for this strategy was 8.1% in the UK and 12.7% in France. Thus, 45.7% of the hospitalizations associated with amoxicillin/erythromycin in France were attributable to antimicrobial resistance. This contrasted with the much lower rate of 14.8% in the UK. For erythromycin/levofloxacin, the proportion of hospitalizations due to resistance was 42.3% in France and 15.1% in the UK.

The impact of resistance was particularly strong for CAP caused by *S. pneumoniae*, where the model predicted a hospitalization rate of only 2.5% in the absence of resistance, compared with predicted results under current 'real' conditions (depending on the strategy) of 10.7–15.7% in France and 3.4–5.5% in the UK. For amoxicillin/erythromycin the impact of cross-resistance was very strong, with erythromycin faring poorly against organisms resistant to amoxicillin. For erythromycin/levofloxacin, when *S. pneumoniae* was the causative pathogen, the proportion of hospitalizations due to antimicrobial resistance was 84.1% in France and 54.5% in the UK.

When the causative pathogen was *H. influenzae*, and treatment was the amoxicillin/erythromycin strategy, the proportion of hospitalizations caused by antimicrobial resistance was 67.1% in France and 45.3% in the UK. Almost no hospi-

Table 4. Model outcomes^a (% of patients): other pathogens

Pathogen/strategy	Rx 1 success ^b	Hospitalized
Atypical/intracellular pathogens		
AMX/ERY	47.5	1.4
ERY/LEV	94.8	0.1
placebo	47.5	5.0
perfect Rx ^c	94.8	0.1
Other bacterial pathogens		
any strategy	50.1	28.2
placebo	10.0	80.0
perfect Rx ^c	91.0	2.2
Viral		
any strategy	47.5	5.0

AMX, amoxicillin; ERY, erythromycin; LEV, levofloxacin; Rx, treatment.

^aThese analyses were not based on country-specific susceptibility data; therefore, they are the same for both countries.

^bRate of clinical success with first-line therapy.

^cThe 'perfect' antimicrobial, i.e. a drug to which all bacterial pathogens are 100% susceptible.

talizations associated with *H. influenzae* and erythromycin/levofloxacin treatment were attributable to resistance.

Sensitivity analysis

All models rely on data that have some degree of uncertainty, and some assumptions. In sensitivity analysis we found that the model was fairly robust to uncertainty in the data and model assumptions, though the exact predictions did vary somewhat.

We estimated that clinical success would be achieved in 90% of cases in which pathogens were susceptible. Lowering the rate of clinical success to 80% had a significant impact on hospitalization rates, causing the rate of hospitalization to rise by an additional 3.2–4%.

The results were moderately sensitive to the proportion of patients who failed initial out-patient therapy who would then be hospitalized. Reducing this rate from 20% to 10% had limited impact for the amoxicillin/erythromycin strategy, resulting in a reduction in hospitalization of <1%. For the erythromycin/levofloxacin strategy, however, the impact was greater, leading to reductions in hospitalization of 1.8–3.2%. Similarly, allowing for 30% of first-line treatment failures to be hospitalized only increased predicted hospitalization by 0.5–0.7% for amoxicillin/erythromycin but by 1.8–3.3% for erythromycin/levofloxacin.

Since few isolates had MICs near the susceptibility breakpoint, allowing a single two-fold dilution shift in the susceptibility breakpoint had little impact except for amoxicillin/erythromycin in France, where a shift that increases susceptibility would reduce the predicted rate of hospitalization from 12.7% to 10.7%.

