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A cost-effectiveness analysis of antimicrobial treatment of community-acquired pneumonia taking into account resistance in Belgium

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Key words: Antimicrobial resistance – Community-acquired pneumonia – Cost-effectiveness analysis – Decision analytic model – Moxifloxacin

ABSTRACT

Objective: This article assesses the cost-effectiveness of outpatient antimicrobial treatment of community-acquired pneumonia (CAP) taking into account resistance in Belgium.

Research design and methods: Our decision analytic model focused on mild to moderate CAP, but did not consider severe CAP. Treatment pathways reflected empirical treatment initiated in the absence of data on CAP aetiology. First-line treatment consisted of moxifloxacin, co-amoxiclav, cefuroxime or clarithromycin. If first-line treatment was unsuccessful, patients were either hospitalised or second-line treatment with a different antimicrobial was initiated. Clinical failure rates were obtained from the published literature or expert opinion. Costs were calculated using published sources from the third-party payer perspective.

Main outcome measures: Effectiveness measures included first-line clinical failure avoided, second-line treatment avoided, hospitalisation avoided and death avoided. Healthcare costs were included, but costs of productivity loss were not considered.

Results: Costs of treating a CAP episode amounted to €144 with moxifloxacin/co-amoxiclav; €222 with co-amoxiclav/clarithromycin; €211 with cefuroxime/moxifloxacin; and €193 with clarithromycin/moxifloxacin. The rate of first-line failure was 5%, 16%, 19% and 18% for these four treatment strategies, respectively. The rate of second-line treatment amounted to 4%, 13%, 16% and 15%, respectively. The hospitalisation rate was 1%, 4%, 4% and 4%, respectively. The death rate was 0.01%, 0.04%, 0.03% and 0.03%, respectively. Sensitivity analyses supported the dominance of moxifloxacin/co-amoxiclav in nearly all scenarios.

Conclusions: First-line treatment of CAP patients with moxifloxacin followed by co-amoxiclav or hospitalisation if required was more effective and less costly as compared with first-line treatment with co-amoxiclav, cefuroxime or clarithromycin.
Introduction

The term ‘community-acquired pneumonia’ (CAP) covers those infections of the lung parenchyma that are not acquired in hospital or a long-term care facility. The incidence, clinical and economic burden of CAP are significant, although Belgian data about these aspects are lacking. CAP is a common infectious disease, with annual incidence rates of 1.6 per 1000 adults in Spain and 11.6 per 1000 adults in Finland. CAP is associated with significant morbidity, is the leading cause of death due to infection in developed countries and is the sixth leading cause of death in the United States. The economic burden of CAP is substantial. In the United States, CAP accounts each year for 10 million physician visits. It is a primary driver of hospital admissions, resulting in about 1 million hospitalisations in the United States per year at an estimated cost of $9 billion. The key component of inpatient costs is the length of hospitalisation.

Patients suffering from CAP generally present with a cough (more than 90% of patients), dyspnea (66%), sputum production (66%) and pleuritic chest pain (50%). Other symptoms may include headache and myalgia. Specific aetiologies, such as Legionella spp., may be associated with gastro-intestinal symptoms. Chest X-rays, examination of the blood and sputum for infectious micro-organisms, and blood tests are commonly used to diagnose individuals with suspected CAP based upon symptoms and physical examination. Several decision rules are available to categorise patients as suffering from either mild, moderate or severe CAP, such as the Pneumonia Severity Index and the CURB-65 score. These decision rules have also been developed to guide treatment.

Patients suffering from mild to moderate CAP are generally treated with oral antimicrobials in the community. Hospitalisation may be required for elderly patients, patients who have underlying chronic illnesses or patients with more serious disease. In the majority of patients, treatment is empirical in that treatment is initiated in the absence of information about the causative pathogen involved in CAP and the antibiotic susceptibility pattern of the isolated organism. The treatment approach to CAP is challenging due to the expanding spectrum of causative pathogens, the rising prevalence of resistance to antimicrobial agents and the increasing pressure to reduce the length of hospitalisation.

These trends have led to a debate about the choice of antimicrobial in the management of CAP. The European Respiratory Society has published clinical guidelines to guide antimicrobial treatment of CAP. With respect to management of CAP in the community, amoxicillin or tetracyclines are recommended. In case of hypersensitivity, newer macrolides, such as clarithromycin, are alternatives in countries with low pneumococcal macrolide resistance. If there is clinically relevant resistance against first-choice agents, treatment with moxifloxacin or levofloxacin may be considered. With respect to management of CAP in hospital, preferred treatment strategies in regions with low resistance rates include piperacillin G, aminopenicillin, co-amoxiclav, cephalosporin II or III; each ± a macrolide. In countries with increased resistance rates, levofloxacin or moxifloxacin may be alternatives. In patients with severe CAP and no risk factors for Pneumococcal aeruginosa, a non-antipseudomonal cephalosporin III + a macrolide or moxifloxacin/levofloxacin is preferred. In patients with severe CAP and risk factors for P. aeruginosa, guidelines recommend an antipseudomonal cephalosporin, an alyureidopenicillin/β-lactamase inhibitor or carbapenem; each with ciprofloxacin.

