JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac070

JAC-Antimicrobial Resistance

Nationwide implementation of online communication skills training to reduce overprescribing of antibiotics: a stepped-wedge cluster randomized trial in general practice

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Received 18 October 2021; accepted 7 June 2022

Objectives: Primary care is responsible for a large proportion of unnecessary antibiotic use, which is one of the main drivers of antibiotic resistance. Randomized trials have found that online communication skills training for GPs reduces antibiotic prescribing for respiratory infections. This study assesses the real-world effect of implementing online communication skills training in general practice.

Methods: In a closed cohort stepped-wedge cluster randomized trial all Belgian GPs were invited to participate in online communication skills training courses (TRACE and INTRO) and provided with linked patient information booklets. The primary outcome was the antibiotic prescribing rate per 1000 patient contacts. Intention-to-treat and per protocol analyses were performed. Trial registration at ClinicalTrials.gov: NCT03265028.

Results: In total, 118 487 observations from 10 375 GPs were included in the analysis. Overall, 299 (2.88%) GPs completed TRACE and 93 (0.90%) completed INTRO, 30 of which completed both. There was no effect of the national implementation of TRACE and INTRO on the population-level antibiotic prescribing rate (prescribing rate ratio [PRR] = 0.99 [95% CI: 0.97–1.02]). GPs who actually completed TRACE prescribed fewer antibiotic prescriptions (PRR = 0.93 [95% CI: 0.90–0.95]).

Conclusions: Inviting GPs to complete an online communication skills training course and providing them with the linked patient information booklets did not reduce antibiotic prescribing. However, GPs who completed TRACE prescribed 7% fewer antibiotics, especially during winter. This suggests a significant decrease in population-wide antibiotic consumption could be achieved by focusing on increasing the uptake of this intervention by identifying and overcoming barriers to participation.

Introduction

Antibiotic resistance poses an increasing threat to public health, making infections harder to treat and causing more severe complications.[1] Overconsumption of antibiotics is one of the main drivers of antibiotic resistance.[2–4] This overconsumption is common in primary care, where patients with lower respiratory tract infections (LRTIs) are prescribed antibiotics, even though these infections are often viral and antibiotics have little to no effect.[5,6]

While GPs are aware of the risks of antibiotic resistance and the limited efficacy of antibiotics in treating LRTIs, prescribing rates remain high.[7,8] Lack of postgraduate training, feeling pressured by the patient, higher patient numbers, shorter

consultation length and diagnostic uncertainty have been identified as factors contributing to higher prescribing rates.[9] Consequently, interventions were developed to address these factors.

GRACE INTRO (INTRO) is an intervention aimed at reducing unnecessary antibiotic prescribing by providing GPs with online training in communication skills and/or training in the use of point-of-care C-reactive protein testing to be linked to a peer-led audit meeting on prescribing.[10] In the communication skills training, GPs learn to gather more information on the patients' concerns and expectations; to provide more information on symptoms, the course of disease, benefits and harms of antibiotic treatment; to agree on a management plan; to sum up the consultation; and to provide guidance about when to reconsult. An interactive booklet is provided, which summarizes relevant patient information on aetiology, self-management, safety-netting advice for LRTIs and antibiotic use. Communication skills and use of the booklet are illustrated through video material. INTRO has been proven effective in reducing antibiotic prescribing (risk ratio = 0.69 [95% CI: 0.54–0.87]),[7,10–14] in a cost-effective way,[15] and for the longer term.[16] TRACE, a shorter and more accessible version of INTRO, was developed by a multidisciplinary team of primary care researchers involved in the development of INTRO and with the input of experts in learning theories. It offers the part of INTRO GPs deemed most effective, namely communication skills training combined with using the booklet.[11] For TRACE the booklet was supported by the European Antibiotic Awareness Day coordinated by ECDC.[17] Both INTRO and TRACE were available through the e-learning platform hosted by the Belgian National Institute for Health and Disability Insurance (NIHDI) and the Federal Public Service of Health. TRACE is accessible online through www.acutecough.org. The first module of TRACE can be completed in 10 min, INTRO in just over half an hour.

This study aimed to evaluate the nationwide implementation of TRACE and INTRO in a pragmatic setting, where several parallel interventions aimed at reducing antibiotic prescribing exist[18] and where GPs decide for themselves about participation. A randomized trial with a stepped-wedge design was selected as the optimal design for this purpose.[19] We hypothesize that inviting all GPs in Belgium to participate in TRACE and INTRO will result in a small (1%–2%) decrease in antibiotic prescriptions at the population level, but translating into large absolute effects due to the large scale at which the intervention is implemented. Secondarily, this study aims to evaluate the effect of actual participation in TRACE or INTRO on GPs' antibiotic prescribing rate. We hypothesize there will be a moderate (5%–10%) decrease in the antibiotic prescribing rate.[20]

Methods

Study design

In a closed cohort, unblinded, stepped-wedge cluster-randomized trial, clusters shift stepwise from the control to the intervention condition. The national implementation study was performed over 17 months. Clusters were defined as the 10 Belgian provinces (5 Flemish, 5 Walloon) and the Brussels Capital Region. These 11 clusters were randomly divided over six sequences, with 2 clusters (1 Flemish, 1 Walloon) crossing over to the intervention condition in each sequence, except for the fifth sequence in which only Brussels changed conditions (see Supplementary data, available at *JAC-AMR* Online). The time between each sequence crossing over from the control to the intervention condition was 1 month. Each cluster provided data on the 6 months before and on the 6 months after crossing over to the intervention condition, making the design balanced at the cluster level. Outcome measures were routinely collected and calculated for all participants in each period. Figure 1 shows when clusters transitioned from the control to the intervention condition. The trial is registered at ClinicalTrials.gov (NCT03265028).

