Effect of two interventions on reducing antibiotic prescription in pharyngitis in primary care

Carl Llor1*, Josep Maria Cots2, Beatriz González López-Valcárcel3, Juan de Dios Alcántara4, Guillermo García5, Javier Arranz6, María José Monedero7, Jesús Ortega8, Vicenta Pineda9, Gloria Guerra10, Manuel Gómez11, Silvia Hernández12, José Paredes13, Marina Cid14 and Carolina Pérez15

1University Rovira i Virgili, Primary Healthcare Centre Jaume I, Tarragona, Spain; 2University of Barcelona, Primary Healthcare Centre La Marina, Barcelona, Spain; 3Department of Quantitative Methods for Economics and Management, University of Las Palmas, Las Palmas de Gran Canaria, Spain; 4Primary Healthcare Centre Bollulos Par del Condado, Huelva, Spain; 5Primary Healthcare Centre La Calzada II, Gijón, Spain; 6Primary Healthcare Centre Arquitecte Bennassar, Palma de Mallorca, Spain; 7Primary Healthcare Centre Rafalena, Castellón, Spain; 8Primary Healthcare Centre Rincón de Soto, La Rioja, Spain; 9Primary Healthcare Centre Serería I, Valencia, Spain; 10Primary Healthcare Centre Escaleritas, Las Palmas de Gran Canaria, Spain; 11Primary Healthcare Centre San Cristóbal, Madrid, Spain; 12Primary Healthcare Centre Jaume I, Tarragona, Spain; 13Primary Healthcare Centre Hostalrich, Girona, Spain; 14Primary Healthcare Centre Teis, Vigo, Spain; 15Primary Healthcare Centre Puntales, Cádiz, Spain

*Corresponding author. Tel: +34-671085857; Fax: +34-977248459; E-mail: carles.llor@urv.cat

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Objectives: To evaluate the effect of two interventions on reducing antibiotic prescription in pharyngitis.

Methods: A prospective, non-randomized, before–after controlled study was carried out in primary care centres throughout Spain. General practitioners (GPs) registered all cases of pharyngitis during a 3 week period before and after two types of intervention in 2008 and 2009, respectively. Full intervention consisted of discussion sessions of the results of the first registry, courses for GPs, guidelines, patient information leaflets, workshops on rapid tests and the use of rapid antigen detection tests (RADTs) in their consulting offices. The physicians in the partial intervention group underwent all the above intervention except for the workshop, and RADTs were not provided. A control group was also included in 2009. Multilevel logistic regression was performed considering the prescription of antibiotics as the dependent variable.

Results: A total of 280 GPs registered cases with pharyngitis (70 partial intervention and 210 full intervention). Fifty-nine new physicians were included as a control group. A total of 6849 episodes of pharyngitis were registered. Antibiotic prescription was significantly lower after intervention for the full intervention group, but not for the partial intervention group. According to the multivariate model, in comparison with the control group, the odds ratio of antibiotic prescription after the intervention was 0.52 (95% confidence interval (95% CI) 0.23–1.18) in the partial intervention group and 0.23 (95% CI 0.11–0.47) in the full intervention group.

Conclusions: Intervention was beneficial for reducing the prescription of antibiotics, but was only statistically significant when the GPs were provided with RADTs.

Keywords: audit, acute pharyngitis, acute tonsillitis, predicting factors

Introduction

Acute pharyngitis is frequently seen in primary care for which uncertain aetiology may result in inappropriate management. Most pharyngitis is viral in origin while group A β-haemolytic Streptococcus (GABHS) is the most common bacterial cause of acute pharyngitis, accounting for ~15%–30% of the cases in children and 5%–15% of cases in adults.1 GABHS has been considered the only commonly occurring form of acute pharyngitis for which antibiotic therapy is indicated.2 Over the past few years, however, cases of bacteraemic infection caused by Fusobacterium necrophorum have been reported in patients aged 15–24 years, extending the cases of pharyngitis that need antibiotic therapy.3 Antibiotic treatment has been shown to shorten the transmission and dissemination of GABHS in the community, reduce the symptomatology compared with an untreated group by a mean of 16 h and prevent suppurative complications.4 Unnecessary antibiotic use plays an important...
role in increasing bacterial resistance and increases medical costs and the risk of drug-related adverse events.\textsuperscript{5} However, the previous literature has indicated that antibiotics are often overprescribed in these patients.\textsuperscript{6–8} This prescription of antibiotics differs considerably among professionals, communities and countries, as does the type of antibiotic administered.\textsuperscript{9} Thus, penicillin V is preferentially prescribed in Scandinavian countries while broader-spectrum antibiotics such as amoxicillin or amoxicillin/clavulanate are mainly used in most European countries.\textsuperscript{9} The evidence shows that in general countries in which more antibiotics are consumed are also those where the most resistant organisms are isolated.\textsuperscript{10}

