THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix 1

Development of enhanced communication skills and booklet intervention

We developed brief internet based training modules using LifeGuide software, using both prior theory and building on previous interventions: internet training and booklet-based format and content for sharing with patients[1;2] and the STAR model for communication training.[3] The materials were piloted in every country and modified according to feedback from interviews with physicians and patients in each country.[4] The booklet was endorsed by the European Antibiotic Awareness Day coordinated by the European Centre for Disease Prevention and Control. To reinforce the communication training group practices were asked to appoint a lead physician who organised a structured meeting where prescribing issues were discussed. The experience of using the patient booklet, and recent cases of LRTI were discussed (participants were asked to document presentation, management and their reflection on consultations for up to 10 recent cases). The pragmatic nature of this study required flexibility in arranging meetings: sometimes meetings in practices were not possible (for example with many single handed practices in Belgium, where meetings between practices were encouraged), and sometimes there was strong preference to have centrally organised meetings (e.g. Poland).

Development of CRP intervention

The text for guidance on the use of CRP was developed based on systematic review evidence[5;6] and the previous IMPAC3T trial[7] and led by Jochen Cals, Hasse Melbye and Paul Little with input from the Network leads and collaborators.

GRACE INTRO web-based training module

The training modules consisted of up to three sections; an introduction (seen by Communication, CRP, and Combined groups) training in communication skills and use of a patient booklet (seen by Communication and Combined groups) and training in using a C-reactive protein point of care (CRP) test (seen by CRP and Combined groups).

1. Introduction

This section presented information describing the problem of antibiotic resistance for healthcare, its relation to antibiotic use, the medicalization of self-limiting illness creating the 'vicious circle' of encouraging re-consultation during subsequent episodes, and the difficulties in determining what patients presenting with LRTI in primary care may benefit from antibiotic treatment. The introduction discusses common concerns Physicians have when deciding whether or not to prescribe antibiotics and explains how physician training in communication skills and/or physician use of CRP point of care testing could potentially assist in the consultation.

C-Reactive Protein (CRP) point of care testing Training

The aim of the training in the use of point of care CRP was to inform physicians about how a point of care CRP result could assist in differentiating self-limiting from serious LRTI and making antibiotic prescribing decisions for LRTI. Physicians were shown how to interpret specific CRP values and how to use the test in their consultations.

The training starts by giving information on the background of CRP point of care testing and providing evidence to support its use in primary care for LRTI. Physicians were encouraged to use the test to differentiate between serious and self-limiting LRTIs. Common misconceptions were discussed. The module stresses that the test cannot distinguish between viral and bacterial infections in primary care and that it is not a stand-alone test, but should always be used alongside history taking and a physical examination.

Relevant cut off points were provided (see Table below). As part of dealing with values in the intermediate range (CRP 20-100 mg/l) delayed prescribing was discussed and presented as an option if illness severity combined with CRP did not warrant immediate antibiotics.

Guidance available to physicians on the cut off points used for CRP values and the relevant treatment options.

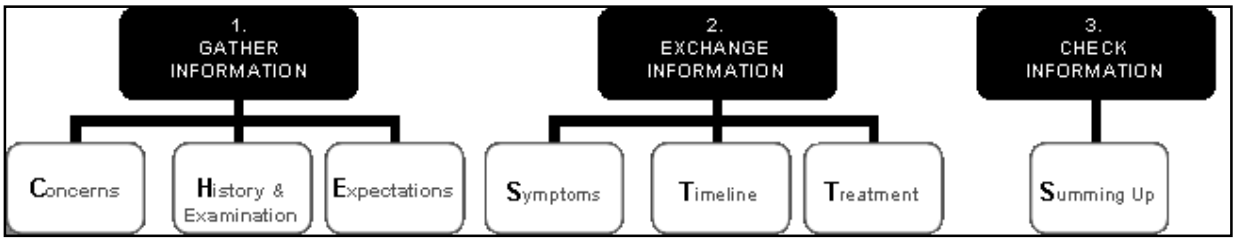
CRP ≤ 20 mg/l
▪ Self-limiting LRTI ▪ Withhold antibiotics
CRP 21-50 mg/l
▪ Majority of patients have self-limiting LRTI ▪ Assessment of signs, symptoms, risk factors and CRP is important ▪ Withhold antibiotics, in most cases
CRP 51-99 mg/l
▪ Assessment of signs, symptoms, risk factors and CRP is crucial ▪ Withhold antibiotics in the majority of cases and consider delayed antibiotics in the minority of cases.
CRP ≥ 100 mg/l
▪ Severe infection ▪ Prescribe antibiotics

The last section of the CRP training included two short video clips which showed the CRP test procedure, including how to take blood by using a finger prick, running the device and obtaining a result within 4 minutes. The training ends with a page summarising the key points of using point of care CRP testing in LRTI in primary care.