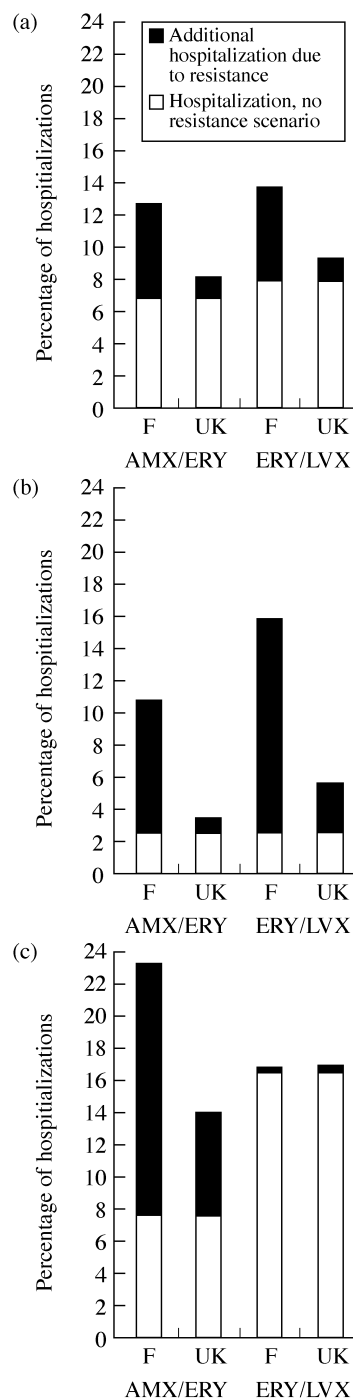


Figure 3. Hospitalization rates in France and the UK: (a) overall, (b) in *S. pneumoniae* and (c) in *H. influenzae*, based on current resistance rates versus a hypothetical zero rate of resistance.

In our baseline analysis, organisms that exhibited *in vitro* resistance by pharmacokinetic/pharmacodynamic standards were assumed to be non-responsive to the drug *in vivo*, although they could still resolve spontaneously. In sensitivity analysis we relaxed this assumption and considered the scenario where half of organisms that are resistant *in vitro* would behave *in vivo* as though they were susceptible. In this

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scenario, predicted hospitalization rates would be lower than in the baseline analysis, but resistance would still be responsible for 27% of hospitalizations in France and 8% in the UK.

Model validation

For validation purposes we required studies that were out-patient based, excluded patients who had already failed treatment, and stated results for first-line success or subsequent hospitalization. There were two studies that met these criteria and were based in the countries studied here.^{29,42} In their 1993–1994 French study of 154 patients initially treated as out-patients, Laurichesse *et al.*⁴² found that most CAP patients were treated initially with either amoxicillin or co-amoxiclav and were successfully treated in 72% of cases. Using the same treatment choices, together with surveillance data from the Alexander Project (www.AlexanderNetwork.com) to estimate antimicrobial resistance in France during the study period, our model generated an initial treatment success rate of 67%, which is similar to the rate found in the study of Laurichesse and colleagues.

The second validation was performed against an out-patient study conducted in the UK by Woodhead *et al.*,²⁹ in which 7.1% of the 198 patients initially treated in the out-patient setting were later admitted to hospital. The most commonly prescribed drug was amoxicillin, the study being conducted in areas of low penicillin resistance in *S. pneumoniae* and β -lactamase production in *H. influenzae*. Resistance rates in general were minimal in the UK at that time (and, indeed, are still relatively low). Thus, the 'no resistance' scenario, especially for amoxicillin, would be expected to be a good comparator. The model estimated hospitalization rates of 6.9% for amoxicillin/erythromycin and 7.9% for erythromycin/levofloxacin, which compare favourably with the hospitalization rate reported by Woodhead and colleagues (7.1%).

Although the US Pneumonia Patient Outcomes Research Team (PORT) study was not conducted in either of the countries included in the analyses here, it included a large, prospective out-patient-based component that is widely cited and used as a benchmark.⁴⁴ Therefore, we also compared our model with this trial. The PORT study took place from 1991 to 1993, a time period in which resistance was very low, and macrolides were the dominant first-line treatment choice.^{43,45} Our model predicted a hospitalization rate of 7.9% for erythromycin/levofloxacin, which is close to the 7.5% rate of subsequent hospitalization found in the PORT study for the 944 patients initially treated as out-patients.

Discussion

CAP is a potentially lethal illness that has a significant impact on utilization of healthcare resources worldwide. Antimicrobial treatment in the out-patient setting is initiated on an

empirical basis. The antimicrobial of choice therefore requires a spectrum of activity that covers all likely pathogens. However, despite the wealth of antimicrobials now available, successful out-patient treatment of CAP poses an ever-increasing challenge in the light of increasing rates of antimicrobial resistance. In recent years, for example, penicillin resistance in common respiratory pathogens has become a major problem worldwide.¹⁰ During the 1980s, >90% of *S. pneumoniae* isolates in the USA were penicillin susceptible and the remainder were penicillin intermediate. However, by the late 1990s one in four isolates showed some level of resistance to penicillin and one in seven showed full resistance.⁴⁶

