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Original Article

Impact of a public commitment charter, a non-prescription pad and an antibiotic information leaflet to improve antibiotic prescription among general practitioners: A randomised controlled study[☆]



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ABSTRACT

Background: This study evaluated the effect of a multifaceted antibiotic stewardship intervention on the overall prescription of systemic antibiotics in primary care. Secondary objectives evaluated the effect on the prescription of broad-spectrum antibiotics and the seasonal variation of both total antibiotic and quinolone prescriptions, as a proxy for unnecessary prescribing.

Methods: This pragmatic, randomised, controlled, before-after intervention study was conducted among general practitioners (GPs) who over prescribe antibiotics in Lorraine, France (Intervention group, n = 109; Control group, n = 236; Before period, 01/10/2017–30/09/2018; After period, 01/10/2018–30/09/2019). The intervention included a public commitment charter, a patient information leaflet and a non-prescription pad. Health Insurance data was obtained to calculate overall and broad-spectrum prescription rate (defined daily doses/1000 consultations) and the seasonal variation of prescriptions (%), by period. The intervention effect was measured with general linear mixed models including three independent variables (group, period and group x period interaction).

Results: Overall, compared to the Before period, GPs in both groups prescribed significantly fewer systemic antibiotics ($p < 0.001$) and broad-spectrum antibiotics ($p < 0.001$) after the intervention was implemented. However, the group x period interaction did not show any evidence that the intervention had an effect on these outcomes. Nevertheless, the intervention did result in a trend towards less seasonal variation in total systemic antibiotic prescription ($p = 0.052$).

Conclusions: A tendency towards an effect of the intervention to reduce unnecessary antibiotic prescribing during winter months was observed. No effect was observed on the overall volume of systemic antibiotic prescription. This study invites discussion about the challenges faced when evaluating non-pharmacological interventions in primary care.

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Introduction

The rise in antibiotic resistance is a major public health threat worldwide, mostly driven by unnecessary and inappropriate antibiotic use [1]. In France, like many European countries, most antibiotics are prescribed in primary care (78% in 2019), mostly by general practitioners (GPs) who are responsible for 72% of these prescriptions [2]. Although antibiotic prescription slowly declined between 2011 and 2019, and markedly in 2020 [3], antibiotic prescription in France is still above the

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European average. European surveillance network (ESAC) data show that in 2021 32% more antibiotics were prescribed in France in primary care than the European average (defined daily doses per 1000 inhabitants per day) [4,5]. Also, around one-third of all prescriptions are considered unnecessary and one-third inappropriate [6]. This means that despite the local antibiotic stewardship strategies implemented over the last twenty years, further efforts are still needed [7].

Among the various antibiotic stewardship strategies developed for primary care [8–10], the reported level of success is diverse. Specifically, several Cochrane reviews reported that point-of-care testing and shared decision making have been shown to be effective, but other multifaceted interventions centred on clinician education and patient information had low level of evidence, preventing any conclusions from being drawn [11–13]. Nevertheless, recent research suggests that educational interventions that target both prescribers and patients, facilitate the doctor/patient communication, and reduce patient expectations to receive an antibiotic may be effective [14–17]. An American study did not show a significant effect of a waiting room educational poster [18] but another found a public commitment charter displayed in examination rooms significantly reduced inappropriate prescriptions [19].

Based on the above-mentioned findings and tools from previous studies [16,19], we designed a multifaceted intervention, called the AntibioCharte intervention, targeting both GPs and patients (see details in section “Intervention”). This intervention includes a public commitment charter highlighting in particular that GPs prescribe antibiotics only when necessary, a non-prescription pad to inform patients why it was not necessary to prescribe an antibiotic in their situation, and a patient information leaflet delivered when an antibiotic was prescribed.

In this context, the main objective of the AntibioCharte study was to evaluate the impact of this multifaceted intervention on the overall prescription of systemic antibiotics. Among secondary objectives addressed in the present manuscript, we also aimed at evaluating the effect of the intervention on broad-spectrum antibiotics and on seasonal variations of both total antibiotic and quinolone prescriptions, as proxy for unnecessary prescribing. A previously published article provides results on the fidelity of GPs regarding the intervention and its acceptability by patients and GPs [20], as part as other secondary objectives of the AntibioCharte study.

Material and methods

Study design, setting, and organisation

The AntibioCharte study was a pragmatic, randomised, controlled, before-after intervention study conducted among GPs in Lorraine, a region in North Eastern France with a population of 2,328,460 inhabitants (according to the 2018 census). It was performed in collaboration with the Regional Health Insurance (RHI) which is the regional division of the French National Health Insurance (NHI) and the regional antibiotic stewardship network (AntibioEst), and funded by the Grand Est Regional Health Agency. The Before period (1st October 2017 and 30th September 2018) preceded the start of the intervention and the After period (1st October 2018 30th September 2019) followed the intervention implementation (1st October 2018). We compared one-year periods to take into account the seasonality of antibiotic prescriptions.