The guidelines of the European Respiratory Society also stated that the selection of antimicrobial needs to reflect local patterns of microbial resistance in addition to the severity of illness, the frequency of specific pathogens and drug safety profiles. With respect to resistance, data from the Belgian Pneumococcal Reference Laboratory indicate that in vitro resistance of Streptococcus pneumoniae to macrolides has increased from 5.2% in 1986 to 36.1% in 2003 in Belgium. Similarly, resistance has grown from 16.4% to 30.2% in the case of tetracyclines and from 2% to 13% in the case of penicillin. On the other hand, pneumococcal resistance was low for fluoroquinolones, remaining below 1% for levofloxacin and being 0% for moxifloxacin over the 1995–2005 period. Antimicrobial resistance can have a substantial impact on outcomes and costs of CAP treatment. There is evidence that CAP patients with pneumococcal resistance may be at greater risk of poor outcomes. Also, if first-line treatment fails due to resistance, additional costs are incurred due to the need for second-line treatment or hospitalisation, or both.

The aim of this article is to assess the cost-effectiveness of empirical outpatient treatment of mild to moderate CAP with moxifloxacin or other antimicrobials (co-amoxiclav, cefuroxime or clarithromycin) in Belgium from the perspective of the third-party payer. Treatment strategies involve oral antimicrobials, are recommended by Belgian guidelines and reflect prevailing treatment pathways in Belgium. The analysis takes into account the presence of antimicrobial resistance in Belgium. In particular, the health economic model investigates whether the higher drug acquisition costs of moxifloxacin are balanced by a lower clinical failure rate and reduced costs of second-line treatment and hospitalisation as a result of a lower resistance rate and a higher clinical success rate.
Methods

A decision analytic model was used to assess the cost-effectiveness of empirical treatment with oral antimicrobials in a population of CAP patients. The model was originally developed for France, Germany and the United States, but the current study adapted the model to reflect empirical antimicrobial treatment of CAP in Belgium. The model adaptation involved the selection of prevalent treatment strategies, antimicrobial resistance data, resource use data and unit cost data pertaining to Belgium. The adapted model adds to the evidence base by presenting, to the best of the authors’ knowledge, the first results on the cost-effectiveness of current antimicrobial treatment pathways in Belgium. Also, the model provides results for a country which has an intermediate level of antimicrobial resistance in CAP pathogens as compared with other European countries such as Germany which has a low level of resistance, or France which has a high level of resistance.

Decision analytic model

Figure 1 represents the decision analytic model of empirical antimicrobial treatment of CAP in Belgium. For each antimicrobial treatment option, the decision tree consists of three arms reflecting the different pathogens, S. pneumoniae, Haemophilus influenzae and the atypical pathogens. For each pathogen, the tree contains two arms, namely susceptible or non-susceptible (resistant) to first-line treatment. Resistance rates vary by the pathogens and treatments considered. If first-line treatment fails, patients are either hospitalised or receive second-line treatment in the community. This is identical for treatment failures occurring in susceptible and resistant isolates. Second-line treatment leads to treatment success or failure. If second-line treatment fails, all patients are hospitalised. Following hospitalisation, patients experience either treatment success (patient is discharged alive) or treatment failure (patient dies in hospital). As the time scale of the model equals the treatment duration of a CAP episode and is, thus, shorter than 1 year, no discounting of costs or outcomes was carried out. Each of the steps of the decision analytic model is described in more detail in the following sections.

Study population

A hypothetical population was considered consisting of patients suffering from mild to moderate CAP (i.e. Fine risk category I–III) and who had not undergone antimicrobial treatment in the previous 3 months. These patients are generally treated empirically in the community. The relative incidence of Fine risk classes in an outpatient population has been reported to be 62%, 26% and 8% for categories I, II and III, respectively. Recalibrating these percentages to add up to 100%, the model applied a relative incidence of 65%, 27% and 8% for categories I, II and III, respectively.

Pathogens

The most common causative microbial pathogens involved in CAP [S. pneumoniae, H. influenzae and the atypical pathogens (Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella spp.)] were considered in the model at their approximate relative isolation frequencies. Estimates were based on observed prevalences across German CAP patients treated initially in the community, reporting 40% for S. pneumonia, 8% for H. influenzae and 12% for atypical pathogens, confirming prevalence estimates from the published literature. Normalising these prevalences to 100% for the purpose of the model generated frequencies of 67% for S. pneumoniae, 10% for H. influenzae and 23% for the atypical pathogens.

