J Antimicrob Chemother 2018; **73**: 3189–3198
doi:10.1093/jac/dky309 Advance Access publication 27 August 2018

Journal of Antimicrobial Chemotherapy

Cost-effectiveness of internet-based training for primary care clinicians on antibiotic prescribing for acute respiratory tract infections in Europe

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Received 6 April 2018; returned 23 May 2018; revised 21 June 2018; accepted 9 July 2018

Objectives: Overprescribing of antibiotics by general practitioners (GPs) is seen as a major driver of antibiotic resistance. Training in communication skills and C-reactive protein (CRP) testing both appear effective in reducing such prescribing. This study assesses the cost-effectiveness (compared with usual care) of: (i) training GPs in the use of CRP testing; (ii) training GPs in communication skills; and (iii) training GPs in both CRP testing and communication skills.

Methods: Economic analyses [cost–utility analysis (CUA) accounting for the cost of antibiotic resistance and cost-effectiveness analysis (CEA)] were both conducted from a healthcare perspective with a time horizon of 28 days alongside a multinational, cluster, randomized, factorial controlled trial in patients with respiratory tract infections in five European countries. The primary outcome measures were QALYs and percentage reduction in antibiotic prescribing. Hierarchical modelling was used to estimate an incremental cost per QALY gained and an incremental cost per percentage reduction in antibiotic prescribing.

Results: Overall, the results of both the CUA and CEA showed that training in communication skills is the most cost-effective option. However, excluding the cost of antibiotic resistance in the CUA resulted in usual care being the most cost-effective option. Country-specific results from the CUA showed that training in communication skills was cost-effective in Belgium, UK and Netherlands whilst training in CRP was cost-effective in Poland.

Conclusions: Internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care if the cost of antibiotic resistance is accounted for.

Introduction

Antibiotic resistance is currently one of the world's leading public health concerns, which places a heavy burden on scarce resources. In the UK, resistant infections such as MRSA are estimated to cost the NHS an additional £1 billion in extra treatments annually[1] and without a resolution 'superbugs' are estimated to cause more deaths than cancer by 2050, costing ∼$100 trillion globally.[2]

The difficulty in determining who will benefit from prescribing, and a desire to satisfy patients' demands, appear to be driving inappropriate and overprescribing of antibiotics by general practitioners (GPs).[3–5] As well as impacting the development of resistance, antibiotic prescribing is associated with significant costs[6]; e.g. NHS in the UK incurs an annual cost of between $35 (£23) and $70 (£47) million in antibiotic prescription costs for acute cough/lower respiratory tract infections alone.[7] Reducing

Table 1. **Sources[a] of valuation data and country contribution to sample size**

Source	Belgium	Netherlands	Poland	Spain	UK
GP visits	1	1	1	1	2
Nurse visits	NA	1	1	1	2
Out-of-hours GP	9	9	9	9	2
Walk-in centre	NA	1	1	1	1
Hospital admissions	1	1	1	1	8
Investigations	7, 9	9	9	9	8
Medication	6	5	1, 9	3, 1	4
Contribution to sample size	318 (7.5%)	329 (7.7%)	1419 (33.3%)	1318 (30.9%)	880 (20.6%)

NA, not applicable.
[a]Key to sources: 1, previous study; 2, Lesley Curtis (www.pssru.ac.uk); 3, www.vademecum.es; 4, British National Formulary (www.bnf.org); 5, Dutch healthcare insurance board (www.medicijnkosten.nl); 6, www.bcfi.be; 7, www.http://riziv.fgov.be; 8, NHS Reference costs; 9, Market basket approach.

inappropriate and overprescribing of antibiotics would thus not only help reduce the problem of antibiotic resistance but also save scarce resources.

The rate of development of new antibiotics has slowed down over the past three decades[8–11] and the antibiotics currently available must be conserved. One way to assist with this protection is to find cost-effective ways of changing the prescribing behaviour of GPs.

Interventions to reduce prescribing, based on persuasion, have generally been ineffective in dealing with the problem,[12,13] and so more recent focus has turned to training GPs in advanced consulting skills and using point-of-care tests. These have resulted in a change in their prescribing behaviour,[14,15] with internet-based training programmes providing a reduction in antibiotic prescribing similar to the standardized methods of training.[16] Such internet-based training was developed by the Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infections in Europe (GRACE) consortium.[4,17,18] The interventions consisted of: (i) training GPs in the use of C-reactive protein testing ('CRP'); (ii) training GPs in communication skills ('communication skills'); and (iii) training GPs in both CRP testing and communication skills ('combined').

