

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

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29 ***Running title: Cost-effectiveness of internet-based training on antibiotics prescribing***

30

31 **Abstract**

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

38 **Methods:** Economic analyses (cost-utility analysis (CUA) accounting for the cost of  
39 antibiotic resistance and cost-effectiveness analysis (CEA)) were both conducted from a  
40 health care perspective with a time horizon of 28 days alongside a multinational, cluster,  
41 randomised, factorial controlled trial in patients with respiratory tract infections in five  
42 European countries. The primary outcome measures were QALYs and percentage reductions  
43 in antibiotic prescribing. Hierarchical modelling was used to estimate an incremental cost-  
44 per-QALY-gained and an incremental cost-per-percentage-reduction in antibiotic prescribing.

45 **Results:** Overall, the results of both the CUA and CEA showed that training in  
46 communication skills is the most cost-effective. However, excluding the cost of antibiotic

47 resistance in the CUA resulted in usual care being the most cost-effective option. Country-  
48 specific results from the CUA showed that training in communication skills was cost-  
49 effective in Belgium, UK and Netherlands whilst training in CRP was cost-effective in  
50 Poland.

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

54

## 55    **Introduction**

56    Antibiotic resistance is currently one of the world's leading public health concerns, which  
57    places a heavy burden on scarce resources. In the UK, resistant infections such as MRSA are  
58    estimated to cost the National Health Service an additional £1 billion in extra treatments  
59    annually<sup>1</sup> and without a resolution 'superbugs' are estimated to cause more deaths than  
60    cancer by 2050, costing about \$100 trillion globally.<sup>2</sup>

61    The difficulty in determining who will benefit from prescribing, and desire to satisfy patients  
62    demands, appear to be driving inappropriate and over-prescribing of antibiotics by general  
63    practitioners (GPs).<sup>3-5</sup> As well as impacting upon the development of resistance, antibiotic  
64    prescribing is associated with significant costs.<sup>6</sup> The National Health Service in the UK  
65    incurs an annual cost of between \$35(£23) and \$70(£47) million in antibiotic prescription  
66    costs for acute cough/lower respiratory tract infections alone for example.<sup>7</sup> Reducing the  
67    inappropriate and over-prescribing of antibiotics would thus not only help reduce the problem  
68    of antibiotic resistance but also save scarce resources.

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

72    Interventions to reduce prescribing, based on persuasion, have generally been ineffective in  
73    dealing with the problem<sup>12-13</sup>, and so more recent focus has turned to training GPs in  
74    advanced consulting skills and using point of care tests. These have resulted in a change in  
75    their prescribing behaviour,<sup>14,15</sup> with internet-based training programmes providing a  
76    reduction in antibiotic prescribing similar to the standardized methods of training.<sup>16</sup> Such  
77    internet-based training was developed by the Genomics to combat Resistance against  
78    Antibiotics in Community-acquired LRTI in Europe (GRACE) consortium.<sup>4,17-18</sup> The

79 interventions consisted of (i) training GPs in the use of C-reactive protein testing ('CRP'), (ii)  
80 training GPs in communication skills ('communication skills') and (iii) training GPs in *both*  
81 CRP testing and communication skills ('combined').

82 Results from the GRACE INTRO trial indicates that all three of these interventions (i) CRP  
83 (ii) communication skills and (iii) combined are effective in changing GP antibiotic  
84 prescribing behaviour.<sup>19</sup> However, in addition to the effectiveness of these interventions, it is  
85 important to determine whether the interventions provide value for money. One study  
86 conducted a cost-effectiveness analysis using reductions in antibiotic prescribing as an  
87 outcome measure and found all three interventions to be cost-effective compared with usual  
88 care.<sup>20</sup> However, no study has assessed the cost-effectiveness of these interventions in a  
89 multinational setting or estimated the country-specific cost-effectiveness of these  
90 interventions. The aim of this study is to assess the cost-effectiveness of these interventions  
91 across five European countries.

92

93 **Patients and methods**

94 ***Patients and settings***

95 The economic analysis was conducted alongside a multinational, cluster, randomised,  
96 factorial controlled trial in which participating practices were randomised to one of four study  
97 groups (i) CRP, (ii) communication skills, (iii) combined and (iv) usual care.<sup>19</sup> The  
98 perspective adopted was that of the health service, including costs to the health service and  
99 health care cost to the patient. Consenting participants who presented with respiratory tract  
100 infections were recruited from primary care networks across five countries in Europe:  
101 Belgium, Netherlands, Poland, Spain, and the United Kingdom (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.<sup>4,17-19</sup>

## **Data collection**

### **Resource use**

The main sources of resource use information were the case report form (CRF) completed by primary care clinicians at the day of the consultation (day 1), and a diary completed by patients over a four-week period starting at day 1. Resource use data were collected on the following: consultations with health professionals, use of medications (over-the-counter and on 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.<sup>21</sup> These costs were inflated to 2016 prices using the consumer price index for each country.<sup>22</sup> Where unit costs were unavailable, a market basket approach<sup>23</sup> 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

124 groups by estimating an average price from a list of drugs within that group. Table 1 gives a  
125 summary of the various sources of unit costs.

### 126 **Intervention costs**

127 For CRP, capital costs were obtained from the manufacturer (Orion Diagnostica) who quoted  
128 an average cost of €1,200. This cost was then annuitized assuming that the machine has a  
129 lifespan of three years, at an interest rate of 3.5%, and a cost-per-patient estimated. The costs  
130 of the reagents used (€7.45 (£6) per patient) were obtained from the provider (Oxford  
131 Biosystems).

132 With respect to the communication skills, the cost of the booklet given to patients, €0.36  
133 (£0.29), was obtained from study coordinators and converted to country equivalent costs  
134 using the market basket approach.<sup>23</sup> For the combined intervention, the cost of the CRP  
135 machine and the cost of booklet estimated above were included.