A multidisciplinary scientific committee, consisting of two infectious diseases physicians, one epidemiologist and one public health specialist, two GPs, one sociologist and pharmacists supervised all scientific aspects and organisational issues during the study period.

Study participants

GPs were identified from the RHI database and were considered eligible if they worked full time in primary care and had overprescribed

antibiotics during the second quarter 2017. Overprescribers were defined as those whom prescribed more than 25 systemic antibiotic courses per 100 patients (aged 16–65 years) without a chronic illness, and if the proportion of patients treated with broad-spectrum antibiotics (i.e., amoxicillin-clavulanate, cephalosporins and fluoroquinolones) exceeded 27% of all patients treated with antibiotics, i.e., GPs who did not reach the objectives set by the NHI as part of the French outpatient pay-for-performance system ‘Remuneration on Public Health Objectives’ (ROSP). Results of these two indicators by GP were available in the RHI database. GPs were excluded if they practiced alternative medicine only or were to retire within two years from the study start.

Randomisation and recruitment

Once each eligible GP had been identified, they were randomised to either the Intervention or Control group. Then, those allocated into the Intervention group were contacted by a delegate from the RHI who explained the study and the AntibioCharte intervention, and the GPs who accepted to participate and provided their written informed consent were enrolled. GPs randomised to the Control group did not receive the AntibioCharte intervention and were informed neither about the study nor that their prescribing data would be anonymously collected, which is allowed by French regulation.

Randomisation was performed in variable block sizes using SAS® software in a ratio 1.5 (Intervention group):1 (Control group) and stratified by rural or urban geographical location. We expected one third of eligible GPs would participate in the Intervention group, which would allow a final ratio of 1:2. To prevent risk of contamination between Intervention and Control groups, GPs selected from the same practice were randomised in the same group, and all GPs from the Intervention group were asked not to provide other GPs with the intervention tools.

Intervention

The AntibioCharte intervention consists of a commitment charter, a patient leaflet and a non-prescription pad. The charter and patient leaflet were created for the study and the pad was developed by the NHI in 2015 but is largely unknown among GPs [21,22]. These three tools were distributed (in paper version only) to GPs enrolled in the Intervention group, to be used during the After period.

The public commitment charter is expected to promote responsible antibiotic use. Participating GPs were asked to sign and display it in their waiting room (Additional file 1). By signing and displaying this charter, the GPs publicly demonstrated their commitment to only prescribe antibiotics when necessary.

The patient information leaflet was to be given to patients when the GP prescribed an antibiotic. This leaflet clearly informed the patient that an antibiotic is prescribed and provided recommendations about the optimal antibiotic use and information about potential side effects (Additional file 2).

The non-prescription explains why prescribing an antibiotic would be unnecessary for the pathology presented. GPs were to give it to patients with an infectious disease that was not treated by antibiotics (Additional file 3). The non-prescription describes the most common symptoms associated with the five most common viral infections, their duration, management recommendations and key messages promoting responsible antibiotic prescribing.

Outcome measures

The primary outcome was the overall prescription rate of systemic antibiotics measured by the mean number of systemic antibiotics (expressed in defined daily doses, DDD) per 1000 consultations, calculated for each GP, for the Before and the After periods [23]. Systemic

antibiotics were defined using the 2017 Anatomical Therapeutic Chemical (ATC) classification system (ATC-J01) [24].

The secondary outcomes were: the broad-spectrum antibiotic prescription rate (DDD/1000 consultations) including amoxicillin-clavulanate (ATC-J01CR02), third-generation cephalosporins (ATC-J01DD) and fluoroquinolones (ATC-J01MA) [25], the seasonal variation of both total antibiotic prescriptions (ATC-J01) and also quinolone prescriptions (ATC-J01M), calculated for each GP and each period as follows [26]:

$$\left[\frac{\text{total number of antibiotic or quinolone prescriptions during the cold months}}{\text{total number of antibiotic or quinolone prescriptions during the warm months}} \right] - 1 \times 100.$$

Seasonal variation of total antibiotic prescriptions and seasonal variation of quinolones are proxy measures for unnecessary antibiotic prescription for viral infections during the cold-weather season. Experts have recommended variation targets of < 20% for systemic antibiotics and < 5–10% for quinolones [23,26].

Data source and collection

We used data retrospectively and routinely collected from the NHI database (SNDS: Système National des Données de Santé). The SNDS contains individual, anonymised and linkable health-related and reimbursement data for almost the entire population (67 million inhabitants) in France. As all antibiotics are reimbursed in France, the SNDS reimbursement data is a reliable proxy measure of antibiotic prescription. The SNDS does not record the indication for which the drugs were prescribed. It is one of the largest databases in the world and it has been extensively used to guide public health policies in France [27,28]. Therefore, the term prescription in this manuscript refers to prescribed antibiotics, dispensed by community pharmacies, reimbursed by the NHI and thus recorded in the SNDS.