Results from the GRACE INTRO trial indicate that all three of these interventions—(i) CRP; (ii) communication skills; and (iii) both combined—are effective in changing GP antibiotic prescribing behaviour.[19] However, in addition to the effectiveness of these interventions, it is important to determine whether the interventions provide value for money. One study conducted a cost-effectiveness analysis (CEA) using reductions in antibiotic prescribing as an outcome measure and found all three interventions to be cost-effective compared with usual care.[20] However, no study has assessed the cost-effectiveness of these interventions in a multinational setting or estimated the country-specific cost-effectiveness of these interventions. The aim of this study is to assess the cost-effectiveness of these interventions across five European countries.

Patients and methods

Patients and settings

The economic analysis was conducted alongside a multinational, cluster, randomized, factorial controlled trial in which participating practices were randomized to one of four study groups: (i) CRP; (ii) communication skills; (iii) CRP and communication skills combined; and (iv) usual care.[19] The perspective adopted was that of the health service, including costs to the health service and healthcare cost to the patient. Consenting participants who presented with respiratory tract infections were recruited from primary care networks across five countries in Europe: Belgium, the Netherlands, Poland, Spain and the UK (England and Wales). The study was approved by ethics committees in all countries and all eligible individuals provided written consent before participating in the study. Full details of the clinical trial and intervention have been published elsewhere.[4,17–19]

Data collection

Resource use

The main sources of resource use information were the case report form completed by primary care clinicians on the day of the consultation (day 1), and a diary completed by patients over a 4 week period starting on day 1. Resource use data were collected on the following: consultations with health professionals, use of medications (over-the-counter and prescription), medical investigations and hospital admissions.

Unit costs

Unit costs specific to each participating country were obtained mainly from national and international sources. In cases where costs were not available, they were obtained from a study previously published by the authors.[21] These costs were inflated to 2016 prices using the consumer price index for each country.[22] Where unit costs were unavailable, a market basket approach[23] was used to estimate a relationship between the UK and the country of interest to obtain this cost. The UK was chosen because all unit costs were available for this setting.

Medications were classified into 13 different groups. As it was not feasible to obtain unit costs for each individual drug for each country, a cost was generated for each of the 13 groups by estimating an average price from a list of drugs within that group. Table 1 gives a summary of the various sources of unit costs.

Intervention costs

For C-reactive protein (CRP), capital costs were obtained from the manufacturer (Orion Diagnostica) who quoted an average cost of €1200. This cost was then annuitized assuming that the machine has a lifespan of 3 years, at an interest rate of 3.5%, and a cost per patient was estimated. The costs of the reagents used [€7.45 (£6) per patient] were obtained from the provider (Oxford Biosystems).

Table 2. Resource use for complete case analysis

	Usual care (*n* = 515)	CRP no communications (*n* = 660)	Communications no CRP (*n* = 740)	CRP plus communications (*n* = 709)
Primary care visits, mean (SD)				
GP visits	0.194 (0.472)	0.355 (0.762)	0.284 (0.713)	0.236 (0.596)
Nurse visits	0.016 (0.206)	0.045 (0.323)	0.103 (0.741)	0.039 (0.263)
Out-of-hours GP visits	0.015 (0.271)	0.006 (0.095)	0.023 (0.182)	0.016 (0.163)
Secondary care visits, mean (SD)				
Hospital emergency visits	0.002 (0.044)	0.003 (0.054)	0.018 (0.134)	0.016 (0.155)
Walk-in centre visits	0.004 (0.087)	0.002 (0.039)	0.022 (0.186)	0.035 (0.383)
Specialist visits	0.004 (0.062)	0.018 (0.155)	0.028 (0.222)	0.023 (0.218)
Admissions	0.010 (0.182)	0.026 (0.379)	0.019 (0.320)	0.030 (0.394)
Prescriptions, *n* (%)				
Antibiotic prescription	307 (59.61)	222 (33.64)	303 (40.95)	242 (34.13)
Over-the-counter medication	346 (67.18)	419 (63.48)	451 (60.95)	441 (62.20)
CRP test	12 (2.33)	441 (66.82)	57 (7.70)	461 (65.02)

With respect to the communication skills, the cost of the booklet given to patients, €0.36 (£0.29), was obtained from study co-ordinators and converted into country equivalent costs using the market basket approach.[23] For the combined intervention, the cost of the CRP machine and the cost of the booklet estimated above were included.

To estimate the cost of the internet-based training, we obtained information on the amount of time GPs spent on it in each arm and estimated the total cost of time spent on training. This value was divided by the number of patients per GP to estimate the cost per patient. GPs spent on average 26.54, 37.44 and 39.76 min on training in the CRP, communication skills and combined intervention arms, respectively. Information on training has been published in a previous study.[4] GPs also received face-to-face training in using the CRP device and a similar approach to that described above was used to estimate a cost per patient in each arm. All costs were converted into Euros using purchasing power parities. In addition to presenting costs in Euros, costs were also presented in pounds sterling. All costs are presented in 2016 prices.

