Research

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Cost effectiveness of amoxicillin for lower respiratory tract infections in primary care:

an economic evaluation accounting for the cost of antimicrobial resistance

Abstract

Background
Lower respiratory tract infections (LRTIs) are a major disease burden and are often treated with antibiotics. Typically, studies evaluating the use of antibiotics focus on immediate costs of care, and do not account for the wider implications of antimicrobial resistance.

Aim
This study sought to establish whether 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 €8216 (£6540) per QALY gained when the cost of resistance was excluded. If the cost of resistance is greater than €11 (£9) 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 — when only multidrug resistance costs and health care costs are included — to €727 135 (£589 856) per QALY gained when broader societal costs are also included.

Conclusion
Economic evaluation of antibiotic prescribing strategies that do not include the cost of resistance may provide misleading results that could be of questionable use to policymakers. However, further work is required to estimate robust costs of resistance.

Keywords
amoxicillin; antibiotic resistance; cost-effectiveness; economic costs; lower respiratory tract infection; quality-adjusted life years.

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 costs[5] 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:

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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[13] were used and inflated using the consumer price index.[14] All costs were converted to Euros (€) using purchasing power parities.[15] 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.[16]

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.[17] 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.[18] 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.[19] 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.[9] 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.[9,20–23] The cost of antibiotic use is borne by society as a whole through the reduction in the effectiveness of the antibiotic. However, this cost is generally not accounted for in economic evaluation studies and possible reasons for this include the fact that the cost may be too small due to uncertainty and time preference, and the difficulties associated with estimating the cost.[9] In addition to this, it has been recognised in recent research that there is currently no good/accurate estimate for the cost of resistance.[24]

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.[6,8,25] Second, it was assumed that the cost of resistance is incurred beyond the 28-day period.[9,23] For the purpose of this study, it was estimated over a 1-year period.[10] 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.[26] Another report stated that the cost of multidrug resistance in the European Union is €1.5 billion annually.[27] And a third, more recent, study estimated the total cost of global resistance to be $100 trillion over a 35-year period.[28] 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,[29,30] 602 million in the EU,[31,32] and 7.3 billion globally.[33] 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

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

Costs	Intervention, € (*n* = 1037)	Control, € (*n* = 1023)	Difference, € (95% CI)[b]
Staff	27.55 (43.11)	26.88 (41.43)	0.67 (–3.18 to 4.43)
Prescribed drug	6.77 (13.10)	5.95 (11.07)	0.82 (–0.36 to 1.81)
Over-the-counter drug	2.28 (6.16)	2.46 (7.06)	–0.18 (–0.72 to 0.40)
Intervention/other drug	6.66 (12.48)	7.75 (14.02)	–1.09 (–2.19 to 0.10)
Other health care	1.22 (13.29)	1.76 (22.05)	–0.54 (–2.32 to 0.79)
Intervention (amoxicillin)	2.75 (2.45)	0	2.75 (2.61 to 2.91)
Total (excluding resistance)	47.23 (50.59)	44.80 (54.84)	2.43 (–2.19 to 6.53)
Health outcomes (EQ-5D-3L)			
EQ-5D-3L baseline	0.760 (0.185)	0.752 (0.192)	0.008 (–0.007 to 0.024)
EQ-5D-3L week 1	0.840 (0.173)	0.824 (0.176)	0.016 (0.002 to 0.033)
EQ-5D-3L week 2	0.908 (0.134)	0.900 (0.134)	0.008 (–0.004 to 0.018)
EQ-5D-3L week 3	0.929 (0.122)	0.925 (0.122)	0.004 (–0.006 to 0.015)
EQ-5D-3L week 4	0.936 (0.107)	0.936 (0.109)	0.0001 (–0.010 to 0.008)

[a]Figures represent the unadjusted difference in costs [b]Bootstrapped CI. EQ-5D-3L = three-level version of EQ-5D questionnaire. SD = standard deviation.