Participants

All Belgian GPs registered with NIHDI as qualified in general medicine were eligible. Exclusion criteria were GPs associated with a hospital, as they potentially did not provide primary care; GPs who worked in a community healthcare centre, as they operate under a different reimbursement system and thus are not adequately represented in the data on reimbursed patient contacts; GPs in training, for which it is unclear how they are represented in the datasets for reimbursed antibiotics and patient contacts; and GPs who had already taken TRACE or INTRO before they were invited. No consent was needed from participants.

Intervention

Upon transition from the control to the intervention condition, participants received a box including an invitation letter for TRACE and INTRO and 30 copies of the linked patient information booklet. Participants were asked to log in with their Belgian electronic identification (e-ID) card to register their NIHDI identification number. However, this was not required to access the course and then participation was not registered. Those who were logged in longer than 10 min, the time approximately needed to complete TRACE, received a certificate of completion. At the end of TRACE, participants were invited to take part in INTRO. Participation in INTRO resulted in an accreditation credit, used to reward GPs who engage in continued education. Registration with their e-ID card was required to claim the accreditation credit.

Outcomes

This study used two routinely collected databases, i.e. one on all reimbursed pharmaceutical products delivered in public pharmacies and one on all reimbursed medical acts as defined by insurance nomenclature (see Supplementary data). The primary outcome was the number of reimbursed prescriptions containing at least one antibiotic prescribed by individual prescribers. Secondary outcomes were number of unique individuals treated with antibiotics, proportion of amoxicillin/clavulanate (ATC J01CR02) on the total amount of amoxicillin (J01CA04; amoxicillin/clavulanate proportion), and proportion of packages prescribed containing second-line antibiotics on the total amount of antibiotic packages (second-line proportion). Second-line antibiotics are tetracyclines (J01A), amoxicillin/clavulanate (J01CR02), cephalosporins (J01DB, J01DC, J01DD, J01DE), macrolides (J01FA), aminoglycosides (J01G) and quinolones (J01MA).[21] Neither TRACE nor INTRO focuses on choice of antibiotics.

The number of unique individuals treated was used to confirm a decrease of prescriptions translated into fewer people receiving any antibiotics and was not the result of the same number of people receiving fewer antibiotics, the former being a better indicator for a decrease in the risk for antibiotic resistance in the population. The amoxicillin/clavulanate proportion and second-line proportion are quality indicators of antibiotic prescribing the Belgian Antibiotic Policy Coordination Committee set national targets for,[22] and feature in the feedback Belgian GPs receive on their prescribing behaviour.[21]

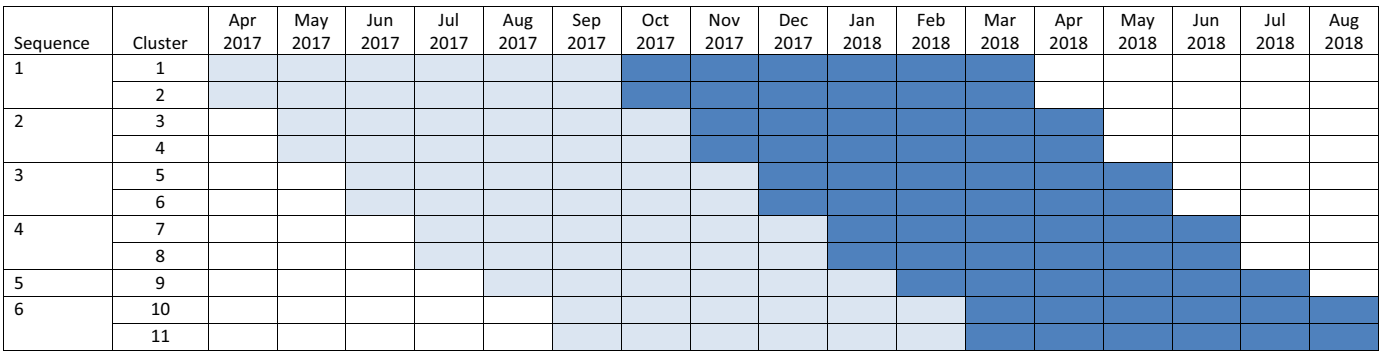

Figure 1. Balanced stepped-wedge design. Clusters in the control condition are marked light blue, clusters in the intervention condition are marked dark blue. In each sequence two clusters shift from the control condition to the intervention condition, except for Sequence 5, which has only one cluster, the Brussels Capital Region.

