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Improvement of antibiotic prescription in outpatient care: a cluster-randomized intervention study using a sentinel surveillance network of physicians

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Objectives: To assess the effectiveness of implementing guidelines, coupled with individual feedback, on antibiotic prescribing behaviour of primary care physicians in Switzerland.

Methods: One hundred and forty general practices from a representative Swiss sentinel network of primary care physicians participated in this cluster-randomized prospective intervention study. The intervention consisted of providing guidelines on treatment of respiratory tract infections (RTIs) and uncomplicated lower urinary tract infections (UTIs), coupled with sustained, regular feedback on individual antibiotic prescription behaviour during 2 years. The main aims were: (i) to increase the percentage of prescriptions of penicillins for all RTIs treated with antibiotics; (ii) to increase the percentage of trimethoprim/sulfamethoxazole prescriptions for all uncomplicated lower UTIs treated with antibiotics; (iii) to decrease the percentage of quinolone prescriptions for all cases of exacerbated COPD (eCOPD) treated with antibiotics; and (iv) to decrease the proportion of sinusitis and other upper RTIs treated with antibiotics. The study was registered at ClinicalTrials.gov (NCT01358916).

Results: While the percentage of antibiotics prescribed for sinusitis or other upper RTIs and the percentage of quinolones prescribed for eCOPD did not differ between the intervention group and the control group, there was a significant increase in the percentage of prescriptions of penicillins for all RTIs treated with antibiotics [57% versus 49%, OR=1.42 (95% CI 1.08–1.89), $P=0.01$] and in the percentage of trimethoprim/sulfamethoxazole prescriptions for all uncomplicated lower UTIs treated with antibiotics [35% versus 19%, OR=2.16 (95% CI 1.19–3.91), $P=0.01$] in the intervention group.

Conclusions: In our setting, implementing guidelines, coupled with sustained individual feedback, was not able to reduce the proportion of sinusitis and other upper RTIs treated with antibiotics, but increased the use of recommended antibiotics for RTIs and UTIs, as defined by the guidelines.

Keywords: ambulatory, guidelines, antibiotic prescribing

Introduction

Antibiotic resistance is increasing rapidly worldwide. While increasing resistance rates were initially mainly described in the hospital setting, resistant microorganisms such as penicillin-resistant *Streptococcus pneumoniae*, community-acquired MRSA and *Escherichia coli* or *Klebsiella* spp. producing ESBLs are increasingly observed in the ambulatory setting. It has been shown previously at the population level that the volume of outpatient antibiotic use in a given area is significantly associated with resistance rates in that area,[1] and even that community antibiotic use may influence resistance rates in the hospital.[2] In addition,

several reports described the association between antibiotic use in primary care and the development of resistance in individual patients.[3,4] In ambulatory medicine, antibiotics are most commonly prescribed for respiratory tract infections (RTIs).[1,5] Broad-spectrum agents are more likely to be prescribed for this indication than narrow-spectrum agents.[5] This is especially menacing as, besides the volume of antibiotics prescribed, the spectrum of antibiotics may also have an impact on the development of resistance, with broad-spectrum antibiotics exerting a higher ecological pressure.[6]

Whether a reduction in antibiotic consumption leads to a reduction in resistance rates is still a matter of debate and seems to depend on the microorganisms and antibiotics tested. While most studies were performed in the hospital setting, where infection control measures could have influenced the results, some studies demonstrated the reversibility of resistance development following reduction in antibiotic consumption in the ambulatory setting.[7–11] As antibiotic prescriptions in ambulatory care exceed antibiotic use in hospitals,[1] improving antibiotic prescription in the ambulatory setting might be even more important in stopping or reversing the increasing antibiotic resistance rates in the ambulatory setting, and indirectly in the hospital setting.

Using the Swiss Sentinel Surveillance Network of physicians,[12] we performed a cluster-randomized intervention study to analyse the influence of detailed antibiotic prescription guidelines on prescription behaviour. The intervention aimed to simultaneously reduce antibiotic prescription rates and modify the antibiotics used in the two most important infections [upper RTIs and uncomplicated lower urinary tract infections (UTIs)]. To improve and sustain the impact of the intervention, guidelines were combined with iterative regular feedback on individual prescription behaviour over 2 years.

