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Influence of bacterial resistances on the efficiency of antibiotic treatments for community-acquired pneumonia

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Abstract The objective of this paper is to perform a cost-effectiveness analysis of the oral antibiotics used in Spain for the ambulatory treatment of community-acquired pneumonia. Our analysis takes into account the influence of bacterial resistances on the cost-effectiveness ratio of antibiotic alternatives from the viewpoint of the public insurer. A deterministic decision analysis model is used to simulate the impact of treatment alternatives on both patients' health and resource consumption. Amoxicillin 1 g may be the most efficient therapy for treating typical pneumonia, as long as the physician is able to discriminate clinically the aetiology of the process with a high degree of reliability. However, for those pathological pictures in which the aetiology cannot be discriminated clinically, and for those in which the consequences of incorrect diagnosis are serious according to clinical criteria, moxifloxacin is the most effective and efficient option.

Keywords Economic evaluation · Cost-effectiveness · Moxifloxacin · Community-acquired pneumonia

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Introduction

Community-acquired pneumonia (CAP) is defined as those infections of the lung parenchyma that originate in the community. Although such infections originate in the community, they are frequently recognised following hospital admission [1].

The incidence of CAP worldwide in adults stands at between 1.6 and 13.4 cases per 1,000 inhabitants per year [2]. The lowest value in this range corresponds to the situation in Spain, according to a population-based study [3] conducted in Catalonia from 1993 to 1995. Treatment is ambulatory in most cases and tends to be empirical, being based on the usual aetiology, the evaluation of the severity of the process, and the risks of unexpected pathogens.

The choice of initial antibiotic is crucial for the correct resolution of the process. From the perspective of health costs, the efficacy of the empirical treatment is very important, since among those patients for whom the initial treatment does not resolve the process, a large proportion are hospitalised. According to the study cited above [2], the direct cost for the public health system of the ambulatory treatment of a patient with CAP was €196 in 2001, whereas if the patient required hospitalisation the figure rose to €1,553.

In the choice of initial antibiotic treatment, in addition to evaluating the patient's risk factors and the severity of the clinical picture, it is important to take into account the resistance pattern developed by some of the pathogens that cause CAP in the specific geographical area under consideration, as a result of which a certain percentage of infections are unresponsive to the action of certain antibiotics. This factor is especially relevant in Spain, where the bacterial resistance

rates of respiratory pathogens are among the highest in Europe [4].

There have been a number of economic evaluation studies on various antibiotic treatments for CAP [5, 6], but whereas there have been evaluations of the bacterial resistance rates on an international scale, this is not the case in Spain.

The purpose of the present work is to carry out an economic evaluation of the oral antibiotics used in Spain for the ambulatory treatment of community-acquired pneumonia, taking into account the impact of bacterial resistances on the effectiveness of each antibiotic treatment. The treatments that are compared here were selected on the basis of expert opinions and clinical practice guidelines. The method used is cost-effectiveness analysis and the perspective adopted is that of the public health system insurer. The impact of uncertainty regarding some of the parameters of the base case on the results of the evaluation is assessed by means of various sensitivity analyses of the key variables.

Methods

Decision model

The analysis is performed using a simple decision analysis model that allows the simulation of both the impact on health (e.g. patients without complications and hospitalisations) and the impact on resource consumption of each treatment evaluated. In the decision tree, the probabilities of each event are fixed, as the model is a deterministic one in which a base case has been defined using the most probable data among those available. The robustness of the base case is evaluated by means of a sensitivity analysis.

The information needed to build the model was drawn from data published on a variety of aspects (efficacy, aetiology, resistance rates, clinical practice guidelines, etc.) and the opinion of various Spanish clinical experts, in order to introduce real practice conditions in the analysis.

Treatments for comparison

The antibiotic treatments included in this economic evaluation were chosen according to the criterion of selecting those treatments recommended by experts and clinical practice guidelines in Spanish health care and which have shown proof of efficacy for the treatment of CAP in the form of controlled clinical trials. The following antibiotic treatments, all of them to be

taken orally and for a duration of 10 days, were chosen:

- 400 mg of moxifloxacin once a day
- 800 mg of telithromycin once a day
- 1,000 mg of amoxicillin three times a day
- 500 mg of clarithromycin twice a day

The experts suggested a treatment consisting of a combination of amoxicillin and clarithromycin or azithromycin, but the lack of suitable controlled clinical trials providing evidence of the efficacy of this treatment ruled out the possibility of including it in the treatments for evaluation.