Statistical methods

The primary outcome was calculated for each month by counting the number of prescriptions containing at least one antibiotic. Similar to what was done by Coenen *et al.*,[23] a prescription was defined as all packages prescribed by the same prescriber to the same individual on the same day. The number of individuals treated was calculated as the number of unique individuals per prescriber who received at least one antibiotic (e.g. a patient prescribed two antibiotics on different days in the same month would be counted as two prescriptions and one unique individual treated).

Generalized linear mixed-effects models (GLMM) were fitted to the available data (see Supplementary data). Different methods are suggested to estimate the treatment effect.[24–29] The first method we used assessed the time-averaged effect of the intervention. The second method measured the effect of the intervention at specific exposure times. For each of these two methods, several models were fitted to the data and the Akaike information criterion was used to select the one that performed best (see Supplementary data).

To evaluate the effect of actual participation in TRACE or INTRO, a prespecified controlled pre-post analysis was performed using models similar to those described above but with an indicator for participation in TRACE or INTRO instead of an indicator for invitation. For GPs who participated in either TRACE, INTRO or both, we included observations of 6 months before the month of participation, the month of participation and the 5 months after participation, reaching an observation window of 1 year. Controls were those participants who did not participate in either TRACE or INTRO. Their observations were included to create a similar 1 year observation window based on the date of invitation to participate in TRACE. As actual participation was not randomized, GP's age category (from under 30 years old to 70 years old and older in increments of 5 years), gender, language (Dutch or French, as registered with NIHDI as preferred language), accreditation status, monthly average patient age, monthly proportion of female patients, monthly proportion of young patients (≤14 years) and monthly proportion of patients with increased insurance benefits were considered for adjustment.

A sensitivity analysis including only observations from GPs who contributed to both the control and intervention condition was performed to evaluate the effect of the changing GP population in the stepped-wedge analysis.

All analyses were performed in R (version 4.0.5) using the glmmTMB and DHARMa packages.[30–32] The estimated effect sizes are reported as prescribing rate ratio (PRR), individuals treated rate ratio (ITRR) or OR, with their 95% CI.

Trial protocol

The trial protocol is not published.

Research ethics review

The analysis of routinely collected reimbursement data is part of the mission and mandate of the NIHDI. No additional ethical review was required.

Results

Participants

The first clusters were invited in October 2017 and the last in March 2018. At the beginning of every month, members of clusters sequenced to cross over to the intervention condition received a box containing the invitation and patient information booklets. Figure 2 shows the number of prescribers and observations included in the analysis. A total of 15 790 prescribers were invited based on their registration as GP with the Federal Public Service of Health; 2311 prescribers were excluded because they worked in a hospital, in a community healthcare centre or were in training. Seventy-two GPs were excluded from the stepped-wedge analysis because they participated in TRACE before being invited, but were included in the pre-post analysis. Patient contacts were counted for 13 407 prescribers. Observations from months in which prescribers had fewer than 25 contacts were omitted. Consequently, 3032 prescribers were excluded because they had fewer than 25 contacts in every month of the study period. A total of 1482 GPs provided data on at least 1 month, but not every month of the study. Overall, 118 487 observations from 10 375 GPs were used in statistical analyses of the stepped-wedge design. The pre-post analysis was performed on 118 509 observations from 10 442 GPs (3 prescribers were omitted because of missing covariates).

Numbers analysed

Table 1 provides a summary of population characteristics for each of the intervention periods. During this study, 4 899 401 unique patients were reimbursed antibiotics prescribed by a GP. GPs made 5 486 295 prescriptions with at least one antibiotic;