Previous research has highlighted the importance of including the cost of antibiotic resistance in economic evaluations assessing interventions in this area.[24,25] As a result of this, the cost of resistance figures generated from a recent study[25] were added to every antibiotic prescription irrespective of the trial arm. The inclusion of these costs was limited to the cost–utility analysis (CUA) since the outcome for the CEA (percentage reduction in antibiotic prescribing) indirectly accounts for antibiotic resistance given the fact that antibiotic prescribing leads to antibiotic resistance.

Health outcomes

Health outcomes were measured using the three-level version of the EQ-5D questionnaire. This instrument comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels: no problems, some problems and severe problems.[26] Patients were asked to complete the EQ-5D-3L questionnaire over the entire 4 week period (at day 1, and at the end of weeks 1, 2, 3 and 4), or until they felt better. EQ-5D-3L index scores were generated using the European Harmonized Tariff[27] and have been validated for use in respiratory disease.[28]

Antibiotic prescribing

Physicians were asked to state whether they prescribed an antibiotic and this information was used to estimate the rate of antibiotic prescribing in each of the trial arms.

Statistical analysis

The economic evaluation comprised two main analyses: CUA (cost per QALY gained), and CEA (cost per percentage reduction in antibiotic prescribing). Both were carried out on an ITT basis. For each participant included in the study, a QALY score over the 4 week period was estimated using the area under the curve approach.[29] Total healthcare costs over the 4 week period were calculated by multiplying the resource items used by the respective unit cost and summing over all items. Missing costs and health outcomes were imputed using a multiple imputation methodology. The technique used was predictive mean matching and the imputation model included 25 imputed datasets.[30]

Multilevel modelling, recommended for the economic evaluation of cluster and multinational trials, was used for data analysis.[31,32] Dependent variables included total cost, QALYs and antibiotic prescribing. The model controlled for day 1 EQ-5D, gender, age, smoking, sex, crepitations, wheeze, pulse rate >100 beats per minute, temperature >37.8°C, respiratory rate, blood pressure and duration of cough. These variables were controlled for to adopt a similar approach to the clinical study. To explore country variation in the cost-effectiveness of the interventions, adjusted country-specific cost-effectiveness estimates were also obtained using a Bayesian approach.[33] Minimally informative prior distributions were placed on all model parameters.[34] All analyses were carried out in STATA 12, Winbugs 14 and R statistical software. Model estimates of the difference in costs, QALYs and antibiotic prescribing were used to derive an incremental cost per QALY gained and an incremental cost per percentage reduction in antibiotic prescribing.

For the CUA, we used the NICE recommended threshold of between £20000 and £30000 (€24655 and €36928) per QALY to judge the cost-effectiveness of the interventions.[35]

A ‘within the table’ analysis was adopted to account for the factorial nature of the trial.[36,37] This method assumes that the interventions are not independent, i.e. the costs and effects of communication skills are influenced by the inclusion of CRP testing and vice versa. This approach, which considers each treatment option individually, was used for the base-case analysis. All interventions were ordered in terms of increasing cost, for costs, QALYs and percentage reduction in antibiotic prescribing for each treatment arm to be compared incrementally. The most cost-effective option was selected based on the principles of dominance [where an intervention is less costly and more effective than the appropriate comparator(s)] and extended (weak) dominance [where an intervention is ruled out if the incremental cost-effectiveness ratio (ICER) is greater than that of a more effective

Table 3. Costs (€) (complete case analysis)

	Usual care (*n* = 515)	CRP no communications (*n* = 660)	Communications no CRP (*n* = 740)	CRP plus communications (*n* = 709)
Primary care visits				
GP visits	3.44 (10.27)	4.68 (11.23)	4.60 (13.90)	3.65 (10.12)
Nurse visits	0.22 (3.12)	0.32 (3.01)	1.36 (9.95)	0.49 (4.71)
Out-of-hours GP visits	5.30 (92.83)	2.04 (32.27)	8.07 (63.65)	5.36 (56.01)
Secondary care visits				
Hospital emergency visits	0.27 (6.22)	0.41 (7.48)	2.60 (18.73)	2.16 (21.30)
Walk-in centre visits	0.09 (2.03)	0.03 (0.90)	0.52 (4.52)	0.78 (7.90)
Specialist visits	0.84 (13.54)	3.75 (31.70)	5.58 (44.60)	4.83 (46.70)
Admissions	4.78 (89.56)	12.20 (179.20)	9.08 (150.58)	13.92 (186.81)
Other costs				
Prescription	11.96 (26.87)	8.74 (19.32)	9.79 (19.04)	11.99 (34.64)
Over-the-counter medication	6.55 (17.36)	4.48 (12.95)	4.52 (12.65)	6.18 (17.32)
CRP test	0.19 (1.23)	5.24 (3.74)	0.28 (1.07)	4.88 (3.79)
Trial intervention cost[a]	0	11.42 (7.45)	5.62 (3.69)	13.43 (8.53)
Resistance cost	105.39 (94.01)	57.29 (84.86)	66.09 (84.49)	60.34 (88.02)

Values are mean (SD).
[a]Cost associated with delivering the trial interventions.