Using a secure SNDS database access and a unique identification number that anonymised the GP, for each antibiotic prescribed in the Intervention and the Control group, we collected the molecule(s), the number of tablets and date dispensed. Also, the allocation group (Intervention or Control), the type of practice (group or solo practice), the practice location (rural, urban) and the number of active patients (i.e., the number of patients the GP saw at least once a year) and the number of consultations per month in 2017, 2018 and 2019 were obtained.

Sample size and statistical analyses

The sample size was based on the hypothesis of a 10% decrease in the prescription rate of all systemic antibiotics in the Intervention group during the After period compared with the Before period, while not changing in the Control group. Considering an α risk of 5%, a power of 90%, and twice the number of GPs in the Control group than in the Intervention group, 67 GPs were required in the Intervention group to show a statistically significant difference. Also, to account for the number of GPs in France who work in a group practice, the number of GPs to be included was multiplied by an estimated coefficient of 1.4. This was based on a mean of three GPs per group practice and an intra-class correlation coefficient of 0.2. Thus, at least 94 GPs would be needed in the Intervention group and 188 in the Control group. Furthermore, it was assumed that around 10–20% of GPs would stop or not apply the intervention, and so the total number of GPs required was increased to 120 in the Intervention group and 240 in the Control group.

A descriptive analysis of the prescription rate and seasonal variation was performed for both groups for the Before and After periods. Antibiotic prescriptions were expressed as a mean and standard deviation in DDD/1000 consultations/year. The seasonal variation was expressed as a mean percentage and standard

deviation. We first compared the GP characteristics between groups, using Chi² tests or the t-tests, according to the variable considered.

The effect of the intervention was calculated using a general linear mixed model analysis (one model for each of the four dependent variables studied: prescription rates for systemic and broad-spectrum antibiotics and the seasonal variation in prescription rates of all systemic antibiotics and quinolones). Three independent variables were included in the model: group (Intervention relative to Control), period (After relative to Before) and interaction between group and period. The estimated effect of each independent variable is presented with standard errors and 95% confident intervals.

All statistical analyses were performed with SAS® version 9.4 (SAS Institute, Inc., Cary, N.C.).

Ethical considerations

The AntibioCharte study was conducted according to the principles of the Declaration of Helsinki and approved by French national ethics committees (Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé [TPS 37763] and Commission Nationale de l'Informatique et des Libertés (CNIL) [Décision DR-2018–199]). All GPs in the Intervention group provided their written informed consent and Control GPs were not informed, according to CNIL DR-2018–199.

Results

Characteristics of general practitioners

Overall, 2073 GPs were assessed for eligibility and 878 met inclusion criteria. The main reason for not being eligible was not overprescribing antibiotics. Among these, 360 were randomised to the Intervention group, of which 109 accepted to participate and were enrolled in the study, and 240 were allocated to the Control group. Fig. 1 illustrates the participant flow.

The practice characteristics of GPs enrolled are shown in Table 1. The groups did not differ in terms of practice type, location and size. Most GPs worked in a solo practice in an urban environment.

Descriptive outcome results

During the study period overall, we observed lower systemic antibiotic prescription rates after the intervention was implemented in both the Control and Intervention groups (Fig. 2a). Also, the prescription rates were lower in the Intervention group compared to the Control group for both periods and throughout the seasonal antibiotic prescription cycle (Fig. 2a and Fig. 3) as were prescription rates for broad-spectrum antibiotics (Fig. 2a).

The seasonal variation in antibiotic prescription including quinolones was also lower in the Intervention group compared to the controls. After the intervention, the seasonal variation in all antibiotic prescription was lower in the Intervention group but higher in the Control group (Fig. 2b).

The effect of the AntibioCharte intervention

Results of prescription rates by group, period and the interaction group x period are shown in Tables 2, 3 and 4.

