Cost effectiveness of amoxicillin for lower respiratory tract infections in primary care: an economic evaluation accounting for the cost of antimicrobial resistance

INTRODUCTION

Acute cough/lower respiratory tract infection (LRTI) is associated with a high rate of morbidity,1 and is responsible for considerable overuse of antibiotics, even though studies have shown that most cases of acute cough/LRTI do not benefit from antibiotic treatment.2 A major difficulty, however, is the problem of differentiating between infections that are likely to benefit from antibiotic treatment and those that will not benefit, which often results in inappropriate prescriptions.3,4 Antibiotic use is also associated with higher costs5 and, more importantly, the development of antibiotic resistance, which itself has economic costs.6,7 A report indicated high correlation between penicillin use and penicillin non-susceptibility,8 suggesting that, despite the difficulties, resistance should be accounted for in assessing the relative costs and benefits of antibiotic treatment.9–11

This study assessed the cost effectiveness of prescribing amoxicillin for acute cough/LRTI compared with placebo in 12 European countries, and explores the implications of accounting for the cost of resistance in estimating the cost effectiveness of antibiotics.

METHOD

Patients and settings

This cost-utility analysis with a time horizon of 28 days was conducted alongside a parallel, randomised trial in which patients received either amoxicillin or placebo.12 The perspective adopted was the health system. A total of 2060 eligible and consenting patients were recruited across 12 European countries: Belgium, France, Germany, Italy, Netherlands, Poland, Slovakia, Slovenia, Spain, Sweden, and the UK (England and Wales). Trial details have been published elsewhere.12

Data collection

Resource use. The main sources of resource use information were the case report form (CRF) completed by primary care physicians, and a diary completed by patients. Resource use data were collected concerning:

- antibiotics (principally amoxicillin) are cost effective in patients with LRTIs, and to explore the implications of taking into account costs associated with resistance.

Design and setting

Multinational randomised double-blinded trial in 2060 patients with acute cough/LRTIs recruited in 12 European countries.

Method

A cost-utility analysis from a health system perspective with a time horizon of 28 days was conducted. The primary outcome measure was the quality-adjusted life year (QALY). Hierarchical modelling was used to estimate incremental cost-effectiveness ratios (ICERs).

Results

Amoxicillin was associated with an ICER of £9216 (£6540) per QALY gained when the cost of resistance was excluded. If the cost of resistance is greater than £11 949 per patient, then amoxicillin treatment is no longer cost effective. Including possible estimates of the cost of resistance resulted in ICERs ranging from £14 730 (£11 949) per QALY gained — to £727 135 (€727 135) per QALY gained — to 14 (£9) per patient,

- costs of care, and do not account for the wider implications of antimicrobial resistance.

- societal costs are also included.

- health care costs are included — to

- lower respiratory tract infection; quality-adjusted life years.

Keywords

amoxicillin; antibiotic resistance; cost-effectiveness; economic costs; lower respiratory tract infection; quality-adjusted life years.
How this fits in
The use of antibiotics for treatment of acute cough/lower respiratory tract infections increases antibiotic resistance. Economic evaluations assessing the use of antibiotics tend to focus on immediate costs of care, and do not account for the wider implications and costs of antimicrobial resistance because of uncertainty, intangibility of these costs, and the difficulty in accurate estimation. This study has shown that economic evaluations of interventions such as antibiotic prescribing may result in misleading conclusions if antibiotic resistance is not accounted for. Future research should focus on how best these costs should be accounted for.

- health professionals — including information on number of visits to the nurse, doctor, and other medical professionals (obtained from the patient diary);
- medication — including information on type and volume of medication that primary care physicians prescribed to patients, as well as information on over-the-counter medication purchased (obtained from both the CRF and the patient diary); and
- referrals to specialists and procedures — including information on numbers and types of referrals (obtained from the CRF).

Unit costs. Country-specific unit costs associated with resource use items were obtained mainly from national and international publications. In cases where they were not available, those from a previous study were used and inflated using the consumer price index. All costs were converted to Euros (€) using purchasing power parities. Costs were also presented in pounds Sterling (£). All costs are presented in 2012 prices.

Health outcomes. Health outcomes were measured using the three-level version of the EQ-5D questionnaire (EQ-5D-3L), which was completed by patients at baseline and weekly until recovery (or for 4 weeks if symptoms were ongoing). EQ-5D-3L index scores were generated using the European Harmonised Tariff.

Data analysis
Data analysis was carried out on an intention-to-treat basis and took an incremental approach. Missing EQ-5D-3L scores and costs were imputed using multiple imputation methodology. Mean differences in costs and QALYs between trial arms were estimated. To avoid biased QALYs, imbalances in baseline utility between the groups were controlled for.

