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Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial

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***Objectives*: To assess the effect of a tailored professional intervention, including academic detailing, on antibiotic prescribing for acute cough.**

***Methods*: In a cluster-randomized controlled before and after study 85 Flemish GPs included adult patients with acute cough consulting in the periods February–April 2000 and 2001. The intervention consisted of a clinical practice guideline for acute cough, an educational outreach visit and a postal reminder to support its implementation in January 2001. Antibiotic prescribing rates and patients' symptom resolution were the main outcome measures.**

***Results*: Thirty-six of 42 GPs received the intervention and 35 of 43 GPs served as controls; 1503 patients were eligible for analysis. Only in the intervention group were patients less likely to receive antibiotics after the intervention [OR_{adj} (95% CI) = 0.56 (0.36–0.87)]. Prescribed antibiotics were also more in line with the guideline in the intervention group [1.90 (0.96–3.75)] and less expensive from the perspective of the National Sickness and Invalidity Insurance Institute {MD_{adj} (95% CI) = −€6.89 [−11.77 − (−2.02)]}. No significant differences were found between the groups for the time to symptom resolution.**

***Conclusions*: An (inter)actively delivered tailored intervention implementing a guideline for acute cough is successful in optimizing antibiotic prescribing without affecting patients' symptom resolution. Further research efforts should be devoted to cost-effectiveness studies of such interventions.**

Keywords: primary care, respiratory tract infections, guidelines, antibacterials, academic detailing

Introduction

In primary care antibiotics are being overprescribed, especially for respiratory tract infections.[1,2] This is also true for the Netherlands[3] with the lowest antibiotic consumption in the European Union: 9 defined daily doses (DDD) per 1000 inhabitants per day.[4] The problem is particularly important for countries such as the UK with a consumption twice, or Belgium with a consumption nearly three times, that of the Netherlands.[4] After all, antibacterial resistance is linked to antibiotic consumption,[5] and it is time for action.[6]

Decreasing the use of antibiotics has been among the most targeted issues of different strategies to improve the use of medicines. Regulatory/financial measures,[7] organizational intervention[8–10] and professional intervention can be distinguished. Professional interventions use primarily evidence-based arguments on effectiveness, safety, cost and sometimes applicability for changing professional practice. Implementing evidence-based guidelines is one of the best-known, and best-studied examples of this approach. Most studies were, however, carried out in the USA, and many targeted hospital prescribing rather than primary care prescribing.[11] Moreover, evidence of their effectiveness from randomized controlled trials is scarce.[12–14]

Specific barriers to change occur at the level of social context and within the broader context of the healthcare structure and culture. In Belgium most GPs are paid a fee for service. There is a plethora of mostly solo practising GPs, competition for patients and open access to secondary care. In contrast to the Netherlands, pharmacotherapy is not discussed on a regular basis in local groups involving pharmacists. Furthermore, there are cultural differences and different attitudes towards respiratory symptoms and antibiotics between Belgium and the Netherlands.[15,16] All these factors may partly explain the large variation in antibiotic consumption between the two countries.[17]

Other barriers to change relate to the credibility of the guideline and to the individual prescriber. Although most GPs are

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aware of the problem of antibiotic resistance at the population level, there may be lack of awareness of the effect of overprescribing in individuals on the probability of future infections with resistant pathogens. Internal barriers within the prescriber relate to knowledge, attitude, but also to the decision process when prescribing an antibiotic. We looked at the antibiotic prescribing decision of Flemish GPs in patients with complaints about coughing, not patients with acute bronchitis.[18] Using qualitative and quantitative research methods we found that non-medical reasons played an important role in the prescribing decision, especially in cases of diagnostic uncertainty.[19,20] Moreover, those reasons favoured antibiotic prescribing. Despite lacking evidence of their effectiveness[21,22] GPs anticipated more 'chagrin' over not prescribing antibiotics than over prescribing them, since antibiotics might prevent them from losing patients as a result of unfulfilled patient expectations or undetected serious disease.

To optimize antibiotic prescribing in Belgium, we developed a context-specific evidence-based guideline for acute cough. The main recommendation is that most patients with acute cough do not need antibiotics. Nevertheless we mentioned first choice antibiotics. Although no single combination of approaches is clearly better than another in implementing guidelines, we preferred the individual approach of academic detailing, and tailored the intervention to identified barriers within GPs.

A cluster-randomized controlled trial (cRCT) was conducted to assess the effect of our intervention on antibiotic prescribing for acute cough. We expected that successful implementation of the guideline would reduce the proportion of patients who were prescribed antibiotics and increase the relative proportion of first choice antibiotics, and that this would not affect the resolution of patients' symptoms.

Materials and methods

Design

We tested the main hypothesis with a cRCT before and after study. General practitioners (GPs) were randomized before the intervention into an intervention group and a control group (Figure 1). Our intervention was preceded by a national public campaign.[23,24] Only the GPs in the intervention group received a tailored intervention to support the implemention of a clinical practice guideline for the management of acute cough in adult patients. Pre-intervention data were collected during a 3 month period in 2000 (pre-test), post-intervention data 1 year later, in 2001, after both interventions (post-test).

Participants

In total 149 GPs not reluctant to take part in further study as assessed by a postal questionnaire study[20] were sent a letter and questionnaire inviting them to join the study. Overall, 85 GPs agreed to participate and a stratified randomization using minimization for sex, university of graduation and age was performed (Table 1). We randomized GPs rather than practices since more than half of the GPs worked single-handed and not all GPs from group practices participated. S.C. made sure that GPs from the same practice ended up in the same group (0 or 1). They were allocated to the same group as the first GP to be randomly allocated from that practice. Afterwards, P.V.R., who was blinded for the composition of the groups, determined whether group 1 became the intervention or the control group by tossing a coin.

We included consultations for acute cough if they concerned immunocompetent patients, 18–65 years, with new or worsening coughing, present for less than 30 days as (one of) the most important complaint(s) and as the reason for first encounter with the GP practice.

The involvement of GPs and patients in the trial is summarized in Figure 1.