Macrolide resistance among common respiratory pathogens is also increasing dramatically in some areas, especially since the introduction of the newer agents of this class, including azithromycin and clarithromycin.^{47–50} In the USA, for example, macrolide resistance in *S. pneumoniae* was reported to have doubled in the 5 years between 1995 and 1999.⁵⁰ Furthermore, it is likely that macrolide resistance genes will spread into new species, since intragenic transfer of macrolide-resistance determinants is possible.⁵¹ Resistance to the fluoroquinolones in streptococci has also begun to emerge.^{52–54} As such, resistance should be an important consideration when choosing an antimicrobial for initial therapy for CAP, although the effect of such resistance on the course of the disease is less clear. The lack of objective clinical data available on this issue, together with the problems associated with designing and conducting suitable prospective clinical studies, means that a modelling approach such as that used here is particularly appropriate to study the effect of resistance on clinical outcomes.

The development of this model is significant for several reasons. Here, the model was used to provide estimates of the impact of antibiotic resistance in adult out-patient CAP. However, using appropriate values for the model parameters it can be customized to different countries and can be used to examine the impact of projected future levels of resistance, compare alternative strategies for treating different patient populations and even explicitly incorporate costs in order to study directly the economic impact of antibiotic resistance.

The model focused on two health outcomes: the proportion of patients expected to achieve clinical success with first-line therapy and the overall rate of subsequent hospitalization. The overall rates of hospitalization varied according to treatment strategy and country, from 8.1% for amoxicillin/erythromycin in the UK to 13.7% for erythromycin/levofloxacin in France. Validation analyses established that the model-generated outcomes were comparable to those observed in published, community-based trials.^{29,42}

An interesting aspect of our model is that we analysed the hypothetical scenario of no resistance in order to assess the impact of resistance on hospitalization rates. The impact of resistance and cross-resistance varied according to country,

treatment strategy and causative pathogen. In France, for example, >40% of hospitalizations were due to antimicrobial resistance, while in the UK resistance was responsible for 15% of hospitalizations. The greatest impact of resistance on hospitalization rate was seen when *S. pneumoniae* was the causative pathogen. This can be partly explained by the substantial cross-resistance between amoxicillin and macrolides (see Table 2). Thus, it appears that resistance may play a major role in hospitalization for CAP in patients treated initially on an out-patient basis.

While the majority of patients with CAP can be effectively treated at home, significant mortality results from those cases requiring hospitalization.^{5,55} One large study of elderly CAP patients found mortality rates of 3–4% in patients initially treated in an out-patient setting,⁵⁶ which suggests substantial subsequent hospitalization and mortality. The model described here suggests that if out-patients are more likely to fail as a result of harbouring resistant strains then they are more likely to require hospitalization. Thus, when a cohort of patients is examined from initial out-patient treatment, those patients with resistant strains will experience higher rates of hospitalization, leading to increased mortality. This logic implies that treatment failure is the cause of subsequent hospitalization for patients originally treated on an out-patient basis. The Pneumonia PORT study found that although the majority of hospitalizations were due to treatment failure, many were due to co-morbid illness.⁴⁴ The study did not, however, report whether those admitted for co-morbid illness were improving in terms of their pneumonia symptoms. Patients may have been hospitalized for co-morbid illness but it may be that most of these patients would not have been admitted if their pneumonia had been treated successfully.

Increased rates of hospitalization are associated not only with greater total mortality but also with considerably greater treatment costs. The cost of CAP management has been studied in Europe and the USA.^{57–59} Guest & Morris⁵⁷ estimated the direct annual costs of CAP to the UK National Health Service during 1992–1993. They found that although about one-third of all episodes was treated in hospital, these episodes accounted for 96% of the annual cost of CAP. A US study also showed that the total direct costs of treatment were due largely to the cost of hospitalizations.⁵⁸ The authors calculated that the total cost of treating CAP was US\$8.4 billion, of which US\$7.5 billion was for in-patient costs. Both studies noted that treatment costs also depended on the duration of hospital stay.^{57,58} Indeed, Fine *et al.*⁵⁹ estimated that a 1 day reduction in the length of stay could yield a mean saving of US\$680 per patient. From these findings it is clear that if antimicrobial resistance leads to higher rates of treatment failure and the need for an increase in either the number or duration of hospital admissions, this will be associated with a huge economic burden.