Table 4. Mean EQ-5D scores over 4 weeks and antibiotic prescribing (complete cases)

	Usual care (*n* = 515)	CRP no communications (*n* = 660)	Communications no CRP (*n* = 740)	CRP plus communications (*n* = 709)
EQ-5D				
Day 1	0.717 (0.216)	0.729 (0.212)	0.693 (0.228)	0.710 (0.223)
Week 1	0.816 (0.197)	0.817 (0.207)	0.786 (0.214)	0.792 (0.210)
Week 2	0.884 (0.176)	0.881 (0.182)	0.864 (0.185)	0.869 (0.186)
Week 3	0.898 (0.170)	0.899 (0.176)	0.894 (0.176)	0.893 (0.174)
Week 4	0.906 (0.165)	0.907 (0.169)	0.903 (0.168)	0.899 (0.169)
Antibiotic prescribing	0.596 (0.491)	0.336 (0.473)	0.409 (0.492)	0.341 (0.474)

Values are mean (SD).

intervention].[38] In addition, all interventions were compared with usual care individually.

Sensitivity analysis

Sensitivity analysis had two main foci. First, the results were compared against country-specific thresholds to determine whether the interventions are cost-effective. This analysis was limited to the CUA, and of the five participating countries only the UK has an explicit threshold [£20000 (€24655) to £30000 (€36928) per QALY gained].[35] There is no explicit threshold in the Netherlands, Belgium, Spain and Poland. However, a value of €20000 per QALY gained is often used in the Netherlands,[39] €35000 per QALY gained has been used to inform decision making in Belgium[40] and in Spain, it has been suggested that the threshold value should lie between €22000 and €25000 per QALY gained.[41] These values were therefore used to represent cost-effectiveness thresholds in the countries mentioned. No threshold value was identified in Poland.

Second, to explore further the impact of including the cost of resistance, sensitivity analysis focused on conducting the economic evaluation without accounting for the cost of antibiotic resistance. This analysis was limited to the CUA since the base-case CUA included the cost of resistance.

Results

A total of 246 practices participated in the study and contributed 4264 participants across five European countries. The country contribution to sample size ranged from 318 (7.5%) in Belgium to 1419 (33.3%) in Poland (Table 1).

Resource use and costs

A breakdown of resource use items is presented in Table 2. Compared with the other interventions, visits to the GP and hospital admissions were lower in the usual care arm. Visits to the GP were highest in the CRP group, whereas visits to the nurse were highest in the communication skills group. As was expected, those in the CRP and combined intervention groups had more CRP tests performed. Approximately 59% of participants in the usual care arm had an antibiotic prescribed compared with ∼34% in the combined intervention arm. Costs associated with resource use items are presented in Table 3. GP costs were highest in the CRP group whereas nurse costs were highest in the communication skills

Table 5. Overall and country-specific cost-effectiveness (CUA)

	Cost (€)[a]	QALY	ICER (€)	ICER (compared with UC) (€)
Overall ($n = 4264$)				
CRP + Comm	94.36	0.0648	dominated by Comm	dominated by UC
UC	92.46	0.065	dominated by Comm	NA
CRP	87.41	0.0651	dominated by Comm	dominates UC
Comm	83.21	0.0651	NA	dominates UC
Belgium ($n = 318$)				
Comm	93.28	0.0651	3450[b]	7120[c]
CRP + comm	92.59	0.0649	7343[d]	8038[c]
CRP	87.45	0.0642	12 900[c]	12 900[c]
UC	86.16	0.0641	NA	NA
Netherlands ($n = 329$)				
CRP + Comm	84.99	0.0649	dominated by CRP	dominated by UC
UC	75.52	0.065	dominated by CRP	NA
CRP	73.41	0.0656	27 186[f]	dominates UC
Comm	54.38	0.0649	NA	211 400[e]
Poland ($n = 1419$)				
UC	143.41	0.0663	49 129[d]	NA
Comm	114.37	0.0656	dominated by CRP	41 486[e]
CRP + Comm	110.95	0.0652	dominated by CRP	29 509[e]
CRP	109.02	0.0656	NA	49 129[e]
Spain ($n = 1318$)				
CRP + Comm	78.71	0.0648	dominated by UC	dominated by UC
CRP	70.86	0.0656	dominated by UC	dominated by UC
UC	66.46	0.0659	1000[f]	NA
Comm	65.86	0.0653	NA	1000[e]
UK ($n = 880$)				
CRP + Comm	106.57	0.0641	dominated by Comm	25 050[c]
UC	101.56	0.0639	dominated by Comm	NA
CRP	98.75	0.0645	dominated by Comm	dominates UC
Comm	98.05	0.0648	NA	dominates UC