136 To estimate the cost of the internet-based training, we obtained information on the amount of  
137 time GPs spent on it in each arm and estimated the total cost of time spent on training. This  
138 value was divided by the number of patients per GP to estimate the cost per patient. GPs  
139 spent on average 26.54 minutes, 37.44 minutes and 39.76 minutes on training in the CRP,  
140 communication skills and combined intervention arms respectively. Information on training  
141 has been published in a previous study.<sup>4</sup> GPs also received face-to-face training in using the  
142 CRP device and a similar approach to that described above was used to estimate a cost per  
143 patient in each arm. All costs were converted to Euros using purchasing power parities. In  
144 addition to presenting costs in Euros, costs were also presented in Pounds Sterling. All costs  
145 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.<sup>24-25</sup> As a result of this, cost of resistance figures generated from a recent study<sup>25</sup> were added to every antibiotic prescription irrespective of the trial arm. The inclusion of these costs was limited to the cost-utility analysis since the outcome for the cost-effectiveness analysis (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.<sup>26</sup> Patients were asked to complete the EQ-5D-3L questionnaire over the entire four 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 Harmonised Tariff<sup>27</sup> and have been validated for use in respiratory disease.<sup>28</sup>

### **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: a cost-utility analysis (CUA; cost per QALY gained) and a cost-effectiveness analysis (CEA; cost per percentage reduction in antibiotic prescribing). Both were carried out on an intention to treat 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.<sup>29</sup> Total healthcare costs over the 4-week period were



170 calculated by multiplying the resource items used by the respective unit cost and summing  
171 over all items. Missing costs and health outcomes were imputed using a multiple imputation  
172 methodology. The technique used was predictive mean matching and the imputation model  
173 included 25 imputed datasets<sup>30</sup>

174 Multilevel modelling, recommended for the economic evaluation of cluster and multinational  
175 trials, was used for data analysis.<sup>31-32</sup> Dependent variables included total cost, QALYs and  
176 antibiotic prescribing. The model controlled for day 1 EQ-5D, gender, age, smoking, sex,  
177 crepitations, wheeze, pulse rate higher than 100 beats per minute, temperature higher than  
178 37.8 degrees Celsius, respiratory rate, blood pressure and duration of cough. These variables  
179 were controlled for in order to adopt a similar approach to the clinical study. To explore  
180 country variation in the cost-effectiveness of the interventions, adjusted country-specific cost-  
181 effectiveness estimates were also obtained using a Bayesian approach.<sup>33</sup> Minimally  
182 informative prior distributions were placed on all model parameters.<sup>34</sup> All analysis was  
183 carried out in STATA 12, Winbugs 14 and R statistical software. Model estimates of the  
184 difference in costs, QALYs and antibiotic prescribing were used to derive an incremental  
185 cost-per-QALY-gained and an incremental cost-per-percentage-reduction in antibiotic  
186 prescribing.

187 For the CUA, we used the NICE recommended threshold of between £20,000 to £30,000  
188 (€24,655 to €36,928) per QALY to judge the cost-effectiveness of the interventions.<sup>35</sup>

189 A 'Within the table' analysis was adopted to account for the factorial nature of the trial.<sup>36-37</sup>  
190 This method assumes that the interventions are not independent i.e. the costs and effects of  
191 communication skills are influenced by the inclusion of CRP testing and vice-versa. This  
192 approach, which considers each treatment option individually, was used for the base-case  
193 analysis. All interventions were ordered in terms of increasing cost, for costs, QALYs and  
194 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 intervention).<sup>38</sup> In addition, all interventions were compared to 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 (£20,000 (€24,655) to £30,000 (€36,928) per QALY gained.<sup>35</sup> There is no explicit threshold in the Netherlands, Belgium, Spain and Poland. However, a value of €20,000 per QALY gained is often used in the Netherlands,<sup>39</sup> €35,000 per QALY gained has been used to inform decision making in Belgium<sup>40</sup> and in Spain, it has been suggested that the threshold value should lie between €22000 and €25000 per QALY gained.<sup>41</sup> These values were therefore used to represent cost-effectiveness thresholds in the countries mentioned. No threshold value was identified in Poland.

Second, to further explore 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.

218     **Results**

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

222     **Resource use and costs**

223     A breakdown of resource use items is presented in Table 2. Compared to the other  
224     interventions, visits to the GP and hospital admissions were lower in the usual care arm.  
225     Visits to the GP were highest in the CRP group, whilst visits to the nurse were highest in the  
226     communication skills group. As was expected, those in the CRP and combined intervention  
227     groups had more CRP tests performed. Approximately 59% of participants in the usual care  
228     arm had an antibiotic prescribed compared to approximately 34% in the combined  
229     intervention arm. Costs associated with resource use items are presented in Table 3. GP costs  
230     were highest in the CRP group whilst nurse costs were highest in the communication skills  
231     group. Costs associated with over-the-counter medication were highest in the usual care arm.

232     **Outcomes**

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

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## 240 **Cost-utility analysis**

241 The CUA results indicate that overall, communication skills is the most cost-effective  
 242 intervention since it dominated all other interventions (Table 5). Compared to usual care,  
 243 both communication skills and CRP were dominant whilst the combined intervention was  
 244 dominated. Country-specific estimates showed that communication skills was the most cost-  
 245 effective intervention in Belgium, UK and Netherlands. CRP is only cost-effective in  
 246 Netherlands if the threshold is above €27,000 (£21,903) per QALY gained. CRP is cost-  
 247 effective in Poland whilst usual care is cost-effective in Spain (Table 5 and Figures 1 and 2).