The analyses here suggest that antibiotic resistance may be a major cause of hospitalization for CAP in adults initially treated in an out-patient setting. If this is true, then one would expect hospitalization rates for CAP to increase during times of increasing resistance. There are, however, two mitigating factors. The first is that most patients hospitalized for CAP have not first been treated as an out-patient. In a meta-analysis of CAP trials, the median rate of prior antibiotic treatment was about one-third.⁶⁰ Similarly, in the US Pneumonia PORT study only about one-quarter of CAP in-patients had been previously treated.⁴⁴ Thus, any increase in hospitalization due to increased out-patient treatment failure is largely diluted by those initially treated as in-patients.

Nonetheless, there are signs that resistance leads to increased hospitalization. Patients initially treated as in-patients are more likely to have severe disease or co-morbidity. Combining the results of two analyses of Medicare in-patient claims, the number of hospitalizations for pneumonia with co-morbid illness or complications [diagnosis-related group (DRG) 89] increased steadily from 1991 to 2000.^{61,62} Admissions for simple pneumonia tend to be otherwise healthy people, many of whom were initially treated as out-patients. These admissions (DRG 90) decreased by 23.7% from 1991 to 1995, but increased by 42.3% from 1995 to 2000. This pattern fits with changes in antibiotic resistance in the USA. Full penicillin resistance in *S. pneumoniae* was <5% during 1992–1994 and 10–15% from 1995 to 1997.⁴⁶ Another study found full penicillin resistance to be 9.5% in 1994–1995 but 21.5% in 1999–2000.¹¹ Thus, we find there is strong circumstantial evidence for a relationship between increasing resistance and increased subsequent hospitalization for out-patient CAP.

The results of our model are based on the premise that *in vitro* susceptibility, according to pharmacokinetic/pharmacodynamic breakpoints, is highly associated with treatment outcome. The few studies that have examined the impact of highly penicillin-resistant pneumococcal disease, which is consistent with the pharmacokinetic/pharmacodynamic approach, as well as a recent case-control study of treatment outcomes in macrolide-resistant bacteraemia,⁴⁰ suggest that this may indeed be the case. However, even if only half of *in vitro* resistant organisms are truly resistant *in vivo*, the model still predicts that resistance accounts for more than a quarter of subsequent hospitalizations for adult CAP in France.

Another potential limitation of this study is the paucity of data regarding hospitalization rates following initial out-patient treatment failure, which we corroborated with medical claims data. Sensitivity analysis showed that halving this rate to 10% had little impact on the amoxicillin/erythromycin strategy, but served to sharply reduce the hospitalization rate for the erythromycin/levofloxacin strategy. Even here, however, the impact of resistance would be substantial.

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The use of surveillance data to estimate antimicrobial resistance rates in the model introduces a further potential limitation. Samples sent to laboratories have a potential selection bias, since microbiological analysis is more commonly carried out in patients who have already failed treatment. Patients who fail treatment may be more likely to be harbouring a resistant pathogen. In this case surveillance data may overestimate resistance rates, thereby leading to an overestimate of hospitalizations in the model. However, even if true resistance rates were just half the rate found in surveillance data, the model estimated that resistance accounted for 27% of the subsequent hospitalizations in France. Thus, even if there were selection bias in the surveillance data, this would not change the conclusions here.

Another assumption in the model was that some infections are inherently non-persisting, i.e. they will resolve even without treatment and would show signs of improvement within 48–72 h of beginning the second round of out-patient therapy. In reality, however, some of these infections would take longer to resolve and might even necessitate switching to a third-line antimicrobial. This would have no bearing on our results since we assumed that patients with these infections would not need to be hospitalized. On the other hand, the model may have a slight bias in favour of underestimation of the hospitalization rate because some patients with inherently non-persisting infections may be hospitalized as a precaution due to co-morbid disease or advanced age.