Methods

Study design and data collection

This open, prospective, cluster-randomized intervention study was performed within the framework of the Swiss Sentinel Surveillance Network (https://www.sentinella.ch), covering 3.1% of all Swiss practitioners in primary care.[12]

Antibiotic prescription data were collected on a weekly basis by the Swiss Federal Office of Public Health (SFOH) from 1 January 2011 to 31 December 2012. Antibiotic prescriptions were categorized into penicillins (including combinations with penicillinase inhibitors), cephalosporins, macrolides, trimethoprim/sulfamethoxazole, quinolones, tetracyclines, glycopeptides, oxazolidinones and other. Diseases were categorized into upper RTIs (including streptococcal angina, otitis media, sinusitis, acute bronchitis, other upper RTIs), lower RTIs [including exacerbated COPD (eCOPD) and pneumonia] and lower uncomplicated UTIs. For each antibiotic prescription, we collected the following dataset: patient age, gender, previous antibiotic therapy since November of the preceding year, perceived patient's attitude to antibiotic prescription ('insistent', 'not insistent'), disease category and the antibiotic group prescribed. In the case of multiple prescriptions only the first prescription per patient and year was analysed. Incomplete datasets were queried continuously by the SFOH, were therefore rare and were removed from the dataset (in total four were missing for 'indication' and five were missing for 'antibiotic class').

Baseline characteristics of each practice were obtained by a separate questionnaire before the start of the study. In an additional survey in the same practices during 4 weeks in spring and 4 weeks in autumn each year, we collected data on the total number of cases with sinusitis or other upper RTIs.

At the end of the study all data were delivered by the SFOH to the Clinical Trials Unit Bern, University of Bern, in Excel format. The study was registered at ClinicalTrials.gov (NCT01358916) and was exempted by the ethics committee from the need to obtain patients' informed consent because treatment followed current guidelines.

Participants

All registered sentinel members as of May 2010 were evaluated for participation in this study. We excluded (i) members of the programme committee and (ii) non-regularly reporting members, defined as members not reporting at least one physician–patient contact in at least 75% of the weeks from August 2009 to July 2010. Finally, 140 members were included and randomly allocated to either the control or the intervention group in a 1:1 ratio.

Intervention

The intervention consisted of two activities: guidelines for antibiotic prescription in RTIs and UTIs, which were developed by the Pediatric Infectious Disease Group of Switzerland and—for adult patients—by an *ad hoc* committee of adult infectious disease specialists. Guidelines included indications for antibiotic use as well as information on the preferred antibiotic regimen (see Supplementary data, available at *JAC* Online). The main focus of the guidelines was to restrict prescriptions to bacterial infections and to preferentially prescribe narrow-spectrum antibiotics, namely penicillins for RTIs and trimethoprim/sulfamethoxazole for uncomplicated lower UTIs. Physicians allocated to the intervention group received these guidelines in November 2010 and again in April 2012. In addition they were provided twice yearly with a reminder, including individual feedback on their antibiotic prescription pattern for all four primary and secondary endpoints, compared with the aggregated data of the other members of the intervention group.

Aim of the study and outcome measures

With this study we aimed to analyse whether an intervention at physician level would be able to influence the prescription pattern of the individual physicians. The primary objectives were: (i) to increase the percentage of prescriptions of penicillins for upper and lower RTIs over all upper and lower RTIs treated with antibiotics; and (ii) to increase the percentage of trimethoprim/sulfamethoxazole prescriptions for uncomplicated lower UTIs over all uncomplicated lower UTIs in adults (≥17 years) treated with antibiotics. The secondary objectives were: (i) to decrease the percentage of quinolone prescriptions for eCOPD over all eCOPD in adults (≥17 years) treated with antibiotics; and (ii) to decrease the percentage of antibiotic prescriptions for sinusitis and other upper RTIs over all diagnosed sinusitis and other upper RTIs.

In addition, we evaluated the primary and secondary objectives at practice level and studied the influence of patient factors (age, gender, attitude to antibiotic prescription) and practice level factors [practice type (one versus more than one physician), practice specialization and language region (French/Italian- versus German-speaking part of Switzerland)] on the effect of the intervention concerning the primary and secondary outcomes. Additional pre-specified objectives were defined and are summarized in the Supplementary data.

Randomization and blinding

Stratified randomization was performed to randomly allocate the practices to the intervention or control arm in a 1:1 ratio. Variables used for stratification were practice specialization (paediatric versus internal or

general), size of cluster (≤100 versus >100 prescriptions per year) and baseline performance of prescription of penicillins for RTIs (≤50% versus >50%) based on data collected between August 2009 and July 2010. Practices were not blinded to allocation.