## 248 **Cost-effectiveness analysis**

249 With respect to the CEA (percentage reduction in antibiotic prescribing as an outcome),  
 250 communication skills was associated with an ICER of €68.08 (£55.23) per percentage  
 251 reduction in antibiotic prescribing when compared to usual care. The ICER for CRP  
 252 compared to communication skills was €176.53 (£143.20) per percentage reduction in  
 253 antibiotic prescribing and the ICER for the combined intervention compared to CRP was  
 254 €338.89 (£274.90) per percentage reduction in antibiotic prescribing (Table 6). Compared to  
 255 usual care, ICERs ranged from €68.08 (£55.23) per percentage reduction in antibiotic  
 256 prescribing with communication skills to €126.21 (£102.38) per percentage reduction in  
 257 antibiotic prescribing with the combined intervention. Country-specific estimates show that  
 258 CRP is the most cost-effective intervention in Belgium. In the Netherlands, CRP is cost-  
 259 effective if society is willing to pay around €72 (£58) per percentage reduction in antibiotic  
 260 prescribing. On the other hand, communication skills is the most cost-effective in Poland,  
 261 Spain and the UK (Table 6 and Figures S1 and S2).

262

## 263    **Sensitivity analysis**

264    In terms of comparing the results to country-specific cost-effectiveness thresholds,  
265    communication skills was cost-effective in Belgium, Netherlands and UK, CRP was cost-  
266    effective in Poland and Usual care was cost-effective in Spain (Table S1).

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

273

## 274    **Discussion**

### 275    **Summary of main findings**

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

## 286    **Strengths and limitations of the study**

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

294    There are also a number of limitations. First, this study is conducted alongside a  
295    multinational, cluster randomised, factorial controlled trial, which presents additional  
296    complexities with respect to the analysis of the data. The factorial nature has the effect of  
297    reducing the sample size for any of the interventions on its own and therefore increasing the  
298    degree of uncertainty in the economic data. In this study, randomisation took place at the  
299    cluster/practice level whilst health economics outcomes such as QALYs were measured at the  
300    level of the individual. However, this has been addressed using methods that account for the  
301    hierarchical nature of the data. Second, assumptions were required to estimate country-  
302    specific unit costs where these were not available. Third, with respect to the CUA, since there  
303    is no European wide cost-effectiveness threshold, this study relied on the UK threshold to  
304    judge the cost-effectiveness of interventions. Other studies have also noted problems with  
305    regards to the choice of cost-effectiveness threshold in a multinational setting.<sup>42</sup> Cost-  
306    effectiveness thresholds used in the Netherlands and Spain are €20,000 and €24,000 per  
307    QALY gained respectively. Fourth, with respect to the CEA, there is no commonly accepted  
308    threshold at which achieving an amount of antibiotic prescribing would be considered cost-  
309    effective. It is therefore difficult to reach a conclusion about the cost-effectiveness of the  
310    interventions based on an accepted threshold for the analysis. This study did not assess the

long-term cost-effectiveness of the interventions under consideration. As a result of this, any long-term issues such as change in practice over time was 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<sup>20</sup> and CRP.<sup>20,43</sup> This study therefore adds to the evidence about the potential benefits of CRP and communication skills, but for the first time in a rigorous experimental multinational context where 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,<sup>25</sup> a result which is similar to what was found in this study.

**Policy implications and implications for future research**

The results of this study indicate that communication skills is 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 where pharmaceutical companies are not successfully channelling enough resources into their development.<sup>2</sup> 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 five-year strategy on antibiotics<sup>44</sup> 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 to usual care, CRP was also found to be cost-effective. Thus, CRP represents a more cost-effective means of reducing unnecessary antibiotic prescribing compared to usual care. However, this was not as cost-effective as communication skills. The National Institute for Health and Care Excellence (NICE) in the UK and Nederlands Huisartsen Genootschap (NHG) in the Netherlands have recommended that point of care CRP testing should be considered for patients presenting with symptoms of LRTI if it is not clear whether antibiotics should be prescribed.<sup>45-46</sup> 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 ‘medicalise’ 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.<sup>47</sup>

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. Whilst withholding antibiotics may lead to a reduction in health in the short-run,<sup>20</sup> 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 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.

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**Transparency declarations**

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**TABLE 1: Source of valuation data and country contribution to sample size**

	Belgium	Netherlands	Poland	Spain	UK
<b>GP Visits</b>	1	1	1	1	2
<b>Nurse Visits</b>	N/A	1	1	1	2
<b>Out of hours GP</b>	9	9	9	9	2
<b>Walk in centre</b>	N/A	1	1	1	1
<b>Hospital Admissions</b>	1	1	1	1	8
<b>Investigations</b>	9	9	9	9	8
<b>Medication</b>	6	5	1,9	3,1	4
<b>Contribution to sample size</b>	318 (7.5%)	329 (7.7%)	1419 (33.3%)	1318 (30.9%)	880 (20.6%)

1= Previous study, 2= Curtis L ([www.pssru.ac.uk](http://www.pssru.ac.uk)), 3= [www.vademecum.es](http://www.vademecum.es), 4= British National Formulary ([www.bnf.org](http://www.bnf.org)), 5= Dutch healthcare insurance board ([www.medicijnkosten.nl](http://www.medicijnkosten.nl)), 6= [www.bcfi.be](http://www.bcfi.be), 7= [www.riziv.fgov.be](http://www.riziv.fgov.be), 8= NHS Reference costs 9= Market basket approach



TABLE 2: Mean (SD) Resource use for complete case analysis

	Usual care (n=515)	CRP no Comm (n=660)	Comm no CRP (n=740)	CRP comm (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 hours GP visits	0.015 (0.271)	0.006 (0.095)	0.023 (0.182)	0.016 (0.163)
SECONDARY CARE VISTIS [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%)

**TABLE 3: Costs (Complete case analysis) (€)**

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

<sup>a</sup> 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 Comm (n=660)	Comm no CRP (n=740)	CRP comm (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			
Antibiotic Prescribing	0.596 (0.491)	0.336 (0.473)	0.409 (0.492)	0.341 (0.474)

TABLE 5: Overall and country-specific cost-effectiveness (Cost-utility analysis)