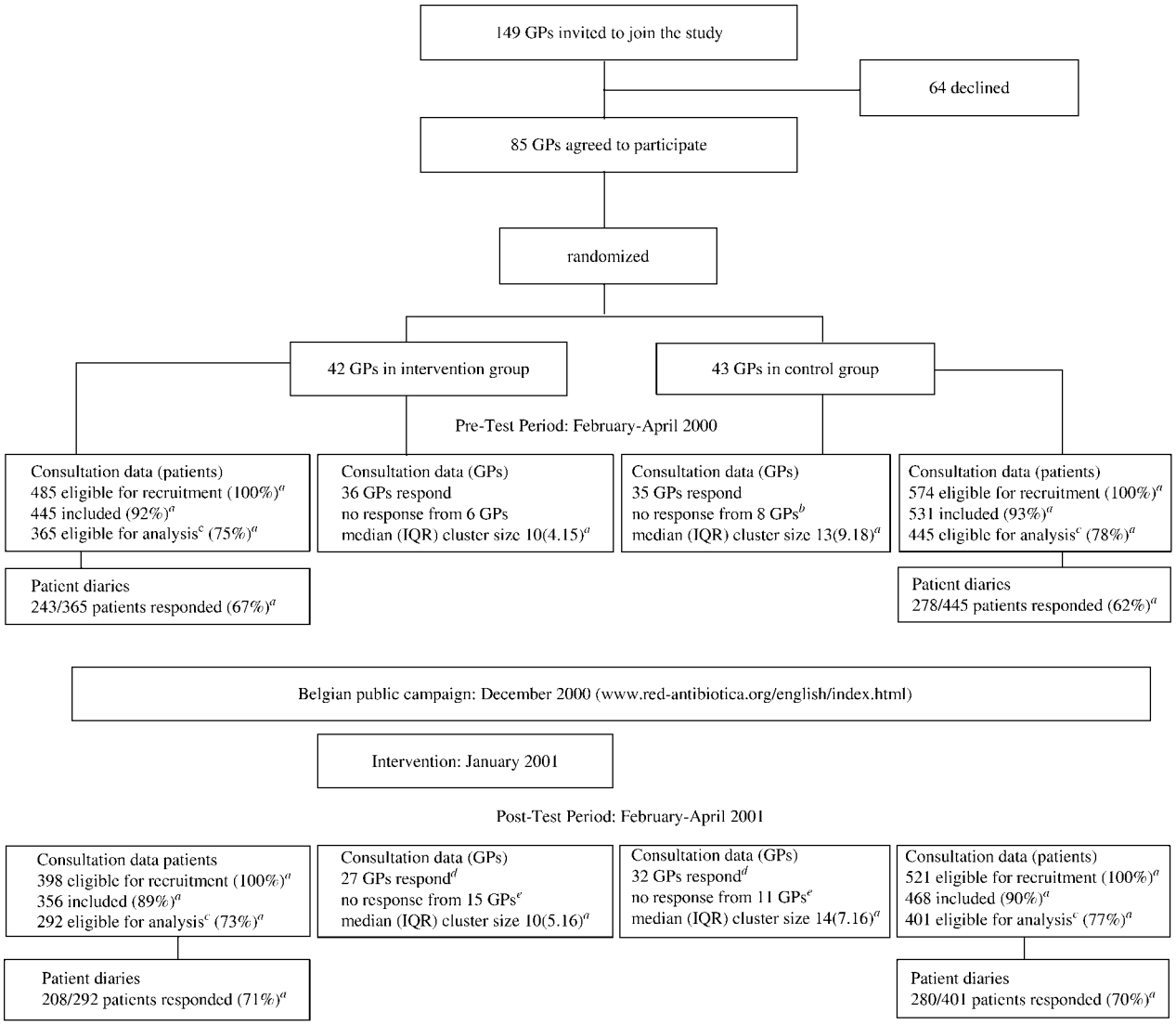
Interventions

Apart from our intervention, all participating GPs received booklets and leaflets of a public campaign initiated in Belgium in November 2000 and continued until December 2000 (Figure 1).[23,24] This campaign also included TV spots and radio messages informing the public on overconsumption and misuse of antibiotics, the resulting resistance problem and the self-limiting character of most frequent infections in the community. All GPs were invited to participate in the cRCT before the pre-test, were reminded of the trial before the post-test by mail and received a fee of €24.79 or €61.97 after each study period depending on their response. After an appointment had been made by telephone they received the material and instructions for data collection by means of a practice visit and a reminder phone call at the start of each registration period. Before the post-test only GPs in the intervention group received our tailored professional intervention (Figure 1), consisting of a clinical practice guideline for the management of acute cough in general practice, an educational outreach visit to GPs based on the principles of academic detailing[25] and a postal reminder of the key messages (Box 1).

An author group of GPs developed a clinical practice guideline according to a standardized methodology defined by the Scientific College of Flemish General Practitioners and in line with the AGREE criteria.[26] Fine-tuning for the specific context of Flemish GPs was based on previous descriptive studies on the management of acute cough and the determinants of antibiotic prescribing.[19,20] The guideline for the intervention was reviewed by a multidisciplinary panel of experts. An educational package was developed in accordance with this guideline and key messages were formulated (Box 1).

All GPs in the intervention group received the guideline by mail and subsequently were contacted by telephone by one of two facilitators. Each time GPs were asked to read the guideline in anticipation of an outreach visit at their practice and to assess the feasibility to comply with its recommendations. The facilitators, a pharmacist and a former medical representative, were trained to perform the educational visits in line with the work of Project Farmaka.[27] They combined the educational visit with the delivery of material and instructions. They rephrased the information in the guideline using simple overheads and emphasizing the key messages. The educational element of this method was a dialogue about perceived barriers to adhering to the guideline, either mentioned by the GP or elicited by the facilitator.

The focus of this dialogue was, however, on dealing with barriers within the individual prescriber, especially in dealing with diagnostic uncertainty. Using a fishbone scheme we presented what was known about the accuracy of history and clinical examination to differentiate between viral and bacterial respiratory infections, upper and lower respiratory infections, and between bronchitis and pneumonia;[28,29] about the validity of a clinical prediction rule to assess prognosis in the case of community-acquired pneumonia;[30] about the effectiveness of antibiotics for acute cough;[21] and about



[a]The proportions of patients eligible fore recruitment (100%) actually included in the study, the proportions of those eligible for analysis.[c] and the proportion of the latter patients responding with patient diaries, as well as the median duster sizes (inter quartile range) were not significantly different between the study groups within each study period, nor between the study periods within each study group using Generalized Estimating Equations and Kruskal Wallis Median Test respectively.
[b]1 GP responding in the Pre-Test did not have consultation data eligible for analysis.[c]
[c]Analysis of the main outcome measures, differences in antibiotic prescribing rates.
[d]Only 27 GPs in the intervention and 29 GPs in the control group responded in both the Pre-Test and the Post-Test
[e]In the intervention group 9 GPs responding in the Pre-Test did not respond in the Post-Test, compared to 6 GPs in the control group.
In the control group 3 GPs not responding in the Pre-Test did so in the Post-Test.