Statistical analysis

We performed an initial power analysis based on data collected for 1 year before study start, which was updated 9 months after study start. Based on 16863 cases with RTIs and 4245 cases with lower UTIs per year, baseline proportions of 46.6% and 18.9% and intra-class correlations of 0.28 and 0.37, we calculated a power of 0.99 and 0.92 to detect an increase in the proportion of penicillin prescriptions to 60% and an increase in the proportion of trimethoprim/sulfamethoxazole prescriptions to 30%, respectively, with a two-sided type I error of 0.05. Exact details of the power calculation are given in the Supplementary data.

Outcomes at patient level were analysed using mixed-effects logistic models that take into account the correlation of data within practices. Adjustment was done for all stratification factors used in the randomization procedure. The influence of other co-factors on the intervention effect was studied by stratified analyses incorporating an interaction term between the co-factor and the intervention into the mixed-effects logistic model.

To compare prescription rates averaged at practice level, we excluded practices with fewer than five cases in total. Absolute differences concerning the proportions of the prescriptions for the study drug between the two groups were derived from linear regression models, adjusting for all stratification factors used in the randomization. We assessed the goodness of fit of linear regression models by R^2. Goodness of fit of mixed-effects logistics models was investigated by plotting deviance residuals against predicted values. The resulting graphs revealed no extreme observations. A more detailed description of the regression analyses is provided in the Supplementary data. In the primary analysis, we used the full analysis set, including all practices as randomized (ITT principle). In sensitivity analyses, we used different adjustment schemes as well as a PP analysis set, where data from practices joining the programme committee of the study during the study, leaving the Sentinel network within 12 months from the start of data collection or notifying <20 prescriptions in total were excluded.

All endpoint definitions and statistical methods were pre-defined in a statistical analysis plan before evaluation of the data and strictly followed during analysis. For the analysis of the primary and secondary endpoints, the data analyst was blinded to the intervention assignment. Once the primary and secondary endpoints were analysed, the data analyst was unblinded. All analyses were done using Stata 12 (Stata Corporation, College Station, TX, USA).

Results

Practice and patient flow

Between randomization and the start of data collection, three practices from the control group (4.3%) and one practice from the intervention group (1.4%) left the sentinel network. Therefore, 67 practices were finally analysed in the control group and 69 in the intervention group.

During the study period, a total of 34682 antibiotic prescriptions were collected. Two thousand seven hundred and twenty-six (17%) out of 16053 prescriptions in the control group and 3004 (16%) out of 18629 prescriptions in the intervention group were excluded from analysis because antibiotics had been prescribed previously, leaving 13327 and 15625 prescriptions for analysis in the control and intervention groups, respectively. The average number (SD) of prescriptions per practice was 199 (156) and 226 (201) in the control and intervention groups, respectively.

Table 1. Baseline characteristics

	Control	Intervention
Practice characteristics		
total, *n*	67	69
practice specialization (paediatric versus internal or general), *n* (%)	8 (11.9)	9 (13.0)
practice size (>100 prescriptions per year at baseline), *n* (%)	41 (61.2)	40 (58.0)
high rate of prescription of penicillins at baseline (>50% for RTIs), *n* (%)	32 (47.8)	31 (44.9)
group practice (>1 physician per practice), *n* (%)	28 (41.8)	26 (37.7)
French/Italian-speaking south-western part of Switzerland (versus German-speaking north-eastern part), *n* (%)	24 (35.8)	22 (31.9)
Patient characteristics		
total, *n*	13327	15625
age, years, median (IQR)	38 (12–61)	33 (10–58)
age category, years, *n* (%)		
0–5	2041 (15.3)	2486 (15.9)
6–16	1709 (12.8)	2665 (17.1)
17–64	6690 (50.2)	7483 (47.9)
≥65	2887 (21.7)	2991 (19.1)
female, *n* (%)	8024 (60.2)	9273 (59.3)
insisting on antibiotics, *n* (%)	1790 (13.4)	1847 (11.8)
indication, *n* (%)		
angina	1976 (14.8)	2736 (17.5)
otitis media	1920 (14.4)	1817 (11.6)
sinusitis	1572 (11.8)	1637 (10.5)
other upper RTIs	1874 (14.1)	2397 (15.3)
acute bronchitis	1868 (14.0)	2211 (14.2)
COPD exacerbation	451 (3.4)	524 (3.4)
pneumonia	799 (6.0)	891 (5.7)
lower UTIs	2867 (21.5)	3412 (21.8)

Baseline characteristics

Baseline characteristics of included practices and patients are shown in Table 1.