Concerning overall systemic antibiotic prescription rates, although the Intervention group prescribed fewer systemic antibiotics than the Control group, irrespective of the period, the difference was not significant (Estimated Effect –59.7 [95% CI: –125.4 to +5.9] $p=0.074$). Moreover, the systemic antibiotic prescription rate was significantly lower after the intervention was implemented, irrespective of the group considered (Estimated Effect –27.9 [95%CI: –41.7 to –14.1] $p < 0.001$). Importantly, no effect of the intervention was observed on antibiotic

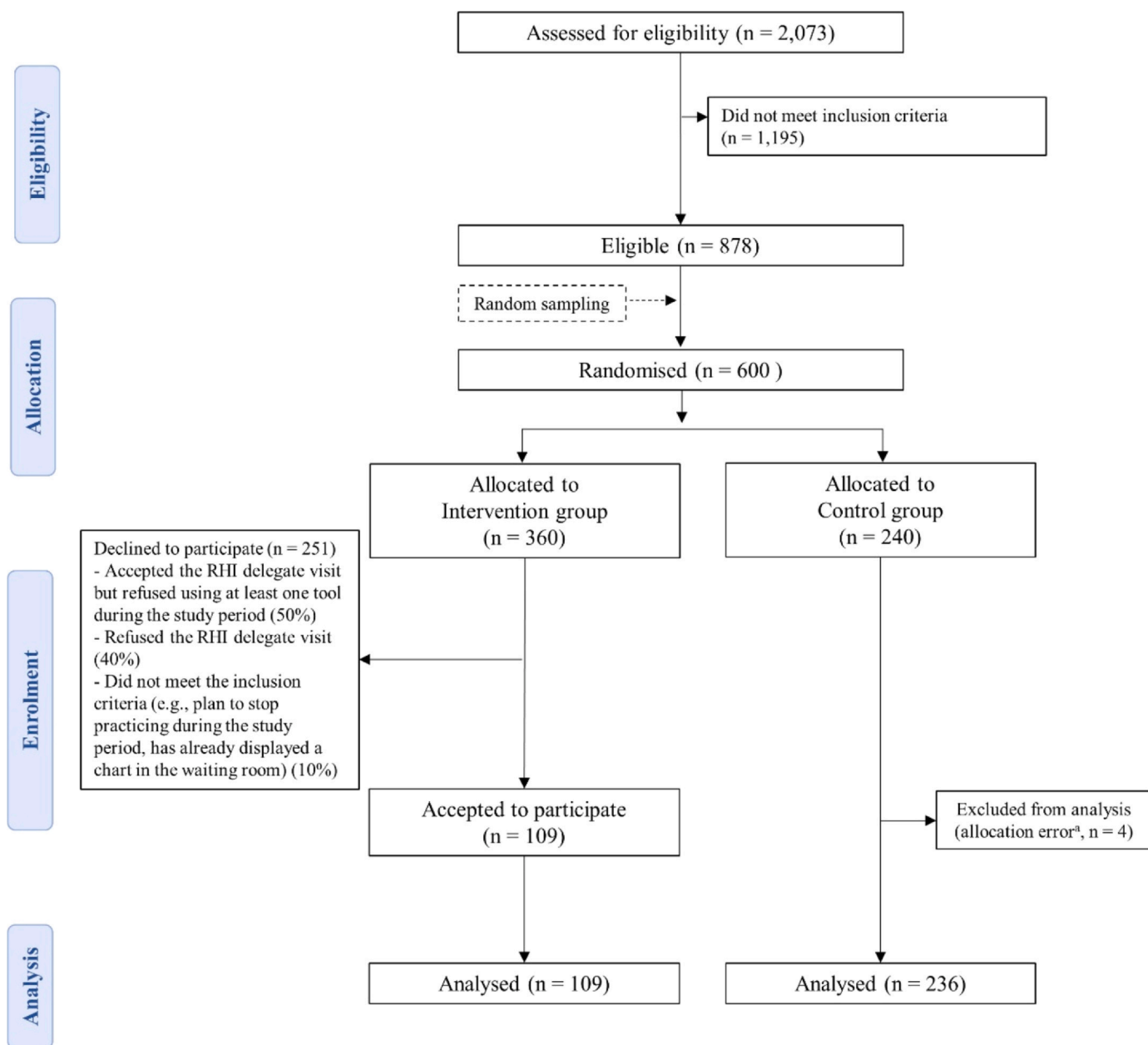


Fig. 1. Flow diagram of the AntibioCharte study RHI: Regional Health Insurance. ^aFour general practitioners have been contacted by a delegate from the RHI when they should not have been.

Table 1
Participating GP characteristics.

	All participants (n = 345)		Control group (n = 236)		Intervention group (n = 109)		P-value ^a
	n	% column or mean (SD)	n	% column or mean (SD)	n	% column or mean (SD)	
Type of practice							0.30
Solo	286	82.9	199	84.3	87	79.8	
Group	59	17.1	37	15.7	22	20.2	
Practice location							0.16
Rural	67	19.4	41	17.4	26	23.9	
Urban	278	80.6	195	82.6	83	76.2	
Number of patients per year							
2017	345	1103 (475)	236	1107 (485)	109	1094 (454)	0.81
2018	345	1143 (500)	236	1136 (510)	109	1159 (478)	0.67
2019	345	1116 (507)	236	1090 (514)	109	1174 (488)	0.15

GPs: general practitioners; SD: standard deviation.