Figure 1. GP and patient flow, and design of the study.

the effect of antibiotic consumption on bacterial resistance in the community and the individual,[31,32] to conclude that after ruling out pneumonia patients with acute cough due to a respiratory infection do not need antibiotics. After all, the possible benefits of antibiotics are outweighed by their cost, and it is not possible to identify those patients who will benefit from antibiotics. Nevertheless, the guideline also recommended amoxicillin or doxycycline as first choice antibiotics if for any reason the GP decides to prescribe antibiotics. We also addressed the effect of patient- and physician-related non-medical reasons on the prescribing decision, especially in cases of diagnostic uncertainty. We demonstrated the mismatch between patients' expectations and GPs' perceptions of these, stressing that the latter are described as important determinants favouring antibiotic prescribing,[33–35] and we instructed the GPs on how to make patients' expectations regarding antibiotic prescribing explicit, and provided different strategies for different patient expectations. To overcome an uncomfortable prescribing decision made for GP-related reasons, we stated that watchful waiting would prevent complications more effectively than antibiotics, and would not jeopardize the doctor–patient relationship. We thus tried to show that managing patients according to the guideline might result in a win-win situation, more satisfied GPs, more satisfied patients

Table 1. Pre-intervention characteristics of study GPs in intervention and control groups[a]

Characteristics	Intervention GPs ($N=27$)	Control GPs ($N=29$)
Figures are number (%)[b]		
men	19 (70)	20 (69)
University of Antwerp graduates	12 (44)	12 (41)
professional training	10 (40)	6 (22)
fee for service	26 (96)	28 (97)
single-handed	13 (48)	15 (52)
GPPTs in practice[c]	9 (33)	3 (10)
part-time	5 (19)	5 (17)
practice in Antwerp	15 (56)	21 (72)
peakflow meter	25 (93)	26 (90)
spirometer	7 (26)	9 (31)
training practice	10 (37)	8 (28)
academic link	10 (37)	9 (31)
records of home visits	21 (78)	25 (86)
computerized records	17 (63)	21 (72)
complementary medicine	1 (4)	1 (3)
Figures are mean (S.D.)		
age (years)	43.6 (8.3)	45.0 (8.1)
patient encounters per week	100 (43)	108 (43)
home visits per week	34 (21)	33 (18)
medical representatives per month	16 (11)	15 (11)
ATC J cost ratio[d]	16.6 (9.0)	14 (6.1)
ATC J volume ratio[d]	3.5 (1.6)	2.9 (1.2)

[a] There were no significant differences between the intervention and the control groups using χ^2 or Student's t test where appropriate when comparing the characteristics of the GPs responding pre-intervention ($n=72$), those responding post-intervention ($n=59$) and those responding pre-intervention and post-intervention ($n=56$). The latter comparison is presented in this table. Responding and non-responding GPs were similar for all characteristics except for 'spirometer': more responding GPs had a spirometer in their practice (16/56 versus 2/29; $P=0.02$).
[b] Denominators vary due to missing values.
[c] GPPT, general practitioner in professional training.
[d] The ratios of the gross amount of antimicrobials for systemic use (ATC J)/the gross amount for all pharmaceutical specialties and the volume (DDD) of ATC J/the volume for all pharmaceutical specialties are both expressed as percentages in individual prescribing feedback from the NSIII to GPs. We asked the participating GPs for these percentages and calculated their mean.

and less antibiotic consumption. We thus tailored the interventions to overcome identified barriers.

All intervention GPs also received one page with the key messages of the guideline by mail as a reminder (Box 1).

Our intervention was initiated in December 2000 and continued until January 2001. The study protocol was approved by the medical ethics committee of the University of Antwerp. Consent was obtained from GPs and patients.

Box 1. Key message of the guideline for acute cough

This guideline concerns patients, aged 12 years or older, whose most prominent complaint is acute cough with or without purulent sputum, not patients with recurrent or chronic cough, chronic obstructive pulmonary disease or patients that have been treated in the preceding week with antibiotics.

First, pneumonia, pulmonary embolism, left ventricular failure (pulmonary edema), pneumothorax, aspiration and irritation by toxic agents should be ruled out by history and clinical examination. Although these are not frequent conditions, and although acute cough may not be the most prominent complaint, these conditions are treatable, and possibly life-threatening. They should not be missed.

If a cause other than a respiratory infection is present (for example asthma, gastroesophageal reflux disease, ACE-inhibitors) management needs to be adjusted accordingly. Even though such conditions may not be obvious in a first encounter, it is worthwhile to take them into account.

If finally a respiratory infection seems to be the most likely cause, it is not feasible to distinguish between viral and bacterial infections. Nevertheless the decision whether to prescribe antibiotics has to be made. Antibiotics are only needed for patients with compromised immunity.*

Besides the scientific arguments, we also recommend that the GP's own agenda and that of the patient be integrated in the final therapeutic decision.

*The guideline also recommended amoxicillin or doxycycline as first choice antibiotics in case it was decided to prescribe antibiotics for any other reason.

Data collection

GPs were asked to collect medical as well as non-medical data for 20 consecutive patients eligible for recruitment (Table 2). If, due to time constraints, this was not possible, one in two or one in three patients were to be included. The GPs kept records of those patients eligible for recruitment but not included. They collected the data themselves on pre-printed forms, with clear instructions about how this should be done. To ensure patient confidentiality, GPs completed the forms using patient identification numbers only. GPs were also asked to deliver a package containing a symptom diary and clear instructions for its use, to all included patients.

Patients were asked to record their symptoms and medication consumption starting the day of the consultation for a maximum of 29 days. Each diary also contained an identification number and was to be returned to the GP in a sealed envelope.