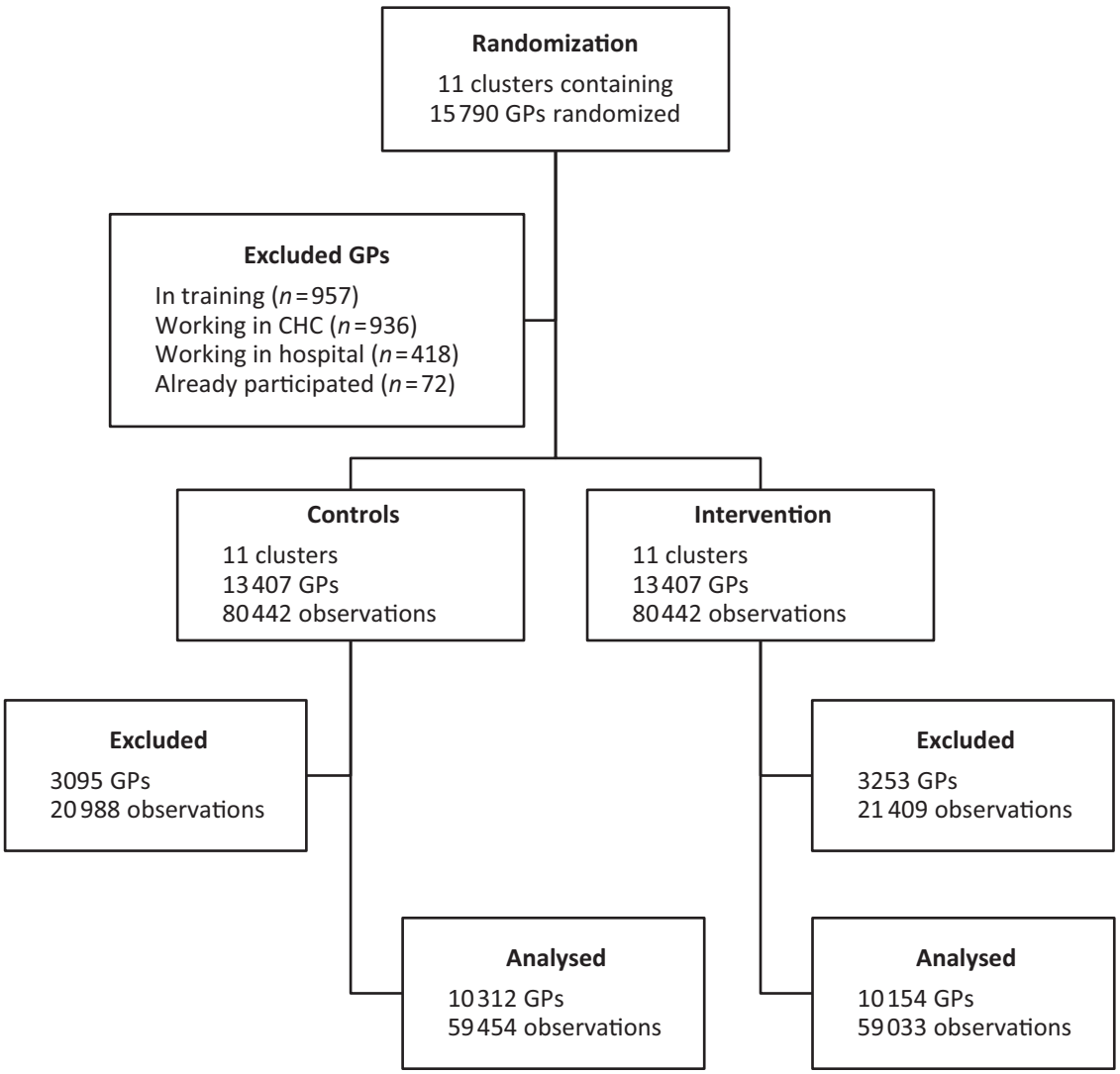

Figure 2. Flow diagram of participants and observations. Observations are monthly individual measurements of the primary outcome. CHC, community healthcare centres.

13.01% of all prescriptions contained at least one antibiotic. In total, 7 862 026 packages of antibiotics prescribed by a GP were reimbursed. Table S1 provides summary measures of population characteristics for each sequence.

Figure S1 shows the change in average prescribing rate over time, with a peak in December, and higher levels of prescribing in the Walloon region. The average prescribing rate per 1000 patient contacts is 122.49 (SD = 81.98) in Belgium, with 142 (SD = 93.64) in Wallonia, 115.02 (SD = 83.79) in Brussels and 111.49 (SD = 77.24) in Flanders. Tables S2–S5 show averages of all outcome measures for every cluster, the intervention and control groups and the total population in every month of the study.

During the 17 months of the study, 269 GPs completed only TRACE, 63 completed only INTRO and 30 completed both. Of the 362 GPs who completed TRACE or INTRO, 70 (21%) did so before they were invited. On the cluster level, this ranged from 0% to 2.4% of the total number of prescribers. These GPs were excluded from the final analysis of the nationwide implementation to avoid contamination bias, but were included again in the pre-post analysis of the effect of participation. GPs who completed and those who did not complete TRACE or INTRO did not differ in the number of antibiotic packages they prescribed in the first 6 months of this study, during which every participant was in the control phase (April 2017–September 2017) (PRR = 1.00 [0.92–1.08]).

Outcomes and estimation

Nationwide implementation

Inviting GPs to the online courses and providing them with patient information booklets did not reduce antibiotic prescribing rates. On average, GPs in the intervention and in the control condition prescribed the same number of antibiotics (PRR = 0.99 [0.97–1.02]), after adjustment for secular time trend. There was no effect during the first month after the intervention (PRR_1 = 1.00 [0.98–1.02]) or subsequent months. Table 2 shows the