^a Differences between the control group and the intervention group were calculated using Chi2 tests for qualitative variables and t-tests for quantitative variables.

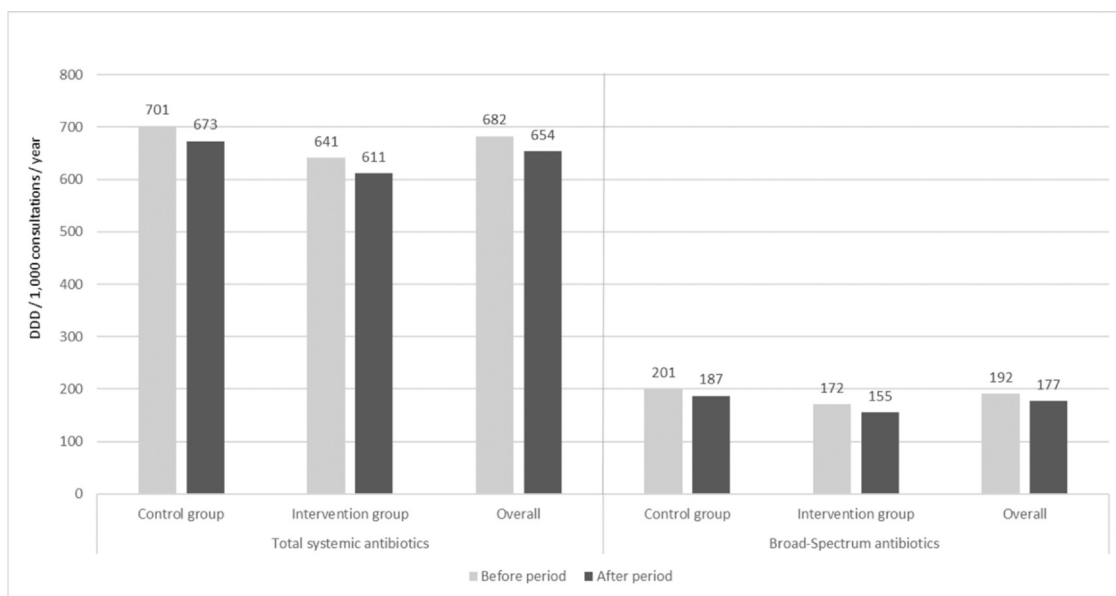


Fig. 2. Descriptive results of the outcomes, by period and by group. a Antibiotic prescription rates of total systemic antibiotics (left) and broad-spectrum antibiotics (right) during the Before and After period (DDD / 1000 consultations / year). b Seasonal variation in total antibiotic prescriptions (left) and quinolones (right). DDD: defined daily dose.

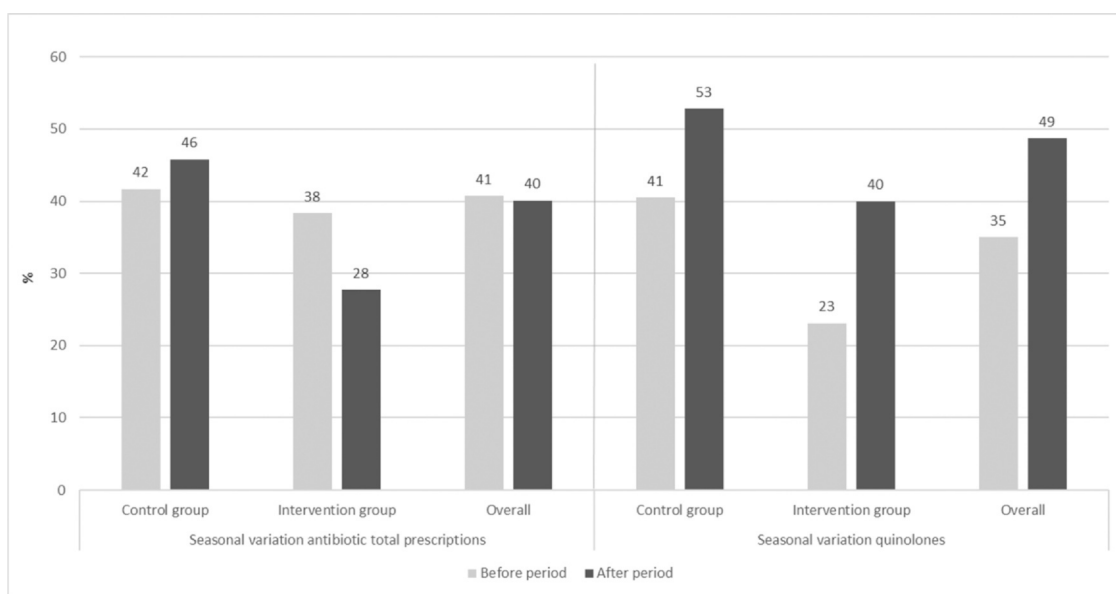


Fig. 2. (continued)

prescriptions as the group x period interaction was not significant (Estimated Effect -2.4 [95%CI: -27.0 to +22.2] p = 0.850) (Table 2).