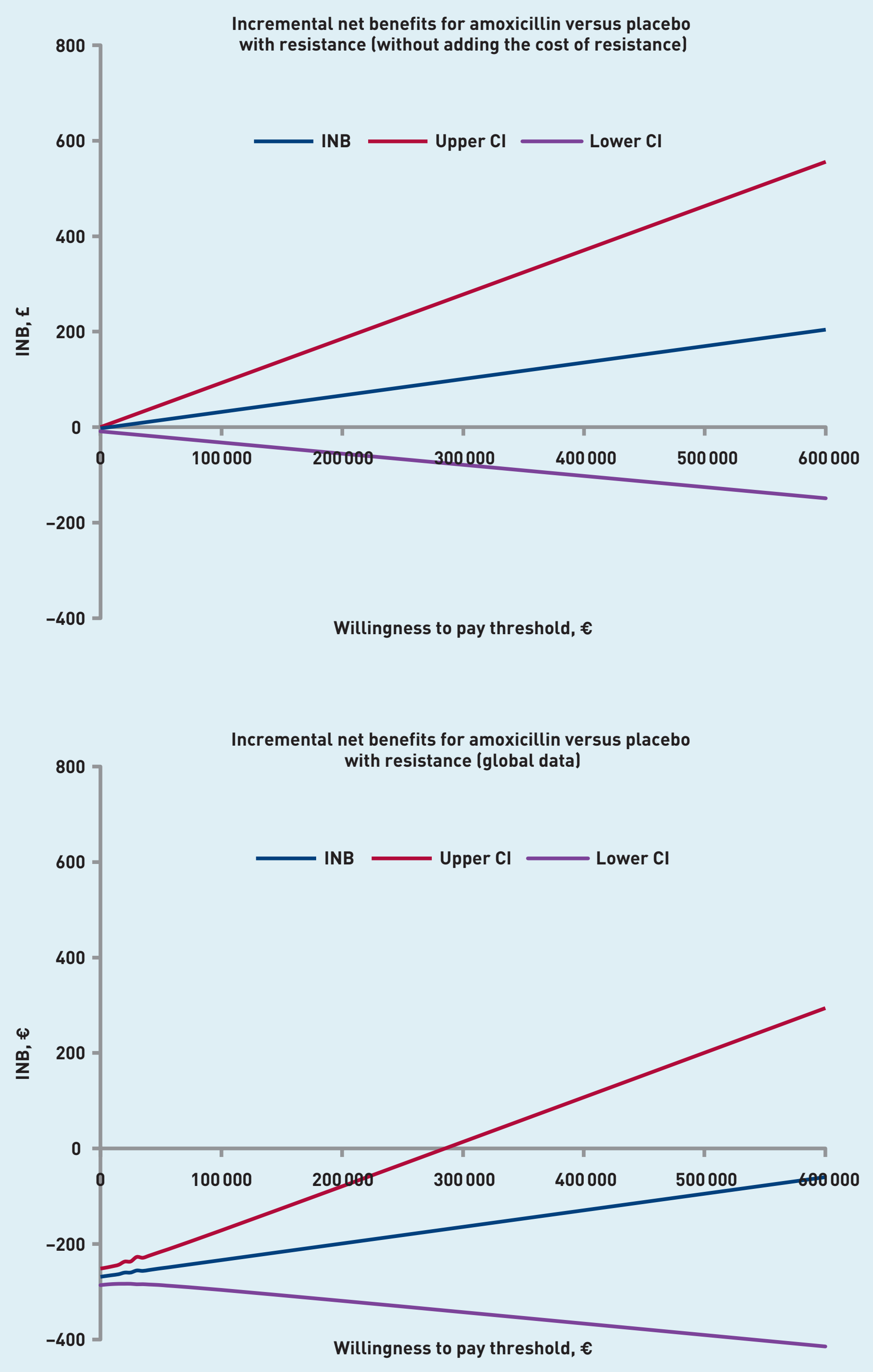

Figure 1. Incremental net benefits with and without the cost of resistance. INB = incremental net benefit.