There were only minor differences between the control and the intervention groups.

Primary objectives

The percentage of prescriptions of penicillins for all treated RTIs was significantly higher in the intervention group [OR 1.42 (95% CI 1.08–1.89); Table 2]. This difference was mainly driven by a high increase in the French/Italian-speaking part of Switzerland [from 35% to 63%, OR 2.81 (95% CI 1.78–4.45)], whereas prescription rates did not differ between groups in the

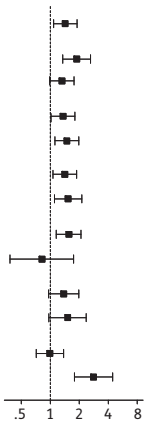
Table 2. Comparison of antibiotic prescription rates between the intervention group and the control group

	Control		Intervention				
	total number of patients treated with antibiotics	%	total number of patients treated with antibiotics	%	ICC	OR (95% CI)	*P* value
Prescriptions of penicillins for RTIs (%)	10460	48.5	12213	56.7	0.27	1.42 (1.08–1.89)	0.01
Prescriptions of SXT for lower UTIs in adults (%)	2744	18.8	3217	35.1	0.44	2.16 (1.19–3.91)	0.01
Prescriptions of quinolones for COPD exacerbation in adults (%)	450	4.7	522	4.8	0.50	1.02 (0.36–2.88)	0.96

ICC, intra-class correlation; SXT, trimethoprim/sulfamethoxazole.
Proportions, ICCs, ORs and *P* values were derived from a mixed-effects logistic model.

Table 3. Comparison of penicillin prescription rate for RTIs among subgroups

		Total number	OR (95% CI)[a]	*P* value[a]	Graph
Overall		22673	1.42 (1.08–1.89)		
Age	0–16 years	8583	1.88 (1.35–2.62)	0.001	
	≥17 years	14090	1.32 (0.99–1.76)		
Gender	male	10573	1.35 (1.01–1.80)	0.13	
	female	12100	1.48 (1.11–1.97)		
Insisting on antibiotics	no	19773	1.41 (1.06–1.88)	0.44	
	yes	2900	1.53 (1.10–2.13)		
Paediatric practice	no	15821	1.55 (1.15–2.09)	0.12	
	yes	6852	0.81 (0.38–1.74)		
Group practice	no	15046	1.37 (0.96–1.97)	0.75	
	yes	7627	1.51 (0.96–2.36)		
Region	German	14213	0.99 (0.71–1.37)	<0.001	
	French/Italian	8460	2.81 (1.78–4.45)		



[a]Calculated from a mixed-effects logistic model with a *P* value for interaction.

German-speaking part of Switzerland (Table 3). The effect of the intervention tended to be smaller in paediatric than in general/internal practices. Interestingly, the effect of intervention was significantly larger in children than in adults. This also held true when looking separately at general and internal practices (*P* value for interaction = 0.002) or paediatric practices (*P* value for interaction = 0.05).

The percentage of trimethoprim/sulfamethoxazole prescriptions for all treated uncomplicated lower UTIs in adults was also significantly higher in the intervention group [OR 2.16 (95% CI 1.19–3.91); Table 2]. Again the difference was much higher in the French/Italian-speaking part of Switzerland [6.8% versus 35%, OR 5.91 (95% CI 2.05–17.00)] than in the German-speaking part of Switzerland [28% versus 36%, OR 1.35 (95% CI 0.68–2.66); Table 4].

Secondary objectives

The percentage of quinolone prescriptions for eCOPD in adults did not differ between groups (Table 2). There were no differences between different subgroups of region, gender, practice type or attitude (data not shown). Analysis of averaged proportions at practice level revealed congruent results (Table 5 and Figure 1). Antibiotics were prescribed in about one-third of all patients with sinusitis or other upper RTIs, irrespective of the group (Table 5).

Sensitivity analysis

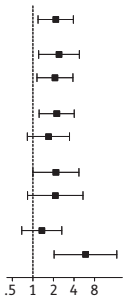
We repeated the main analysis (i) without any adjustment, (ii) adjusting additionally for age and gender and (iii) using the PP analysis set. All of these additional analyses led to results very similar to those of the main analysis (data not shown).