The diagnosis of streptococcal pharyngitis also differs between different countries. In many countries only clinical criteria are used to make the diagnosis while in others these criteria are complemented with rapid antigen detection tests (RADTs). It has been shown that physicians who use these point-of-care tests use antibiotics less frequently to treat pharyngitis.\textsuperscript{11–13} The Happy Audit study, an acronym for Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the Treatment of respiratory tract infections, is an interventional study financed by the European Union, the main objective of which has been to strengthen the surveillance of respiratory tract infections in primary healthcare in Europe through the development of intervention programmes targeting general practitioners (GPs) and changing people’s habits towards prudent use of antimicrobial agents. This study involves the participation of GPs from six countries (Denmark, Sweden, Lithuania, Russia, Spain and Argentina).\textsuperscript{14,15} Spain has historically been one of the European countries with the highest antibiotic prescription rate with the greatest number of antimicrobial resistances among respiratory microorganisms, although this has progressively decreased in recent years.\textsuperscript{15} In addition, Spain is the only country in which two types of intervention were undertaken—one that was more intense and another that was partial in nature including a control group of physicians to allow the objective of the study to be achieved: evaluation of the effect of two interventions on lowering the prescribing of antibiotics in pharyngitis.

Patients and methods
Study design
A prospective, non-randomized, before–after controlled study was performed in primary care clinics in Spain. Three groups of professionals were included. (i) A full intervention group, made up of GPs from eight Autonomous Communities. This intervention consisted of presentation sessions and discussion of the results of the first registry of pharyngitis patients, training courses in the diagnosis and treatment of respiratory tract infections, discussion of guidelines, patient information leaflets, workshops on rapid tests and the introduction of RADTs in the consulting office. (ii) Another group of GPs from the Autonomous Community of Catalonia was assigned to a partial intervention that included all of the above intervention except for the workshop on diagnostic methods and RADTs. The first registry was made of the two groups of professionals prior to the intervention in January and February 2008 and a second registry was made after the intervention in January and February 2009. (iii) Another group of professionals (control group) from another two Autonomous Communities only did the registry in 2009 with no previous intervention. Considering that the population size was 4100 physicians in 2008, with a percentage of antibiotic prescription of 30%, a mean cluster size of 48 and sampling error of 4%, the number of physicians to be included in the sample assigned to the full intervention group was 72. The number of physicians working in the two communities assigned to the control group was 1745 in 2008, and taking into account the same figures for the remaining variables, the number of physicians to be included was 70.

The data were registered according to the methodology of the Audit Project Odense described by Munck et al.\textsuperscript{16} which follows a prospective self-registry methodology in which a simple reporting sheet is used. All the participants were instructed to fill out a template with all the patients with pharyngitis during a 3 week period, covering a total of 15 working days. On this sheet the physician attending the patient noted different concrete parameters of medical care, including the age and gender of the patient, the number of days of symptoms, presenting signs (fever, coughing, odynophagia, tender cervical glands, tonsillar exudate), suspected tonsillitis or not, aetiological suspicion (viral or bacterial), performance of RADTs, antibiotic treatment or not and the type of antibiotic administered, allergy or not to penicillin, whether the patient requested antibiotic or not and transfer to another healthcare setting or not.

Approval was obtained from the Ethics Committee Board Fundació Jordi Gol i Gurina. The project was conducted in accordance with the EU Directive of Good Clinical Practice. During the audit cycle, the participating primary care physicians were exposed to different interventions, but the patients did not undergo any intervention. Therefore, the patients were not asked for informed consent. However, patients were informed about the objective of the project and they were told that specific clinical information related to the consultation would be entered into a database.