Enhanced Communication skills training and use of patient information booklet

The aim of the communication skills training was to facilitate physicians in using specific patient centred communication skills in the acute cough consultation, using three elements of an effective consultation: to gather information about patient beliefs and expectations, exchange information and agree management, and check patient understanding and concordance. Each of these has steps for the physician to follow (see Figure 1 below). The acronym of these seven steps is CHESTTS which helps ease of recollection in the English version of GRACE INTRO.

Furthermore, it was outlined how a patient booklet could be helpful in the consultation (with a focus on exchanging information and shared decision-making). The web pages presented information, backed by research evidence, to explain how a booklet could help to address patient concerns and maintain patient satisfaction. Physicians were encouraged to make use of tick boxes in the booklet to highlight specific sections which were relevant to individual patients in order to personalise the information. An online discussion forum was also provided for participating physicians but was used by relatively few.



A diagram showing the three elements of an effective consultation and the steps involved in each of these to be carried out by a GP.

The last section of the communication skills training presented eight short video clips to give examples of how each of the seven tasks above could be achieved in the consultation. For 'Treatment' two videos were displayed; one giving advice about the appropriate use of antibiotics and one video clip giving advice on self-management of acute cough. The video clips were shot in a physician office with a qualified physician giving advice to an actor playing the role of a patient with acute cough. The training ends with a page summarising the key points of communication skills training module.

Details of responses in post intervention survey

The sample who completed the post-intervention survey comprised 147 men and 199 women with a mean age of 42.3 (s.d. 8.9), who had practised for a mean of 19.2 (s.d. 9.6) years. Most respondents reported completing the website training alone (189/230, 82.2%), but the remainder completed it as a group. The mean time members of the intervention groups spent on the website was 35.5 mins, with considerable variation (s.d. 28.1 mins). Time spent on the website differed between groups ($F(2,310) = 6.05$, $p = .003$). The CRP group had the shortest duration (26.5 mins, s.d. 20.5), differing significantly on post hoc group comparisons from the communication group (37.4 mins, s.d. 28.9) and combined group (mean = 39.8 mins, s.d. 30.5). Of the 159 Physicians who responded to the post-intervention question about how their seminar was organised, most took part in a practice based seminar with multiple Physicians (70/159; 44.03%), some engaged in self-reflection alone i.e. they did not do a seminar (28/159; 17.61%), a minority of practices met together (44/159; 27.67%) and the remaining practices held a multi-practice teleconference.

Variance of Random effects for GP, practice and Network.

Most of the variance in random effects was due to GP and practice while network contributed very little: the model with GP, practice and network was not significantly better than GP and practice model (LR test p=0.960). The ICCs for antibiotic prescribing were 0.13 for physicians 0.13, 0.05 for Practices, and 0.001for Networks when controlling for antibiotic prescribing.

	***Single level model not controlling for antibiotic prescribing**	***Three level model not controlling for antibiotic prescribing**	***Three level model also controlling for Antibiotic Prescribing at baseline**	**ICC not controlling for baseline antibiotic prescribing**	**ICC controlling for baseline antibiotic prescribing**
GP	1.56	0.68	0.5	0.15	0.13
Practice	1.33	0.38	0.18	0.08	0.05
Network	0.166	0.17	0.004	0.04	0.001

*Single level model: GP only, Practice only, and Network only;

Three level model: GP, Practice and Network in model

Individual group model whole trial cohort: Characteristics of individual group (n (%) or mean (SD))