Discussion

In this cluster-randomized trial, antibiotic prescription guidelines and regular feedback on individual prescription behaviour resulted in an increase in the use of penicillins for upper RTIs and

Table 4. Comparison of trimethoprim/sulfamethoxazole prescription rate for uncomplicated lower UTIs in adults among subgroups

		Total number	OR (95% CI)[a]	*P* value[a]	Graph
Overall		5961	2.16 (1.19–3.91)		
Gender	male	1032	2.41 (1.21–4.77)	0.48	
	female	4929	2.10 (1.14–3.86)		
Insisting on antibiotics	no	5238	2.23 (1.23–4.04)	0.23	
	yes	723	1.69 (0.83–3.44)		
Group practice	no	3825	2.17 (1.00–4.72)	0.97	
	yes	2136	2.12 (0.83–5.41)		
Region	German	4466	1.35 (0.68–2.66)	0.02	
	French/Italian	1495	5.91 (2.05–17.00)		



[a]Calculated from a mixed-effects logistic model with a *P* value for interaction.

Table 5. Comparison of antibiotic prescription rates at practice level

	Control		Intervention		Difference in proportion	
	total (*n*)	%	total (*n*)	%	(95% CI)[a]	*P* value[a]
Prescribing rate of penicillins for RTIs treated with antibiotics	67	48.7	68	55.8	8.0 (2.3–13.6)	0.006
Prescribing rate of SXT for lower UTIs in adults treated with antibiotics (internal/general practices only)	57	26.4	55	39.0	12.4 (3.3–21.6)	0.009
Quinolone prescribing rate for COPD exacerbation in adults treated with antibiotics (internal/general practices only)	28	10.5	33	13.3	2.2 (−7.6–12.1)	0.66
Prescription rate for all diagnosed sinusitis and other upper RTIs	66	34.4	67	32.5	−1.2 (−10.5–8.2)	0.80

SXT, trimethoprim/sulfamethoxazole.
[a]Absolute differences between groups and corresponding CI and *P* values were derived from a linear regression model adjusting for all stratification factors used in the randomization. The goodness of fit of the models, expressed as R^2, was 0.48, 0.05, 0.05 and 0.02 from top to bottom.

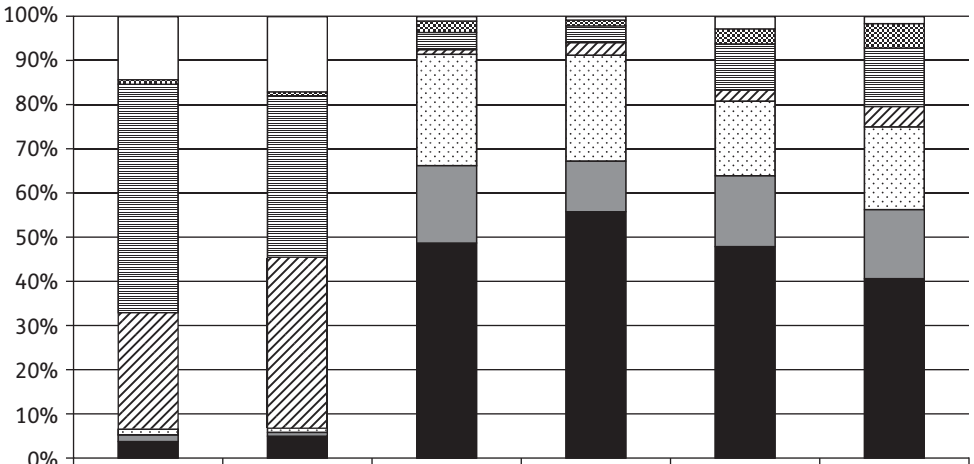
trimethoprim/sulfamethoxazole for uncomplicated lower UTIs, but did not affect the total amount of antibiotics prescribed for sinusitis or other upper RTIs. This is in agreement with other studies, demonstrating that using printed material and feedback for physician education was not able to improve their prescribing or only improved it by a small amount, whereas patient-based interventions or even more multifaceted interventions could reduce antibiotic prescribing.[13–15] In general, active clinical education strategies seem to be more efficient than passive strategies,[13,16] and training in enhanced communication skills could be one important element of these strategies.[17,18] In addition, the effect of even complex intervention programmes may depend on the infections studied.[19]

Our intervention was successful in (i) increasing the percentage of prescriptions of penicillins for all RTIs treated with antibiotics, paralleled by a decrease in cephalosporin use, while macrolide consumption was stable, and (ii) increasing the percentage of trimethoprim/sulfamethoxazole prescriptions for all uncomplicated lower UTIs treated with antibiotics, paralleled by a decrease in the quinolone prescription rate. For both indications, the increase was significantly more pronounced in the French/Italian-speaking region of Switzerland, which is known to have higher outpatient antibiotic prescription rates than the German-speaking part of Switzerland.[20,21]