Perspective of the analysis and time horizon

The analysis was performed from the perspective of the Spanish public health system insurer. Consequently, only direct costs for the National Health System are taken into consideration.

The time horizon of the model was designed to match the resolution of the episodes, either through successful first-time or second-time antibiotic treatment or by the patient's admission to hospital due to the failure of the antibiotic treatments. In both cases, the time horizon was quite short (10–20 days), so it was not necessary to use a discount rate either in the costs or in the units of effectiveness.

Estimation of the effectiveness of the antibiotic treatments

The model follows a two-step process to estimate the effectiveness values of the different treatments. Firstly, a distinction is made in the decision tree between patients who had strains with bacterial resistances to the treatment drug and those who did not. These calculations were made on the basis of data for the incidence of the most frequent pathogens that cause CAP and their bacterial resistance rates (as observed in Spain) to the various antibiotic treatments included in the analysis.

Secondly, the efficacy of the treatments is estimated on the basis of reviewing the international literature on controlled clinical trials on CAP in which one of the objects of comparison was one of the treatments selected above. These efficacy data are applied to the percentage of patients who did not have strains that were resistant to the treatment drug. This procedure is equivalent to assuming that in the selected trials there were no infections with resistance to the antibiotic treatments evaluated. In the percentage of patients with strains showing bacterial resistances to the treat-

ment drug evaluated it is assumed that the initial antibiotic treatment always fails.

Figure 1 shows the structure of the decision tree once the percentage of infections resistant to the antibiotic treatment has been determined.

Estimation of the percentage of patients with infections resistant to the treatment

It is assumed that CAP can be due to any of four possible organisms causing infection: the pathogen *Streptococcus pneumoniae*, the pathogen *Haemophilus influenzae*, atypical pathogens, and viruses. The data on the incidence of each of these organisms in Spain as used in the base case were obtained from a study conducted in 1996 and 1997 [7] (Table 1).

On the basis of these data on the incidence of organisms causing CAP, a series of prior assumptions were made in order to determine in the model what percentage of these organisms are resistant to the treatment antibiotic:

- 100% of CAP cases of viral origin are successfully resolved/cured spontaneously, regardless of the empirical antibiotic treatment used.
- Infections caused by atypical pathogens do not display bacterial resistances to any of the treatments.
- Bacterial resistances to treatment with telithromycin are identical to those to treatment with moxifloxacin. This assumption is due to the impossibility

of finding evidence regarding the resistance rates of the main pathogens to telithromycin, as this antibiotic had only recently become available on the Spanish market at the time of the study.

Using the data on the incidence of organisms causing CAP and the data provided by two studies [4, 8] for bacterial resistances in Spain of the pathogens *Streptococcus pneumoniae* and *Haemophilus influenzae* to the antibiotics evaluated (see Tables 2 , 3), the model determines the percentage of patients affected by strains with bacterial resistance to the drug evaluated.

As can be seen in Fig. 1, one of the assumptions made in the model is that any antibiotic treatment of an infection caused by a strain with medium or low susceptibility to that antibiotic (i.e. resistant strains) will result in failure. In the case of treatment with amoxicillin it has been assumed that failure is the outcome only in the case of low-susceptibility strains, as this is a high-dosage treatment.

Estimation of efficacy

The clinical literature on the efficacy of the antibiotics analysed in this study in treating CAP was reviewed by searching on the Medline database. The period search was from January 1998 to February 2004, with the keywords "community acquired pneumonia", "clinical trial" and the selected antibiotic treatments (only oral treatments). The resulting papers were further