	Follow-up period				Baseline period
	Control	CRP	Communication	Both	
Gender (female)	553/870 (64%)	670/1062 (63%)	758/1170 (65%)	753/1162 (65%)	4218/6771 (62%)
Age	50.5 (17.4)	51.1 (17.7)	51.3 (17.1)	50.9 (17.2)	49.6 (18.6)
Non-smoker (past or current)	471/870 (54%)	570/1062 (54%)	596/1170 (51%)	577/1162 (50%)	N/A
Illness duration prior to the index consultation (days)	7.6 (6.1)	8.3 (7.8)	7.6 (6.0)	7.3 (6.4)	7.8 (7.2)
Respiratory rate (breaths/minute)	17.2 (5.7)	17.4 (5.8)	16.9 (4.9)	17.4 (5.5)	N/A
Temperature (degrees C)	36.7 (0.9)	36.7 (0.8)	36.8 (0.9)	36.8 (0.9)	N/A
Lung disease (COPD or Asthma)	128/838 (15%)	205/1043 (20%)	213/1154 (18%)	217/1152 (19%)	N/A
*Mean severity score (all symptoms)	2.0 (0.5)	2.0 (0.6)	1.9 (0.5)	2.0 (0.5)	1.8 (0.5)
*Mean severity of cough	3.1 (0.8)	3.0 (0.8)	3.1 (0.8)	3.2 (0.7)	3.0 (0.8)
Sputum production	689/866 (80%)	846/1059 (80%)	976/1172 (83%)	947/1162 (82%)	5355/6771 (79%)

* Mean severity symptoms rated 1='no problem', 2= 'mild problem',
3='moderate problem', 4 ='severe problem'

Individual group model whole trial cohort: Effectiveness of intervention in individual groups

	Control	**CRP**	**Communication**	**Both**
Crude percentage antibiotic prescribed	58% (508/870)	35% (368/1062)	41% (476/1170)	32% (366/1162)
Basic risk ratio	1.00	0.54 (0.40, 0.68; <0.001)	0.69 (0.54, 0.85; <0.001)	0.46 (0.35, 0.60; <0.001)
Adjusted risk ratio	1.00	0.53 (0.36, 0.74; <0.001)	0.68 (0.50, 0.89; 0.003)	0.38 (0.25, 0.55; <0.001)

New or worsening symptoms				
Crude percentage	12% (102/861)	20% (207/760)	23% (259/1101)	17% (192/1141)
Basic risk ratio	1.00	1.91 (1.26, 2.77;p=0.003)	2.22 (1.49, 3.15; p<0.001)	1.49 (0.96,2.22; p=0.069)
Adjusted risk ratio	1.00	1.75 (1.12, 2.60;p=0.014)	2.12 (1.41,3.02; p<0.001)	1.54 (0.99, 2.29; p=0.056)
Diary Symptom score (for days 2-4)				
Crude mean	**1.75 (0.95)**	**1.70 (1.00)**	**1.81 (1.02)**	**1.86 (1.02)**
Basic mean difference		**-0.01 (-0.017,0.144; p=0.892)**	**0.09 (-0.06, 0.24;p=0.252)**	**0.08 (-0.07,0.23; p=0.308)**
Adjusted mean difference		**0.01 (-0.12,0.15; p=0.904)**	**0.06 (-0.07,0.20; p=0.357)**	**0.08 (-0.05,0.22; p=0.223)**
Resolution of moderately bad symptoms				
Median (IQR)	**5 (3,7)**	**5 (3,8)**	**6 (3,10)**	**6 (3,10)**
Basic Hazard ratio	**1.00**	**0.97 (0.82, 1.15; p=0.728)**	**0.85 (0.72, 1.00; p=0.051)**	**0.86 (0.73, 1.01; p=0.072)**
Adjusted Hazard ratio	**1.00**	**0.87 (0.74, 1.03; p=0.114)**	**0.79 (0.67, 0.92; p=0.004)**	**0.77 (0.65, 0.91; p=0.002)**

Factorial and Individual group results for LRTI and URTI subgroups

There was no significant difference between patients with LRTI and URTI (interaction term for antibiotic prescribing between RTI and CRP group 1.15 (p=0.569) and 1.51 (p=0.851) between RTI type and communication group) but since the power to assess interactions was limited the individual results for LRTI and other RTIs are shown below.