Antimicrobial treatment

Antimicrobial treatments represented current treatment pathways in Belgium and were based on Belgian guidelines relating to treatment of CAP in the community. First-line treatment consisted of moxifloxacin (a fluoroquinolone), co-amoxiclav (a beta-lactam), cefuroxime (a beta-lactam) or clarithromycin (a macrolide). If first-line treatment was unsuccessful as determined at a follow-up visit, some patients were hospitalised or a second-line treatment was initiated. A hospitalisation rate following first-line treatment failure of 15.4% was used. Second-line treatments were co-amoxiclav (if first-line treatment with moxifloxacin failed), clarithromycin (if first-line treatment with co-amoxiclav failed) and moxifloxacin (if first-line treatment with clarithromycin or cefuroxime failed). Regimens of first-line and second-line treatment amounted to a daily dose of 400 mg of moxifloxacin during 10 days; a daily dose of 2625 mg of co-amoxiclav during 10 days; a daily dose of 1500 mg of cefuroxime during 10 days and a daily dose of 1000 mg of clarithromycin during 5 days. If second-line treatment was unsuccessful, all patients were hospitalised. Antimicrobial treatment in hospital was assumed to be identical for all patients in order to avoid introducing variability as the model focuses on patients treated in the community.
Figure 1. Decision analytic model to determine the cost-effectiveness of antimicrobial treatment of CAP in the community
Clinical failure rates

The model is based on the premise that clinical failure can occur due to two main reasons: lack of response to treatment in patients with susceptible pathogens and failure due to the presence of antimicrobial-resistant pathogens.

The failure rate in susceptible pathogens was estimated on the basis of antimicrobial success rates from published clinical trials in CAP. Meta-analyses were not suitable for use in the model as they did not focus on the population considered. A wide range of efficacy data was found in the literature due to differences in trial design, treatment setting, patient population, duration of treatment, trial size, outcome measures used, etc. Our estimates were based on those clinical trials that could be matched as far as possible to the patient population, causative pathogens, time horizon, dosage and outcome measures considered in our analysis. The antimicrobial success rate was calculated as the simple average of selected studies. The obtained antimicrobial success rates were 95% for moxifloxacin\(^{25-28}\), 90% for co-amoxiclav\(^{29}\), 90% for cefuroxime\(^{30}\) and 93% for clarithromycin\(^{25,31,32}\).

The failure rate in antimicrobial-resistant pathogens was estimated on the basis of antimicrobial resistance data from published surveillance studies. The majority of samples considered in surveillance studies relate to hospitalised patients. However, a recent study showed that the prevalence of resistant isolates in a hospitalised and community setting is similar for community-acquired pathogens\(^{33}\), thus enabling us to generalise surveillance data to the community setting. Antimicrobial resistance data related to Belgium or were derived from published sources in the absence of Belgian data.

For *S. pneumoniae*, the Clinical and Laboratory Standards Institute (CLSI) breakpoints were used to define susceptibility and resistance of a pathogen as these breakpoints represent the ‘gold standard’ and are used internationally in trials. For *H. influenzae*, pharmacokinetic/pharmacodynamic (PK/PD) breakpoints were used, except for moxifloxacin, for which CLSI breakpoints were applied\(^{34}\). The use of PK/PD rather than CLSI breakpoints had a major effect on the resistance rate in *H. influenzae*. PK/PD breakpoints for *H. influenzae* were used in the base case analysis because they are thought to better reflect clinical success/failure containing information on both *in vitro* and *in vivo* on time and eradication and because they have been validated in animal models and clinical studies in otitis media and sinusitis\(^{34-36}\). No CLSI breakpoints have been developed for the atypical pathogens as no resistance has been observed in these pathogens.

In Belgium, surveillance studies from 1995 to 2005 have consistently found 0% resistance of *S. pneumoniae* to moxifloxacin\(^{15,16}\). There were no reports of moxifloxacin resistance from the Alexander Project (1998–2000)\(^{34}\) and from the PROTEKT study (1999–2000)\(^{37}\) in *H. influenzae* isolates. Atypical isolates have not demonstrated any resistance to moxifloxacin and are assumed to be 100% susceptible.

Beta-lactams are among the most effective agents for the treatment of *S. pneumoniae*, with >90% of isolates in Belgium being susceptible. Resistance rates of 0% and 9.2% have been reported to co-amoxiclav and cefuroxime, respectively, for Belgium\(^{38}\). In *H. influenzae*, the model used resistance rates of 0% to co-amoxiclav and 22.1% to cefuroxime\(^{34}\). As the beta-lactams are not active against the atypical pathogens, the model assumed a 100% resistance rate of atypical pathogens to co-amoxiclav and cefuroxime.