Fig. 1 Decision tree. Resistant strains are those with low and medium susceptibility to the respective drugs, except in the case of amoxicillin, for which they are only those with low susceptibility. *HC* Hospital casualty, *H* hospitalisation, *PC* primary care. All antibiotic treatment alternatives are modelled under the same assumptions on (organisms causing the infection, and resistances). Telithromycin branch tree is identical to the Moxifloxacin one and Clarithromycin branch is identical to the Amoxicillin one
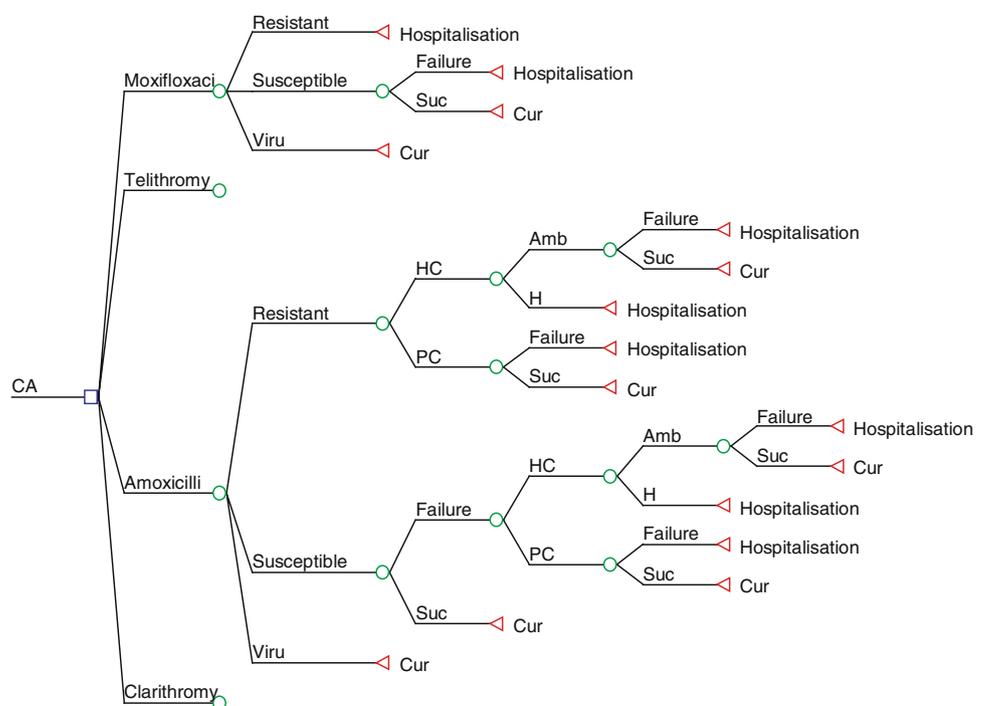
Table 1 Incidence of organisms causing CAP

Pathogen	Proportion of cases
Streptococcus pneumoniae	0.40
Haemophilus influenzae	0.10
Atypical pathogens	0.35
Viruses	0.15

Source: own data, based on [7]

Table 2 Bacterial resistances of infections caused by *Streptococcus pneumoniae*

Antibiotic	Percentage of strains with medium or low susceptibility	Percentage of strains with low susceptibility
Amoxicillin	0.109	0.049
Clarithromycin	0.369	0.369
Moxifloxacin	0.004	0.004

Source: own data, based on [4, 8]

Table 3 Bacterial resistances of infections caused by *Haemophilus influenzae*

Antibiotic	Percentage of strains with medium or low susceptibility	Percentage of strains with low susceptibility
Amoxicillin	0.302	0.277
Clarithromycin	0.256	0.015
Moxifloxacin	0.000	0.000

Source: own data, based on [4, 8]

narrowed down to those clinical trials that fulfilled the requirements of being controlled, randomised and double blind. This selection was reviewed and approved separately by the two clinical authors, in order to ensure that the evidence to be used would be of the best possible quality. Table 4 provides information about the studies that were selected (which were comparative two-by-two studies) and the efficacy value, defined as clinical cure at the final follow-up visit (approximately 30 days after the beginning of the treatment) in the population by protocol, of each treatment according to results obtained combining the data published in these trials.