Comm, communications training; UC, usual care; NA, not applicable (this is the reference case).
[a]Costs includes the costs associated with antibiotic resistance.
[b]Compared with training in both CRP testing and communication skills.
[c]Compared with UC.
[d]Compared with CRP training.
[e]ICER value represents a comparison of UC versus the respective intervention since the ICER generated from a comparison of the respective intervention with UC represents a willingness to accept a loss in benefit, rather than a willingness to pay for a gain in benefit.
[f]Compared with communication skills training.

group. Costs associated with over-the-counter medication were highest in the usual care arm.

Outcomes

There was an improvement in the health of participants over the 4 week period as shown by the EQ-5D scores. The scores at 4 weeks were higher than those at day 1 in all four treatment arms (Table 4). Overall, antibiotic prescribing was highest in the usual care group and lowest in the combined intervention group (Table 4).

CUA

The CUA results indicate that overall, communication skills is the most cost-effective intervention since it dominated all other interventions (Table 5). Compared with usual care, both communication skills and CRP were dominant whereas the combined intervention was dominated. Country-specific estimates showed that communication skills were the most cost-effective intervention in Belgium, the UK and the Netherlands. CRP is only cost-effective in the Netherlands if the threshold is >€27000 (£21903) per QALY gained. CRP is cost-effective in Poland whereas usual care is cost-effective in Spain (Table 5 and Figures 1 and 2).

CEA

With respect to the CEA (percentage reduction in antibiotic prescribing as an outcome), communication skills was associated with an ICER of €68.08 (£55.23) per percentage reduction in antibiotic prescribing when compared with usual care. The ICER for CRP