Table 1. Characteristics of prescribers by control and intervention condition

Variable	Control ($n=10\,312$)	Intervention ($n=10\,154$)
Sex, female, *n* (%)	4046 (39.2)	4008 (39.5)
Age, years, *n* (%)		
Younger than 30	490 (4.8)	497 (4.9)
30–34	946 (9.2)	946 (9.3)
35–39	651 (6.3)	649 (6.4)
40–44	762 (7.4)	753 (7.4)
45–49	987 (9.6)	976 (9.6)
50–54	936 (9.1)	929 (9.2)
55–59	1700 (16.5)	1687 (16.6)
60–64	1854 (18.0)	1833 (18.1)
65–69	1299 (12.6)	1229 (12.1)
Older than 70	684 (6.6)	652 (6.4)
Missing	3	3
Language, French, *n* (%)	4480 (43.4)	4400 (43.3)
Accreditation status, accredited, *n* (%)	9601 (93.1)	9439 (93.0)
Patient contacts per month, mean (SD)	368.95 (242.48)	392.76 (253.42)
Packages of antibiotics prescribed, mean (SD)	63.16 (60.74)	69.65 (67.39)
Prescriptions with antibiotic, mean (SD)	43.12 (38.68)	49.51 (45.55)
Prescribing rate, mean (SD)	118.83 (77.02)	126.18 (86.53)
Individuals treated with antibiotics, mean (SD)	38.40 (34.54)	44.32 (40.70)
Rate of individuals treated, mean (SD)	105.97 (68.72)	113.10 (77.77)
Patient age, years, mean (SD)	53.89 (8.82)	53.10 (8.81)
Patient sex, % female, mean (SD)	58.90 (7.41)	58.82 (7.38)
Young patients, %, mean (SD)	7.68 (5.53)	8.50 (5.80)
Patients with increased reimbursement status, %, mean (SD)	27.69 (13.67)	26.92 (13.47)
Participated in TRACE, *n* (%)	—	299 (2.94)
Participated in INTRO, *n* (%)	—	93 (0.92)

Averages are expressed per month. Rates are expressed per 1000 patient contacts. Young patients are patients under the age of 15 years. A single prescription can contain one or multiple packages.
SD, standard deviation.

estimated effect sizes. Figure 3(a) shows the estimated average number of antibiotic prescriptions in the intervention and control conditions across the study period.

The number of unique individuals treated did not decrease (ITRR = 0.99 [0.97–1.02]). The population-averaged amoxicillin/clavulanate proportion did not change (OR = 1.01 [0.98–1.04]), nor did the population-averaged proportion of second-line antibiotics (OR = 0.99 [0.97–1.02]). Table S6 shows the estimates of all models.

Participation in online training

Following participation in TRACE only, the time-averaged number of antibiotic prescriptions declined by 7% (PRR = 0.93 [0.90–0.95]), an estimated difference of 8.60 fewer [−8.00 to −9.00] antibiotic prescriptions per 1000 patient contacts. The prescribing rate did not decline following participation in INTRO only (PRR = 0.99 [0.93–1.06]). The interaction effect between the two courses was insignificant (PRR = 0.97 [0.87–1.08]). Table 3 shows the estimated effect sizes. Figure 3(b) shows the estimated average number of antibiotic prescriptions among those who did or did not participate in TRACE across the study period.

The effect of participation in TRACE only was most pronounced in the first month of participation, in which the prescribing rate declined by 10% ($PRR_1 = 0.90$ [0.87–0.93]). It gradually faded in the subsequent months ($PRR_2 = 0.93$ [0.90–0.97]; $PRR_3 = 0.94$ [0.91–0.98]; $PRR_4 = 0.95$ [0.91–0.99]; $PRR_5 = 0.95$ [0.92–0.99]) and became insignificant in the last month of follow-up ($PRR_6 = 0.97$ [0.93–1.01]).

The effect of participation on the rate of individuals treated showed a similar pattern. Following participation in TRACE only, the rate of individuals treated declined by 7% (ITRR = 0.93 [0.91–0.95]), meaning on average 7.90 fewer [−7.50 to −8.30] individuals per 1000 patient contacts. The effect was most pronounced in the first months after the intervention ($ITRR_1 = 0.90$ [0.87–0.93]; $ITRR_2 = 0.94$ [0.90–0.97]; $ITRR_3 = 0.94$ [0.91–0.98]; $ITRR_4 = 0.95$ [0.92–0.99]) and became insignificant in the last 2 months of follow-up ($ITRR_5 = 0.96$ [0.92–1.00]; $ITRR_6 = 0.98$ [0.94–1.02]).

There was no effect on the quality of antibiotic prescribing. The population-averaged amoxicillin/clavulanate proportion did not change ($OR_{TRACE} = 0.99$ [0.91–1.07]; $OR_{INTRO} = 1.02$ [0.83–1.24]), nor did the population-averaged proportion of second-line antibiotics ($OR_{TRACE} = 1.00$ [0.94–1.06]; $OR_{INTRO} = 1.01$ [0.87–1.17]). Table S7 shows the estimates of all models.

To evaluate if the effect of participation in TRACE was different among different regions in Belgium, an interaction with region was added to a model containing only an indicator for participation in TRACE, covariates, random intercepts for prescriber and cluster, and random effects for temporal autocorrelation at the level of the cluster and of the prescriber. Adding the interaction did not improve the model (X^2 [df = 2] = 1.564, $P = 0.456$).