Concerning broad-spectrum antibiotics, the Intervention group prescribed significantly fewer antibiotics than the Control group, irrespective of the period (Estimated Effect -29.3 [95%CI: -51.7 to -7.0] p = 0.010) and significantly fewer broad-spectrum antibiotics were prescribed after the implementation of the intervention, irrespective of the group (Estimated Effect -13.5 [95%CI: -19.0 to -8.0] p < 0.001). However, once again, we did not show an intervention effect (Estimated Effect -3.0 [95% CI: -12.8 to +6.8] p = 0.543) (Table 3).

Concerning the seasonal variation in antibiotic prescriptions, the effect of the intervention tended towards significance for all systemic antibiotics (Estimated Effect -14.7 [95%CI: -29.6 to +0.14] p =

0.052) but not for quinolones (Estimated Effect 4.4 [95%CI: -22.8 to +31.6] p = 0.750) (Table 4).

Discussion

Overall summary of results

AntibioCharte study was designed to evaluate the effect of a multifaceted intervention to engage GPs and support patients to use antibiotics appropriately, with a strong focus on reducing unnecessary antibiotic prescribing. We found fewer systemic, including broad spectrum antibiotics, were prescribed overall, following the implementation of the intervention. However, this downward trend did not differ significantly between Intervention and Control groups.

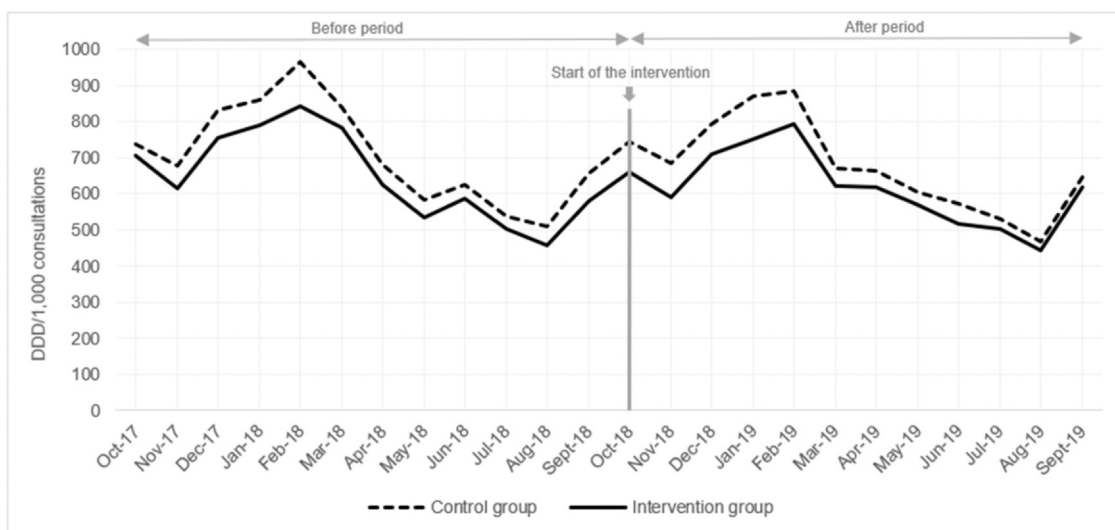


Fig. 3. Prescription rate of all systemic antibiotics by GPs in the Control group and in the Intervention group, by month (DDD / 1000 consultations). DDD: defined daily dose; GP: general practitioner.

Table 2
Effect of the Intervention on overall systemic antibiotic prescription rate (DDD / 1000 consultations).

Variable	Estimated effect (SE)	95% CI	P-value
Intercept	701.1 (18.8)	[664.2–738.0]	< 0.001
Group (reference: Control group)	-59.7 (33.4)	[- 125.4–5.9]	0.074
Period (reference: Before period)	-27.9 (7.0)	[- 41.7 to - 14.1]	< 0.001
Group x period interaction ^a	-2.4 (12.5)	[- 27.0–22.2]	0.850

CI: confidence interval; DDD: defined daily dose; SE: standard error

^a Difference (After period – Before period) in the Intervention group versus difference (After period – Before period) in the Control group were estimated using a general linear mixed model analysis.

Table 3
Effect of the Intervention on the broad-spectrum^a antibiotic prescription rate (DDD / 1000 consultations).