Table 4 Efficacy of the treatments analysed

Antibiotic treatment	Efficacy (CI 95%)	Information source
Moxifloxacin	0.910 (0.866–0.955)	[9, 10]
Telithromycin	0.887 (0.836–0.939)	[11, 12]
Amoxicillin	0.876 (0.823–0.929)	[10, 12]
Clarithromycin	0.885 (0.834–0.937)	[9, 11]

CI Confidence interval with a probability of 95%

Resource consumption

Hospitalisation

In the case of the treatments with moxifloxacin and telithromycin, the model assumes that failure is always followed by hospitalisation. In the treatments with clarithromycin and amoxicillin, the model assumes a 50% probability that the patient will need to visit a primary care centre to initiate a second or rescue antibiotic treatment with moxifloxacin, and a 50% probability that the patient will need to go to a hospital casualty service, according to consensus view of experts. In the latter case, it has been assumed that there is a 50% probability of hospitalisation, while the remaining 50% is the probability of initiating a second ambulatory antibiotic treatment. The model assumes that failure of the second ambulatory antibiotic treatment is always followed by hospitalisation, and that admission is followed by a hospital stay of 8.87 days in the pneumology service. This value was obtained from the value for the average stay of the group related to diagnosis No. 89, simple pneumonia in patients over 17 years of age with complications, according to data for 2002 provided by the Spanish Ministry of Health and Consumer Affairs [13].

Second or rescue antibiotic treatment

When the initial antibiotic treatment fails and a second antibiotic treatment is administered, it is assumed that the antibiotic chosen is moxifloxacin.

Visits to primary care centres

In addition to those determined by the decision tree, the model assumes one visit at the beginning of the treatment, and another visit at the end of the ambulatory treatment (initial treatment or following failure of the initial treatment) when successful.

Visits to hospital casualty services

In addition to those determined by the decision tree, the model assumes that hospitalisation is always preceded by a visit to casualty.

Diagnostic tests

The model assumes that the treatment is empirical and that therefore no tests are conducted in the diagnosis of CAP. After the failure of the first treatment the following tests are performed: chest radiograph,

sputum test, Gram stain and a conventional culture (independently of whether the patient visits a primary care centre or casualty). No further tests are conducted in the event of failure of the rescue antibiotic.

Pharmaceuticals

The model only considers the use of antibiotic drugs. In the branches of the tree with successful antibiotic treatment (whether in the first or the second treatment), the duration of the treatment is 10 days. It is assumed that if an antibiotic treatment fails it is discontinued after 2 days independently of whether it is the initial or the second treatment.

Unit costs

The unit costs used in the analysis are shown in Table 5, all of them expressed in 2004 euros. The costs of acquiring the pharmaceuticals were obtained from the Catalogue of Proprietary Medicinal Products [14]. The unit cost per complete treatment was calculated on the basis of the average cost per daily dose, obtained from the packages whose dosage best matched the doses required to complete the treatment. It is assumed that there is no co-payment by the patient towards the cost of the drugs. Average wages of health professionals and the costs of other health resources were estimated on the strength of a database of Spanish health costs [15].

Sensitivity analysis

In the base case of the study, we adopted the values and assumptions described above. In order to test the robustness of the results we conducted a series of univariate sensitivity analyses, altering the values of the variables as described below.

Table 5 Average unit costs (in 2004 euros) used in the base case of the analysis

Resource	Average unit cost (range)	Source
Moxifloxacin(10 days)	49.30	[14]
Telithromycin (10 days)	70.20	[14]
Amoxicillin (10 days)	8.49	[14]
Clarithromycin (10 days)	31.99	[14]
Chest radiograph	18.77 (4.47–38.75)	[15]
Sputum test, Gram stain	3.82 (1.09–10.53)	[15]
Conventional sputum culture	13.55 (6.59–19.6)	[15]
Primary care visit	7.93 (5.38–13.93	[15]
Hospital casualty visit	60.27 (24.57–103.19)	[15]
1 day stay in a hospital pneumology service	304.82 (171.86–423.02)	[15]

– Efficacy rates: we used a 95% confidence interval of statistical significance.
– Unit costs: we used the extreme values shown in Table 5.
– Resistance pattern: we performed one analysis assuming that only infections with low susceptibility to the respective antibiotics lead to treatment failure, and another analysis assuming the inexistence of bacterial resistances.
– Aetiology: we assumed that there were no atypical infections.

Type of economic evaluation and decision tree analysis

The economic evaluation is of the cost-effectiveness type. The two units of effectiveness used are the number of patients without complications (successful initial antibiotic treatment) and the number of patients admitted to hospital.

These units of effectiveness were chosen because the model does not consider the possibility of deaths, and therefore precludes a measurement more frequently used in economic evaluation studies such as life-years gained.