Similarly, an interaction effect was added to assess if the effect of participation in TRACE was different during the winter months, when patients consult more frequently because of LRTIs. Adding the interaction changed the previous effects estimates. While prescribers who participated typically prescribed 5% less antibiotics, as opposed to prescribers who did not participate (PRR = 0.95 [0.92–0.98]), they prescribed 10% less in winter (PRR = 0.90 [0.85–0.95]).

Ancillary analysis

The pre-planned sensitivity analysis, including 117 575 observations from 10 091 GPs, did not substantially change the estimates or their interpretation. Neither did repeating the analysis including GPs who participated before they were invited as if they had been invited in the month they participated.

Discussion

Nationwide implementation of TRACE and INTRO by sending all GPs an invitation to participate in these online communication

Table 2. Effect estimates of the implementation of TRACE

	Prescribing rate			Individuals treated rate			AMC proportion			Second-line proportion		
	PRR	95% CI	*P*	ITRR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Time-averaged effect	0.99	0.97–1.02	0.635	0.99	0.97–1.02	0.549	1.01	0.98–1.04	0.502	0.99	0.97–1.02	0.667
Time since invitation												
1 month	1.00	0.98–1.02	0.967	1.00	0.98–1.02	0.898	1.01	0.98–1.05	0.463	0.99	0.97–1.02	0.553
2 months	1.00	0.97–1.03	0.849	1.00	0.96–1.03	0.780	1.01	0.97–1.05	0.681	1.00	0.96–1.04	0.992
3 months	1.03	0.99–1.08	0.169	1.03	0.98–1.07	0.230	1.00	0.95–1.06	0.852	1.03	0.98–1.08	0.248
4 months	1.04	0.99–1.10	0.148	1.04	0.98–1.09	0.198	1.00	0.94–1.07	0.933	1.02	0.96–1.08	0.560
5 months	1.05	0.98–1.11	0.169	1.04	0.98–1.11	0.227	1.02	0.95–1.09	0.634	1.02	0.95–1.10	0.583
6 months	1.05	0.97–1.13	0.212	1.04	0.97–1.13	0.284	1.01	0.93–1.09	0.838	0.99	0.91–1.08	0.861

P values are based on Wald tests. The prescribing rate is the number of monthly antibiotic prescriptions per 1000 patient contacts. The individuals treated rate is the number of unique individuals treated with antibiotics per 1000 patient contacts. The AMC proportion is the number of AMC packages prescribed on the total number of amoxicillin packages prescribed. The second-line proportion is the number of second-line antibiotics packages on the total of antibiotic packages.
AMC, amoxicillin/clavulanate.

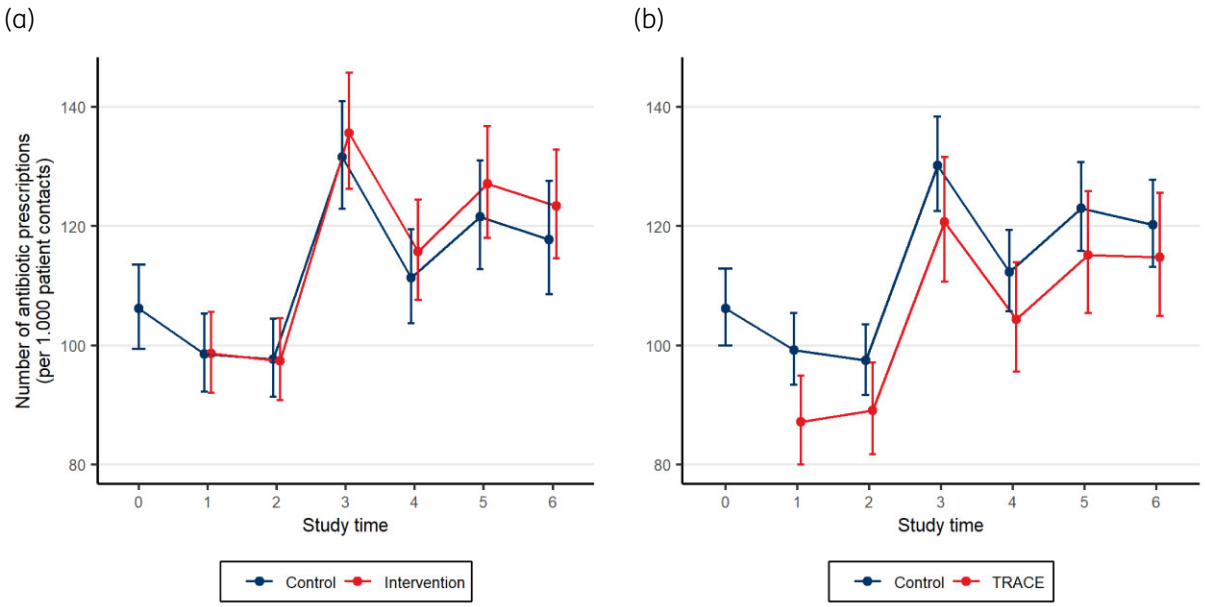

Figure 3. The estimated average number of antibiotic prescriptions of all antibiotics and 95% CI across the study period comparing (a) the intervention group with the control group after the nationwide implementation and (b) GPs who participated in TRACE with those who did not participate, while controlling for participation in INTRO and other covariates.

skills courses and linked patient information booklets did not reduce antibiotic prescribing on a population level. The lack of effect could be explained by the low participation rate of GPs in the first 6 months after being invited.