In RTIs, the intervention was more effective in children. There is some indication that the intervention was less effective in paediatric practices than in general or internal practices; however, the difference was non-significant (*P* value for interaction = 0.12). Two hypotheses may explain this difference. First, as amoxicillin syrup is widely used in all paediatric practices for RTIs, as reflected by an amoxicillin prescription rate for RTIs of 82.1% in the control group, improvement in this subgroup is hardly possible, also taking into account the contraindications, namely allergic reactions. Second, the paediatric guidelines existed before this study began. They were not advertised in the control group, but nevertheless were available on the internet, which might have further reduced the effect of the intervention.

Prescription of quinolones for lower RTIs in adults should only be considered when there are clinically relevant bacterial resistance rates against all first-choice agents.[11] Nevertheless, we were not able to reduce quinolone use in COPD exacerbations. We suppose that this is due to the already very low quinolone prescription rate and the relative low number of patients in this group.

So far, antibiotic stewardship programmes have mainly been recommended for hospitals. For outpatient care only a few recommendations are offered, largely because of the paucity of data regarding effective interventions.[22] There are few studies describing the effect of an outpatient antimicrobial stewardship



	Control	Intervention	Control	Intervention	Control	Intervention
	lower UTI		RTI		eCOPD	
☐ Others	14.3	17.0	1.1	0.7	2.7	1.6
▩ Tetracyclines	0.7	0.9	2.3	1.4	3.4	5.6
▤ Quinolones	52.1	36.5	3.9	3.9	10.5	13.3
▨ SXT	26.4	39.0	1.2	2.6	2.6	4.6
⁙ Macrolides	1.3	1.0	25.3	24.1	16.8	18.7
▒ Cephalosporins	1.5	0.6	17.5	11.6	16.1	15.5
■ Penicillins	3.6	5.0	48.7	55.8	47.8	40.7

Figure 1. Antibiotic prescription rates averaged at practice level for treated RTIs, lower UTIs in adults (internal/general practices only) and eCOPD in adults (internal/general practices only) in the control and intervention groups. SXT, trimethoprim/sulfamethoxazole.

intervention on the selection of the preferred antibiotic. In a cross-sectional study Bhattacharyya *et al.*[14] observed an increase in the proportion of patients treated with amoxicillin as the agent of choice from 8.1% to 29.4% after publication of treatment guidelines for sinusitis in adults. In another study[22]—using a 1 h education session, quarterly audits and regular feedback as intervention tools—broad-spectrum prescriptions for RTIs in a paediatric population were reduced from 26.8% to 14.3%, which compares well with the absolute increase in prescription of penicillins of 13.4% in patients below age 17 in our study.

Our study has several strengths. Randomization was done by practice and there were no significant differences between the groups. Data analysis proved to be very stable, as ITT analysis, PP analysis and analysis at practice and patient levels all led to congruent results.

There were some limitations in our study. First, practices were not blinded to allocation and practices participating in the sentinel network are probably not representative of all Swiss physicians. However, we believe that the high interest of study physicians in infectious diseases and knowledge of the study design probably led to better results in the control group, which would rather underestimate the effect of our study. Second, the cluster-randomized design did not allow prescription patterns to be studied within individual practices. Third, we do not have any data on the duration of therapy or the DDDs used. Fourth, we were not able to identify which part of the intervention was most effective. Fifth, we did not analyse whether outcomes were different between groups, although there are some data in the literature showing that outcomes and satisfaction of patients are not influenced by the prescription pattern.[16,18] Sixth, we did not measure the sustainability of the effect, but there is some evidence that effects may be sustained for years.[17] Seventh, as participants did not cover a complete geographical region, we were not able to study the effect of this intervention on resistance prevalence.

We conclude that publication of guidelines and individual feedback to prescribers may influence prescription behaviour. It may be easier to modify the preferred antibiotic than the total antibiotic prescription rate. Knowledge of the size of the effect in individual subgroups is important for better targeting of further interventions.

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Transparency declarations

We affirm that the manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

We declare: no support from any organization for the submitted work besides the acknowledged financial support from anresis.ch; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work. A. K. reports grants from ESCMID and personal fees from ArjoHuntleigh for an independent lecture outside the submitted work.

Supplementary data

Supplementary data are available at *JAC* Online (http://jac.oxfordjournals.org/).

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