	Cost <sup>a</sup>	QALY	ICER	ICER (compared to UC)
<b>Overall (n=4264)</b>				
<b>CRP&amp;Comm</b>	94.36	0.0648	Dominated by Comm	Dominated by UC
<b>Usual care</b>	92.46	0.065	Dominated by Comm	N/A <sup>f</sup>
<b>CRP</b>	87.41	0.0651	Dominated by Comm	Dominates UC
<b>Comm</b>	83.21	0.0651	N/A <sup>f</sup>	Dominates UC
<b>Belgium (n=318)</b>				
<b>Comm</b>	93.28	0.0651	3450 <sup>c</sup>	7120 <sup>b</sup>
<b>CRP&amp;comm</b>	92.59	0.0649	7343 <sup>c</sup>	8038 <sup>b</sup>
<b>CRP</b>	87.45	0.0642	12900 <sup>b</sup>	12900 <sup>b</sup>
<b>Usual care</b>	86.16	0.0641	N/A <sup>f</sup>	N/A <sup>f</sup>
<b>Netherlands (n=329)</b>				
<b>CRP&amp;Comm</b>	84.99	0.0649	Dominated by CRP	Dominated by UC
<b>Usual care</b>	75.52	0.065	Dominated by CRP	N/A <sup>f</sup>
<b>CRP</b>	73.41	0.0656	27,186 <sup>c</sup>	Dominates UC
<b>Comm</b>	54.38	0.0649	N/A <sup>f</sup>	N/A
<b>Poland (n=1419)</b>				
<b>Usual care</b>	143.41	0.0663	49129 <sup>c</sup>	N/A <sup>f</sup>
<b>Comm</b>	114.37	0.0656	Dominated by CRP	41486 <sup>g</sup>
<b>CRP&amp;Comm</b>	110.95	0.0652	Dominated by CRP	29509 <sup>g</sup>
<b>CRP</b>	109.02	0.0656	N/A <sup>f</sup>	49129 <sup>g</sup>
<b>Spain (n=1318)</b>				
<b>CRP&amp;Comm</b>	78.71	0.0648	Dominated by Usual care	Dominated by UC
<b>CRP</b>	70.86	0.0656	Dominated by Usual care	Dominated by UC
<b>Usual care</b>	66.46	0.0659	1000 <sup>d</sup>	N/A <sup>f</sup>
<b>Comm</b>	65.86	0.0653	N/A <sup>f</sup>	1000 <sup>g</sup>
<b>UK (n=880)</b>				
<b>CRP&amp;Comm</b>	106.57	0.0641	Dominated by Comm	25050 <sup>b</sup>
<b>Usual care</b>	101.56	0.0639	Dominated by Comm	N/A <sup>f</sup>
<b>CRP</b>	98.75	0.0645	Dominated by Comm	Dominates UC
<b>Comm</b>	98.05	0.0648	N/A <sup>f</sup>	Dominates UC

<sup>a</sup> Costs includes the costs associated with antibiotic resistance <sup>b</sup> Compared to usual care <sup>c</sup> Compared to CRP training <sup>d</sup> Compared to communication skills training <sup>e</sup> Compared to training in both CRP testing and communication skills <sup>f</sup> not applicable, this is the reference case <sup>g</sup> ICER value represents a comparison of usual care versus the respective intervention since the ICER generated from a comparison of the respective intervention with usual care represents a willingness to accept a loss in benefit, rather than a willingness to pay for a gain in benefit. UC=usual care

**TABLE 6: Overall and country-specific cost-effectiveness (Cost-effectiveness analysis)**

	<b>Cost<sup>a</sup></b>	<b>Outcome</b>	<b>ICER</b>	<b>ICER (compared to UC)</b>
<b>Overall (n=4264)</b>				
<b>CRP + Comm</b>	60.32	0.8003	338.8889 <sup>b</sup>	126.209 <sup>b</sup>
<b>CRP</b>	49.34	0.7679	176.5343 <sup>d</sup>	95.44643 <sup>b</sup>
<b>Comm</b>	39.56	0.7125	68.8019 <sup>b</sup>	68.8019 <sup>b</sup>
<b>Usual care</b>	27.96	0.5439	N/A <sup>f</sup>	N/A <sup>f</sup>
<b>Belgium (n=318)</b>				
<b>CRP + Comm</b>	62	0.8216	323.4528 <sup>b</sup>	234.3308 <sup>b</sup>
<b>CRP</b>	52.07	0.7909	26.85393 <sup>d</sup>	203.7946 <sup>b</sup>
<b>Comm</b>	49.68	0.7019	26350 <sup>b</sup>	26350 <sup>b</sup>
<b>Usual care</b>	33.81	0.7013	N/A <sup>f</sup>	N/A <sup>f</sup>
<b>Netherlands (n=329)</b>				
<b>CRP + Comm</b>	58.47	0.8409	1929.73 <sup>c</sup>	126.6091 <sup>b</sup>
<b>CRP</b>	44.19	0.8335	72.67583 <sup>b</sup>	72.67583 <sup>b</sup>
<b>Usual care</b>	26.21	0.5861	Dominated by Comm	N/A <sup>f</sup>
<b>Comm</b>	26	0.7894	N/A <sup>f</sup>	Dominates UC
<b>Poland (n=1419)</b>				
<b>CRP + Comm</b>	61.3	0.7366	189.8754 <sup>c</sup>	81.94658 <sup>b</sup>
<b>CRP</b>	49.11	0.6724	92.14953 <sup>d</sup>	55.44933 <sup>b</sup>
<b>Comm</b>	44.18	0.6189	46.00962 <sup>b</sup>	46.00962 <sup>b</sup>
<b>Usual care</b>	34.61	0.4109	N/A <sup>f</sup>	N/A <sup>f</sup>
<b>Spain (n=1318)</b>				
<b>CRP + Comm</b>	47.5	0.8044	Dominated by CRP	162.4065 <sup>b</sup>
<b>CRP</b>	39.53	0.8156	145.0094 <sup>d</sup>	100.5685 <sup>b</sup>
<b>Comm</b>	31.83	0.7625	78.13688 <sup>b</sup>	78.13688 <sup>b</sup>
<b>Usual care</b>	23.61	0.6573	N/A <sup>f</sup>	N/A <sup>f</sup>
<b>UK (n=880)</b>				
<b>CRP + Comm</b>	74.46	0.8066	202.439 <sup>c</sup>	112.511 <sup>b</sup>
<b>CRP</b>	59.52	0.7328	170.1754 <sup>d</sup>	95.16466 <sup>b</sup>
<b>Comm</b>	49.82	0.6758	82.03317 <sup>b</sup>	82.03317 <sup>b</sup>
<b>Usual care</b>	23.11	0.3502	N/A <sup>f</sup>	N/A <sup>f</sup>