For macrolides, there are two main resistance mechanisms in *S. pneumoniae*, the *mefA* genotype was believed to confer mainly low-level resistance (MICs 1–32 mg/L), whereas the *ermB* genotype was expected to result in mainly high-level resistance (MICs ≥ 8 mg/L)\(^{37}\). Until recently, it was believed that macrolides would be expected to retain efficacy against a proportion of macrolide-resistant strains with *mefA* and low MICs (1–4 mg/L), but be ineffective against *ermB* strains\(^{38}\). However, recent evidence has indicated that both mechanisms can result in a high level of resistance. The model used estimates of resistance rates to clarithromycin of 23.7% for *S. pneumoniae* and 100% for *H. influenzae*\(^{43,39}\). For atypical pathogens, no resistance has been reported to clarithromycin.

Rates of clinical failure due to resistance were estimated for each pathogen. As the published literature did not provide quantitative evidence on this relationship, a number of assumptions were made based on the opinion of clinical experts. For moxifloxacin, co-amoxiclav and cefuroxime, the model assumed that 50% of resistant isolates of *S. pneumoniae* resulted in clinical failure. Also, for clarithromycin, a 50% clinical failure rate was assumed for both *mefA* resistance and for strains with *ermB* resistance (± *mefA*). This was based on the premise that even in case of treatment failure, host defence mechanisms can overcome resistance and still result in clinical success. Clinical failure rates for resistant isolates of *H. influenzae* were assumed to be 50% for all antimicrobials considered. As atypical pathogens are not resistant to moxifloxacin and clarithromycin, the clinical failure rate due to resistance was assumed to be 0%. Finally, a spontaneous cure rate of 65% (or a clinical failure rate of 35%) was assumed when co-amoxiclav or cefuroxime was used to treat an atypical pathogen.
Mortality

Data from the PORT study indicated that the mortality rate of Fine category I, II and III patients treated for CAP in the community was 0.1%. As the mortality rate in the community is very small, the mortality rate was considered to be zero. For hospitalised patients, the mortality rate of Fine category I, II and III patients of 0.9%, as obtained from the PORT study, was used in the model. The PORT study also provided an estimate of the mortality rate in the intensive care unit of 37%.10

Resource use and costs

Resource use was derived from the literature. Unit costs were obtained from RIZIV/INAMI, the national insurance company which acts as the Belgian third-party payer40, or from published sources in the absence of Belgian data. Where needed, costs were inflated to 2006.

Daily reimbursed costs of antimicrobial treatment amounted to 4.12€ for moxifloxacin 400mg; 2.47€ for co-amoxiclav 2625 mg; 2.94€ for cefuroxime 1500 mg and 2.75€ for clarithromycin 1000 mg40. Antimicrobial treatments were prescribed at the first consultation for a period of 10 days for moxifloxacin, co-amoxiclav and cefuroxime, and for a period of 5 days for clarithromycin8. Evaluation of treatment success took place after 3 days. If first-line treatment was failing, patients were either hospitalised or second-line treatment with a different antimicrobial was initiated. As the costs of the first-line treatment had been incurred, the full 10-day or 5-day cost of treatment was included in the model for patients failing first-line treatment. Similarly, patients failing second-line treatment also incurred the full cost of this treatment prior to hospitalisation.

Patients who sought medical advice for CAP incurred a general practitioner (GP) office visit (at a reimbursed cost of 16.71€), a GP home visit (19.95€), a specialist office visit (20.41€) or an emergency room visit (16.71€)40. The frequency of initial visits was estimated at 61% for GP office visits, 19% for GP home visits, 18% for specialist office visits and 2% for emergency room visits41. The initial visit was followed by one follow-up visit after 3 days to assess the efficacy of treatment. The same frequency of the different visit types was assumed for this follow-up visit, with the exception of emergency room visits which were assumed to be followed by a GP office visit. This generated a frequency of follow-up visits of 63% for GP office visits, 19% for GP home visits, 18% for specialist office visits and 0% for emergency room visits5. In case of treatment failure, the costs of another visit were included to assess the efficacy of second-line treatment. If second-line treatment failed, no further GP visits were included prior to hospitalisation.

CAP guidelines advise the use of an initial chest X-ray (at a reimbursed cost of 9.96€) to diagnose CAP and a follow-up chest X-ray (11.95€) to ascertain that the infection has disappeared following treatment16,40. Initial chest X-rays were performed in 39% of patients and follow-up chest X-rays were conducted in 35% of patients24. A white blood cell count was assumed for all patients failing treatment (at a reimbursed cost of 20€)90. Susceptibility testing is not generally carried out in the community setting and was included in total hospital costs14.

The reimbursed hospitalisation cost for CAP patients admitted to the regular ward included all costs related to treatment and diagnostic tests and amounted to 3150.64€40. Based on a study comparing costs of patients surviving and dying in hospital, costs of surviving patients were multiplied by 1.45 to obtain hospitalisation costs for patients dying in hospital2. Similarly, based on French data comparing costs of patients admitted to a regular ward or the intensive care unit, a multiplier of 1.63 was used to calculate costs of patients admitted to the intensive care unit43.

 Costs related to adverse events were not included due to the low incidence rates of adverse events in antimicrobial treatment44. As a result, the impact of these costs on the cost-effectiveness of antimicrobial treatment strategies is expected to be limited.