LRTI Factorial analysis

		Control for CRP	**CRP**	**Control for Communication**	**Communication**
Antibiotics Prescribed	**Crude percentage**	51% (834/1625)	35% (620/1773)	48% (733/1535)	39% (721/1863)
	Basic risk ratio	1.00	0.57 (0.46, 0.69; p<0.001)	1.00	0.74 (0.61, 0.88; p=0.001)
	Adjusted risk ratio	1.00	0.53 (0.39, 0.68; p<0.001)	1.00	0.66 (0.51, 0.84; p<0.001)
New or worse symptoms	**Crude percentage**	20% (305/1556)	20% (342/1721)	18% (265/1489)	21% (382/1788)
	Basic Risk Ratio (	1.00	1.04 (0.79, 1.36; p=0.766)	1.00	1.24 (0.94, 1.60; p=0.125)
	Adjusted risk ratio	1.00	1.04 (0.77, 1.37; p=0.790)	1.00	1.28 (0.97, 1.66; p=0.086)
Diary Symptom score (for days 2-4)	**Crude mean**	1.83 (0.03)	1.82(0.03	1.77 (0.03)	1.88(0.03)
	Basic mean difference		-0.03 (-0.15, 0.09; p=0.617)		0.10 (-0.02, 0.22; p=0.109)
	Adjusted mean difference		0.01 (-0.08, 0.11; p=0.782)		0.06 (-0.04, 0.16; p=0.234)
Resolution of moderately bad symptoms	***Crude median (IQR)***	*5 (3,9)*	*6 (3,9)*	*5 (3,8)*	*6 (3,10)*
	Basic Hazard ratio)	*1.00*	*0.99 (0.87, 1.12; p=0.829)*	*1.00*	*0.88 (0.77, 0.99; p=0.033)*
	Adjusted Hazard ratio	*1.00*	*0.92 (0.81, 1.03; p=0.157)*	*1.00*	*0.86 (0.76, 0.97; p=0.014)*

URTI Factorial analysis

		Control for CRP	CRP	Control for Communication	Communication
Antibiotics Prescribed	**Crude percentage**	36% (150/415)	25% (114/451)	36% (143/397)	26% (121/469)
	Basic risk ratio	1.00	0.62 (0.42, 0.88; p=0.006)	1.00	0.66 (0.45, 0.92; p=0.013)
	Adjusted risk ratio	1.00	0.50 (0.31, 0.79; p=0.002)	1.00	0.82 (0.53, 1.18; p=0.313)
Worsening of illness	**Crude percentage**	14% (56/406)	13% (57/438)	11% (44/390)	15% (69/454)
	Basic risk ratio	1.00	1.04 (0.58, 1.79; p=0.876)	1.00	1.66 (0.93, 2.77; p=0.087)
	Adjusted risk ratio	1.00	0.99 (0.56, 1.69; p=0.977)	1.00	1.72 (0.96,2.86; p=0.065)
Diary Symptom score (for days 2-4)	**Crude mean**	1.57 (0.05)	1.64 (0.05)	1.54 (0.05)	1.66 (0.05)
	Basic mean difference		0.10 (-0.08, 0.27; p=0.276)		0.11 (-0.06, 0.29; p=0.211)
	Adjusted mean difference		-0.01 (-0.17, 0.15; p=0.876)		0.14 (-0.02, 0.30; p=0.093)
Resolution of moderately bad symptoms	***Crude median (IQR)***	*4 (3,8)*	*5 (3,7)*	*4 (3,7)*	*5 (3,10)*
	Basic Hazard ratio	*1.00*	*0.96 (0.80, 1.17; p=0.712)*	*1.00*	*0.84 (0.69, 1.02; p=0.077)*
	Adjusted Hazard ratio	*1.00*	*0.95 (0.77, 1.18; p=0.652)*	*1.00*	*0.77 (0.62, 0.95; p=0.015)*