Variable	Estimated effect (SE)	95% CI	P-value
Intercept	200.8 (6.4)	[188.2–213.4]	< 0.001
Group (reference: Control group)	-29.3 (11.4)	[- 51.7 to - 7.0]	0.010
Period (reference: Before period)	-13.5 (2.8)	[- 19.0 to - 8.0]	< 0.001
Group x period interaction ^b	-3.0 (5.0)	[- 12.8–6.8]	0.543

CI: confidence interval; DDD: defined daily dose; SE: standard error

^a Amoxicillin-clavulanate, third-generation cephalosporins and fluoroquinolones

^b Difference (After period – Before period) in the Intervention group versus difference (After period – Before period) in the Control group were estimated using a general linear mixed model analysis.

Table 4
Effect of the Intervention on the seasonal variation of all systemic antibiotic prescriptions and seasonal variation of quinolone prescriptions (%).

Variable	Estimated effect (SE)	95% CI	P-value
Seasonal variation of all systemic antibiotics use			
Intercept	41.7 (3.0)	[35.8–47.6]	< 0.001
Group (reference: Control group)	-3.4 (5.3)	[- 13.9–7.1]	0.526
Period (reference: Before period)	4.1 (4.3)	[- 4.3–12.4]	0.335
Group x period interaction ^a	-14.7 (7.6)	[- 29.6–0.14]	0.052
Seasonal variation of quinolone use			
Intercept	40.5 (5.6)	[29.5–51.6]	< 0.001
Group (reference: Control group)	-17.4 (10.0)	[- 37.1–2.2]	0.082
Period (reference: Before period)	12.4 (7.8)	[- 2.9–27.8]	0.112
Group x period interaction ^a	4.4 (13.8)	[- 22.8–31.6]	0.750

CI: confidence interval; SE: standard error

^a Difference (After period – Before period) in the Intervention group versus difference (After period – Before period) in the Control group were estimated using a general linear mixed model analysis.

Furthermore, we found that the effect of the intervention tended towards significance for the seasonal variation in all systemic antibiotic prescriptions, but not for quinolones.

Effect of the intervention and comparison with the literature

Importantly, we found that the AntibioCharte intervention tended to reduce the seasonal variation, by decreasing the number of antibiotic prescriptions during the cool season (group \times period interaction: Estimated Effect -14.7 $p=0.052$). This suggests that the intervention may have encouraged GPs to reduce unnecessary antibiotic prescribing for viral infections, mostly acute upper and lower respiratory infections that occur during the cool seasons. This hypothesis is strengthened by the lack of effect observed on the seasonal variations of quinolones, usually prescribed in primary care for urinary tract infections, which remain stable throughout the year [29]. The non-prescription, which explains why an antibiotic prescription was unnecessary, may have been particularly effective to reduce unnecessary prescribing among the three AntibioCharte tools employed. This tool may have helped some patients and GPs to change their attitude towards needing an antibiotic and to support shared decision making. Indeed, the previously published acceptability evaluation of the AntibioCharte intervention indicated that both GPs and patients preferred the non-prescription pad among the three intervention tools [20]. This positive tendency towards fewer unnecessary antibiotic prescriptions is consistent with a commitment poster intervention assessed in America, in which inappropriate systemic antibiotic prescribing for acute respiratory infections was significantly reduced, relative to standard practice [19]. Although Meeker et al. attributed the success of their commitment poster to GPs making a public commitment to responsible antibiotic prescription, they also suggested that the poster may have informed patients about responsible antibiotic prescription and so engaged them in making a shared decision. That Meeker et al. found a significantly reduced inappropriate antibiotic prescribing rate, while we only found a tendency towards reduction may be explained by the shared decision-making culture being relatively recent in France compared to America [30,31]. However, our result on the positive tendency to reduce the seasonal variation of total antibiotic prescription should be interpreted with caution as the Intervention group may have been affected by selection bias. Indeed, the Control GPs were not informed that they had been selected for a study and that their prescribing data were being collected. On the contrary, GPs who accepted to participate and enrolled in the Intervention group may have done so as they were already aware about the need to prescribe antibiotics appropriately and so were more sensitive to significantly improving their prescription practices than the Control GPs. This explanation is supported by the group effect observed in the analysis (overall systemic antibiotics: -59.7 , $p=0.074$; broad-spectrum antibiotics: -29.3 , $p=0.010$), the Intervention GPs prescribing less antibiotics than the controls, irrespective of the period.

However, as our study design prevented us from collecting detailed GP data, we were not able to compare extensively GP's characteristics of both groups, and then to conclude about a selection bias (see Limitations). If present, this selection bias may have resulted in an over or underestimated effect of the intervention, preventing us from drawing a robust conclusion about the effect of the intervention.

On the contrary, our study did not show any effect of the AntibioCharte intervention on the overall systemic and broad-spectrum antibiotic prescription rates. Possibly, the intervention may have lacked effect as the study was conducted in a context of decreasing antibiotic prescriptions in primary care over the last ten years [4]. This follows ongoing efforts coordinated at national level by the French Health Ministry and at regional level by Regional Health Authorities to reduce inappropriate and unnecessary systemic antibiotic prescription [3,7].