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

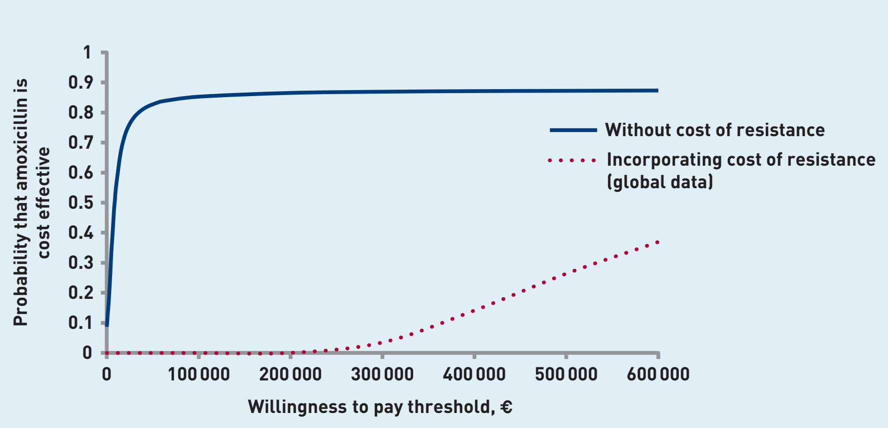

Figure 2. Cost-effectiveness acceptability curve (amoxicillin versus placebo) with and without resistance.

importance of estimating costs and effects jointly.[34] This study found that amoxicillin is associated with a cost-effectiveness ratio of €8216 (£6540) per QALY gained, indicating that the intervention is cost effective if the cost of resistance is ignored. The threshold at which the cost of resistances makes a difference to this decision is, however, low — between around €6 (£5) and €11 (£9) for the current NICE thresholds. With the inclusion of possible values for the cost of resistance, the resulting ICERs indicated that amoxicillin is not cost effective in most cases. The only exception was with the European data where amoxicillin was shown to be cost effective with the inclusion of the respective estimated cost of resistance. However, it should be noted that the European estimated cost of resistance did not include broader societal costs.

Table 2. Cost effectiveness of amoxicillin versus placebo[a]

Cost effectiveness excluding the cost of antimicrobial resistance	
Difference in costs between amoxicillin and placebo groups, € (95% CI)	3.04 (–1.36 to 7.44)
Difference in QALYs gained (95% CI)	0.00037 (–0.0002 to 0.0009)
ICER, €	8216 per QALY gained
Cost effectiveness including cost of resistance (US data)	
Difference in costs between amoxicillin and placebo groups, € (95% CI)	81.47 (75.45 to 87.49)
Difference in QALYs gained (95% CI)	0.00037 (–0.0002 to 0.0009)
ICER, €	220 189 per QALY gained
Cost effectiveness including cost of resistance (EU data)	
Difference in costs between amoxicillin and placebo groups, € (95% CI)	5.45 (1.06 to 9.85)
Difference in QALYs gained (95% CI)	0.00037 (–0.0002 to 0.0009)
ICER, €	14 730 per QALY gained
Cost effectiveness including cost of resistance (global data)	
Difference in costs between amoxicillin and placebo groups, € (95% CI)	269.04 (251.87 to 286.22)
Difference in QALYs gained (95% CI)	0.00037 (–0.0002 to 0.0009)
ICER, €	727 135 per QALY gained

[a]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

Cost effectiveness excluding the cost of resistance	
Difference in costs between amoxicillin and placebo groups, € (95% CI)[a]	0.34 (–6.55 to 7.23)
Difference in QALYs gained (95% CI)	–0.0009 (–0.002 to 0.0002)
ICER	Amoxicillin dominated

[a]95% CIs. ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life year.

Strengths and limitations

The study has some limitations. First, this is a placebo-controlled trial and, as such, the intervention may not be compared with the most relevant alternatives.[35] Second, given there is no European-wide threshold, the study had to rely on the UK cost-effectiveness threshold. Third, the method used to estimate the cost of resistance assumes that current prescriptions lead to current costs and that there is a linear relationship between prescribing and resistance. However, in practice the impact will be lagged and there may be a non-linear relationship, particularly in primary care settings. This analysis also assumes that the cost of resistance is the same across all antibiotics regardless of antibiotic class and the sector of care in which it was prescribed, whereas in reality this cost could vary with the type of antibiotic used and the patient case-mix. For example, broad-spectrum antibiotics are more likely to be associated with a higher level of resistance and a higher cost of resistance. Thus, the cost of resistance estimates used in this study may not be specific to amoxicillin prescribed in primary care for acute cough/LRTI. Although the authors attempted to include costs from a number of sources, there were major limitations associated with this data. For example, the €1.5 billion value in a European setting is an underestimate of the cost of resistance since it was limited to selected multidrug-resistant bacteria and appears not to have included wider societal costs beyond health care. The $100 trillion value could also be an overestimate of the costs.

