Supplemental materials for: Little P, Stuart B, Francis N, et al. Antibiotic prescribing for acute respiratory tract infections 12 months after communication and CRP training: a randomized trial. Ann Fam Med. 2019;17(2):125-132.

Supplemental 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 ^{23 33} and the STAR model for communication training ¹³. The materials were piloted in every country and modified according to feedback from interviews with clinicians and patients in each country²². 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^{34 35} and the previous IMPAC3T trial⁸ 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

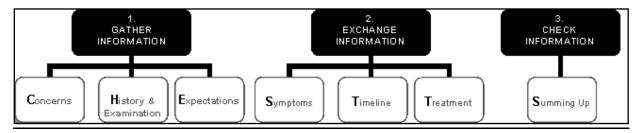
This section presented information describing the problem of antibiotic resistance for healthcare, its relation to antibiotic use, the medicalization of self-limiting illness creating the 'vicious circle' of encouraging re-consultation during subsequent episodes, and the difficulties in determining what patients presenting with LRTI in primary care may benefit from antibiotic treatment. The introduction discusses

common concerns Clinicians 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.

2. Enhanced Communication skills training and use of patient information booklet

The aim of the communication skills training was to facilitate clinicians 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. Clinicians 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 clinicians 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.

3. 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 clinicians about how a point of care CRP result could assist in differentiating self-limiting from serious LRTI and making antibiotic prescribing decisions for LRTI. Clinicians 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. Clinicians 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 clinicians on the cut off points used for CRP values and the relevant treatment options.

$CRP \le 20 \text{ mg/l}$

- 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.

$CRP \ge 100 \text{ mg/l}$

- 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.

Appendix 2.

Table 5.- Characteristics of individual group (n (%) or mean (SD))

	Final 12 months follow-up				Initial 3 months follow-up period			Baseline	
	Control	CRP	Communic'n	Both	Control	CRP	Commun'n	Both	
Gender	730/1244	736/1220	740/1219	884/1479	553/870	670/1062	758/1170	753/1162	4218/6771
(female)	(59%)	(60%)	(61%)	(60%)	(64%)	(63%)	(65%)	(65%)	(62%)
Age in years	50.6 (18.5)	51.8	52.8 (19.0)	50.8 (18.7)	50.5	51.1	51.3	50.9	49.6
(mean (SD))		(18.7)			(17.4)	(17.7)	(17.1)	(17.2)	(18.6)
Illness	512/1244	520/1220	514/1219	678/1479	424/863	570/1054	614/1164	558/1155	3,542/6717
duration	(41%)	(43%)	(42%)	(46%)	(49%)	(54%)	(53%)	(48%)	(53%)
prior to the									
index									
consultation									
>5 days									
Respiratory	39/1244	57/1220	26/1218	76/1479	63/846	82/1020	38/1030	41/1145	N/A
rate (> 25	(3%)	(5%)	(2%)	(5%)	(7%)	(8%)	(3%)	(4%)	
breaths/min.)									
Temperature	165/1244	120/1220	126/1219	260/1479	96/849	106/1004	132/1153	174/1148	N/A
(>38°C)	(13%)	(10%)	(10%)	(18%)	(11%)	(11%)	(11%)	(15%)	

Table 6 - Comparison of characteristics of patients and antibiotic prescribing from practices which provided follow-up compared with overall cohort (n (%) or mean (SD))