Given the multinational nature of this study, hierarchical modelling (with explanatory variables stratified into patient and country levels) was used to estimate cost per QALY gained, as well as incremental net monetary benefits (INB). To determine the probability of antibiotics being cost effective, a cost-effectiveness acceptability curve (CEAC) was constructed using the approach of Hoch and colleagues. The National Institute for Health and Care Excellence’s (NICE) recommended threshold of between £20 000 and £30 000 (between €24 655 and €36 982) per QALY was used to judge the cost effectiveness of the interventions. All analyses were carried out in Stata 12 and Microsoft Excel®. Due to the short length of the study period (4 weeks), discounting was not required.

Accounting for the cost of resistance
The issue of whether the cost of antibiotic resistance should be included in economic evaluations has been highlighted in previous studies. Further, antibiotic resistance has been considered to be a negative externality associated with the use of antibiotics, which implies that the current consumer of the antibiotic does not bear the full cost. In addition to this, it has been recognised in recent research that there is currently no good/accurate estimate for the cost of resistance.

As a result, the authors’ main approach was to estimate the threshold cost of resistance that would change the decision as to whether amoxicillin is cost effective or not, based on the NICE threshold of £20 000 to £30 000 (€24 655 to €36 982) per QALY gained. This was done using ‘what-if’ analysis in Excel. As a secondary analysis, the authors estimated possible values for the cost of resistance based on the currently available data in order to determine whether it would make a difference to the results. Due to the challenges associated with estimating this cost and the lack of available
data, the following assumptions were made. First, it was assumed that there is a positive linear relationship between numbers of prescriptions and levels of resistance, and that prescriptions are the main cause of antibiotic resistance. Second, it was assumed that the cost of resistance is incurred beyond the 28-day period. For the purpose of this study, it was estimated over a 1-year period. Third, it was assumed that the cost of resistance is similar for all antibiotics, regardless of the antibiotic class, and whether or not the prescription was from primary, secondary, or tertiary care.

A literature search revealed three possible values for the cost of resistance. One study estimated the annual cost of resistance in the US to be $55 billion annually. Another report stated that the cost of multidrug resistance in the European Union is €1.5 billion annually. And a third, more recent, study estimated the total cost of global resistance to be $100 trillion over a 35-year period. This is equivalent to $2.8 trillion annually.

Estimates of the annual number of prescriptions were also obtained from the literature — 328 million for the US, 602 million in the EU, and 7.3 billion globally. To estimate the annual cost-per-prescription, given the assumption that antibiotic prescribing is the main cause of resistance, the cost of resistance was divided by the annual number of prescriptions for each of the three scenarios described above. A γ distribution was used to account for the uncertainty around the cost of resistance estimates. Resistance costs were then added to the trial cost for each patient who received amoxicillin as well as those who had received an antibiotic prescription, irrespective of whether they were randomised to receive amoxicillin or placebo.

Sensitivity analysis
Sensitivity analysis was carried out to determine whether amoxicillin is cost effective in patients aged ≥60 years.

RESULTS
Baseline characteristics
Data were obtained from 2060 patients who met the inclusion criteria. Of these, 1037 (50.3%) were randomised to receive amoxicillin, and 1023 (49.7%) to placebo. Average ages were similar in the intervention and control groups. A total of 595 (28.8%) patients were aged ≥60 years.

Resource use and cost
Patients in the control group had more visits to their GP and nurse than patients in the intervention group, whereas patients receiving amoxicillin had more out-of-hours GP visits. The amoxicillin group was associated with higher costs per patient (€47.23 (£38.32)) than the control group (€44.80 (£36.34)) (Table 1).

Health outcomes
The mean EQ-5D-3L score at baseline was 0.760 (0.185) for the intervention group and 0.752 (0.192) for the control group (0.008 [0.007 to 0.024]). The mean EQ-5D-3L score at week 1 was 0.840 (0.173) for the intervention group and 0.834 (0.176) for the control group (0.006 [0.002 to 0.033]). The mean EQ-5D-3L score at week 2 was 0.908 (0.134) for the intervention group and 0.900 (0.134) for the control group (0.008 [0.004 to 0.018]). The mean EQ-5D-3L score at week 3 was 0.929 (0.122) for the intervention group and 0.925 (0.122) for the control group (0.004 [0.006 to 0.015]). The mean EQ-5D-3L score at week 4 was 0.936 (0.107) for the intervention group and 0.936 (0.109) for the control group (0.000 [0.010 to 0.008]).