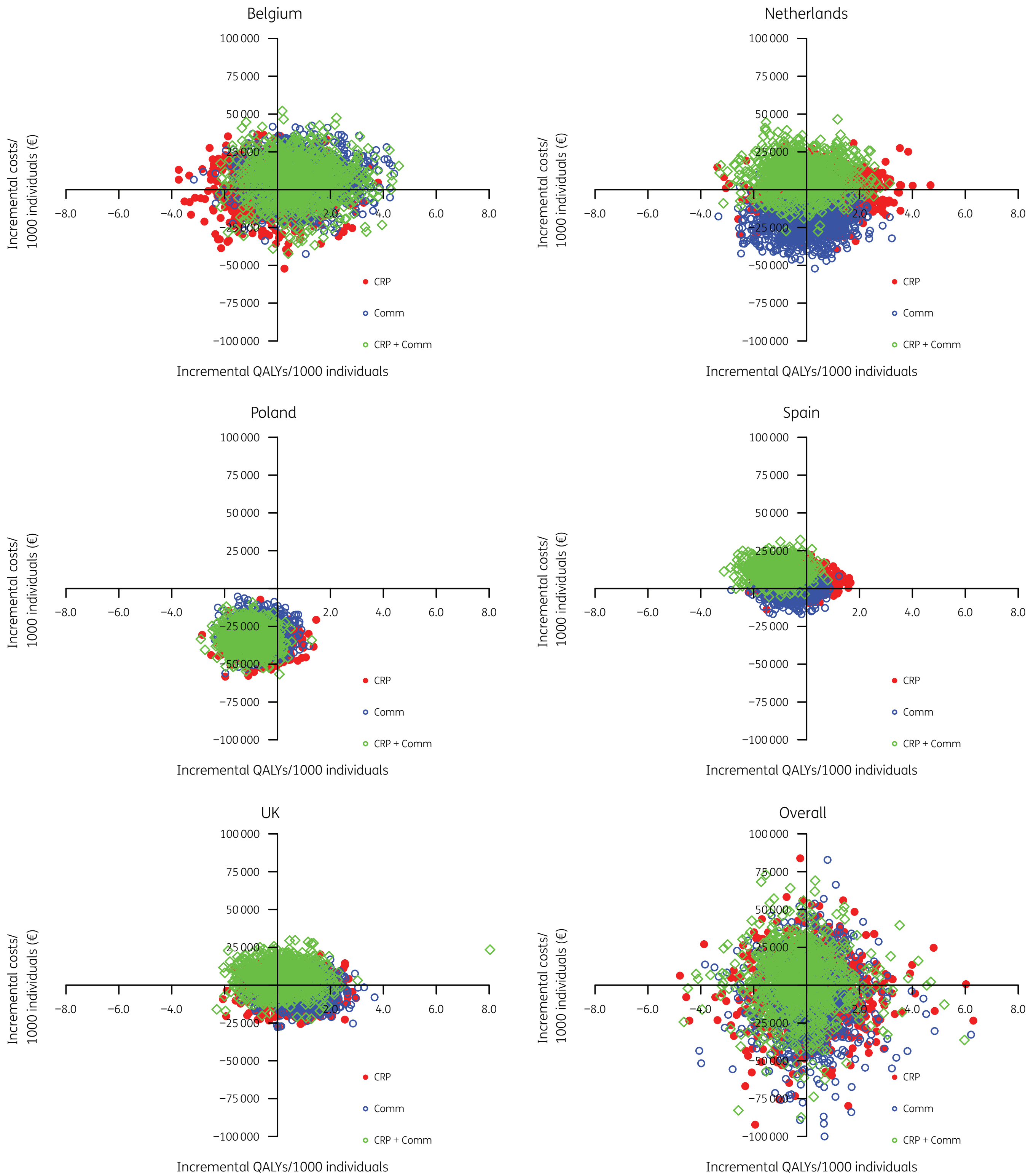

Figure 1. Cost-effectiveness plane (CUA). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

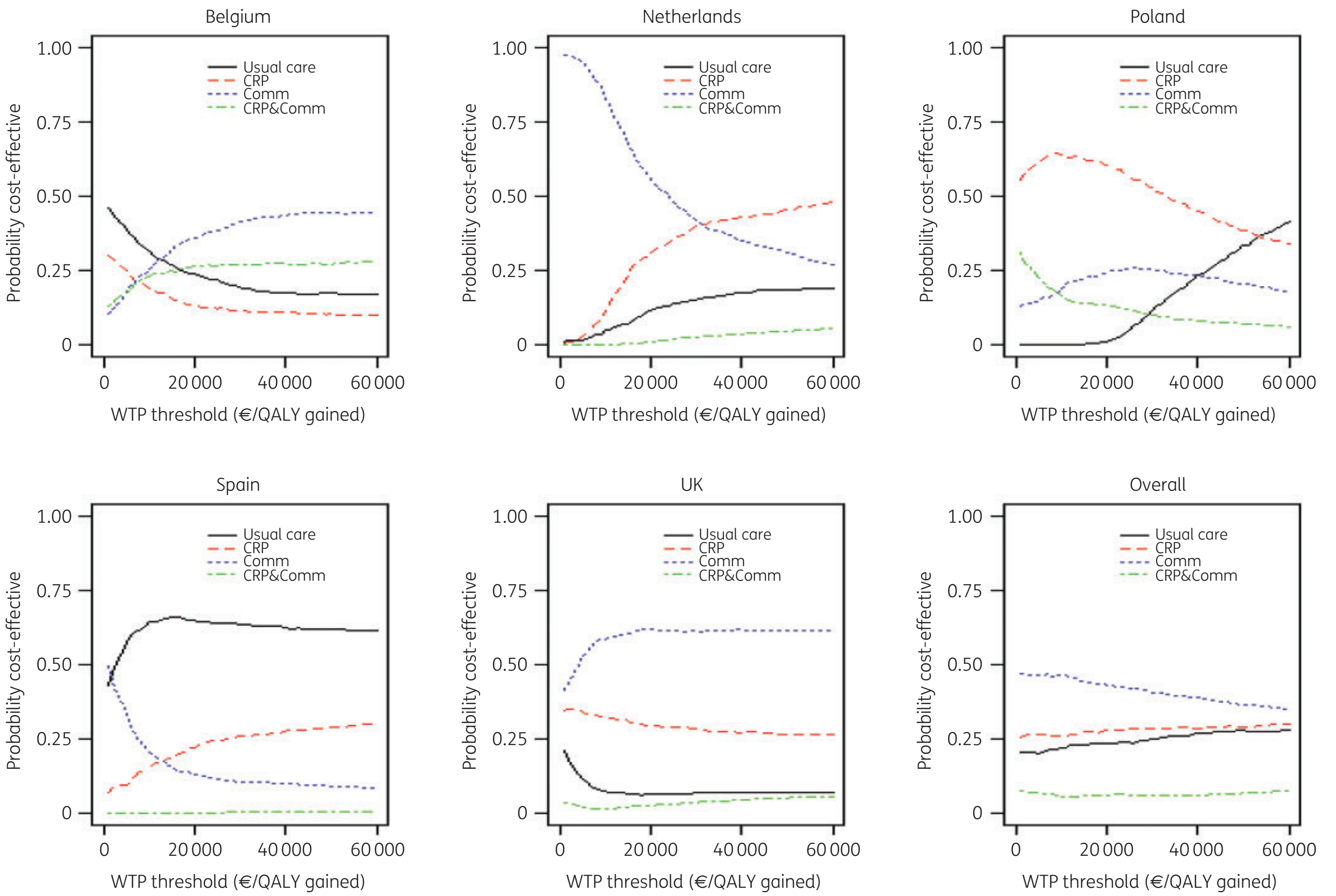

Figure 2. Cost-effectiveness acceptability curves (CUA). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*. WTP, willingness to pay; Comm, communications training.