<sup>a</sup> Costs excludes the costs associated with antibiotic resistance <sup>b</sup> Compared to usual care <sup>c</sup> Compared to CRP training <sup>d</sup> Compared to communication skills training <sup>e</sup> Compared to training in both CRP testing and communication skills <sup>f</sup> not applicable, this is the reference case UC=usual care

Figure 1: Cost-effectiveness plane (cost-utility analysis)

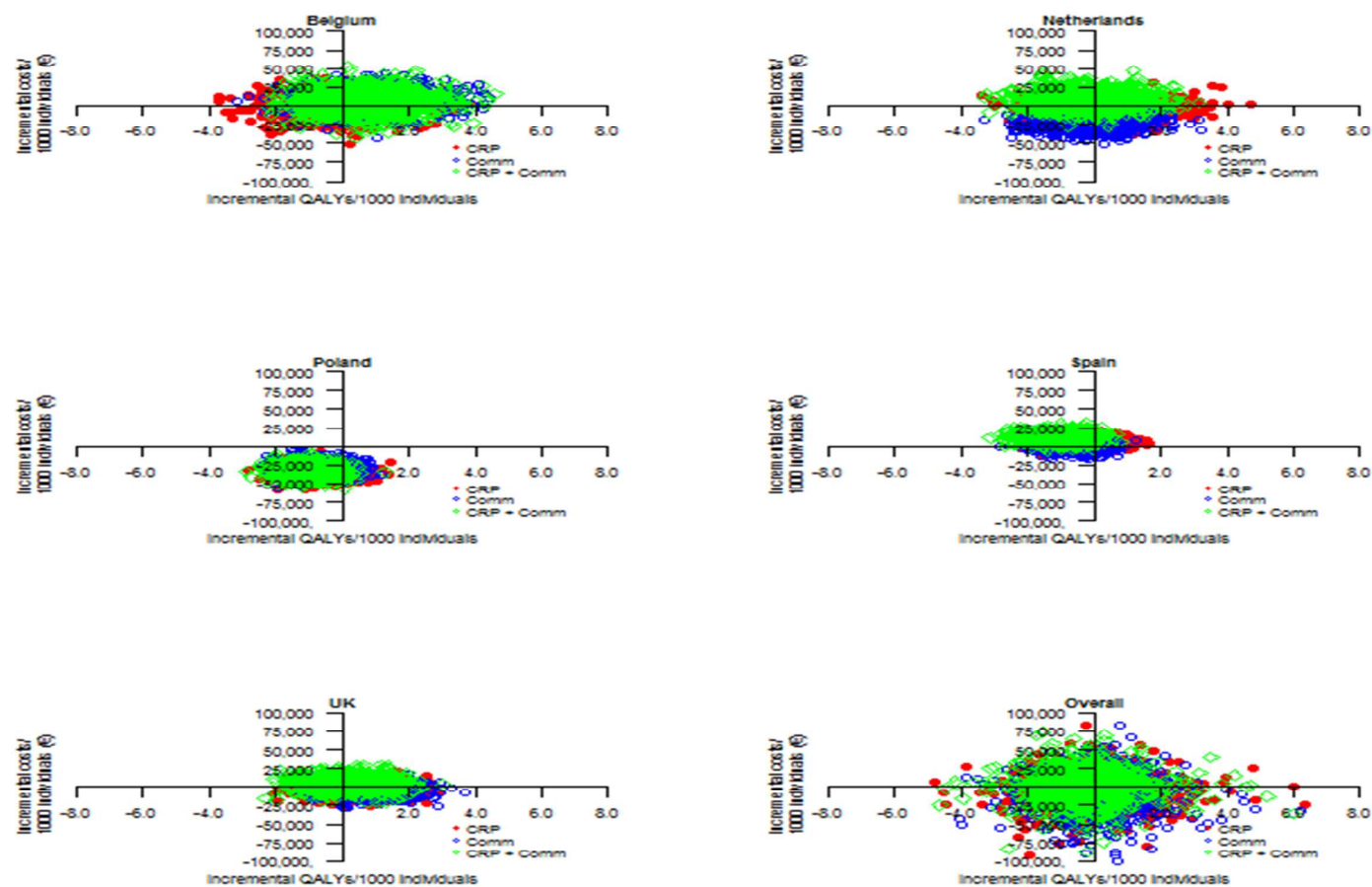
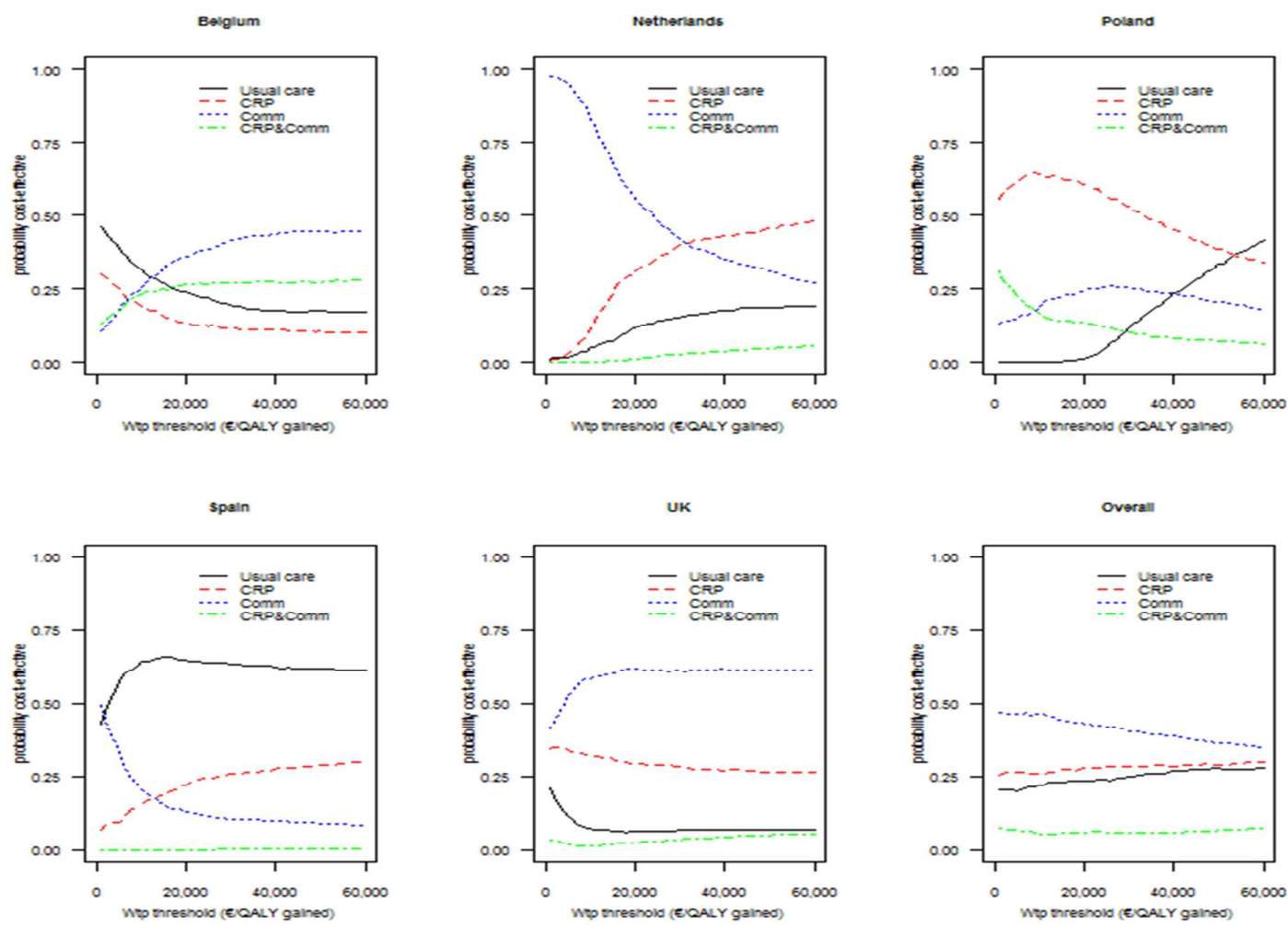