Finally, the assumption that all second-line treatment failures would be hospitalized is, obviously, a simplification. In reality, there are patients who are able to have a third round of out-patient therapy. Some of these patients have non-persisting infections and these did not affect our results. However, our model slightly overestimates hospitalization due to those patients with persisting infection who are able to have a third round of out-patient therapy and respond. When considering the entire cohort of CAP patients, this group is likely to be very small. Overall, despite the various potential limitations of the model, it performed well in validation tests against published community-based studies. This suggests that whatever bias may have been created by the assumptions of the model, the magnitude of this bias is small.

There are both clinical and economic arguments for aiming to reduce rates of hospitalization in patients with CAP. Out-patient treatment strategies must, therefore, be chosen carefully to optimize the chances of achieving a cure and thereby avoiding the need for hospitalization. The choice of first-line therapy should be made based on the spectrum of activity of the drug, local resistance patterns and activity against pathogens that are least likely to resolve spontaneously. Owing to cross-resistance, the choice of second-line therapy can present a challenge.

The findings of this study indicate that first-line treatment success is of great importance in reducing subsequent hospi-

talizations for out-patient CAP. This would seem to suggest that newer antimicrobials should be used for first-line therapy. However, the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group and the British Thoracic Society have recommended that fluoroquinolones be reserved for second-line treatment for fear of inducing greater fluoroquinolone resistance.^{39,63} Indeed, fluoroquinolone-resistant *S. pneumoniae* has reached significant levels in some countries, which is causing alarm.⁶⁴ Thus clinicians are faced with a dilemma.

In conclusion, the data generated using this probability model suggest that antimicrobial resistance and cross-resistance may have an impact on health outcomes in out-patients receiving treatment for CAP, including increased rates of hospitalization. Hospitalization is associated with poorer clinical outcomes, including increased mortality, and increased treatment costs. Therefore, out-patient treatment strategies should be developed to maximize the likelihood of cure and thereby minimize the need for hospitalization.

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References

1. Meyer, R. D. & Finch, R. (1992). Community-acquired pneumonia. *Journal of Hospital Infection* **22**, Suppl. A, 51–9.
2. Almirall, J., Bolibar, I., Vidal, J., Sauca, G., Coll, P., Niklasson, B. *et al.* (2000). Epidemiology of community-acquired pneumonia in adults: a population-based study. *European Respiratory Journal* **15**, 757–63.
3. Bartlett, J. G., Dowell, S. F., Mandell, L. A., File, T. M., Jr, Musher, D. M. & Fine, M. J. (2000). Practice guidelines for the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases* **31**, 347–82.
4. Lave, J. R., Lin, C. J., Fine, M. J. & Hughes-Cromwick, P. (1999). Cost of treating patients with community-acquired pneumonia. *Seminars in Respiratory Critical Care Medicine* **20**, 189–97.
5. Fine, M. J., Smith, M. A., Carson, C. A., Mutha, S. S., Sankey, S. S., Weissfeld, L. A. *et al.* (1996). Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *Journal of the American Medical Association* **275**, 134–41.
6. Fine, M. J., Auble, T. E., Yealy, D. M., Hanusa, B. H., Weissfeld, L. A., Singer, D. E. *et al.* (1997). A prediction rule to identify low-risk

patients with community-acquired pneumonia. *New England Journal of Medicine* **336**, 243–50.

7. Bartlett, J. G. & Mundy, L. M. (1995). Community-acquired pneumonia. *New England Journal of Medicine* **333**, 1618–24.

8. Lynch, J. P., 3rd (2000). Community-acquired pneumonia: risk factors and specific causes. *Journal of Respiratory Diseases* **21**, 457–68.

9. Felmingham, D. & Grüneberg, R. N. (2000). The Alexander Project 1996–1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. *Journal of Antimicrobial Chemotherapy* **45**, 191–203.

10. Sahm, D. F., Jones, M. E., Hickey, M. L., Diakun, D. R., Mani, S. V. & Thornsberry, C. (2000). Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997–1998. *Journal of Antimicrobial Chemotherapy* **45**, 457–66.

11. Doern, G. V., Heilmann, K. P., Huynh, H. K., Rhomberg, P. R., Coffman, S. L. & Brueggemann, A. B. (2001). Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. *Antimicrobial Agents and Chemotherapy* **45**, 1721–9.

12. Sloas, M. M., Barrett, F. F., Chesney, P. J., English, B. K., Hill, B. C., Tenover, F. C. *et al.* (1992). Cephalosporin treatment failure in penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. *Pediatric Infectious Diseases Journal* **11**, 662–6.