Base case analysis

The base case analysis calculated incremental cost-effectiveness ratios (ICERs) using the following equation:

\[ \text{ICER} = \frac{(C_1 - C_0)}{(E_1 - E_0)} \]

where \( C_1 \) is the cost of the intervention; \( C_0 \) is the cost of the alternative with which the intervention is compared; \( E_1 \) and \( E_0 \) are the respective health outcomes of intervention and comparator.

The intervention was a strategy consisting of first-line treatment with moxifloxacin and second-line treatment with co-amoxiclav if required. The three comparator strategies were co-amoxiclav/clarithromycin, cefuroxime/moxifloxacin, and clarithromycin/moxifloxacin. Effectiveness was assessed in terms of the rate of first-line clinical failures, of second-line treatments required, of hospitalisations required and of mortality. A strategy is said to dominate the comparator when it is both less expensive and more effective.

Sensitivity analysis

One-way deterministic sensitivity analyses were carried out to ascertain the robustness of ICERs by varying key
input parameters over plausible ranges. The sensitivity analyses set all antimicrobial success rates at 100% with a view to isolating the impact of antimicrobial resistance on ICERs. To assess the impact of changes in resistance level, resistance rates for *S. pneumoniae* and *H. influenzae* were changed from −50% to +50% of base case rates for each of the antimicrobials considered. The clinical failure rate for resistant isolates was reduced from 50% to 20%. CLSI resistance rates were used for *H. influenzae* instead of PK/PD resistance rates.

To explore the impact of hospitalisation, hospitalisation costs were either increased or decreased by 50%. Also, the base case analysis assumed no admissions to the intensive care unit. In the deterministic sensitivity analysis, a rate of admittance to the intensive care unit for hospitalised patients of 4.9% was used, based on the Fine category mix of the population9. Furthermore, the analysis explored the impact of first-line treatment failure resulting in no hospitalisation, but always leading to second-line treatment in the community.

Viruses were not considered in the base case analysis as the main focus is on antimicrobial resistance and viruses are insensitive to antimicrobial treatment. The deterministic sensitivity analysis considered viruses as these are often mistaken for microbial pathogens and are treated empirically with antimicrobials. Normalised frequencies used in the sensitivity analysis were 20% for viruses, 54% for *S. pneumoniae*, 8% for *H. influenzae* and 18% for the atypical pathogens23. Finally, to equalise the effect of second-line treatment, an analysis was performed in which all second-line treatments were changed to moxifloxacin. A similar analysis was conducted with co-amoxiclav as second-line treatment for all treatment strategies.

A probabilistic sensitivity analysis based on a 100000-iteration Monte Carlo simulation was performed in *Microsoft Excel* using the add-on programme @RISK. Such an analysis requires that a probability distribution is assigned to each input parameter. Hospitalisation unit costs and antimicrobial success rates were assumed to have a triangular distribution. The beta distribution was chosen for resistance rates. Spontaneous cure rates and clinical failure rates for resistant isolates were assumed to be distributed as uniform random variables. For each iteration, the simulation drew input parameters at random from their statistical distributions and calculated cost and effectiveness pairs.

At the end of the 1000 iterations, the joint statistical distribution for costs and effectiveness was represented as a cloud of points on the cost-effectiveness plane. Cost-effectiveness acceptability curves representing the probability that the moxifloxacin/co-amoxiclav strategy is cost-effective for a range of cost-effectiveness thresholds were also drawn.

## Results

### Base case analysis

Table 1 presents the cost-effectiveness results of the base case analysis. A strategy consisting of first-line treatment with moxifloxacin and second-line treatment with co-amoxiclav dominated each of the three comparator strategies (co-amoxiclav/clarithromycin, cefuroxime/moxifloxacin and clarithromycin/moxifloxacin). The cost of treating a CAP episode with moxifloxacin/co-amoxiclav was 35%, 32% and 26% less than treatment with co-amoxiclav/clarithromycin, 221.97

<table>
<thead>
<tr>
<th></th>
<th>Moxifloxacin/ co-amoxiclav</th>
<th>Co-amoxiclav/ -clarithromycin</th>
<th>Cefuroxime/ moxifloxacin</th>
<th>Clarithromycin/ moxifloxacin</th>
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<tr>
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<td>Hospitalisation</td>
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<td>4.28%</td>
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<td>Deaths</td>
<td>0.01%</td>
<td>0.04%</td>
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Note: ICER = incremental cost-effectiveness ratio
**Table 2.** Deterministic sensitivity analysis in terms of first-line clinical failures avoided