The GPs held a patient reference sheet with the names of patients against those numbers. This enabled them to assess and improve their patients' response. They sent all completed data collection

Table 2. Characteristics of patients with acute cough: consultation data [figures are numbers (%) unless otherwise stated]

Characteristic	Pre-intervention (2000)		Post-intervention (2001)	
	intervention ($n=365$)	control ($n=445$)	intervention ($n=292$)	control ($n=401$)
Demographic				
men	156 (43)	191 (43)	118 (40)	172 (43)
predicted mean age[a] (95% CI)	41.9 (40.3–43.5)	40.9 (39.4–42.4)	40.2 (38.5–42.0)	41.7 (40.1–43.2)
History and risk				
asthma	26 (7)	61 (14)	21 (7)	32 (8)
COPD (CARA)	27 (7)	39 (9)	23 (8)	30 (7)
heart failure[a]	3 (1)	7 (2)	0 (0)	6 (1)[b]
ACE-inhibitor	9 (2)	14 (3)	5 (2)	8 (2)
CV-disease[a]	8 (2)	10 (2)	1 (0)	6 (1)
aspiration risk	0 (0)	10 (2)	0 (0)	4 (1)[b]
liver disease[a]	3 (1)	13 (3)	1 (0)	8 (2)
renal disease[a]	2 (1)	7 (2)	0 (0)	2 (0)[b]
neoplastic disease[a]	3 (1)	9 (2)	2 (1)	4 (1)
thrombo-embolic risk	5 (1)	39 (9)	3 (1)	25 (6)[c,d]
smoking	119 (33)	158 (36)	80 (27)	135 (34)
Circumstance				
high workload	196 (54)	242 (54)	153 (52)	243 (61)
sick impression	158 (43)	197 (44)	112 (38)	171 (43)
request for antibiotics	37 (10)	88 (20)	27 (9)	66 (16)
request for another medication	175 (48)	216 (49)	163 (56)	180 (45)
Symptom				
predicted mean duration of cough (95% CI)	5.6 (4.9–6.2)	6.5 (5.9–7.1)	5.2 (4.6–5.9)	5.7 (5.1–6.3)[c,e]
sputum	198 (54)	285 (64)	159 (54)	222 (55)[c,e]
fever	94 (26)	149 (33)	64 (22)	114 (28)
runny nose	221 (61)	287 (64)	179 (61)	235 (59)
headache	177 (48)	232 (52)	146 (50)	198 (49)
muscle ache	119 (33)	168 (38)	86 (29)	122 (30)
sore throat	227 (62)	242 (54)	173 (59)	214 (53)
wheezing	61 (17)	89 (20)	52 (18)	81 (20)
shortness of breath	98 (27)	134 (30)	79 (27)	110 (27)
chest pain	108 (30)	159 (36)	92 (32)	138 (34)
loss of appetite	99 (27)	130 (29)	62 (21)	82 (20)[e]
limited activity	164 (45)	221 (50)	105 (36)	167 (42)
Sign				
altered consciousness[a]	3 (1)	8 (2)	0 (0)	2 (0)
pulse rate >125/min[a]	4 (1)	8 (2)	0 (0)	2 (0)
respiratory rate >30/min	3 (1)	11 (2)	0 (0)	5 (1)
temperature >38°C[a]	39 (11)	63 (14)	22 (8)	39 (10)
systolic BP <90 mmHg[a]	16 (4)	7 (2)	6 (2)	13 (3)
less vesicular breathing	49 (13)	70 (16)	32 (11)	36 (9)
wheezing	68 (19)	78 (18)	49 (17)	63 (16)
ronchi	95 (26)	118 (27)	71 (24)	70 (17)[e]
crepitations	18 (5)	32 (7)	13 (4)	26 (6)
percussion dullness	1 (0)	9 (2)	2 (1)	5 (1)
Higher risk[a]	142 (39)	175 (39)	98 (34)	147 (37)

Table 2. (*Continued*)

Characteristic	Pre-intervention (2000)		Post-intervention (2001)	
	intervention ($n = 365$)	control ($n = 445$)	intervention ($n = 292$)	control ($n = 401$)
Investigation				
radiograph	7 (2)	23 (5)	3 (1)	11 (3)
sputum analysis	0 (0)	12 (3)	1 (0)	4 (1)[b]
infection parameters	4 (1)	12 (3)	5 (2)	10 (2)
serology	1 (0)	7 (2)	2 (1)	9 (2)
other	0 (0)	26 (6)	6 (2)	9 (2)[b]
Prescriptions				
referral	3 (1)	18 (4)	1 (0)	12 (3)[c]
sick leave	124 (34)	193 (43)	107 (37)	165 (41)
follow-up contact	25 (7)	57 (13)	29 (10)	33 (8)
medication	318 (87)	388 (87)	285 (98)	377 (94)

[a] We constructed the variable 'Higher risk'. It was derived from Fine *et al.*[30] and equals 1, if the patient's age is >50 or if the patient has congestive heart failure, cerebrovascular disease, liver disease, renal disease or neoplastic disease, or has altered consciousness, pulse rate >125/min, respiratory rate >30/min, temperature >38°C or systolic blood pressure >90 mmHg, and equals 0 otherwise. This also enabled significance testing of variables for which no estimation was possible.
[b] No estimation possible.
[c] Significant differences between intervention and control in pre-intervention.
[d] Significant differences between intervention and control in post-intervention.
[e] Significant differences between pre-intervention and post-intervention in control group. There were no significant differences between pre-intervention and post-intervention in intervention group.

material to S.C. for analysis. The data collection method had been previously piloted.

Outcomes

The primary outcome was the antibiotic prescribing rate by GPs for adult patients with acute cough. We were also interested in the type of antibiotic prescribed, if any, and whether any change in antibiotic prescribing affected symptom resolution. Finally, we measured the medication cost per patient from the perspective of the National Sickness and Invalidity Insurance Institute (NSIII). We compared data from the control group with data from the intervention group in each study period, and pre-intervention data with post-intervention data in each study group.