Nevertheless, the study also has strengths. First, it was carried out in several countries across Europe and, as a result, the finding is likely to be generalisable. Second, this study has been able to show the threshold cost of resistance that would change the decision as to whether amoxicillin is cost effective or not. Third, although the estimation of resistance costs was somewhat speculative, this study has attempted to include this cost in the estimation of cost effectiveness. Given the importance of this issue, it is preferable to make some assumptions about the costs imposed by resistance than to ignore them entirely. The sensitivity of the results to the cost of resistance also highlights the importance of the issue.

Comparison with existing literature

Previous studies have highlighted the need for the inclusion of the cost of antimicrobial resistance in economic evaluations of this sort,[9] but they tend not to be incorporated because of uncertainty, intangibility, and/or difficulty in accurate estimation. In addition, methods to estimate these costs have not been developed.[9] For the first time, this study has provided a valid estimate of the threshold cost of resistance and attempted to include possible estimates of the cost of resistance and found that it had an effect on the results of the study in most cases, suggesting both that incorporating the cost of resistance in the economic evaluation of antibiotic interventions is important, and that it can make a difference to findings. In this study, the threshold cost of resistance was estimated at €6.08 (£4.98) per patient for a cost-effectiveness threshold of €24 655 (£20 000) per QALY. This is a clear indication that the actual cost of resistance does not need to be too high in order to change the decision with respect to the cost effectiveness of an intervention.

Implications for research and practice

This study has shown that amoxicillin is not cost effective in a sub-group of patients who were aged ≥60 years, and this therefore adds to the literature, which suggests that there needs to be better targeting of antibiotics.[6,36] Mechanisms for better targeting include the use of delayed prescribing, training, and diagnostic tools, which have been shown to be effective.[37–40] The results of this study highlight the great importance that should be attached to additional research into improved methods for estimating the costs associated with resistance, but also suggest that there is a possibility that prescription of antibiotics for LRTI may not be cost effective. The authors' final recommendation is that all economic evaluations of interventions where antibiotics are used should attempt to incorporate a cost for resistance.

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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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REFERENCES