Table 1. Cost of amoxicillin versus placebo, and associated health outcomes [mean [SD]]

<table>
<thead>
<tr>
<th>Costs</th>
<th>Intervention, € (n = 1037)</th>
<th>Control, € (n = 1023)</th>
<th>Difference, € (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff</td>
<td>27.55 (43.11)</td>
<td>26.88 (41.43)</td>
<td>0.67 [–3.18 to 4.43]</td>
</tr>
<tr>
<td>Prescribed drug</td>
<td>6.77 (13.10)</td>
<td>5.95 (11.07)</td>
<td>0.82 [–0.36 to 1.81]</td>
</tr>
<tr>
<td>Over-the-counter drug</td>
<td>2.28 (6.16)</td>
<td>2.46 (7.06)</td>
<td>–0.18 [–0.72 to 0.40]</td>
</tr>
<tr>
<td>Intervention/other drug</td>
<td>6.66 (12.48)</td>
<td>7.75 (14.02)</td>
<td>–1.09 [–2.19 to 0.10]</td>
</tr>
<tr>
<td>Other health care</td>
<td>1.22 (13.29)</td>
<td>1.76 (22.05)</td>
<td>–0.54 [–2.32 to 0.79]</td>
</tr>
<tr>
<td>Intervention (amoxicillin)</td>
<td>2.75 (2.45)</td>
<td>0</td>
<td>2.75 (2.61 to 2.91)</td>
</tr>
<tr>
<td>Total (excluding resistance)</td>
<td>47.23 (50.59)</td>
<td>44.80 (54.84)</td>
<td>2.43 [–2.19 to 6.53]</td>
</tr>
</tbody>
</table>

Health outcomes (EQ-5D-3L) 0.760 (0.185) for the intervention group and 0.752 (0.192) for the control group (0.008 [0.007 to 0.024]). The mean EQ-5D-3L score at week 1 was 0.840 (0.173) for the intervention group and 0.834 (0.176) for the control group (0.006 [0.002 to 0.033]). The mean EQ-5D-3L score at week 2 was 0.908 (0.134) for the intervention group and 0.900 (0.134) for the control group (0.008 [0.004 to 0.018]). The mean EQ-5D-3L score at week 3 was 0.929 (0.122) for the intervention group and 0.925 (0.122) for the control group (0.004 [0.006 to 0.015]). The mean EQ-5D-3L score at week 4 was 0.936 (0.107) for the intervention group and 0.936 (0.109) for the control group (0.000 [0.010 to 0.008]).

4Figures represent the unadjusted difference in costs. 5Bootstrap CI. EQ-5D-3L = three-level version of EQ-5D questionnaire. SD = standard deviation.
higher in the amoxicillin group than in the control group, and increased over the 4-week period in both groups (Table 1).

Cost effectiveness

The difference in cost between the amoxicillin and placebo groups was €3.04 (£2.42) before accounting for the cost of resistance. The difference in QALYs between the two groups was 0.00037 (Table 2). Amoxicillin was associated with an ICER of €8216 (£6540) per QALY gained when the cost of resistance was excluded. The ICER was below the NICE-recommended threshold, and the INB of amoxicillin at £20 000 (£24 655) per QALY gained was positive (Figure 1), suggesting that amoxicillin is cost effective when the cost of resistance is ignored. The CEAC shows that, at a willingness-to-pay threshold of £20 000 (£24 655) per QALY gained, there is an 80% chance that amoxicillin is cost effective (Figure 2).

Accounting for the costs of resistance

The threshold for the cost of resistance was estimated at €6.08 (£4.98) for £20 000 per QALY threshold, and €10.64 (£8.68) for £30 000 per QALY. With the inclusion of possible values for the cost of resistance, the difference in cost between amoxicillin and placebo groups was €81.47 (£66.09), €5.45 (£4.42), and €269.04 (£218.25) with the US, European, and global data respectively, and the resulting ICERs were €220 189 (£178 618), €14 730 (£11 949), and €727 135 (£589 856) per QALY gained with the US, European, and global data respectively. The only instance where the cost of resistance was lower than the threshold value occurred when the European data were applied (Table 2).

Sensitivity analysis: cost effectiveness of amoxicillin in older patients

Amoxicillin was found to be more costly in patients who are aged ≥60 years, and also found to be slightly less effective in this group of patients, indicating that amoxicillin is not cost effective in this patient group (Table 3).