Sample size

Sample size was calculated with antibiotic prescribing for acute cough as the primary outcome. Before the pre-test no data were available regarding the antibiotic prescribing rate for acute cough nor about the Intra-cluster Correlation Coefficient (ICC) needed to adjust the sample size because GPs rather than patients were randomized. Therefore we calculated the sample size with a method that takes into account the number of events, the expected effect and the power of the study, but not the ICC. We thus acted as if patients were randomized, and assumed a minimum of 20 patients for each practice and a worst case control group rate of 50%. Under these assumptions we anticipated a power of 90% to detect a difference of 10% in rate between the two groups at the 5% significance level with 30 practices in each study group. We anticipated adjustment of the sample size for cluster randomization and loss to follow up. Therefore we planned to randomize 40 GPs in each group and to adjust the number of patients to be included per practice for the post-test according to the ICC found in the pre-test.

Statistical methods

We applied cluster-specific methods taking into account the dependence among patients of the same GP, known as the clustering effect: GPs rather than patients were randomized, and variance in how patients were managed would be partly explained by the GP.[36]

We used logistic regression to test for an effect of our intervention on antibiotic prescribing (Box 2).

To test for differences in medication cost a linear regression model with random intercept was used to account for within-GP correlation. To test for differences in time to symptom resolution we used Cox's proportional hazard regression. Data were analysed assuming independence and standard errors were then corrected for within-GP correlation using a robust estimator. All models were estimated with SAS v8.02 (SAS System for Windows 8.02; SAS Institute Inc., Cary, NC, USA). All other analyses were performed with Statistica v6.0. (Statistica for Windows 6.0; StatSoft, Inc., Tulsa, OK, USA).

Results

GP flow and characteristics

The randomized GPs were similar to other Flemish GPs (invited) with respect to age and sex distribution.

They all received the material and instructions for data collection. Six GPs in the intervention arm and seven GPs in the control arm did not respond in the pre-test (Figure 1). We did not get data eligible for the analysis of the main outcome

Box 2. *Analysis of cluster data*

To assess the effect of a tailored intervention on GPs' antibiotic prescribing for acute cough, we first estimated a logistic model: logit $p(X) = \beta 0 + \beta 1\ G + \beta 2\ P + \beta 3\ G*P$, where $p(X)$ is the probability of an antibiotic prescription, G is a dichotomous variable for the study groups, which equals zero for the control and one for the intervention group, P is a dichotomous variable for the study period, which equals zero for the pre-test and one for the post-test. The same kind of model was used to test for significant differences of the covariates. All significant covariates in this analysis were included in the above model as possible confounders. Then from this multivariable analysis non-significant covariates were removed, eliminating one by one the covariates with least significant type 3 score statistics. We adjusted logistic regression estimates for clustering within our data (patients are nested within GPs).[36] We used generalized estimating equations (GEEs).[37] By testing the hypothesis H0:$\beta 1 = 0$ we were able to test for differences between control and intervention groups during the pre-test.

Second, we considered the model without the effect of the study group, i.e. a model assuming baseline prescribing to be similar. We assumed prescribing rates to be equal in both study groups before the intervention, an assumption which should hold with randomization. Furthermore cross-sectional pre-intervention data in cluster trials rarely provide (statistically) useful insights and often confuse interpretation.[38]

Under this assumption we tested for differences between control and intervention groups after the intervention by testing the hypothesis H0: $\beta 3 = 0$.

By testing the hypothesis H0: $\beta 2 = 0$ we were able to test for differences between pre-intervention and post-intervention periods in the control group.

By testing the hypothesis H0: $\beta 2 + \beta 3 = 0$ we were able to test for such differences in the intervention group.

measures from one control GP (age or duration of cough not in line with inclusion criteria or unknown). In the intervention arm 36 GPs received the entire intervention (33/36 responding and 3/6 non-responding GPs). On average the educational visit lasted 22 min (S.D. 10 min; range: 5–60 min). Of those responding in the pre-test nine GPs in the intervention arm and six GPs in the control arm did not respond in the post-test. Three GPs were recovered for the post-test in the control arm. This left 27 of 42 GPs in the intervention arm and 32 of 43 GPs in the control arm for the post-test. Loss to follow up was due to motivational problems regarding data collection and similar in both study groups. No significant differences were found between the intervention and control GPs, nor between responding GPs and the non-responding group for the same characteristics, including pre-intervention antibiotic use in cost and volume (Table 1).

Patient flow and characteristics

Consultation data. The GPs collected data for 1978 patients eligible for recruitment: in the pre-test 485 in the intervention group, 574 in the control group; in the post-test 398 and 521, respectively (Figure 1). They included 1800 patients in the study (445, 531, 356 and 468, respectively), of which 1503 patients were eligible for analysis of the primary outcome (365, 445, 292 and 401, respectively). Comparing between the four groups, by which we mean comparing between both study groups within each study period and between both study periods within each study group, the median cluster sizes were similar (Figure 1). Likewise similar proportions of patients eligible for recruitment were actually included in the study, and eligible for analysis. The proportions of male patients were not different whether patients eligible for recruitment were included in the study or not. Only in the post-intervention control group was the proportion of male patients eligible for recruitment greater in those eligible for analysis than in those not eligible for analysis. Of the patients eligible for recruitment the patients included and those eligible for analysis were younger than those not included, and not eligible for analysis, respectively.

Table 2 shows the characteristics of the patients with acute cough eligible for analysis by study group for the pre-intervention and the post-intervention periods. Except for the risk of thrombo-embolic disease, duration of cough, the presence of sputum, ronchi, loss of appetite and a referral, patient characteristics were similar (Table 2).

Patients in the intervention group were less likely to be at risk for thrombo-embolic disease in the pre-test [odds ratio (OR) (95% CI) = 0.17 (0.05–0.60)] and the post-test [OR = 0.15 (0.03–0.79)]. They were less likely to produce sputum [OR = 0.68 (0.47–0.98)], less likely to be referred [OR = 0.23 (0.06–0.68)] and coughing significantly less days before consulting in the pre-test only [estimated difference (ED) (95% CI) = 0.96 (0.12–1.80)]. In the post-test, patients in the control group were coughing significantly less days before consulting compared with the pre-test [ED = 0.79 (0.12–1.46)] They were also less likely to produce sputum [OR = 0.68 (0.48–0.97)], or have loss of appetite [0.60 (0.39–0.93)] or ronchi [0.58 (0.34–1.00)].