<table>
<thead>
<tr>
<th>Description</th>
<th>Input value</th>
<th>Costs (€)</th>
<th>First-line failure</th>
<th>ICERS</th>
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<td><strong>Effect of resistance</strong></td>
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<td><strong>Range of resistance</strong></td>
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<td><strong>S. pneumoniae</strong></td>
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<td>236.91</td>
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<td>Clarithromycin/moxifloxacin</td>
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<td><strong>Effect of clinical failure rates</strong></td>
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<td><strong>Effect of choice of resistance rates for H. influenzae</strong></td>
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<td>Viruses</td>
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<td><strong>First-line treatment</strong></td>
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<td>All moxifloxacin second-line comparison</td>
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<td>143.53</td>
<td>258.65</td>
<td>286.51</td>
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Note: CLSI = Clinical and Laboratory Standards Institute; ICER = incremental cost-effectiveness ratio
### Table 3. Deterministic sensitivity analysis in terms of hospitalisations avoided

<table>
<thead>
<tr>
<th>Description</th>
<th>Input value</th>
<th>Costs (E)</th>
<th>Hospitalisation rate</th>
<th>ICERs</th>
</tr>
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<tbody>
<tr>
<td>Effect of resistance</td>
<td>All clinical success rates set at 100%</td>
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<td></td>
<td></td>
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<tr>
<td>Range of resistance</td>
<td>Moxifloxacin</td>
<td>143.53</td>
<td>221.97</td>
<td>211.16</td>
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<tr>
<td>S. pneumoniae and H. influenzae</td>
<td>Moxifloxacin</td>
<td>143.53</td>
<td>221.97</td>
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<tr>
<td>Effect of clinical failure rates</td>
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<td>143.53</td>
<td>221.97</td>
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<tr>
<td>for resistant isolates</td>
<td>Clarithromycin</td>
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<td>236.91</td>
<td>211.16</td>
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<td>Co-amoxiclav/cefuroxime</td>
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<td>221.97</td>
<td>199.46</td>
<td>192.79</td>
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<td>Effect of choice of resistance rates for</td>
<td>CLSI resistance rates</td>
<td>143.53</td>
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<td>H. influenzae</td>
<td>All moxifloxacin second-line</td>
<td>129.92</td>
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<td>Effect of hospitalization</td>
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<td>154.29</td>
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<td>Hospitalisation rate 0% following first-line failure</td>
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<td>157.61</td>
<td>125.37</td>
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<td>All moxifloxacin second-line</td>
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<td>258.65</td>
<td>286.51</td>
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Note: CLSI = Clinical and Laboratory Standards Institute; ICER = incremental cost-effectiveness ratio
cefoxime/moxifloxacin or clarithromycin/moxifloxacin, respectively. The moxifloxacin/co-amoxiclav strategy offered lower rates of first-line clinical failures, of second-line treatments required, of hospitalisations required and of mortality, than the three comparator strategies.

Deterministic sensitivity analysis

Deterministic one-way sensitivity analyses were carried out for the effectiveness measures of first-line clinical failures avoided (see Table 2) and hospitalisations avoided (see Table 3). Results are extremely robust to change, with moxifloxacin/co-amoxiclav remaining the dominant strategy in nearly all scenarios. This is driven primarily by the absence of resistance to moxifloxacin and the high clinical success rate associated with moxifloxacin. There are only two scenarios for which moxifloxacin/co-amoxiclav is not the dominant strategy: (a) when the clarithromycin clinical failure rate is reduced from 50% to 20% while keeping the failure rate for moxifloxacin unchanged and (b) when first-line treatment failure did not result in any hospitalisation, but initiated only second-line treatment in the community.

The first scenario decreased clinical failure rates from 50% to 20% using 5% decrements (i.e. the following values were tested for each antimicrobial: 50%, 45%, 40%, 35%, 30%, 25% and 20%). Only the results for 20% are presented in Tables 2 and 3). Adjusting clinical failure rates of moxifloxacin, co-amoxiclav and cefuroxime incrementally did not change any results significantly, nor did reducing clarithromycin clinical failure rates incrementally from 50% to 25%. However, once clarithromycin clinical failure rates were decreased to 20%, the clarithromycin/moxifloxacin strategy became less costly than the moxifloxacin/co-amoxiclav strategy (139.27€ vs. 143.53€). This is due to an improved clinical profile for clarithromycin combined with the lower cost of treatment with clarithromycin therapy in Belgium (13.76€ vs. 41.20€ for treatment with moxifloxacin). Effectiveness measures remain favourable for the moxifloxacin/co-amoxiclav strategy, resulting in ICERs of 79.44€ per first-line failure avoided and 707.45€ per hospitalisation avoided. However, it may be considered unrealistic to assume that the clinical failure rate for clarithromycin is 20% whereas the clinical failure rate for moxifloxacin is 50%.

The second scenario for which moxifloxacin/co-amoxiclav lost its dominant position is in the unlikely event of no hospitalisations following first-line treatment failure. In this situation, the clarithromycin/moxifloxacin strategy became less costly than the moxifloxacin/co-amoxiclav strategy (110.83€ vs. 123.43€) since the higher level of clarithromycin resistance can no longer result in direct hospitalisation after a first regimen of clarithromycin without an outpatient second-line treatment of moxifloxacin first administered. Effectiveness measures remained in favour of the moxifloxacin/co-amoxiclav strategy. This resulted in ICERs of moxifloxacin/co-amoxiclav as compared with clarithromycin/moxifloxacin of 96.03€ per first-line clinical failure avoided and 10 192.01€ per hospitalisation avoided.