	Final 12 months	Initial 3 months	Initial 3 months	Baseline
	follow up	follow up in those	follow up	
		who provided 12		
		months follow up		
		data		
Gender (female)	2,891/4830	2,112/3280	2,734/4264	4218/6771 (62%)
	(59.8%)	(64.39%)	(64.1%)	
Age in years (mean (SD))	51.6 (18.8)	51.1 (17.6)	51.0 (17.4)	49.6 (18.6)
Non-smoker (past or	N/A	2561/3280 (78.1%)	3340/4264 (78.3%)	N/A
current)				
Illness duration prior to the	2,097/4830	1,649/3265	2,166/4236	3,542/6717 (53%)
index consultation >5 days	(43.4%)	(50.5%)	(51.1%)	
Respiratory rate (>25	178/4830 (3.7%)	184/3190 (5.8%)	224/4122 (5.42%)	N/A
breaths/minute)				
Temperature	639/4830 (13.2%)	408/3235 (12.6%)	508/4154 (12.2%)	N/A
(>38 degrees C)				
Sputum production	N/A	2631/3271	3,448/4249	5355/6771
		(80.4%)	(81.2%)	(79%)
Percentage prescribed	53.7%	55.5%	55.6%	55.3%
antibiotics at baseline				

Appendix 3.

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/URTI Factorial analysis

		Control	CRP	Control for	Communication
		for CRP		Communication	
LRTI					
Antibiotics	Crude	672/1293	728/1424 (51.12%)	673/1217	727/1500 (48.50%)
Prescribed	percentage	(51.97%)		(55.30%)	
	Basic risk ratio	1.00	0.97 (0.89-1.05;	1.00	0.94 (0.86-1.00;
			p=0.439)		p=0.074)
	Adjusted risk	1.00	0.79 (0.59-1.03;	1.00	0.75 (0.56-0.97;
	ratio		p=0.082)		p=0.024)
URTI					
Antibiotics	Crude	292/940	265/923 (28.71%)	289/907 (31.86%)	268/956 (28.03%)
Prescribed	percentage	(31.06%)			
	Basic risk ratio	1.00	0.94 (0.81-1.08;	1.00	0.94 (0.81-1.09;
			p=0.373)		p=0.445)
	Adjusted risk	1.00	0.81 (0.57-1.10;	1.00	0.83 (0.59-1.12;
	ratio		p=0.188)		p=0.232)

LRTI/URTI Individual group analysis

LRTI	Usual care	CRP	Communication	Combined
Crude percentage antibiotic prescribed	378/642 (58.88%)	295/575 (51.30%)	294/651 (45.16%)	433/849 (51.00%)
Basic risk ratio	1.00	0.86 (0.59-1.13;	0.75 (0.50-1.01;	0.72 (0.49-0.98;
		p=0.333)	p=0.064)	p=0.036)
Adjusted risk ratio	1.00	0.76 (0.47-1.06;	0.71 (0.45-0.99;	0.59 (0.36-0.86;
		p=0.112)	p=0.046)	p=0.003)
URTI	Usual care	CRP	Communication	Combined
Crude percentage antibiotic prescribed	180/486 (37.04%)	109/421 (25.89%)	112/454 (24.67%)	156/502 (31.08%)
Basic risk ratio	1.00	0.74 (0.48-1.08;	0.75 (0.49-1.08;	0.80 (0.53-1.14;
		p=0.104)	p=0.138)	p=0.240)
Adjusted risk ratio	1.00	0.58 (0.36-0.92;	0.60 (0.37-0.94;	0.67 (0.42-1.01;
		p=0.018)	p=0.023)	p=0.053)

REFERENCES

- 1. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, Dieleman JP, Verheij TJ. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. J Antimicrob Chemother. 2004;54(6):1116-1121.
- 2. Petersen I, Johnson A, Islam A, et al. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. BMJ 2007;335:982 (10 November), doi:10.1136/bmj.39345.405243.BE.
- 3. Kroening-Roche JC, Soroudi A, Castillo EM, Vilke GM. Antibiotic and bronchodilator prescribing for acute bronchitis in the emergency department. J Emerg Med. 2012;43(2):221-227.
- 4. Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. BMJ. 2009;338:b2242.
- 5. Smith S, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Cochrane Database Syst Rev. 2014;1(3): CD000245.
- 6. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. Lancet Infect Dis. 2013;13(2):123-129. 10.1016/S1473-3099(12)70300-6.