Results

Base case

The results of the base case, according to bacterial resistance rates reported in Tables 2 and 3, are shown in Tables 6 and 7. With the assumptions and values of the data used in the base case, treatment with moxifloxacin is dominant with respect to the other antibiotic treatments evaluated (lower cost and greater effectiveness). In the base case, the average cost per typical patient treated with moxifloxacin is lower than that of the other treatments evaluated and the effectiveness of the treatment, measured in terms of patients free of complications or patients not requiring hospitalisation, is greater.

If we break down the average cost per patient in each treatment according to the type of resources used (pharmaceuticals, visits to primary care services or hospital casualty, and hospitalisation) we see that in all the treatments the largest part of the cost is incurred due to the resource consumption caused by hospitalised patients. This breakdown is shown in Table 8.

Sensitivity analysis

With the aim of analysing the impact of uncertainty on some of the main parameters used in the base case, we

Table 6 Results of the analysis in the base case (effectiveness in terms of number of patients without complications)

Antibiotic treatment	Percentage of patients without complications	Average cost (€) per typical patient treated	Incremental cost per additional patient without complications
Moxifloxacin	92.23	279.20	Dominant alternative
Clarithromycin	74.91	283.30	Dominated alternative
Telithromycin	90.28	352.10	Dominated alternative
Amoxicillin	54.65	458.50	Dominated alternative

Table 7 Results of the analysis in the base case (effectiveness in terms of number of patients hospitalised)

Antibiotic treatment	Percentage of patients hospitalised	Average cost (€) per typical patient treated	Incremental cost per hospitalisation avoided
Moxifloxacin	92.23	279.20	Dominant alternative
Clarithromycin	92.04	283.30	Dominated alternative
Telithromycin	90.28	352.10	Dominated alternative
Amoxicillin	85.61	458.50	Dominated alternative

carried out several univariate sensitivity analyses, the results of which can be seen in Tables 9 and 10. The assumptions employed in the sensitivity analyses affect the efficacy values of the treatments, the unit costs of the resources, the proportion of low-susceptibility strains, the presence of bacterial resistances and the existence of infections caused by atypical pathogens.

When the measure of effectiveness is the number of patients free of complications, moxifloxacin continues to be the dominant treatment alternative only when we take into account the upper limits of the confidence interval of the efficacy data, or the upper limit of the range of variation of the unit costs (assumptions 1 and 4 in Table 9). In the remaining assumptions considered in the sensitivity analysis, the treatment with moxifloxacin dominates (with greater efficacy and lower costs) the treatments with telithromycin and amoxicillin. Treatment with moxifloxacin suggests greater effectiveness than that with clarithromycin, but also a higher cost per additional patient without complications when we consider the lower limit of the confidence interval of the efficacy data (€242.30), the lower limit of the range of variation of the unit costs (€27.80), and likewise when we only consider the proportion of strains with low susceptibility to determine failures due

to bacterial resistances (€104.30) or when we assume the inexistence of infections caused by atypical pathogens (€960.90). In the absence of bacterial resistances (assumption 6 in Table 9), clarithromycin dominates telithromycin and amoxicilin treatments, and moxifloxacin presents a high incremental cost per additional patient without complications when compared to clarithromycin (€6,353.90).

When the measure of effectiveness is the number of patients not requiring hospitalisation, the results of the sensitivity analysis are very similar to those outlined above (see Table 10). Moxifloxacin continues to be the dominant treatment alternative even when we take into account the upper limits of the confidence interval of the efficacy data, or the upper limit of the range of variation of the unit costs (assumptions 1 and 4 in Table 10). When we use the lower limit of the unit costs, the incremental cost per hospitalisation avoided by means of treatment with moxifloxacin as compared with clarithromycin is €2,554.40. However, clarithromycin is the dominant alternative when we consider the lower limit of the confidence interval of the efficacy data (assumption 2 in Table 10), and also when we use only the proportion of low-susceptibility strains to determine failures due to bacterial resistances (assumption 5 in Table 10), and when we assume the absence of bacterial resistances (assumption 6 in Table 10). And, amoxicilin appears as the dominant alternative when we assume the inexistence of infections caused by atypical pathogens (assumption 7 in Table 10).