DISCUSSION

Summary

This study assessed the cost effectiveness of amoxicillin for patients presenting to primary care with acute cough/LRTI. To the best of the authors’ knowledge, no other study has done this in a multinational setting, or in patients aged ≥60 years. The results showed that amoxicillin is associated with a higher cost and the difference in QALYs between groups was not statistically different, which is in line with the main study’s findings that suggest marginal benefits from antibiotics in acute cough/LRTI.12 The insignificant difference in QALYs between groups seems to suggest that cost effectiveness should be established based on a comparison of costs between the two groups. However, within the current paradigm, it is considered best practice that cost-effectiveness analysis should be conducted, because of the
Figure 2. Cost-effectiveness acceptability curve (amoxicillin versus placebo) with and without resistance.

Table 2. Cost effectiveness of amoxicillin versus placebo

<table>
<thead>
<tr>
<th>Cost effectiveness excluding the cost of antimicrobial resistance</th>
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</thead>
<tbody>
<tr>
<td>Difference in costs between amoxicillin and placebo groups, € (95% CI)</td>
<td>3.04 (–1.36 to 7.44)</td>
</tr>
<tr>
<td>Difference in QALYs gained (95% CI)</td>
<td>0.00037 (–0.0002 to 0.0009)</td>
</tr>
<tr>
<td>ICER, €</td>
<td>8216 per QALY gained</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost effectiveness including cost of resistance (US data)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in costs between amoxicillin and placebo groups, € (95% CI)</td>
<td>81.47 (75.45 to 87.49)</td>
</tr>
<tr>
<td>Difference in QALYs gained (95% CI)</td>
<td>0.00037 (–0.0002 to 0.0009)</td>
</tr>
<tr>
<td>ICER, €</td>
<td>220 189 per QALY gained</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost effectiveness including cost of resistance (EU data)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in costs between amoxicillin and placebo groups, € (95% CI)</td>
<td>5.45 (1.06 to 9.85)</td>
</tr>
<tr>
<td>Difference in QALYs gained (95% CI)</td>
<td>0.00037 (–0.0002 to 0.0009)</td>
</tr>
<tr>
<td>ICER, €</td>
<td>14 730 per QALY gained</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost effectiveness including cost of resistance (global data)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in costs between amoxicillin and placebo groups, € (95% CI)</td>
<td>269.04 (251.87 to 286.22)</td>
</tr>
<tr>
<td>Difference in QALYs gained (95% CI)</td>
<td>0.00037 (–0.0002 to 0.0009)</td>
</tr>
<tr>
<td>ICER, €</td>
<td>727.135 per QALY gained</td>
</tr>
</tbody>
</table>

*Figures obtained from the regression analysis/hierarchical model. ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life year.

Table 3. Sensitivity analysis: cost effectiveness of amoxicillin in patients aged ≥60 years

<table>
<thead>
<tr>
<th>Cost effectiveness excluding the cost of resistance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in costs between amoxicillin and placebo groups, € (95% CI)</td>
<td>0.34 (–6.55 to 7.23)</td>
</tr>
<tr>
<td>Difference in QALYs gained (95% CI)</td>
<td>–0.0009 (–0.0002 to 0.0002)</td>
</tr>
<tr>
<td>ICER</td>
<td>$100 trillion</td>
</tr>
</tbody>
</table>

*95% CIs. ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life year.
This study was funded as part of GRACE (Genomics to combat resistance against antibiotics in community-acquired LRTI in Europe; www.grace-lrti.org/portal/en-gb/homepage), a European Commission funded project within the Sixth Framework Programme (grant agreement 518226), and supported by the Research Foundation, Flanders, Belgium (FWO) (G•0274•08N), and the European Science Foundation (ESF), in the framework of the Research Networking Programme TRACE (http://www.esf.org/coordinating-research/research-networking-programmes/biomedical-sciences-med/current-esf-research-networking-programmes/translational-research-on-antimicrobial-resistance-and-community-acquired-infections-in-europe-trace.html). The funding source had no role in study design, data collection, analysis, report writing, or submission.

Ethical approval
The study was approved by ethics committees in all participating countries, and all patients provided written consent before participating.

Provenance
Freely submitted; externally peer reviewed.

Competing Interests
Joanna Coast reports grants from the European Union Sixth Framework Programme during the conduct of the study. Samuel Coenen reports grants from the European Commission Sixth Framework Programme, from the Research Foundation, Flanders, Belgium, and from the ESF, in the framework of the Research Networking Programme TRACE, during the conduct of the study. Raymond Oppong reports grants from the European Commission Sixth Framework Programme during the conduct of the study. Theo Verheij reports grants from the European Commission during the conduct of the study. All other authors declare no competing interests.

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5. Little P. Delayed prescribing of antibiotics for upper respiratory tract infection: with clear guidance to patients and parents it seems to be safe. BMJ 2005; 331(7512): 301–302.