Analysis of the effect of taking up the invitation and undertaking the online training suggests TRACE reduces antibiotic prescribing and reduces the number of individuals treated with antibiotics. The estimates for INTRO were not significant, but this could be due to the small number of GPs ($n=93$) who completed INTRO. Effectiveness of INTRO and its active ingredients (enhanced communication skills training, patient information booklet and, in Belgium to a lesser extent, peer-led audit meetings on prescribing) was already established through trials.[10–16] TRACE, focusing on communications skills training and use of the patient information booklet, had not yet been evaluated. This study provides evidence for its effectiveness in a pragmatic setting. This effect is not mediated through participation in INTRO. The effect of TRACE was not sustained longer than 6 months, which is in contrast with previous studies on longitudinal effects of INTRO and other similar interventions, which

Table 3. Effect estimates of participation in TRACE and/or INTRO

	Prescribing rate			Individuals treated rate			AMC proportion			Second-line proportion		
	PRR	95% CI	*P*	ITRR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
TRACE	0.93	0.90–0.950	**<0.001**	0.93	0.91–0.95	**<0.001**	0.99	0.91–1.07	0.807	1.00	0.94–1.06	0.919
INTRO	0.99	0.93–1.06	0.781	0.99	0.93–1.05	0.665	1.02	0.83–1.24	0.886	1.01	0.87–1.17	0.889
TRACE × INTRO	0.97	0.87–1.08	0.591	0.96	0.86–1.07	0.419	0.97	0.67–1.39	0.849	0.85	0.65–1.11	0.229
Time since participation												
TRACE: 1 month	0.90	0.87–0.93	**<0.001**	0.90	0.87–0.93	**<0.001**	1.00	0.88–1.14	0.977	1.00	0.91–1.1	0.999
TRACE: 2 months	0.93	0.90–0.97	**<0.001**	0.94	0.90–0.970	**<0.001**	0.96	0.84–1.09	0.528	0.95	0.86–1.04	0.263
TRACE: 3 months	0.95	0.91–0.98	**0.003**	0.94	0.91–0.98	**0.001**	1.01	0.88–1.16	0.867	0.99	0.9–1.09	0.868
TRACE: 4 months	0.95	0.91–0.99	**0.011**	0.95	0.92–0.99	**0.018**	0.96	0.84–1.11	0.598	0.98	0.88–1.08	0.668
TRACE: 5 months	0.96	0.92–1.00	**0.034**	0.96	0.92–1.00	0.054	0.89	0.77–1.02	0.094	0.94	0.85–1.05	0.265
TRACE: 6 months	0.97	0.93–1.02	0.256	0.98	0.94–1.02	0.372	1.11	0.96–1.29	0.157	1.08	0.97–1.20	0.176
INTRO: 1 month	0.99	0.93–1.06	0.748	0.97	0.91–1.03	0.341	0.85	0.65–1.10	0.213	0.84	0.69–1.00	0.056
INTRO: 2 months	0.96	0.90–1.04	0.323	0.96	0.90–1.04	0.317	1.12	0.84–1.48	0.440	1.07	0.87–1.32	0.496
INTRO: 3 months	1.01	0.94–1.10	0.727	1.01	0.94–1.09	0.822	0.91	0.69–1.22	0.540	0.91	0.74–1.12	0.387
INTRO: 4 months	0.93	0.85–1.02	0.142	0.93	0.85–1.01	0.098	0.90	0.65–1.25	0.528	0.92	0.73–1.17	0.505
INTRO: 5 months	0.97	0.88–1.07	0.510	0.96	0.88–1.06	0.444	1.17	0.84–1.62	0.355	1.01	0.79–1.29	0.933
INTRO: 6 months	0.96	0.87–1.06	0.451	0.98	0.89–1.08	0.718	1.40	1.00–1.97	0.050	1.27	0.99–1.64	0.063

P values are based on Wald tests. The prescribing rate is the number of monthly antibiotic prescriptions per 1000 patient contacts. The individuals treated rate is the number of unique individuals treated with antibiotics per 1000 patient contacts. The AMC proportion is the number of AMC packages prescribed on the total number of amoxicillin packages prescribed. The second-line proportion is the number of second-line antibiotics packages on the total of antibiotic packages.

Significant differences are indicated in bold.

AMC, amoxicillin/clavulanate.

showed sustained effects over longer periods of time.[16,33,34] While GPs who participated in the INTRO trials showed a higher engagement to participate, our pragmatic study also included GPs with less initial engagement. This highlights the importance of initial motivation, engagement and peer support to establish and maintain long-term change in antibiotic prescribing.