13. Catalan, M. J., Fernandez, J. M., Vazquez, A., Varela de Seijas, E., Suarez, A. & Bernaldo de Quiros, J. C. (1994). Failure of cefotaxime in the treatment of meningitis due to relatively resistant *Streptococcus pneumoniae*. *Clinical Infectious Diseases* **18**, 766–9.

14. Dagan, R., Abramson, O., Leibovitz, E., Greenberg, D., Lang, R., Goshen, S. *et al.* (1997). Bacteriologic response to oral cephalosporins: are established susceptibility breakpoints appropriate in the case of acute otitis media? *Journal of Infectious Diseases* **176**, 1253–9.

15. del Castillo, F., Baquero-Artigao, F. & Garcia-Perea, A. (1998). Influence of recent antibiotic therapy on antimicrobial resistance of *Streptococcus pneumoniae* in children with otitis media in Spain. *Pediatric Infectious Diseases Journal* **17**, 94–7.

16. Cassiere, H. A. & Niederman, M. S. (1998). Community-acquired pneumonia. *Disease-a-Month* **44**, 613–75.

17. File, T. M., Jr (2002). Appropriate use of antimicrobials for drug-resistant pneumonia: focus on the significance of β -lactam-resistant *Streptococcus pneumoniae*. *Clinical Infectious Diseases* **34**, Suppl. 1, S17–26.

18. Metlay, J. P. (2002). Update on community-acquired pneumonia: impact of antibiotic resistance on clinical outcomes. *Current Opinion in Infectious Diseases* **15**, 163–7.

19. Friedland, I. R. (1995). Comparison of the response to antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. *Pediatric Infectious Diseases Journal* **14**, 885–90.

20. Pallares, R., Linares, J., Vadillo, M., Cabellos, C., Manresa, F., Viladrich, P. F. *et al.* (1995). Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *New England Journal of Medicine* **333**, 474–80.

21. Einarsson, S., Kristjansson, M., Kristinsson, K. G., Kjartansson, G. & Jonsson, S. (1998). Pneumonia caused by penicillin-non-susceptible and penicillin-susceptible pneumococci in adults: a case control study. *Scandinavian Journal of Infectious Diseases* **30**, 253–6.

22. Metlay, J. P., Hofmann, J., Cetron, M. S., Fine, M. J., Farley, M. M., Whitney, C. *et al.* (2000). Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. *Clinical Infectious Diseases* **30**, 520–8.

23. Ewig, S., Ruiz, M., Torres, A., Marco, F., Martinez, J. A., Sanchez, M. *et al.* (1999). Pneumonia acquired in the community through drug-resistant *Streptococcus pneumoniae*. *American Journal of Respiratory Critical Care Medicine* **159**, 1835–42.

24. Feikin, D. R., Schuchat, A., Kolczak, M., Barrett, N. L., Harrison, L. H., Lefkowitz, L. *et al.* (2000). Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. *American Journal of Public Health* **90**, 223–9.

25. Turett, G. S., Blum, S., Fazal, B. A., Justman, J. E. & Telzak, E. E. (1999). Penicillin resistance and other predictors of mortality in pneumococcal bacteremia in a population with high human immunodeficiency virus seroprevalence. *Clinical Infectious Diseases* **29**, 321–7.

26. Sinus and Allergy Health Partnership. (2000). Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngology—Head and Neck Surgery* **123**, 1 Part 2, 5–31.

27. Marchant, C. D., Carlin, S. A., Johnson, C. E. & Shurin, P. A. (1992). Measuring the comparative efficacy of antibacterial agents for otitis media: the ‘Pollyanna phenomenon’. *Journal of Pediatrics* **120**, 72–7.

28. Fang, G. D., Fine, M. J., Orloff, J., Arisumi, D., Yu, V. L., Kapoor, W. *et al.* (1990). New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. *Medicine* **69**, 307–16.

29. Woodhead, M. A., Macfarlane, J. T., McCracken, J. S., Rose, D. H. & Finch, R. G. (1987). Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* **i**, 671–4.

30. Macfarlane, J. T., Colville, A., Guion, A., Macfarlane, R. M. & Rose, D. H. (1993). Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* **341**, 511–4.