Figure 2: Cost-effectiveness acceptability frontier (cost-utility analysis)







**Table S1: Cost-effectiveness based on country-specific thresholds**

<b>Country</b>	<b>Country-specific threshold</b>	<b>Intervention most cost-effective at country-specific threshold</b>
Belgium	Explicit threshold is not used. However, a value of €35,000 has been used to inform decision making	Communication skills most cost-effective
Netherlands	€20,000 per QALY gained	Communication skills most cost-effective
Spain	An explicit threshold is not used. However, a recent study suggests that it should lie between €22,000 and €25,000 per QALY	Usual care most cost-effective
Poland	Explicit threshold not used	CRP most cost-effective
UK	£20,000 to £30,000 per QALY	Communication skills most cost-effective

**Table S2: Sensitivity analysis (Cost-utility analysis excluding cost of resistance)**

	Cost	Outcome	ICER
<b>Overall (n=4264)</b>			
CRP&Comm	60.08	0.0648	Dominated by comm
CRP	48.82	0.0651	Dominated by comm
Comm	39.64	0.0651	114,700 <sup>b</sup>
Usual care	28.17	0.065	N/A <sup>f</sup>
<b>Belgium (n=318)</b>			
CRP&Comm	61.95	0.0649	Dominated by comm
CRP	52.08	0.0642	Dominated by comm
Comm	49.58	0.065	17578 <sup>b</sup>
Usual care	33.76	0.0641	N/A <sup>f</sup>
<b>Netherlands (n=329)</b>			
CRP&Comm	58.32	0.0648	Dominated by CRP
CRP	44.06	0.0656	29533 <sup>b</sup>
Usual care	26.34	0.065	2200 <sup>d</sup>
Comm	26.12	0.0649	N/A <sup>f</sup>
<b>Poland (n=1419)</b>			
CRP&Comm	61.33	0.0653	Dominated by UC
CRP	49.13	0.0657	Dominated by UC
Comm	44.01	0.0656	Dominated by UC
Usual care	34.57	0.0663	N/A <sup>f</sup>
<b>Spain (n=1318)</b>			
CRP&Comm	47.46	0.0648	Dominated by UC
CRP	39.52	0.0656	Dominated by UC
Comm	31.82	0.0653	Dominated by UC
Usual care	23.73	0.0658	N/A <sup>f</sup>
<b>UK (n=880)</b>			
CRP&Comm	74.38	0.0641	Dominated by comm
CRP	59.34	0.0645	Dominated by comm
Comm	49.82	0.0648	29657 <sup>b</sup>
Usual care	23.13	0.0639	N/A <sup>f</sup>