Our contradicting results on implementation and active participation could be because participation was voluntary and in a real-life setting. As a result, invitation did not result in high participation rates. Our results suggest GPs who complete TRACE effectively reduce their antibiotic prescribing, but we only registered a small number of GPs who completed the course. Identifying determinants of participation and their relation to antibiotic prescribing can help to target interventions to those GPs who are less inclined to follow a training course and/or to change their antibiotic prescribing by removing barriers and/or adding other incentives to participate. Our descriptive analysis shows prescribing rates remain high especially in the winter and the Walloon region. Future interventions could focus on this region as it has the most potential for improvement. Repeating the intervention at the start of every winter might help to maximize the effect, especially since our pre-post analysis shows TRACE's effectiveness doubles during winter. Despite regional differences in antibiotic prescribing, we found that the effect of participation in TRACE was the same across all regions. This could indicate other countries can expect similar effect sizes of similar interventions. The intervention had no impact on antibiotic prescribing quality. However, we did not expect a change in prescribing quality since neither TRACE nor INTRO focus on prescribing first-choice antibiotics when antibiotics are indicated. These indicators were included because GPs are familiar with them through the individual feedback they receive on their prescribing behaviour.

Strengths and limitations

All Belgian GPs were invited to participate, making estimations very precise. While no blinding was applied, we assume most GPs were unaware of this study being conducted. As we used routinely collected data to measure their antibiotic prescribing, data collection posed no intrusion on their daily prescribing habits. Consequently, this study offers a real-life glimpse into daily antibiotic prescribing practices.

On the other hand, stepped-wedge designs are susceptible to contamination when subjects are exposed to the intervention before they were sequenced. Twenty-one percent of GPs who completed TRACE or INTRO did so before they were invited and were omitted from the stepped-wedge analysis. However, our ancillary analysis showed reincluding these prescribers did not change results.

Failure to adjust for secular time trends in the analysis of stepped-wedge designs could lead to biased estimates of intervention effects.[35] We accounted for the secular trend in antibiotic prescribing by adding a fixed categorical time effect and random calendar time effects to the fitted models, thereby imposing various correlation structures for observations within clusters. Despite our comprehensive model-based attempt to accommodate the secular trend, other cluster-specific time effects with different assumptions about the underlying association structure

are possible.[35] Hence, some confounding of the intervention effect with time could persist, potentially biasing our results.

We had no information on reason for consultation or diagnosis. Our online communication course focuses on LRTI, but we were unable to focus our analysis on only those consulting for LRTI. This could have contributed to an underestimation of the effect compared with other, less pragmatic trials. We did however find that the effect of participation is greater during winter when more patients consult their GP because of LRTIs. Future research could focus more on antibiotic prescribing among patients consulting for LRTI.

Registered participation in the online course was low. Only 2.78% of invited GPs completed TRACE or INTRO. We did not assess use of the linked booklet, nor did we have information on the number of GPs participating without using their e-ID, required to register them as participants. Therefore, we were not able to assess if the small effect sizes originate from a lack of interest or failure to take the course, to register participation or to apply the communication skills in practice.

Conclusions

National implementation of online communication skills training by inviting all GPs to take part and providing them with linked patient information booklets did not reduce antibiotic prescribing. However, antibiotic prescribing lowered among individual GPs who actually participated in TRACE, particularly during the winter. In other words, while passive invitation does not seem effective, this study adds to the evidence that online communication training results in reduced antibiotic prescribing and indicates future research needs to focus on increasing intervention uptake. After all, a significant decrease in population-wide antibiotic consumption could be achieved by increasing the participation of GPs, especially in winter.

Funding

This work was supported as follows. Herman Goossens of the University of Antwerp coordinated both the Network of Excellence GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe), which produced the GRACE INTRO e-learning and was granted by the European Commission's sixth framework programme (grant agreement no. 5198226), and the Research Networking Programme TRACE (Translation Research on Antimicrobial resistance and Community-acquired infections in Europe; www.esf.org/trace), which produced the TRACE e-learning and was granted by the European Science Foundation. The University of Antwerp supported the translation of the TRACE and GRACE intervention into French. BAPCOC (Belgian Antibiotic Policy Coordination Committee) supported the national implementation of the TRACE and GRACE interventions. NIHDI (National Institute for Health and Disability Insurance) and the Federal Public Service of Health hosted the TRACE and GRACE e-learning courses on their joint e-learning platform and provided a certificate and accreditation points for participation. Robin Bruyndonckx was funded as a postdoctoral researcher by FWO Flanders (Fonds Wetenschappelijk Onderzoek – Vlaanderen).

Transparency declarations

None to declare.

Author contributions

Conceptualization, led by S.C. with contribution from all authors; methodology, led by L.D., S.Ab., R.B. and S.C. and agreed by all authors; analysis, L.D. with contribution from S.Ab., R.B. and S.C.; interpretation all authors; writing—original draft preparation, L.D., S.Ab., R.B. and S.C.; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Supplementary data

Supplementary data, including Figure S1 and Tables S1 to S7, are available at *JAC-AMR* Online.

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