The sensitivity analysis shows the high sensitivity of the results of the base case to the presence or absence of bacterial resistances. In the extreme hypothesis of the absence of any type of bacterial resistances

Table 8 Breakdown of average cost according to type of resource

Antibiotic treatment	Drugs (%)	Visits and tests (%)	Hospitalisation (%)
Moxifloxacin	16.6	8.1	75.3
Telithromycin	18.4	6.9	74.7
Amoxicillin	4.6	10.6	84.9
Clarithromycin	12.1	12.0	76.0

Table 9 Sensitivity analysis (effectiveness in terms of patients without complications)

Antibiotic treatment	Percentage of patients without complications	Average cost (€) per typical patient treated	Incremental cost per additional patient without complications
Assumption 1: efficacy according to upper limit of CI			
Moxifloxacin	96.01	175.02	Dominant alternative
Clarithromycin	78.39	230.98	Dominated alternative
Telithromycin	94.66	232.10	Dominated alternative
Amoxicillin	57.04	396.52	Dominated alternative
Assumption 2: efficacy according to lower limit of CI			
Moxifloxacin	88.44	383.30	€242.30
Clarithromycin	71.42	342.04	–
Telithromycin	85.89	472.12	Dominated alternative
Amoxicillin	52.25	524.79	Dominated alternative
Assumption 3: lower limit of range of variation of unit costs			
Moxifloxacin	92.23	177.93	€27.80
Clarithromycin	74.91	173.11	–
Telithromycin	90.28	226.78	Dominated alternative
Amoxicillin	54.65	263.38	Dominated alternative
Assumption 4: upper limit ofrange of variation of unit costs			
Moxifloxacin	92.23	378.39	Dominant alternative
Telithromycin	90.28	473.22	Dominated alternative
Amoxicillin	54.65	648.77	Dominated alternative
Clarithromycin	74.91	393.99	Dominated alternative
Assumption 5: use only of percentage of low-susceptibility strains to determine failures due to bacterial resistances			
Moxifloxacin	92.23	279.20	€104.30
Clarithromycin	77.04	263.30	–
Telithromycin	90.28	352.10	Dominated alternative
Amoxicillin	54.65	458.50	Dominated alternative
Assumption 6: absence of bacterial resistances			
Moxifloxacin	92.37	275.10	€6,353.90
Clarithromycin	90.24	139.50	–
Telithromycin	90.42	348.20	Dominated alternative
Amoxicillin	58.79	418.80	Dominated alternative
Assumption 7: nonexistence of infections caused by atypical pathogens			
Moxifloxacin	92.87	261.40	€960.90
Amoxicillin	84.07	176.80	–
Telithromycin	91.11	329.30	Dominated alternative
Clarithromycin	67.58	352.10	Dominated alternative

CI Confidence interval

(assumption 6 in Tables 9 , 10), either treatment with clarithromycin becomes the dominant alternative (Table 10) or the incremental cost per additional patient treated with moxifloxacin without complications is notably high (Table 9). This result underlines the impact of the presence and the level of bacterial resistances of the population with CAP to be treated in each geographical area on the choice of an efficient antibiotic treatment.

Discussion

With the information available, it is complex and in most cases difficult to evaluate pharmacological therapy clinically or economically with the aim of supplying information for decision-making. Information on outcomes, which is necessary in order to carry out such evaluations, is obtained primarily from controlled clinical trials which, although they guarantee a good level of internal validity, are prone to limitations when it comes to extrapolating the consequences to actual clinical practice.

This problem exists when evaluating any pharmacological therapy, but the case of antibiotics is perhaps one of the most complex. Although clinical trials with these drugs provide information of great importance regarding their relative efficacy and their safety profile, the resistance patterns that exist in different environments in many cases make it impossible to extrapolate outcomes directly to specific environments.