31. Ruiz-González, A., Falguera, M., Nogués, A. & Rubio-Caballero, M. (1999). Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *American Journal of Medicine* **106**, 385–90.

32. Jacobs, M. R., Bajaksouzian, S., Zilles, A., Lin, G., Pankuch, G. A. & Appelbaum, P. C. (1999). Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 US surveillance study. *Antimicrobial Agents and Chemotherapy* **43**, 1901–8.

33. Craig, W. A. (2001). The hidden impact of antibacterial resistance in respiratory tract infection. Re-evaluating current antibiotic therapy. *Respiratory Medicine* **95**, Suppl. A, S12–9.

34. Canadian Coordinating Office for Health Technology Assessment. (1997). Macrolides in community-acquired pneumonia and otitis media. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Issue 8, 1–14.

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35. Carbon, C., Léophonte, P., Petitpretz, P., Chauvin, J. P. & Hazebrucq, J. (1992). Efficacy and safety of temafloxacin versus those of amoxicillin in hospitalized adults with community-acquired pneumonia. *Antimicrobial Agents and Chemotherapy* **36**, 833–9.
36. Lode, H., Garau, J., Grassi, C., Hosie, J., Huchon, G., Legakis, N. *et al.* (1995). Treatment of community-acquired pneumonia: a randomized comparison of sparflaxacin, amoxicillin–clavulanic acid and erythromycin. *European Respiratory Journal* **8**, 1999–2007.
37. Donowitz, G. R., Brandon, M. L., Salisbury, J. P., Harman, C. P., Tipping, D. M., Urick, A. E. *et al.* (1997). Sparflaxacin versus cefaclor in the treatment of patients with community-acquired pneumonia: a randomized, double-masked, comparative, multicenter study. *Clinical Therapeutics* **19**, 936–53.
38. Mundy, L. M., Oldach, D., Auwaerter, P. G., Gaydos, C. A., Moore, R. D., Bartlett, J. G. *et al.* (1998). Implications for macrolide treatment in community-acquired pneumonia. *Chest* **113**, 1201–6.
39. Heffelfinger, J. D., Dowell, S. F., Jorgensen, J. H., Klugman, K. P., Mabry, L. R., Musher, D. M. *et al.* (2000). Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Archives of Internal Medicine* **160**, 1399–408.
40. Lonks, J. R., Garau, J., Gomez, L., Xercavins, M., Ochoa De Echaguen, A., Gareen, I. F. *et al.* (2002). Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. *Clinical Infectious Diseases* **35**, 556–64.
41. Backhouse, R. J., Kapasi, M., Noble, I. & Hutton, J. (1995). Modelling the use of three antibiotics in the management of community-acquired pneumonia. *British Journal of Medical Economics* **8**, 195–210.
42. Laurichesse, H., Robin, F., Gerbaud, L., Pochet, P., Gourdon, F., Beytout, J. *et al.* (1998). Empirical therapy for nonhospitalized patients with community-acquired pneumonia. *European Respiratory Journal* **11**, 73–8.
43. Felmingham, D. & Grüneberg, R. N. (1996). A multicentre collaborative study of the antimicrobial susceptibility of community-acquired, lower respiratory tract pathogens 1992–1993: the Alexander Project. *Journal of Antimicrobial Chemotherapy* **38**, Suppl. A, 1–57.
44. Fine, M. J., Stone, R. A., Singer, D. E., Coley, C. M., Marrie, T. J., Lave, J. R. *et al.* (1999). Processes and outcomes of care for patients with community-acquired pneumonia. *Archives of Internal Medicine* **159**, 970–80.
45. Gilbert, K., Gleason, P. P., Singer, D. E., Marrie, T. J., Coley, C. M., Obrosky, S. *et al.* (1998). Variations in antimicrobial use and cost in more than 2,000 patients with community-acquired pneumonia. *American Journal of Medicine* **104**, 17–27.
46. Centers for Disease Control and Prevention. (1998). Preventing emerging infectious diseases: a strategy for the 21st century. Overview of the updated CDC plan. *MMWR Morbidity and Mortality Weekly Report* **47**, 1–14.
47. Baquero, F. (1999). Evolving resistance patterns of *Streptococcus pneumoniae*: a link with long-acting macrolide consumption? *Journal of Chemotherapy* **11**, Suppl. 1, 35–43.