Statistical analysis
The data were analysed with the Stata v.11 statistical program, performing univariate descriptive statistics and homogeneity tests of antibiotic prescription for each group between the physicians who completed the study and those who did not. A multilevel logistic regression model was estimated with two levels: contacts with pharyngitis and physicians. Antibiotic prescription was considered as the dependent variable (yes/no). The variables of interest were the use of RADTs and the five clusters of physicians (control group, full intervention group before and after the intervention and the partial intervention group before and after the intervention). The model was also adjusted for covariables age and gender, signs presented, diagnosis and patient demand for antibiotics. The physician effect was random on the intercept (Model 1). In addition, an alternative specification (Model 2) added a random differential medical effect after the intervention for the two intervention groups. Models were estimated with adaptive Gaussian quadrature with seven quadrature points per level.\textsuperscript{17} The likelihood ratio test was used to test Model 1 versus Model 2. After having estimated Model 2, the Bayesian a posteriori prediction of both random effects was calculated. The equality of means of the random effect between the groups was compared using ANOVA. The goodness of fit was assessed by using the Wald test of the model, with the deviance test to compare alternative models.\textsuperscript{18} Statistical significance was considered with $P<0.05$.

Results
A total of 332 primary care physicians were invited to participate voluntarily in the study in 2008, with 235 being assigned to the full intervention group and 97 to the partial intervention group. Of these two groups, 309 physicians registered the first audit in
2008 (93.1%) and 281 professionals carried out the intervention in 2008 and made the second registry in January–February 2009 (84.6%). A total of 280 GPs (210 full intervention and 70 partial intervention) registered contacts with pharyngitis. Of the 59 physicians invited to participate as the control group in 2009, all accepted to fill in the registry. Figure 1 shows the general scheme of the study. In 2008, a total of 3562 cases of pharyngitis were registered, 359 of which corresponded to physicians who left the study. Among the latter, antibiotics were prescribed in 151 cases (42.1%), a percentage similar to that observed among physicians who continued in the study (1317/3203; 41.1%). In the remaining analyses the results of the physicians who left the study were not considered.

The five groups of physicians registered a total of 6849 episodes of pharyngitis. In 2008 3203 cases were reported with another 3646 in 2009. As shown in Figure 2, antibiotic prescription was greater in the control group (50.1%). Antibiotic prescription did not decrease after the partial intervention, but did do so after the full intervention with a global reduction from 40.7% to 21.2%.

In our study, only the full intervention group had access to RADTs after the intervention. Rapid tests were used in 1088 patients out of the 2135 cases of pharyngitis attended by physicians assigned full intervention in 2009 (51%), its use being more frequent as the number of Centor criteria increased (Table 1). Nevertheless, only 763 out of the 1088 RADTs performed (70%) were carried out in patients with two or more Centor criteria as recommended in the guidelines, and in 139 contacts of the remaining 902 cases (15.4%) the test should have been done but was not.

Multilevel logistic regression results
A multilevel logistic regression model of two levels was estimated including contacts with pharyngitis (n=6849) and physicians (n=339). The Wald test of the model was 11149.47 ($P<0.001$). The sensitivity of the model was 88.2% and its specificity 90.6%. In this multilevel logistic regression analysis (Table 2) a negative result in the rapid test is interpreted as a
very important preventive factor for prescription [95% confidence interval (95% CI) 0.004–0.014]. On adjustment for covariates, there were no significant differences in prescription between the partial intervention and control groups or in the effect of partial intervention on the probability of prescription. Prior to the intervention the full intervention group did not significantly differ from the control group although the odds ratio (OR) was 0.54 (95% CI 0.27–1.06). However, the full intervention group presented an intense and significant preventive effect for prescription. The OR estimated versus the control group was 0.23 (95% CI 0.11–0.47). With regard to the other covariables, older age showed a greater probability of antibiotic prescription. Likewise, signs and symptoms had a significant effect on antibiotic prescription except for cough. It is of note that prescribers were very susceptible to demand for antibiotic by the patient (OR 20.6; 95% CI 11.2–37.6).

The random part of the model included two effects of the physicians on the probability of prescribing, one for all and another specific for those in the intervention groups after the audit (Table 3). Both random effects were significant (95% CI 1.67–2.16 and 1.60–2.30, respectively) and correlated negatively (r = 0.56). The random general effect on the intercept indicates that the physicians were heterogeneous in their prescription patterns. The specific random experimental effect indicates that heterogeneity among the physicians diminished after both the partial (only audit) and complete (including RADTs in the consulting office) interventions. The global medical effect was very significant ($\chi^2$ 835.67; P < 0.0001). The $\chi^2$ test was greater than in the alternative specifications.