compared with communication skills was €176.53 (£143.20) per percentage reduction in antibiotic prescribing and the ICER for the combined intervention compared with CRP was €338.89 (£274.90) per percentage reduction in antibiotic prescribing (Table 6). Compared with usual care, ICERs ranged from €68.08 (£55.23) per percentage reduction in antibiotic prescribing with communication skills to €126.21 (£102.38) per percentage reduction in antibiotic prescribing with the combined intervention. Country-specific estimates show that CRP is the most cost-effective intervention in Belgium. In the Netherlands, CRP is cost-effective if society is willing to pay ∼€72 (£58) per percentage reduction in antibiotic prescribing. On the other hand, communication skills is the most cost-effective in Poland, Spain and the UK (Table 6 and Figures S1 and S2, available as Supplementary data at *JAC* Online).

Sensitivity analysis

In terms of comparing the results with country-specific cost-effectiveness thresholds, communication skills were cost-effective in Belgium, the Netherlands and the UK, CRP was cost-effective in Poland and usual care was cost-effective in Spain (Table S1).

The results of the sensitivity analysis, which excludes the cost of antibiotic resistance, are presented in Table S2 and Figures S3 and S4, and they show that, overall, usual care is cost-effective if the cost of antibiotic resistance is not accounted for. The country-specific estimates also show that, with the exception of Belgium where communication skills were cost-effective, usual care is the most cost-effective intervention in all other countries when the cost of antibiotic resistance is not included.

Discussion

Summary of main findings

This study evaluated the cost-effectiveness (compared with usual care) of: (i) training GPs in the use of CRP testing; (ii) training GPs in communication skills; and (iii) training GPs in both CRP testing and communication skills. In terms of cost per percentage reduction in antibiotic prescribing, overall, communication skills was the most cost-effective intervention. Similarly, the CUA also showed that communication skills was the most cost-effective intervention. However, the country-specific estimates were not consistent across the CUA and the CEA. The only country where communication skills was cost-effective across both the CUA and CEA was the UK. Compared with usual care, both communication skills and CRP are cost-effective. Sensitivity analysis in which the cost of resistance was not included in the CUA led to a scenario in which usual care was the most cost-effective intervention overall.

Table 6. Overall and country-specific cost-effectiveness (CEA)

	Cost (€)[a]	Outcome	ICER (€)	ICER (compared with UC) (€)
Overall ($n = 4264$)				
CRP + Comm	60.32	0.8003	338.8889[b]	126.209[b]
CRP	49.34	0.7679	176.5343[c]	95.44643[b]
Comm	39.56	0.7125	68.8019[b]	68.8019[b]
UC	27.96	0.5439	NA	NA
Belgium ($n = 318$)				
CRP + Comm	62	0.8216	323.4528[b]	234.3308[b]
CRP	52.07	0.7909	26.85393[c]	203.7946[b]
Comm	49.68	0.7019	26 350[b]	26 350[b]
UC	33.81	0.7013	NA	NA
Netherlands ($n = 329$)				
CRP + Comm	58.47	0.8409	1929.73[d]	126.6091[b]
CRP	44.19	0.8335	72.67583[b]	72.67583[b]
UC	26.21	0.5861	dominated by Comm	NA
Comm	26	0.7894	NA	dominates UC
Poland ($n = 1419$)				
CRP + Comm	61.3	0.7366	189.8754[d]	81.94658[b]
CRP	49.11	0.6724	92.14953[c]	55.44933[b]
Comm	44.18	0.6189	46.00962[b]	46.00962[b]
UC	34.61	0.4109	NA	NA
Spain ($n = 1318$)				
CRP + Comm	47.5	0.8044	dominated by CRP	162.4065[b]
CRP	39.53	0.8156	145.0094[c]	100.5685[b]
Comm	31.83	0.7625	78.13688[b]	78.13688[b]
UC	23.61	0.6573	NA	NA
UK ($n = 880$)				
CRP + Comm	74.46	0.8066	202.439[d]	112.511[b]
CRP	59.52	0.7328	170.1754[c]	95.16466[b]
Comm	49.82	0.6758	82.03317[b]	82.03317[b]
UC	23.11	0.3502	NA	NA

Comm, communications training; UC, usual care; NA, not applicable (this is the reference case).
[a]Costs excludes the costs associated with antibiotic resistance.
[b]Compared with UC.
[c]Compared with communication skills training.
[d]Compared with CRP training.

Strengths and limitations of the study

There are several strengths to this study. First, the factorial nature of the study enabled the relative cost-effectiveness of four different interventions to be explored within the same trial. Second, this study utilized data from five different European countries and so the findings may be more generalizable than those obtained from previous studies conducted in single country settings. Third, the study presented country-specific cost-effectiveness estimates, and, fourth, this study explored the implications of accounting for antibiotic resistance in economic evaluations.