- 7. Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579-587.
- 8. Cals JW, Butler CC, Hopstaken RM, Hood K, Dinant GJ. 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. 10.1136/bmj.b1374.
- 9. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010;8(2):124-133.
- 10. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev. 2005;(4):CD003539.
- 11. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2007;(4):CD000409.
- 12. van der Velden A, Pijpers E, Kuyvenhoven M, et al. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. BJGP 2012;62:e801-e07(7).
- 13. Butler CC, Simpson SA, 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. 10.1136/bmj.d8173.
- 14. Kumar S, Little P, Britten N. Why do Gps prescribe antibiotics for sore throat? A grounded theory interview study of general practitioners. BMJ 2003;326:(18 January):138.
- 15. Cornford CS. Why patients consult when they cough: a comparison of consulting and non-consulting patients. Br J Gen Pract. 1998;48(436):1751-1754.
- 16. Minnaard MC, de Groot JA, Hopstaken RM, et al. The added value of C-reactive protein measurement in diagnosing pneumonia in primary care: a meta-analysis of individual patient data. CMAJ. 2017;189(2):E56-E63.
- 17. National Institute for Health and Care Excellence. NICE clinical guideline 191: Pneumonia in adults diagnosis and management. NICE. 2014.
- 18. Verheij T, Hopstaken R, Prince JM. NHG-Standaard Acuut hoesten. [Dutch College of General Practitioners Guidelines on Acute Cough 2011, updated 2013]. Huisarts Wet. 2011;54(2):68-92.
- 19. Woodhead M, Blasi F, Ewig S, et al.; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections—full version. Clin Microbiol Infect. 2011;17(Suppl 6):E1-E59.

- 20. Little P, Stuart B, Francis N, et al.; GRACE consortium. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet. 2013;382(9899):1175-1182. 10.1016/S0140-6736(13)60994-0.
- 21. Oppong R, Smith RD, Little P, et al. Cost-effectiveness of internet-based training for primary care clinicians on antibiotic prescribing for acute respiratory tract infections in Europe. J Antimicrob Chemother. 2018;73(11):3189-3198. 10.1093/jac/dky309.
- 22. Anthierens S, Tonkin-Crine S, Douglas E, et al; GRACE INTRO study team. 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. 10.1186/471-2296-13-101.
- 23. Francis NA, Butler CC, 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.
- 24. Coenen S, Van Royen P, Michiels B, et al. Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. J A C 2004;54(3):661 (doi:10.1093/jac/dkh374)-672.
- 25. Welschen I, Kuyvenhoven M, Hoes A, et al. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. BMJ 2004;329:431 (21 August), doi:10.1136/bmj.38182.591238.EB.
- 26. Adams G, Gulliford M, Ukoumunne O, et al. Patterns of intra-cluster correlation from primary care research to inform study design and analysis. J Clin Epidemiol 2004 Aug;57(8):785-94 2004;57:785-94.
- 27. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690-1691.
- 28. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. BMJ. 1997;314(7082):722-727.
- 29. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ. 2001;322(7282):336-342.
- 30. Yardley L, Douglas E, Anthierens S, et al.; GRACE consortium. Evaluation of a web-based intervention to reduce antibiotic prescribing for LRTI in six European countries: quantitative process analysis of the GRACE/INTRO randomised controlled trial. Implement Sci. 2013;8:134. 10.1186/748-5908-8-134.

- 31. Anthierens S, Tonkin-Crine S, Cals J, et al. Clinicians' views and experiences of interventions to enhance the quality of antibiotic prescribing for acute respiratory tract infections. J Gen Intern Med. 2015;30(4):408-416. 10.1007/s11606-014-3076-6.
- 32. Cals JW, De Bock L, Beckers PJ, et al. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year followup of a cluster randomized trial. Ann Fam Med. 2013;11(2):157-164. 10.1370/afm.1477.
- 33. 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(4):e66.
- 34. van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ. 2005;331(7507):26.
- 35. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. Fam Pract. 2009;26(1):10-21.