48. Kataja, J., Huovinen, P. & Seppälä, H. (2000). Erythromycin resistance genes in group A streptococci of different geographical origins. The Macrolide Resistance Study Group. *Journal of Antimicrobial Chemotherapy* **46**, 789–92.
49. Tait-Kamradt, A., Davies, T., Appelbaum, P. C., Depardieu, F., Courvalin, P., Petitpas, J. *et al.* (2000). Two new mechanisms of macrolide resistance in clinical strains of *Streptococcus pneumoniae* from Eastern Europe and North America. *Antimicrobial Agents and Chemotherapy* **44**, 3395–401.
50. Hyde, T. B., Gay, K., Stephens, D. S., Vugia, D. J., Pass, M., Johnson, S. *et al.* (2001). Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *Journal of the American Medical Association* **286**, 1857–62.
51. Brisson-Noël, A., Arthur, M. & Courvalin, P. (1988). Evidence for natural gene transfer from Gram-positive cocci to *Escherichia coli*. *Journal of Bacteriology* **170**, 1739–45.
52. Bast, D. J., Low, D. E., Duncan, C. L., Kilburn, L., Mandell, L. A., Davidson, R. J. *et al.* (2000). Fluoroquinolone resistance in clinical isolates of *Streptococcus pneumoniae*: contributions of type II topoisomerase mutations and efflux to levels of resistance. *Antimicrobial Agents and Chemotherapy* **44**, 3049–54.
53. Lister, P. D. (2000). Emerging resistance problems among respiratory tract pathogens. *American Journal of Managed Care* **6**, Suppl. 8, S409–18.
54. Yan, S. S., Fox, M. L., Holland, S. M., Stock, F., Gill, V. J. & Fedorko, D. P. (2000). Resistance to multiple fluoroquinolones in a clinical isolate of *Streptococcus pyogenes*: identification of *gyrA* and *parC* and specification of point mutations associated with resistance. *Antimicrobial Agents and Chemotherapy* **44**, 3196–8.
55. Gilbert, K. & Fine, M. J. (1994). Assessing prognosis and predicting patient outcomes in community-acquired pneumonia. *Seminars in Respiratory Infection* **9**, 140–52.
56. Dean, N. C., Silver, M. P., Bateman, K. A., James, B., Hadlock, C. J. & Hale, D. (2001). Decreased mortality after implementation of treatment guideline for community-acquired pneumonia. *American Journal of Medicine* **110**, 451–7.
57. Guest, J. F. & Morris, A. (1997). Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *European Respiratory Journal* **10**, 1530–4.
58. Niederman, M. S., McCombs, J. S., Unger, A. N., Kumar, A. & Popovian, R. (1998). The cost of treating community-acquired pneumonia. *Clinical Therapeutics* **20**, 820–37.
59. Fine, M. J., Pratt, H. M., Obrosky, D. S., Lave, J. R., McIntosh, L. J., Singer, D. E. *et al.* (2000). Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. *American Journal of Medicine* **109**, 378–85.
60. Christiansen, K. (1996). Community-acquired pneumonia: epidemiologic and clinical considerations. *Clinical Microbiology and Infection* **1**, Suppl. 2, S23–9.
61. Baine, W. B., Yu, W. & Summe, J. P. (2001). Epidemiologic trends in the hospitalization of elderly Medicare patients for pneumonia, 1991–1998. *American Journal of Public Health* **91**, 1121–3.
62. Centers for Medicare & Medicaid Services. 100% MEDPAR inpatient hospital fiscal years 1998–2000, short stay inpatient by state. [On-line.] <http://www.cms.gov/statistics/medpar/default.asp> (12 November 2002, date last accessed).

63. British Thoracic Society. (2001). BTS guidelines for the management of community-acquired pneumonia in adults. *Thorax* **56**, *Suppl 4*, IV1–64.

64. Pérez-Trallero, E., Garcia-Rey, C., Martin-Sanchez, A. M., Aguilar, L., Garcia-de-Lomas, J. & Ruiz, J. (2002). Activities of six

different quinolones against clinical respiratory isolates of *Streptococcus pneumoniae* with reduced susceptibility to ciprofloxacin in Spain. Spanish Surveillance Group for Respiratory Pathogens (SAUCE Program). *Antimicrobial Agents and Chemotherapy* **46**, 2665–7.