Table 10 Sensitivity analysis (effectiveness in terms of patients hospitalised)

Antibiotic treatment	Percentage of patients hospitalised	Average cost (€) per typical patient treated	Incremental cost per hospitalisation avoided
Assumption 1: efficacy according to upper limit of CI			
Moxifloxacin	3.99	175.02	Dominant alternative
Clarithromycin	6.13	230.98	Dominated alternative
Telithromycin	5.34	232.10	Dominated alternative
Amoxicillin	12.19	396.52	Dominated alternative
Assumption 2: efficacy according to lower limit of CI			
Clarithromycin	10.03	342.04	Dominant alternative
Moxifloxacin	11.56	383.30	Dominated alternative
Telithromycin	14.11	472.12	Dominated alternative
Amoxicillin	16.75	524.79	Dominated alternative
Assumption 3: lower limit of range of variation of unit costs			
Moxifloxacin	7.77	177.93	€2,554.40
Clarithromycin	7.96	173.11	–
Telithromycin	9.72	226.78	Dominated alternative
Amoxicillin	14.39	263.38	Dominated alternative
Assumption 4: upper limit of range of variation of unit costs			
Moxifloxacin	7.77	378.39	Dominant alternative
Telithromycin	9.72	473.22	Dominated alternative
Amoxicillin	14.39	648.77	Dominated alternative
Clarithromycin	7.96	393.99	Dominated alternative
Assumption 5: use only of percentage of low-susceptibility strains to determine failures due to bacterial resistances			
Clarithromycin	7.29	263.30	Dominant alternative
Moxifloxacin	7.77	279.20	Dominated alternative
Telithromycin	9.72	352.10	Dominated alternative
Amoxicillin	14.39	458.50	Dominated alternative
Assumption 6: absence of bacterial resistances			
Clarithromycin	3.10	139.50	Dominant alternative
Moxifloxacin	7.63	275.10	Dominated alternative
Telithromycin	9.58	348.20	Dominated alternative
Amoxicillin	13.08	418.80	Dominated alternative
Assumption 7: nonexistence of infections caused by atypical pathogens			
Amoxicillin	5.05	176.80	Dominant alternative
Moxifloxacin	7.13	261.40	Dominated alternative
Telithromycin	8.89	329.30	Dominated alternative
Clarithromycin	10.29	352.10	Dominated alternative

CI Confidence interval

Certain microorganisms display much higher resistance rates in Spain than in other geographical environments [4]. We will not go into the reasons for this situation here, but clearly it constitutes a hindrance to the direct extrapolation of the results obtained in the treatment of infectious pathologies with various antibiotics in other countries. This limitation is particularly important in pathologies that can have serious effects on health and that tend to be treated empirically, as is the case with community-acquired pneumonia, given that the resistances displayed by common pathogens restrict the use of certain drugs in conditions of real practice, whereas these same drugs used in experimental conditions in other environments with a different resistance pattern may obtain good results.

One illustrative example of this is the case of the new active quinolones used against the pneumococcus. Although clinical trials, carried out mostly in the USA, detect no differences in efficacy between these drugs and the usual alternatives (beta-lactams and macrolides), the resistance pattern of the pneumococcus to beta-lactams and macrolides is very different in Spain, thus contradicting the external validity of these trials.

The aim of our evaluation was to assess the efficiency of those drugs for the empirical treatment of community-acquired pneumonia for which quality basic experimental information was available, also taking into consideration the aetiological and resistance characteristics existing in Spain. To our mind, the incorporation of these variables makes this information

more useful for decision-makers than the basic information obtained from clinical trials.

The results of the base analysis indicate that, considering the habitual pathogens and their resistances in the Spanish environment, moxifloxacin may be the treatment that achieves the best results both in terms of clinical efficacy, and in economic terms. However, this conclusions are higly sensitive to resistance rate assumptions.

Integrating the whole health care process and the consequences derived from the efficacy of the treatments is the only logical way to provide coherent information from a health system perspective. Measuring only the direct cost of the pharmacological therapy does not necessarily lead to efficient decision-making.

The study conducted here has obvious limitations that must be taken into account when drawing conclusions, although we have attempted to mitigate them in some cases by means of sensitivity analysis.

The first of these limitations comes as a result of the information used. Epidemiological data on the organisms involved in this pathology and their resistance patterns in Spain are relatively scarce, both for economic evaluations and for any level of decision-making. This point is obviously important, because in the absence of differences regarding resistances, or with other aetiological patterns, the results would have been very different. With the information we had at our disposal, it is difficult to guarantee that the epidemiological pattern considered is the real one, especially with respect to the participation of each causal pathogen and its resistance pattern. Nevertheless, the data we used in this study are those that are available, and are the same ones used by the administration and scientific societies when making recommendations.