These efforts have exposed GPs to multiple communication, education and incentive antibiotic stewardship interventions to adopt responsible antibiotic prescribing practices [32]. Indeed, prescription rates were significantly lower for both groups after the intervention and a period effect was observed for both systemic and broad-spectrum antibiotics.

The reason for a lack of intervention effect on the overall and broad-spectrum antibiotic prescription rates is possibly complex and multifactorial [33,34]. Probably, persisting patient and GP barriers contributed to the Intervention's lack of effect. Some previously reported GP-related factors include diagnostic uncertainty, difficulty in changing prescribing habits and not having time to adopt antibiotic stewardship strategies. Patients sometimes also pressure GPs to prescribe antibiotics, particularly older patients with comorbidities [35,36]. One recent quantitative survey conducted in France reported that 33% of GPs felt pressure from patients to prescribe antibiotics [37]. Also, a recent survey found that 96% of GPs declared being confronted with requests for antibiotics when faced with a viral infection (sometimes: 53%; often: 43%) [38]. Similarly, a recent qualitative study highlighted that the general public in France perceived antibiotics as being the only solution for a rapid cure and did not perceive antibiotic resistance as a personal responsibility [39].

These results raise the important question of the methodological issues related to evaluating non-pharmacological interventions in primary care that may have contributed to our findings. Indeed, a recent systematic research had identified inherent limitations, heterogeneous evaluation methods in research in primary care and few studies reporting sustainable effects of interventions [40]. However, little is known to date about the optimal designs to evaluate the effectiveness of non-pharmacological interventions in the general population.

Strengths and limitations

This study has a pragmatic design that allowed the intervention to be evaluated in real-life conditions. Furthermore, the data sources used to measure the outcomes were robust, reliable, health administrative databases. Considerable thought and care went into designing this study in line with recent recommendations on antimicrobial stewardship intervention evaluation [41], considering evaluation methods for non-pharmacological interventions are heterogeneous in primary care research today [42]. However, several methodological issues were faced in this study. Firstly, the SNDS database gives information on prescribed antibiotics that have been dispensed by community pharmacies and might thus underestimate the overall number of antibiotic prescriptions. However, this underestimation is probably low as patients put high pressure to get antibiotics and there is no reason to think it differed significantly between the two study groups. Secondly, although an interrupted time-series analysis is recommended for evaluating antibiotic stewardship interventions, it was not performed as originally planned [41]. Despite obtaining 24 months of data (12 months before and 12 months after the intervention' implementation), there was insufficient data to obtain a robust model, considering the marked seasonal effect of antibiotic prescription, which is much more important in primary care than in hospitals.

Thirdly, as previously mentioned, GPs who accepted being part of the Intervention group were probably more aware about antibiotic stewardship and had more appropriate antibiotic prescription practices than those of the Control group. This may have led to a selection bias and an over or underestimation of the effect on the outcomes. However, this design was intentionally chosen to control a potential Hawthorne effect with which the Control GPs may modify their prescribing practices as part of being involved in the study and having their antibiotic prescription monitored [43]. So, the Hawthorne effect may underestimate the real effect of the intervention and lead to negative results. In a recent meta-analysis from

Berkhout et al., the overall odd-ratio of the Hawthorne effect computed in primary care was 1.41 (95% CI: 1.13–1.75) [43].

Fourthly, the participation rate in the Intervention group was slightly lower than expected, leading to insufficient recruitment in the Intervention arm (109 participating GPs vs 120 expected). These recruitment difficulties in the Intervention group (30% of GPs agreed to participate) may have been exacerbated by RHI delegate involvement which may have been negatively perceived, as a way to reduce antibiotic expenditures [21]. Also, the sample size was based on a 10% decrease in overall prescription rate of systemic antibiotics in the Intervention group and no change in the Control group, but we found a smaller decrease than expected in the Intervention group and a decrease in the Control group. All these elements have reduced the statistical power of the study, and may partly explain the negative results on overall systemic and broad-spectrum antibiotics.

Lastly, for acceptability reasons in the Intervention group and legal reasons in the control group (not informed about the study), data available on GPs and patients' characteristics were limited to prevent us to identify any GP included in the present study. This information may however have been useful to check for selection bias, and then to adjust analyses for potential confounders.

Conclusions

Our study found a tendency towards an effect of the AntibioCharte intervention to reduce unnecessary antibiotic prescribing during winter months. However, we did not find any effect of the AntibioCharte intervention on the overall systemic and broad-spectrum antibiotic prescription rates. This study opens the discussion about the challenges associated with research methodology concerning the evaluation of non-pharmacological interventions in primary care.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jiph.2023.11.027](https://doi.org/10.1016/j.jiph.2023.11.027).

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