Patient diaries. Patient diaries of 1009 patients eligible for analysis were available: in the pre-test 243 in the intervention group, 278 in the control group, in the post-test 208 and 280, respectively (Figure 1). Comparing the four groups, the proportion of patients eligible for analysis responding with patient diaries is similar. Except for age, duration of coughing, smoking, ACE-inhibitors and percussion dullness, the characteristics of the patients eligible for analysis were similar whether patients responded with patient diaries or not. Patients responding with patient diaries were significantly older [estimated difference (95% CI) = 4.00 years (2.57–5.42)], and coughing not as long [0.57 days (0.04–1.11)]. They were more likely to be taking ACE-inhibitors [OR = 3.62 (95% CI = 1.17–11.2)] and less likely to be smoking [0.57 (0.44–0.73)] or have a clinical examination positive for percussion dullness [0.33 (0.15–0.93)]. Comparing the presence of complaints on the day of the

consultation (= day 1) from these patients' diaries between the four groups, only for fever and headache were differences found between the study periods (Table 3). Patients in the control group were less likely to suffer from fever [0.62 (0.43–0.89)] and patients in the intervention group were more likely to suffer from headache [1.64 (1.08–2.48)] in the post-test.

Comparing the number of complaints on the day of the consultation, patients in the control group suffer from less complaints in the pre-test compared with the post-test [estimated difference (95% CI) = 0.50 (0.04–0.95)], and compared with the intervention group [0.52 (0.15–0.90)].

Outcome

Outcome data were collected for 1503 consultations for acute cough. The ICC for primary outcome was highly significant, indicating that cluster-specific analytical methods were appropriate (Table 4).

Use of antibiotics. Table 4 shows the prescription rate of antibiotics and the percentage difference in change of prescription rate for patients in the intervention and the control groups. In the pre-test, antibiotic prescribing rates were not significantly different between the intervention and control groups [OR (95% CI) = 1.09 (0.68–1.76); OR_{adj} (95% CI) = 1.28 (0.76–2.16)], adjusted for duration of cough and presence of sputum). Using a model assuming similar pre-intervention antibiotic prescribing rates in both study groups, an assumption which should hold with randomization, patients in the intervention group were less likely to receive an antibiotic after our intervention compared with controls [OR_{adj} = 0.56 (0.36–0.87)]. Also, comparing the antibiotic prescribing rate between the pre-test and the post-test, only patients in the intervention group were less likely to receive antibiotics after the intervention (OR_{adj} = 0.56 (0.39–0.81), than patients in the control group [OR_{adj} = 1.01 (0.76–1.33)].

Type of antibiotics used. Pre-intervention prescribing rates of recommended antibiotics were not significantly different between the intervention and control groups [OR = OR_{adj} = 1.05 (0.52–2.12)]. Under the assumption of equal baseline prescribing, patients in the intervention group were more likely to receive amoxicillin or doxycycline than patients in the control group [OR_{adj} = 1.90 (0.96–3.75)] (Table 4). Also comparing the antibiotic prescribing rate between the pre-test and the post-test, only patients in the intervention group were more likely to receive the recommended antibiotics after the intervention [OR_{adj} = 1.98 (1.19–3.29)], and not patients in the control group [OR_{adj} = 1.03 (0.61–1.78)].

Cost of antibiotics. Looking at the medication cost from the perspective of the NSIII means looking at the reimbursement cost of prescribed medication. Since for many prescribed drugs

Table 4. Rate of use and percentage difference in change of use of (recommended) antibiotics

	Intervention	Control
Use of antibiotics		
pre-intervention	43.0 (157/365)	37.8 (168/445)
post-intervention	27.4 (80/292)	28.7 (115/401)
percentage change	−15.6	−9.1
percentage difference	−6.5	
OR (95% CI)[a]/ICC[b]	0.74 (0.51–1.08)/0.18	
OR_{adj} (95% CI)[c]/ICC[b]	0.56 (0.36–0.87)/0.22	
Use of recommended antibiotic		
pre-intervention	40.1 (63/157)	37.5 (63/168)
post-intervention	53.8 (43/ 80)	37.4 (43/115)
percentage change	+13.6	−0.1
percentage difference	+13.7	
$OR_{(adj)}$ (95% CI)[a]/ICC[b]	1.90 (0.96–3.75)/0.12	

[a] Odds ratios are based on the model assuming equal prescribing rates in intervention and control group in the pre-intervention period (see Box 2).
[b] Intra-cluster correlation coefficient.
[c] Adjusted for the presence of sputum, ronchi, loss of appetite and duration of cough.

Table 3. Characteristics of patients with acute cough: data from patient diaries [figures are numbers (%)]

	Pre-intervention (2000)		Post-intervention (2001)	
	intervention (n = 243)	control (n = 278)	intervention (n = 208)	control (n = 280)
Complaint on day 1				
coughing	239 (98)	275 (99)	205 (99)	273 (98)
sputum	149 (61)	177 (64)	112 (54)	170 (61)
fever	62 (26)	98 (35)	56 (27)	71 (25)[a]
runny nose	150 (62)	175 (63)	128 (62)	160 (57)
sore throat	139 (57)	160 (58)	111 (53)	148 (53)
headache	117 (48)	151 (54)	126 (61)	159 (57)[b]
muscle ache	80 (33)	114 (41)	65 (31)	106 (38)
loss of appetite	89 (37)	110 (40)	74 (36)	97 (35)
shortness of breath	84 (35)	113 (41)	75 (36)	94 (34)
wheezing	49 (20)	72 (26)	45 (22)	62 (22)
chest pain	87 (36)	108 (39)	65 (31)	95 (34)
Reconsultation	57 (23)	55 (20)	40 (19)	61 (22)
Hospitalization	0 (0)	1 (0)	2 (1)	0 (0)[c]

[a] Significant differences between pre-intervention and post-intervention in control.
[b] Significant differences between pre-intervention and post-intervention in intervention group.
[c] No estimation possible.

for acute cough no reimbursement is made, significance testing of the medication cost in all patients is hampered by distributional problems. We tested for differences in reimbursement cost in the subset of patients who were prescribed an antibiotic. Since antibiotics represent the only reimbursed group of prescribed medication in this subset of patients, we actually tested for differences in antibiotic cost. The antibiotic cost was lower in the intervention group after our intervention compared with the control group {Mean Difference $(MD)_{adj}$ (95% CI) = −€6.89 [−11.77−(−2.02)]}, and compared with the pre-test {MD_{adj} = −€6.11 [−9.97−(−2.24)]} (Table 5).