Another major limitation is that the model of decisions and outcomes used is necessarily simplistic, and puts all patients in the same situation. For example, the outcome of a typical pneumonia is not necessarily the same as that of an atypical one. The former is more severe and the outcome can be much more harmful. In our scenario, they are assessed as equal, which to some extent is tantamount to making a general underestimation of those alternatives that are not of use against atypical pathogens (basically amoxicillin).

This simplistic approach and the lack of available information leads us to neglect the discriminatory value of clinical diagnosis in the model (the physician's ability to discriminate clinically between a typical and an atypical pneumonia), as in our model the reaction to a clinical picture of pneumonia is to start the treatment, and the possibility of screening or distinguishing a typical pneumonia from an atypical one is not taken into account. This is not the case in real practice, and often the physician can estimate clinically (on the basis of the symptoms) or demographically (on the basis of the patient's demographic or pathological characteristics) the probabilities of the clinical picture being typical or atypical, or the relevance of covering or not covering both possibilities with the treatment. This point is very relevant to the analysis, because if the physician can screen with a high degree of reliability according to the cause (typical or atypical pathogen) the most efficient treatment may vary.

In the sensitivity analysis, we observe that if we eliminate the presence of atypical pathogens the treatment with the best cost-effectiveness ratio is amoxicillin 1 g, with moxifloxacin being the second choice. No doubt the same would occur if we analysed only atypical pneumonias, where possibly the macrolides (clarithromycin in our case) would be the most efficient option.

Another shortcoming of the analysis is the absence of one therapy used empirically in real practice by physicians, namely amoxicillin in association with clarithromycin, the theoretical justification of which is to cover the whole spectrum when there is doubt as to the nature of the causal pathogen (whether it is typical or atypical) or when, according to clinical criteria, the consequences of mistaking the clinical picture might be very serious. Unfortunately, there is no clinical information on this combination that met our criteria for the inclusion of studies so that we could add it to our analysis.

One example of the possible consequences of incorporating clinical criteria into the choice of treatment and using the amoxicillin/clarithromycin combination can be found in the quasi-experimental study by Torres et al. [16], in which the treatment was allocated according to clinical criteria (moxifloxacin, amoxicillin, clarithromycin or a combination of the last two) to 564 patients and the outcome was followed up. The efficacy of the various regimens is the same: 95.3% efficacy for moxifloxacin and 93.7% for the group amoxicillin, clarithromycin or the combination of both. We did not include this study in our analysis, as it was not a clinical trial as such, and obviously its internal validity is limited, but it can give us an idea of the degree of success of clinical diagnosis.

The rest of the results obtained in the study, both in the base case and in the sensitivity analysis, indicate that the model is robust in all respects, with the exception of the limitations mentioned above. The results do not vary substantially when minimum or maximum costs are used, nor when a certain amount of

change is introduced into the resistance pattern. As mentioned above, the only point that notably influences the results is the inclusion or otherwise of atypical pathogens in the model.

We can draw the following conclusions from the results of the study:

1. Amoxicillin 1 g may be the most efficient therapy for treating presumed pneumococcal pneumonia, as long as the physician is able to discriminate the aetiology of the process clinically with a high degree of reliability.
2. For those pathological pictures in which the aetiology cannot be discriminated clinically, and for those in which the consequences of incorrect diagnosis are serious according to clinical criteria, moxifloxacin could represent an effective and efficient option, specially under the assumptions of the base case adopted in this study.

Another issue that should be stressed in the analysis is the importance for decision-making on pharmacological therapy of considering the whole set of actions and outcomes of the treatment and the pathology as broadly and comprehensively as possible. The direct cost of the drugs, though relevant, is a small part of the total cost, and decisions based solely on this parameter may generate responses that overall are inefficient for the system.

It should also be noted that this integrated view of health care is not the most usual one in our health system, where costs and outcomes are given meaning and importance in a compartmental fashion, and not only when deciding which drug to use. Thus, in primary care, from an economic viewpoint, the use of a more expensive drug means an additional cost even if it reduces health care costs in other areas, and in hospital care the basic problem in the best of cases is how to minimise the costs of the internal care process.

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