<sup>a</sup> Costs excludes the costs associated with antibiotic resistance <sup>b</sup> Compared to usual care <sup>c</sup> Compared to CRP training <sup>d</sup> Compared to communication skills training <sup>e</sup> Compared to training in both CRP testing and communication skills <sup>f</sup> not applicable, this is the reference case UC=usual care

Figure S1: Cost-effectiveness plane (Cost-effectiveness analysis)

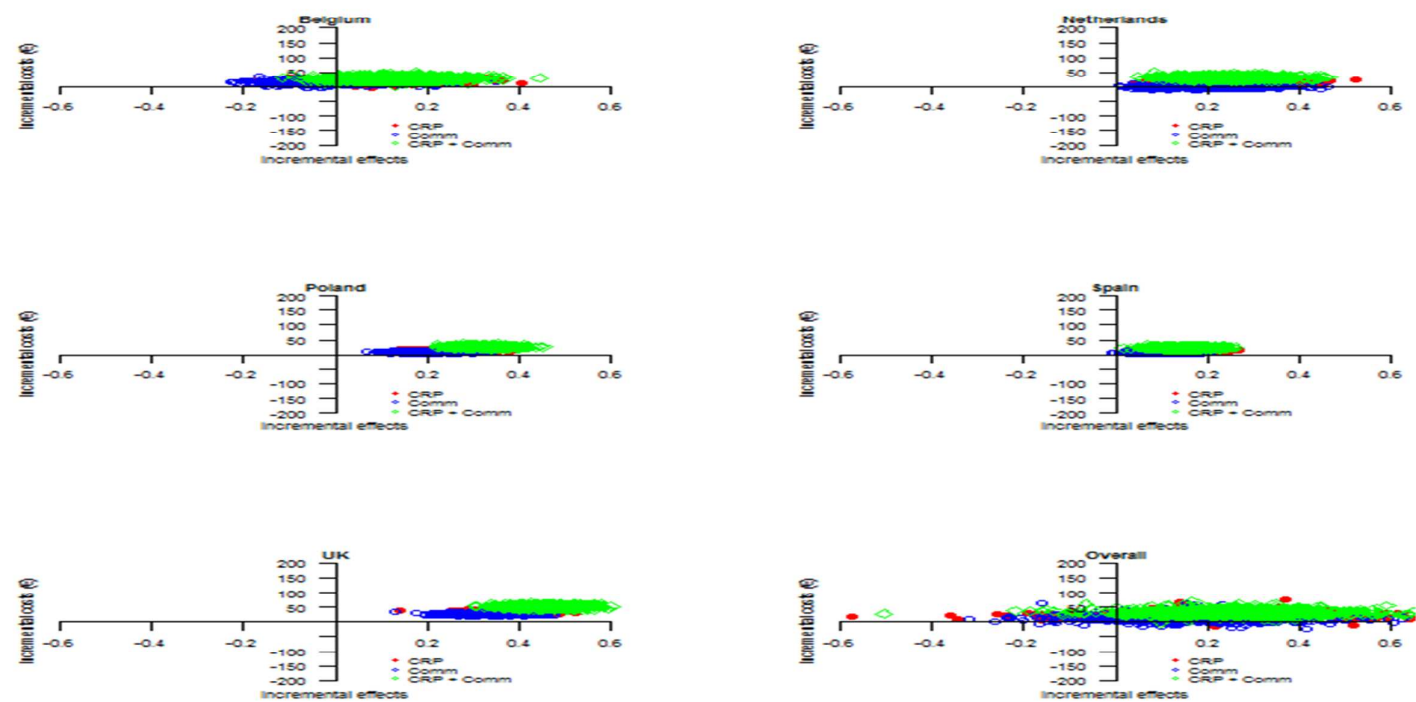


Figure S2: Cost-effectiveness acceptability curve (Cost-effectiveness analysis)