Time to symptom resolution. Concerning the use of antibiotics and the kind of antibiotics used the same conclusions can be drawn from the subset of patients responding with patient diaries. Comparing the time to resolution of all symptoms and time to return to the activity and the health status of before the illness, no significant difference was found between the patients in the intervention group and those in the control group after our intervention (Figure 2). Reconsultation and hospitalization rates were also similar (Table 3).

Other analyses. Large variations occurred among the included GPs in the prescription of antibiotics and in the extent of change for this outcome measure (Figure 3). The change in antibiotic prescription rates was not different in the first month compared with the last 2 months of the post-test.

Table 5. Mean and difference in change of medication cost in the subset of patients with an antibiotic prescription from the perspective of the NSIII

Medication cost	Intervention	Control
Pre-test	22.86	21.48
Post-test	16.75	22.35
Change	−6.11	+0.87
Difference	−6.97	
MD (95% CI)[a]	−6.76 [−12.30−(−1.89)]	
MD_{adj} (95% CI)[b]	−6.89 [−11.77−(−2.02)]	

[a] Mean difference is based on the model assuming equal medication cost in intervention and control group in the pre-test period (see Box 2).
[b] Adjusted for presence of sore throat.

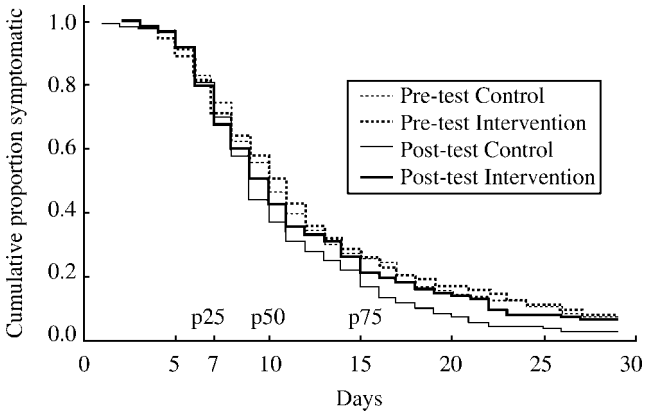


Figure 2. Symptom resolution of patients with acute cough: graph of time to symptom resolution versus cumulative proportion of symptomatic patients (Kaplan–Meier).

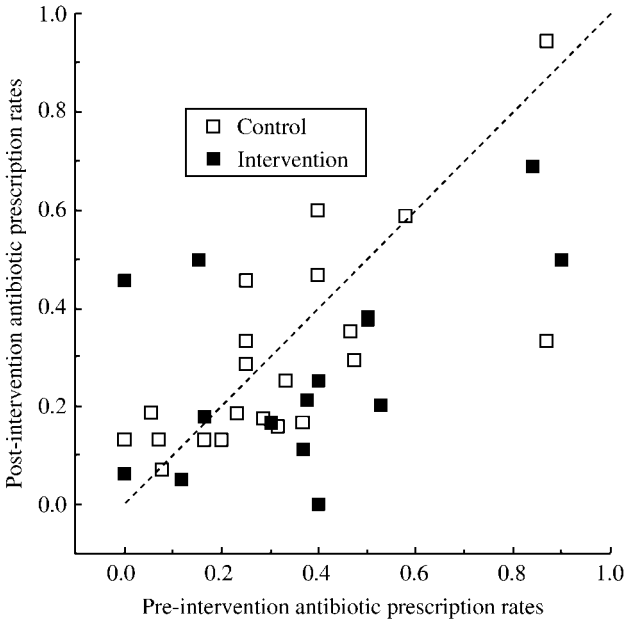


Figure 3. Rate of antibiotic use in consultations for acute cough before and after the tailored interventions from all practices with more than 10 consultations in each period.

Discussion

We were able to show that a tailored intervention to implement a guideline for acute cough optimized GPs' antibiotic prescribing for adult patients with acute cough. Compared with controls, patients in the intervention group were prescribed less antibiotics. If GPs in the intervention group prescribed antibiotics, these were more in line with the guideline, although not significant at the 5% significance level. No significant differences were found in the resolution of patients' symptoms.

This kind of trial should not only contribute to evidence of the effect, but also to understanding of the mechanism.

The evidence of effect

Study limitations. The results may be biased due to the recruitment and non-response of GPs and patients. The recruited GPs did not differ from the other 64 GPs approached for this study nor from the other 108 GPs responding in the questionnaire study,[20] as we reported elsewhere.[39] However, more male GPs agreed to participate (63/85 versus 36/64: $P = 0.02$, versus 64/108: $P = 0.03$, respectively). Furthermore, their age and sex distribution is similar to national averages. No response was due to motivational problems regarding data collection and was similar in both study groups. Responding and non-responding GPs, and GPs in both study groups were similar also for pre-intervention antibiotic prescribing. Since GPs were responsible for selecting patients into the trial, there was a possibility of selection bias. However, we do not believe there is evidence that in the intervention group other patients were selected in the post-intervention period. Attempting to audit that patients were in fact consecutive patients we asked GPs to keep records of those

patients eligible for recruitment but not included. The proportion of patients eligible for recruitment actually included in the study, the proportion of the included patients eligible for analysis and the proportion of the latter patients responding with patient diaries, as well as the median cluster size was similar in both study groups and study periods. It was not feasible to increase the sample size for the post-test because GPs were unable to include more than 10 patients on average per study period.

Furthermore, the characteristics of the patients in the intervention group post-intervention did not differ from the characteristics of the patients in the intervention group pre-intervention, nor did they differ from the characteristics of the patients in the control group post-intervention, except for thrombo-embolic risk. The latter difference, however, already existed pre-intervention.

We only registered information on variables that were a priori identified as influencing the antibiotic prescribing decision. All these variables were tested for significance. The likely impact of type I errors is limited to the effect of the covariates duration of cough, and the presence of sputum, ronchi and of loss of appetite on antibiotic prescribing. The significant differences found for these characteristics all point in the same direction, suggesting that these findings represent a true difference rather than a difference due to chance.