There are also a number of limitations. First, this study is conducted alongside a multinational, cluster randomized, factorial controlled trial, which presents additional complexities with respect to the analysis of the data. The factorial nature has the effect of reducing the sample size for any of the interventions on its own and therefore increasing the degree of uncertainty in the economic data. In this study, randomization took place at the cluster/practice level and health economics outcomes such as QALYs were measured at the level of the individual. However, this has been addressed using methods that account for the hierarchical nature of the data. Second, assumptions were required to estimate country-specific unit costs when these were not available. Third, with respect to the CUA, as there is no Europe-wide cost-effectiveness threshold, this study relied on the UK threshold to judge the cost-effectiveness of interventions. Other studies have also noted problems regarding the choice of cost-effectiveness threshold in a multinational setting,[42] and as indicated earlier, there are differing thresholds suggested across the countries in this study. Fourth, with respect to the CEA, there is no commonly accepted threshold at which achieving a specific amount of antibiotic prescribing would be considered cost-effective. It is therefore difficult to reach a conclusion about the cost-effectiveness of the interventions based on an accepted threshold for the analysis. This study did not assess the long-term cost-effectiveness of the interventions under consideration. Because of this, any long-term issues such as change in practice over time were not assessed. Finally, the use of estimates of the costs of antibiotic resistance is problematic given the difficulty of making such estimates.

Comparison with other studies

Other studies have reached similar conclusions about the cost-effectiveness of communication skills[20] and CRP.[20,43] This study therefore adds to the evidence of the potential benefits of CRP and communication skills, but for the first time in a rigorous experimental multinational context in which the interventions have been assessed across a number of European countries. One previous study also concluded that ignoring the cost of antibiotic resistance in economic evaluations could lead to misleading conclusions,[25] a result similar to that found in this study.

Policy implications and implications for future research

The results of this study indicate that communication skills are cost-effective in terms of reducing antibiotic prescribing, and the intervention may offer a cost-effective way of preserving the effectiveness of the available antibiotics in an era when pharmaceutical companies are not successfully channelling enough resources into their development.[2] Training GPs in advanced, relevant communication skills might also help to preserve the effectiveness of new antibiotics if and when they become available. Prescribing antibiotics to patients who are likely to benefit is one of the aims of the UK government's 5 year strategy on antibiotics[44] and the widespread use of advanced, specific communication skills is likely to help achieve this aim since the intervention is both effective and cost-effective in terms of reducing antibiotic prescribing.

Compared with usual care, CRP was also found to be cost-effective. Thus, CRP represents a more cost-effective means of reducing unnecessary antibiotic prescribing compared with usual care. However, this was not as cost-effective as communication skills. NICE in the UK and Nederlands Huisartsen Genootschap in the Netherlands have recommended that point-of-care CRP testing should be considered for patients presenting with symptoms of lower respiratory tract infection if it is not clear whether antibiotics should be prescribed.[45,46] Similarly, Belgium has implemented training in communication skills at the national level. However, if governments and policy makers choose to adopt these interventions, the current cost of implementing them on a large scale needs to be considered. The other issue that needs to be considered is whether the widespread use of testing will 'medicalize' largely self-limiting illnesses (by creating the perception that consulting for a test is necessary to decide whether treatment is necessary) and thus increase consultations, potentially reducing efficiency and limiting the ability to reduce antibiotic prescribing.[47]

The interventions considered in this study (communication skills and CRP) are primarily aimed at reducing the prescription of antibiotics by GPs and a potential question is whether the QALY, which is focused primarily on measuring health gain, should be the main outcome measure for interventions of this type. While withholding antibiotics may lead to a reduction in health in the short run,[20] this may be considered acceptable in the context of prescribing antibiotics for future use, with the subsequent future health gain for the individual and society that it implies. It is therefore suggested that the impact of antibiotic resistance should be accounted for in all economic evaluations of interventions that consider antibiotic use. Our study attempted to account for this by including a cost of resistance in the analysis and this clearly had a significant impact on the results that we obtained. The implication of not accounting for resistance is that policy makers may be led to believe that such an intervention may not provide value for money and not implement interventions that do not appear cost-effective because the resistance costs are excluded. However, there are clear benefits to society when antibiotic prescribing is reduced. This study recommends that future research should focus on how to capture and include the cost of resistance in economic evaluations.

In conclusion, internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care if the cost of antibiotic resistance is accounted for.

Funding

This study was supported by the European Commission Framework Programme 6, the National Institute for Health Research and the Research Foundation Flanders.

Transparency declarations

None to declare.

Supplementary data

Figures S1–S4 and Tables S1 and S2 appear as Supplementary data at *JAC* Online.

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