1. World Health Organization. *Antimicrobial resistance*. Factsheet No. 194. Revised January 2002. www.who.int/mediacentre/factsheets/fs194/en/ (accessed 13 Jun 2016).
2. Butler CC, Hood K, Verheij T, *et al*. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009; **338:** b2242.
3. Cals JW, Hopstaken RM, Butler CC, *et al*. Improving management of patients with acute cough by C-reactive protein point of care testing and communication training (IMPAC3T): study protocol of a cluster randomised controlled trial. *BMC Fam Pract* 2007; **8:** 15.
4. Virkki R, Juven T, Rikalainen H, *et al*. Differentiation of bacterial and viral pneumonia in children. *Thorax* 2002; **57(5):** 438–441.
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.
6. Coast J, Smith R. Antimicrobial resistance: can economics help? *Eurohealth* 2001; **7(2):** 32–33.
7. Ciesla G, Leader S, Stoddard J. Antibiotic prescribing rates in the US ambulatory care setting for patients diagnosed with influenza, 1997–2001. *Respir Med* 2004; **98(11):** 1093–1101.
8. Goossens H, Ferech M, Vander Stichele R, Elseviers M. ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365(9459):** 579–587.
9. Coast J, Smith RD, Millar MR. Superbugs: should antimicrobial resistance be included as a cost in economic evaluation? *Health Econ* 1996; **5(3):** 217–226.
10. Costelloe C, Metcalfe C, Lovering A, *et al*. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340:** c2096.
11. Malhotra-Kumar S, Lammens C, Coenen S, *et al*. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; **369(9560):** 482–490.
12. Little P, Stuart B, Moore M, *et al*. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13(2):** 123–129.
13. Oppong R, Coast J, Hood K, *et al*. Grace-01 Study Team. Resource use and costs of treating acute cough/lower respiratory tract infections in 13 European countries: results and challenges. *Eur J Health Econ* 2011; **12(4):** 319–329.
14. World Bank. Consumer price index. 2016. http://data.worldbank.org/indicator/FP.CPI.TOTL?page=6 (accessed 13 Jun 2016).
15. Organisation for Economic Co-operation and Development. OECD Purchasing power parities. 2012. http://stats.oecd.org/index.aspx?queryid=22519 (accessed 13 Jun 2016).
16. Greiner W, Weijnen T, Nieuwenhuizen M, *et al*. A single European currency for EQ-5D health states. *Eur J Health Econ* 2003; **4(3):** 222–231.
17. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York, NY: John Wiley & Sons, 2004.
18. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of 'community acquired' syncope. *BMC Health Serv Res* 2006; **6(1):** 68.
19. Appleby J, Devlin N, Parkin D. NICE's cost effectiveness threshold. *BMJ* 2007; **335(7616):** 358–359.
20. Laxminarayan R, Brown GM. Economics of antibiotic resistance: a theory of optimal use. *J Environ Econ Manag* 2001; **42(2):** 183–206.
21. Coast J, Smith R, Millar M. An economic perspective on policy to reduce antimicrobial resistance. *Soc Sci Med* 1998; **46(1):** 29–38.
22. Smith R, Coast, J. *The economic burden of antimicrobial resistance: why it is more serious than current studies suggest*. Technical Report 2012. London: London School of Hygiene and Tropical Medicine, 2012. http://researchonline.lshtm.ac.uk/639028/1/DH_AMR_final_report_30-10-12_with_appendix.pdf (accessed 13 Jun 2016).
23. Reed SD, Laxminarayan R, Black DJ, Sullivan SD. Economic issues and antibiotic resistance in the community. *Ann Pharmacother* 2002; **36(1):** 148–154.
24. Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ* 2013; **346:** f1493.
25. Bruyndonckx R, Hens N, Aerts M, *et al*. Exploring the association between resistance and outpatient antibiotic use expressed as DDDs or packages. *J Antimicrob Chemother* 2015; **70(4):** dku525.
26. Centers for Disease Control and Prevention. *Antimicrobial resistance: no action today, no cure tomorrow*. World Health Day: Media Fact Sheet. 7 Apr 2011. http://www.cdc.gov/media/releases/2011/f0407_antimicrobialresistance.pdf (accessed 13 Jun 2016).
27. European Centre for Disease Prevention and Control, European Medicines Agency. *The bacterial challenge: time to react*. Joint technical report. Stockholm: ECDPC, 2009. http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (accessed 13 Jun 2016).
28. O'Neill J, Review on Antimicrobial Resistance. *Antimicrobial resistance: tackling a crisis for the health and wealth of nations*. 2014. http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed 13 Jun 2016).
29. Hicks LA, Taylor TH Jr, Hunkler RJ. US outpatient antibiotic prescribing, 2010. *N Engl J Med* 2013; **368(15):** 1461–1462.
30. United States Government Accountability Office. *Antibiotic resistance: data gaps will remain despite HHS taking steps to improve monitoring*. Report to the Committee on Agriculture, House of Representatives. GOA-11-406. 2011. http://www.gao.gov/assets/320/319110.pdf (accessed 13 Jun 2016).
31. European Centre for Disease Prevention and Control. *Summary of the latest data on antibiotic consumption in the European Union*. Stockholm: ECDPC, 2014. http://ecdc.europa.eu/en/eaad/Documents/antibiotic-consumptio-ESAC-Net-2014-EAAD.pdf (accessed 13 Jun 2016).
32. Eurostat. Population on 1 January. http://ec.europa.eu/eurostat/tgm/table.do?tab=table&language=en&pcode=tps00001&tableSelection=1&footnotes=yes&labeling=labels&plugin=1 (accessed 13 Jun 2016).
33. Van Boeckel TP, Gandra S, Ashok A, *et al*. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; **14(8):** 742–750.
34. Dakin H, Wordsworth S. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. *Health Econ* 2013; **22(1):** 22–34.
35. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The *BMJ* Economic Evaluation Working Party. *BMJ* 1996; **313(7052):** 275–283.
36. Chung A, Perera R, Brueggemann AB, *et al*. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ* 2007; **335(7617):** 429.
37. Oppong R, Jit M, Smith RD, *et al*. Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. *Br J Gen Pract* 2013; DOI: 10.3399/bjgp13X669185.
38. Moore M. Antibiotics: time to act. *Br J Gen Pract* 2013; DOI: 10.3399/bjgp13X668447.
39. Spurling G, Del Mar CB, Dooley L, *et al*. Delayed antibiotics for respiratory infections. *Cochrane Database Syst Rev* 2013; **4:** CD004417.
40. Little P, Stuart B, Francis N, *et al*. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; **382(9899):** 1175–1182.