The professional intervention. Adjusting the main outcome measure, the antibiotic prescribing rate, for these differences, patients in the intervention group were less likely to receive an antibiotic prescription compared with controls after our intervention.

We might have underestimated the rates for antibiotic prescription because the practitioners may not have registered this information correctly in some instances on the pre-printed forms we provided. This is unlikely to have differed between the groups and is therefore unlikely to have affected the results. It is possible that we underestimated the reduction in the prescription of antibiotics for acute cough. We do not know how often patients were told that antibiotics normally are not necessary but received an antibiotic prescription for use 'if needed'. However, we know from the patient diaries that patients in the intervention group did not purchase or take the prescribed antibiotics less often than patients in the control group. Figure 3 shows the importance of using adequately sized cluster-randomized controlled trials to evaluate interventions to support the implementation of guidelines. Large variations exist in practice and in the extent of change among practices.

The public campaign. A national campaign, which coincided with our professional intervention, provided health education for the general public. Though the study does not, and did not set out to, compare the effect of the coincidence of a national public campaign and a professional intervention, the design of our study also allowed us to test for an effect of the national public campaign on the antibiotic prescription rates for acute cough. We agree with Flottorp *et al.*[40] that uncontrolled or inadequately controlled before and after evaluations in selected practices are likely to have spurious results that are, at best, difficult to interpret. Nonetheless, the similarities of the effectiveness of our intervention when assessing differences between the intervention and control groups after our intervention and when assessing pre-post differences in the intervention group, together with the absence of pre-post differences in the control group, when adjusting for differences in patient characteristics, suggests that the national campaign had no effect on antibiotic prescribing after our intervention.

In contrast to the public campaign our professional intervention resulted not only in a reduction of antibiotic consumption, it also changed the type of antibiotics prescribed from less desirable to more desirable antibiotics.

Price to pay. This trial on the implementation of a guideline to optimize antibiotic prescribing not only looked at prescribing as outcome, but took patient outcomes into account as well. Though antibiotics are not needed for most patients with acute cough, indiscriminately reducing antibiotic use will withhold some patient subgroups from the benefits of antibiotics. A retrospective study recently showed a weak association between lower rates of antibiotic prescribing and increased community-acquired pneumonia mortality in England and Wales.[41] Still, evidence for possible harm of our approach is limited. In our study less and other antibiotics prescribed by the GP did not affect the time to symptom resolution of the patients in the intervention group compared with the controls after our intervention, nor did it affect reconsultation or hospitalization rates. Furthermore, the potential increase of serious complication[42] must be weighed against the potential adverse effects.[43]

Another notable aspect of our study was the short duration of the educational intervention compared with some other studies that have used repeated education over several weeks; for example, to improve adolescent health care.[44] Despite the responding GPs being visited more than 15 times per month by medical representatives, a single outreach visit resulted in the desired changes during follow up.

We reached 36 of 42 GPs with our complete intervention at a total cost of €8514.22 (intervention material, training facilitators and visits), or €236.51 per GP visited. The intervention resulted in a significant reduction in the reimbursement cost for antibiotics from the perspective of the NSIII of nearly €7 per patient.

Understanding the mechanism

Recently, Gross & Pujat[45] concluded that for implementing guidelines for appropriate antimicrobial usage multifaceted implementation methods seem to be the most successful. Although more complex interventions to implement guidelines tend to be most effective, their effectiveness varies, they require more resources and it is difficult to know which interventions to use. Identifying barriers to change and tailoring interventions to address these is a logical approach to selecting appropriate interventions. Still, the effectiveness of tailored interventions remains uncertain.[40] Two recent cRCTs reported the effect of interventions addressing either general practices[40] or primary healthcare teams,[46] not individual GPs. In contrast to the small effect of a tailored intervention on the antibiotic prescribing rates for sore throat,[40] the small effect of educational outreach visits on the uptake of pneumococcal vaccination, and no effect of such visits, coinciding with a national campaign, on influenza vaccination,[46] our intervention had a substantial effect on antibiotic prescribing.

Instead of a 'one size fits all' approach, we really tailored the interventions to the needs of individual general practitioners. Tailoring the intervention at this level might have greater effect. After all, individual approaches seem to have a greater impact on prescribing than group approaches.[47,48] The individual

approach of face-to-face meetings, and academic detailing, to improve antibiotic prescribing proved to be successful in eight studies in primary care.[44] Furthermore, we actively supported the GPs with outreach visits and we might have identified important barriers to change. Our educational programme addressed mainly the issues relating to the individual prescriber's barriers to change, focusing on non-medical reasons for prescribing. We did not provide individual feedback on prescribing nor on decision criteria.[49] Studies of scoring rules for sore throat have failed to show that they lower the rates for antibiotic prescription.[50,51]

We have not identified trials of the implementation of a guideline for acute cough similar to ours. The key messages of the pre-final version of the guideline used for this cRCT are the same as those of the final version,[52] also available now for all GPs at http://www.wvvh.be. Although our evidence base was rather poor, and uncertainty about the evidence may affect doctor's behaviour, identifying, understanding and modifying tacit expert knowledge and promoting the ownership of change amongst professionals appeared to be more important in altering behaviour in accordance with the guideline.[53]

If we also distinguish between an agenda for action and one for future research, the evidence of effectiveness supports this implementation strategy of the guideline to optimize antibiotic prescribing on a larger scale. Further research efforts should be devoted to understanding the interaction between public campaigns and professional interventions and to cost-effectiveness studies. Whereas the public campaign transiently reduced antibiotic consumption and saved money,[23,24] the involvement of the prescribers has the potential of influencing the prescribing decision as well, for example, the type of antibiotics prescribed. In addition interventions to optimize antibiotic prescribing should prospectively monitor the incidence of serious complications of respiratory tract infections.

Conclusions

The described strategy to support the implementation of the guideline, tailored to address identified barriers to the optimization of antibiotic prescribing for acute cough, achieved the goals of the public campaign: 'Antibiotics: Use them less often, but better'.

This trial is assigned the International Standard Randomized Controlled Trial Number (ISRCTN) ISRCTN09811591 by Current Controlled Trials Ltd.

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Conflict of interest statements

None declared.

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