LRTI Individual group analysis

	Control	**CRP**	**Communication**	**Both**
Crude percentage antibiotic prescribed	62%(420/674)	36% (313/861)	44% (414/951)	34%(307/912)
Basic risk ratio	1.00	0.52 (0.38, 0.67; p<0.001)	0.68 (0.52, 0.84; p<0.001)	0.44 (0.32, 0.58; p<0.001)
Adjusted risk ratio	1.00	0.53 (0.35, 0.74; p<0.001)	0.67 (0.46, 0.88; p=0.002)	0.35 (0.23, 0.53; p<0.001)
New or worsening symptoms				
Crude percentage	13% (86/666)	22% (179/823)	25% (219/890)	18% (163/898)
Basic risk Ratio	1.00	1.77 (1.19, 2.55; p=0.007)	2.05 (1.39, 2.87; p<0.001)	1.42 (0.93, 2.09; p=0.099)
Adjusted risk ratio	1.00	1.67 (1.09,2.48; p=0.021)	1.97 (1.32, 2.80; p=0.001)	1.47 (0.96, 2.18; p=0.080)
Diary Symptom score (for days 2-4)				
Crude mean	1.84 (0.04)	1.72 (0.04)	1.83 (0.04)	1.93 (0.04)
Basic Mean difference		-0.09 (-0.27, 0.09; p=0.324)	0.04 (-0.13, 0.22; p=0.636)	0.06 (-0.11, 0.24; p=0.486)
Adjusted mean difference		-0.03 (-0.18, 0.12; p=0.707)	0.02 (-0.12, 0.16; p=0.775)	0.07 (-0.08, 0.22; p=0.347)
Resolution of moderately bad symptoms				
Median (IQR)	5 (3,8)	5 (3,8)	6 (3,10)	6 (4,10)
Basic Hazard ratio	1.00	0.99 (0.82, 1.18; p=0.877)	0.87 (0.71, 1.04; p=0.139)	0.86 (0.72, 1.03; p=0.106)
Adjusted Hazard ratio	1.00	0.89 (0.74, 1.07; p=0.212)	0.83 (0.70, 0.99; p=0.044)	0.78 (0.65, 0.93; p=0.007)

URTI Individual group analysis

	Control	**CRP**	**Communication**	**Both**
Crude percentage antibiotic prescribed	**45% (88/196)**	**27% (55/201)**	**28% (62/219)**	**24% (59/250)**
Basic risk ratio	**1.00**	**0.55 (0.33, 0.87; p=0.008)**	**0.59 (0.35, 0.91; p=0.014)**	**0.41 (0.24, 0.68; p<0.001)**
Adjusted risk ratio	**1.00**	**0.48 (0.23, 0.87; p=0.013)**	**0.78 (0.43, 1.21; p=0.302)**	**0.43 (0.21, 0.76; p=0.002)**
New or worsening symptoms				
Crude percentage	8% (16/195)	14% (28/195)	19% (40/211)	12% (29/243)
Basic risk Ratio	1.00	2.15 (0.88, 4.52; p=0.093)	3.09 (1.36, 5.82; p=0.008)	2.01 (0.83, 4.22; p=0.118)
Adjusted risk ratio	1.00	2.03 (0.78, 4.47; p=0.010)	3.09 (1.33, 5.89; p=0.010)	2.07 (0.85, 4.37; p=0.106)
Diary Symptom score (for days 2-4)				
Crude mean	1.44 (0.07)	1.63 (0.08)	1.69 (0.08)	1.64(0.07)
Basic Mean difference		0.25 (-0.01, 0.50; p=0.057)	0.26 (0.01, 0.51; p=0.044)	0.22 (-0.02, 0.47; p=0.075)
Adjusted mean difference		0.16 (-0.08, 0.40; p=0.186)	0.30 (0.07, 0.53; p=0.010)	0.16 (-0.07, 0.38; p=0.168)
Resolution of moderately bad symptoms				
Median (IQR)	3.5 (3,6)	4 (3,7)	5 (3,11)	6 (3,10)
Basic Hazard ratio	1.00	0.88 (0.66, 1.16; p=0.367)	0.77 (0.58, 1.01; p=0.061)	0.80 (0.61, 1.05; p=0.103)
Adjusted Hazard ratio	1.00	0.81 (0.59, 1.11; p=0.184)	0.66 (0.48, 0.89; p=0.007)	0.71 (0.53, 0.96; p=0.024)

References

1 Francis N, Butler C, Hood K, Simpson S, Wood F, Nuttall J. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ* 2009; **339:** b2885.

2 Yardley L, Joseph J, Michie S, Weal M, Wills G, Little P. Evaluation of a web-based intervention providing tailored advice for self-management of minor respiratory symptoms: exploratory randomized controlled trial. *J Med Internet Res* 2010; **12:** e66.

3 Butler C, Simpson S, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012; **344:** d8173.

4 Anthierens S, Tonkin-Crine S, Douglas E, et al. General practitioners' views on the acceptability and applicability of a web-based intervention to reduce antibiotic prescribing for acute cough in multiple European countries: a qualitative study prior to a randomised trial. *BMC Fam Pract* 2012; **13:** 101.

5 van der Meer V, Neven AK, van den Broek PJ, Assendelft WJJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 2005; **331:** 26.

6 Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. *Fam Pract* 2009; **26:** 10–21.

7 Cals J, Butler C, Hopstaken R, Hood K, Dinant G. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; **338:** b1374.