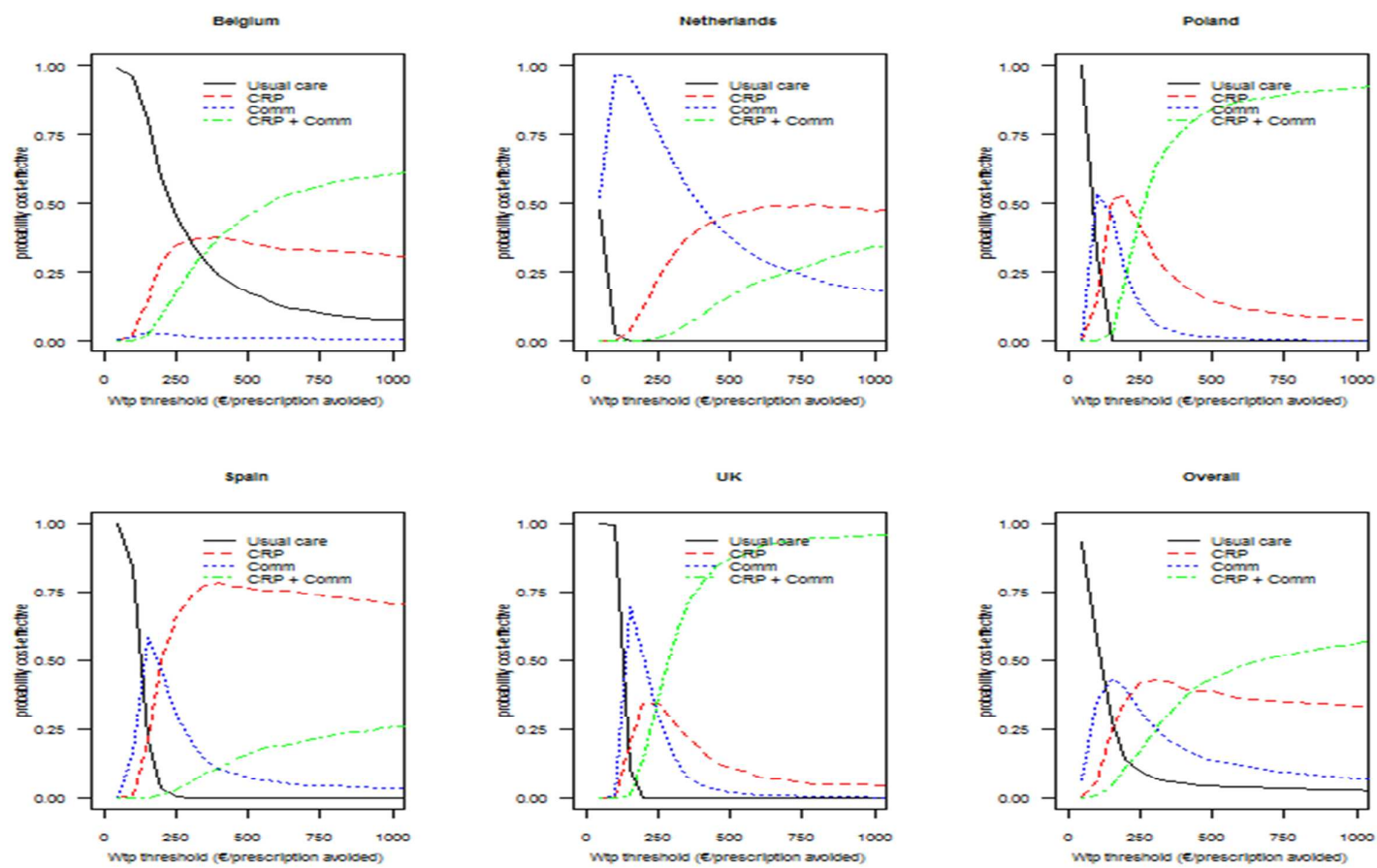


Figure S3: Sensitivity analysis (Cost-effectiveness plane excluding cost of resistance)

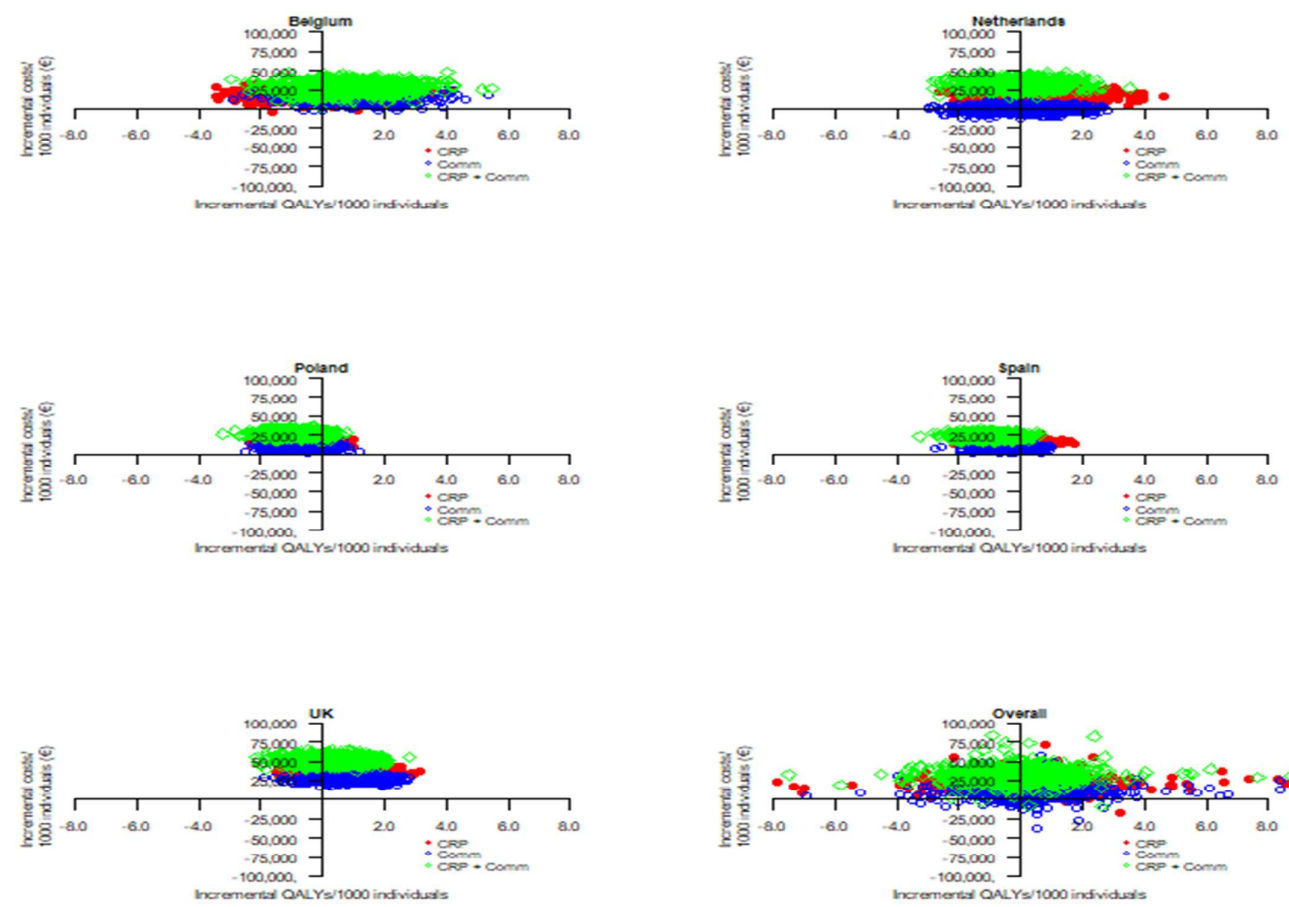


Figure S4: Sensitivity analysis (Cost-effectiveness acceptability frontier excluding the cost of resistance)