There was little impact on results of setting all antimicrobial success rates at 100%. This was due to the low prevailing levels of resistance. Adjusting resistance rates by 50% had little effect on results, in particular those of moxifloxacin or co-amoxiclav treatments as both have S. pneumoniae resistance rates of 0%. Results were also robust to the use of CLSI rather than PK/PD resistance rates for H. influenzae, 50% increases and decreases to hospitalisation costs, the allowance of admissions to the intensive care unit, the inclusion of viruses as a ‘causative’ pathogen, and the standardisation of second-line treatments to either moxifloxacin or co-amoxiclav.

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses were carried out of incremental cost-effectiveness results expressed as cost per first-line clinical failure avoided. Figure 2 shows the scatter plot of 1000 ICER results comparing moxifloxacin/co-amoxiclav with co-amoxiclav/clarithromycin on the cost-effectiveness plane and a 95% confidence ellipse. The moxifloxacin/co-amoxiclav strategy has a 99.4% probability of dominating co-amoxiclav/clarithromycin. Similarly, the moxifloxacin/co-amoxiclav strategy has a 99.9% probability of dominating cefuroxime/moxifloxacin (see Figure 3) and a 92.4% probability of dominating clarithromycin/moxifloxacin (see Figure 4). If decision makers are willing to pay a maximum amount of, for instance, 200€ per first-line clinical failure avoided, the cost-effectiveness acceptability curves demonstrate that the probability of moxifloxacin/co-amoxiclav being cost-effective is 99.5%, 100% and 98.5% as compared with co-amoxiclav/clarithromycin (see Figure 5), cefuroxime/moxifloxacin (see Figure 6) and clarithromycin/moxifloxacin (see Figure 7), respectively.

Discussion

This study assessed the cost-effectiveness of various empirical antimicrobial strategies to treat CAP in the community in Belgium. The base case analysis showed that first-line/second-line treatment with moxifloxacin/co-amoxiclav dominated all other strategies
Cost-effectiveness of antimicrobial treatment of CAP in Belgium

Martin et al.

747

under all effectiveness measures considered (first-line clinical failure avoided, second-line treatment avoided, hospitalisation avoided and deaths avoided). The deterministic and probabilistic sensitivity analyses demonstrated that results are extremely robust to change, with moxifloxacin/co-amoxiclav remaining the dominant strategy in nearly all scenarios. From a clinical perspective, these results indicate that the absence of resistance to moxifloxacin and the high clinical success rate associated with moxifloxacin leads to moxifloxacin/co-amoxiclav being the most effective and least expensive option in most cases.

This model was developed to assess the impact of resistance for CAP patients treated in the community. Treatment guidelines are available in most countries, though these are not always followed in general practice. This model demonstrated the economic and clinical effects of a possible policy change, as moxifloxacin may currently be under-utilised in Belgium for the treatment of CAP. The analysis was based on three commonly prescribed and less costly comparators, substantially penalising moxifloxacin, which is 67%, 40% and 199% more costly than co-amoxiclav, cefuroxime and clarithromycin,

Figure 2. Cost-effectiveness plane of moxifloxacin/co-amoxiclav versus co-amoxiclav/clarithromycin in terms of cost per first-line clinical failure avoided

Figure 3. Cost-effectiveness plane of moxifloxacin/co-amoxiclav versus cefuroxime/moxifloxacin in terms of cost per first-line clinical failure avoided

Figure 4. Cost-effectiveness plane of moxifloxacin/co-amoxiclav versus clarithromycin/moxifloxacin in terms of cost per first-line clinical failure avoided
Figure 5. Cost-effectiveness acceptability curve of moxifloxacin/co-amoxiclav versus co-amoxiclav/clarithromycin in terms of cost per first-line clinical failure avoided.

Figure 6. Cost-effectiveness acceptability curve of moxifloxacin/co-amoxiclav versus cefuroxime/moxifloxacin in terms of cost per first-line clinical failure avoided.

Figure 7. Cost-effectiveness acceptability curve of moxifloxacin/co-amoxiclav versus clarithromycin/moxifloxacin in terms of cost per first-line clinical failure avoided.
hospitalisation rates exceeding the rates observed in the Spanish study amounted to 8–14%. These hospitalisation rates can be attributed to the inclusion of patients suffering from severe CAP (i.e. Fine category I–V) in the French study, whereas our study was limited to patients suffering from mild to severe CAP (i.e. Fine category I–III). Hospitalisation rates in a Spanish study amounted to 8–14%. These hospitalisation rates exceeded the rates observed in our study because the Spanish model assumed higher hospitalisation rates following first-line treatment failure. For example, the Spanish study assumed that treatment failure with moxifloxacin is always followed by hospitalisation. This does not reflect current treatment pathways in Belgium, where around 85% of patients failing treatment with moxifloxacin start second-line treatment in the community and approximately 15% of patients are hospitalised.