**Discussion**

This study demonstrates that an intervention aimed at achieving more prudent use of antibiotics for pharyngitis by GPs is able to reduce the prescription of antibiotics and this reduction is much greater and statistically significant when these professionals are offered the possibility of performing RADTs in their offices. Inclusion of the two levels of patients and GPs in our model allowed estimation of the inclination to prescribe antibiotics of each physician and compare whether the intervention reduced the heterogeneity among the participating physicians. The results of this study demonstrate the high degree of heterogeneity among primary care physicians in the tendency to prescribe antibiotics prior to the intervention, which was reduced after both the partial and complete interventions.
One limitation of the study was that the clinical outcomes of the patients were not taken into account and thus, it is not known whether the percentage of complications or clinical failure differed between the groups. Nonetheless, the registry sheet included the transfer of patients to hospital. Another limitation that should be regarded in this type of study is that the mere fact of performing an audit may influence prescribing habits. However, the reliability of the Audit Project Odense methodology demonstrated in various projects carried out in other European countries is very high and is very well correlated with actual prescribing in medical offices. Although this was not a clinical trial, which may be considered a limitation of the study, we analysed the results with multivariate multilevel analysis, which allowed comparison of the physicians and determination of whether the effect of the intervention reduced not only antibiotic prescription but also variability among physicians. Another limitation is the unequal numbers of practitioners included in the study groups. Even though the number of physicians finally recruited in the partial intervention group coincided with the number calculated, the physicians in the full intervention group were clearly oversampled and the number of professionals in the control group was slightly underestimated, although this difference was marginal. Nevertheless, the greatest strength of this study is the large number of physicians included. In addition, <10% of the professionals who carried out the first registry left the study. Another strength of this study is inherent in the reality of our country and most of the European countries in which RADTs are not incorporated into primary care and, therefore, the effect of their use can be better established and can also be compared with the partial intervention, which was exactly the same, but without the use of these tests.

Many studies have been performed to determine the effectiveness of different types of intervention in reducing the prescription of antibiotics in pharyngitis. Not all interventions achieve positive results particularly when used alone. According to a review of the Cochrane Library, only interventions taking combinations such as these into account, including result feedback, interactive educational sessions and strategies aimed at patients, achieve a reduction in the prescription of antibiotics in supposedly viral respiratory infections. On the other hand, the use of printed educational material or audit and feedback alone resulted in no or only small changes in prescribing. Interactive educational meetings, such as those undertaken in this study, appear to be more effective than didactic lectures. Despite multifaceted interventions combining physicians, patients and public education being the most successful in reducing antibiotic prescribing for inappropriate indications, the effectiveness of these interventions is, in fact, only modest. Nonetheless, to date, few studies have been performed to determine the modification in antibiotic prescription in pharyngitis with the introduction of RADTs and, in these cases, the reduction in antibiotic prescription is usually more important than with other types of intervention. McIsaac et al. reported a 45% reduction in antibiotic prescription in adults using RADTs compared with empirical treatment. Worrall et al. reported a percentage of antibiotic prescription of 58% among physicians who did not use RADTs and of 27% among those who did use this rapid test. Similarly, in another primary care study carried out in Switzerland, the use of RADTs reduced antibiotic prescribing from 60% to 37%. Curiously, in recent studies carried out in paediatrics, in which the incidence of streptococcal infection is higher, greater reductions in percentages of antibiotic prescription were observed among the physicians assigned to RADTs, ranging from 22% to 28%. Perhaps the results of our study could lead to the design of clinical trials with different levels of intervention that also consider this or other rapid tests, improvements in doctor–patient communication and patient empowerment such as those recently suggested by Altiner et al. and Cals et al. and combinations of these.

In conclusion, despite the exaggerated use of antibiotics and the growing development of bacterial resistance, only a small number of approaches within the primary care setting have been shown to be effective in reducing the global use of antibiotics. The results of the present study, which included an important number of GPs with the implementation of a simple methodology, a 15 day registry of pharyngitis before and after two types of intervention, demonstrate that an intervention aimed at both professionals and patients to encourage the prudent use of antibiotics in pharyngitis achieves a reduction in the prescription of antibiotics. However, this reduction is much more important if primary care offices are provided with apparatus for RADTs. We believe that the pragmatic nature of our study enhances generalization of the results to other countries where these rapid tests are not routinely used.

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**Transparency declarations**

C. L. declares having received rapid diagnostic tests free of charge from Leti, Genzyme, Axis-Shield and Orion Diagnostica for investigational...
studies. Furthermore he declares that Leti covered the travel and accommodation costs for seeking the inclusion of physicians in a control group in the Happy Audit study and covered the accommodation costs during an international congress on respiratory disease in primary care in 2010. He declares not having received honoraria from any laboratory. All other authors: none to declare.

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