An economic evaluation examined the cost-effectiveness of antimicrobial treatment of CAP in France, United States and Germany. Our Belgian study supports the findings of this international study, where first-line treatment with moxifloxacin followed by co-amoxiclav dominated all other treatments for all outcome measures in the three countries considered. Another economic evaluation, using a different model, was set in Spain. The authors found that first-line treatment with moxifloxacin followed by clarithromycin, telithromycin or amoxicillin in that moxifloxacin treatment was less expensive and more effective in terms of the number of patients without complications and the number of patients hospitalised.

This model suffers from a number of limitations. As the aim of the study was to examine the cost-effectiveness of initial antimicrobial treatment in the community, the model included patients suffering from mild-to-moderate CAP. By limiting the analysis to Fine categories I–III, the patient population is relatively healthy. As a consequence, our cost-effectiveness results cannot be extrapolated to patient populations that have a different mix of Fine categories. For instance, patients suffering from severe CAP (i.e. Fine category IV–V) are likely to have a higher mortality rate in the community, hospitalisation rate and in-hospital mortality rate, influencing the cost-effectiveness of antimicrobial treatment strategies.

The majority of patients classified as Fine category I–III are treated in the community with some requiring hospitalisation. In our model, all patients are hospitalised following second-line treatment failure. This is the case for the majority of patients, although some patients may still receive a third treatment in the community. The effect of changes in the hospitalisation rate was also tested in the sensitivity analysis, with little effect on the ICERs.

Our model of treatment pathways is necessarily simplistic and reflects empirical treatment in Belgium. Antimicrobial treatment in the community is often empirical. The empirical approach is also the prevailing method of drug selection. However, empirical treatment does not always reflect real clinical practice where data on the pathogen and the susceptibility may be available following first-line treatment failure. If the physician can adopt, with a high degree of reliability, the antimicrobial treatment strategy according to the cause, the most efficient treatment strategy may vary.

Estimates of several input parameters in Belgium were unknown and, in these cases, international data were relied upon. With respect to antimicrobial resistance data, the model used Belgian data when available and used international resistance data in the absence of Belgian data. The deterministic and probabilistic sensitivity analyses showed that cost-effectiveness results were robust to changes in resistance rates. With respect to resource utilisation, the analysis drew on French data on the frequency of physician visits, the frequency of diagnostic tests and the hospitalisation rate for CAP patients. For instance, the hospitalisation rate following first-line treatment failure of 15.4% for France was used in our model. This was because the French estimate related to a similar patient population to that considered in our model (i.e. patients initially treated in the community) and because of similar treatment patterns between Belgium and France. Nevertheless, although the French health care system may be similar in many aspects to the Belgian system, the results may not present an accurate picture of Belgian resource utilisation and costs for CAP.

Rates of clinical failure due to resistance were assumed for each CAP pathogen. There is no published literature documenting the link between resistance and clinical failure. Therefore, the calculations of failure rates were based on the opinion of clinical experts. A previous version of this model, developed for the United States, was compared to empirical data on treatment failure and results were very comparable, thus validating the assumption that only 50% of resistant pathogens results in clinical failure.
Indirect costs due to productivity loss were not included in this model as the perspective was that of the Belgian third-party payer. The inclusion of indirect costs is expected to result in even more positive outcomes for the moxifloxacin/co-amoxiclav strategy. The patient population considered in the model includes a large percentage of the working population and as moxifloxacin treatment entails fewer clinical consequences, this would result in less time off-work and, hence, less productivity loss.

Despite its limitations, this study reports on one of the few models in CAP that assess both costs and outcomes associated with antimicrobial treatment taking into account bacterial resistance. Its results can aid local decision makers to allocate scarce health care resources. Future modelling work in this domain would benefit from more recent data on resistance. There is also a need for studies that examine the relationship between resistance and clinical failure.

Conclusions

First-line/second-line empirical treatment of CAP patients with moxifloxacin/co-amoxiclav is a dominant strategy as compared with other current treatment strategies in Belgium. Treatment with moxifloxacin is more effective in terms of first-line clinical failure, need for second-line treatment and hospitalisation as compared with first-line treatment with co-amoxiclav, cefuroxime or clarithromycin. As a consequence, total healthcare costs of treating a CAP episode with moxifloxacin/co-amoxiclav are lower than costs of comparator strategies, despite the higher drug cost of moxifloxacin. These results demonstrate that it is more cost-effective to select an antimicrobial as first-line treatment that is more effective, i.e. with lower resistance and a higher clinical success rate.

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Cost-effectiveness of antimicrobial treatment of CAP in Belgium Martin et al. 751