Title

Interventions to reduce antibiotic prescribing for lower respiratory tract infections.

Happy Audit study

Authors

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Abstract

This before-after study was aimed to evaluate the effect of two interventions on lowering the prescription of antibiotics in lower respiratory tract infections (LRTI) in Spain.
General practitioners (GP) registered all cases with LRTIs during 3-week periods before and after an intervention, in 2008 and 2009. Two types of intervention were considered: full intervention (FIG) consisting in discussion sessions of the results of the first registry, courses for GPs, guidelines, patient information leaflets, workshops on rapid tests and use of the C-reactive protein (CRP) test. GPs in the partial intervention group (PIG) underwent all the above intervention except for the workshop on rapid tests and they did not have access to CRP. A multilevel logistic regression analysis was performed considering the prescription of an antibiotic as the dependent variable.

Two hundred ten physicians were assigned to FIG and 70 to PIG. In 2009, 58 new physicians were included as a control group. 5,385 LRTIs were registered. Compared with the control group the odds ratio of antibiotic prescription after the intervention in the PIG was 0.42 (95%CI: 0.22-0.82), being 0.22 (95%CI: 0.12-0.38) in the FIG.

Intervention led to a reduction in the prescription of antibiotics, mainly when CRP testing was available.

**Key words:** Audit. Lower respiratory tract infections. C-reactive protein. Antibiotics.

Unnecessary use of antibiotics plays an important role in increasing bacterial resistance and medical costs as well as the risk of drug-related adverse events [1]. The most frequent indication for antibiotic prescription in the North-western hemisphere is lower respiratory tract infections (LRTI) [2]. Acute bronchitis accounts for 80% of LRTIs [3, 4], and despite evidence of little or no benefit with antibiotics, approximately three-quarters of LRTIs are treated with antimicrobial agents in most of these countries.
Clinical signs and symptoms are unreliable for distinguishing viral from bacterial LRTI [8, 9]. Diagnostic uncertainty increases the likelihood of inappropriate antibiotic prescription and, when in doubt, general practitioners (GP) opt for antibiotic prescription in case of possible pneumonia since routine chest radiographies for all patients with LRTI is neither feasible nor appropriate in primary care [10]. The C-reactive protein (CRP) is a promising biomarker for improving the assessment of LRTI in primary care and has shown to perform better in predicting the diagnosis of pneumonia than any individual or combined clinical symptoms and signs in LRTI [11, 12]. The CRP rapid test is feasible and easy to perform in the community setting since it takes approximately three minutes to obtain the result, can utilize serum, plasma or whole blood, organized laboratories are not needed and can be used by clinicians or nursing staff [13]. Moreover studies comparing this rapid test with the routine CRP laboratory test have shown a very good correlation thereby demonstrating its reliability [14].

Few studies have evaluated the role of these rapid tests on antibiotic prescription in primary care. Furthermore, these studies have been performed in countries with low antibiotic prescription rates [15-20]. Compared to other European countries, Spain has historically had a high outpatient antimicrobial consumption rate and a high proportion of respiratory microorganisms with resistance to common antibiotics, although this has progressively decreased in recent years [21,22]. The aim of this study was to evaluate the effect of two interventions on lowering the prescription of antibiotics in LRTIs in primary care in our country.

MATERIAL AND METHODS

Study population
A prospective non-randomized controlled before-after study was performed in primary care clinics in Spain. This study constitutes part of the Happy Audit project, a study financed by the European Commission, the main objective of which was to strengthen the surveillance of respiratory tract infections in primary healthcare through the development of intervention programmes targeting general practitioners and changing people’s habits towards prudent use of antimicrobial agents [23]. GPs from six countries have participated in this study (Denmark, Sweden, Lithuania, Russia, Spain and Argentina). However, Spain was the only country in which two types of interventions were undertaken. The interventions only differed in the training and access to the use of a CRP point of care test.

Detailed information about the study method and the intervention can be found in the study protocol [23]. Briefly, the data were registered according to the methodology of the Audit Project Odense described by Munck et al [24], which follows a prospective self-registry methodology in which a simple reporting sheet is used. Approval was obtained from the Ethical Committee Board Fundació Jordi Gol i Gurina (registration number: 44154). All the participants were instructed to fill out a template with all the patients with LRTIs during a 3-week period in the winter months of 2008 (first registry) and 2009 (second registry), covering a total of fifteen working days in both periods. On this sheet the physician attending the patient noted different specific parameters of medical care, including the age and gender of the patient, the number of days of symptoms, presenting signs – fever, coughing, dyspnoea, increase in sputum volume, purulence of sputum-, diagnosis – acute bronchitis, acute exacerbation of chronic bronchitis or chronic obstructive pulmonary disease (COPD), pneumonia-, aetiologic suspicion (viral or bacterial), performance of chest X-ray and CRP rapid tests, antibiotic
treatment or not, allergy or not to penicillin, whether the patient requested an antibiotic or not and referral to another healthcare setting or not.

Three groups of professionals were included: 1) A full intervention group (FIG), made up of GPs from eight Autonomous Communities. This intervention consisted in presentation sessions and discussion of the results of the first registry, training courses on the diagnosis and treatment of LRTIs, discussion of guidelines, patient information leaflets, workshops on rapid tests and the introduction of the CRP test in the consulting office. The workshops took place approximately two months before the second registry. Physicians were instructed not to use the CRP as a stand-alone test but rather to use it as an additional test in case of doubt, withholding antibiotic therapy with CRP values lower than 20 mg/l and prescribing an antibiotic with values > 100 mg/l. 2) Another group of general practitioners from Catalonia were assigned to a partial intervention (PIG) which included all the above intervention except for the workshop on diagnostic methods and the CRP tests. 3) The control group included professionals from two other Autonomous Communities who only did the registry in 2009, with no previous intervention.

**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 among the physicians who completed the study and those who did not. A multilevel logistic regression model was estimated with two levels: the patients with LRTIs and the physicians. Antibiotic prescription was considered as a dependent variable. The variables of interest were the use of the CRP and the five clusters of physicians (control group, FIG before and after the intervention and the PIG before and after the
intervention). The model was also adjusted for covariables: age and gender, days with symptoms, signs presented, diagnosis, patient demand for antibiotics, X-ray request and radiographic results positive for consolidation. The physician effect was modelled as a random intercept and, in addition, the model included a specific random effect on the FIG after the intervention. Once the model had been estimated the Bayesian posterior predictor of both random effects was calculated [25]. Statistical significance was considered with a p value <0.05.

RESULTS

A total of 332 GPs were invited to voluntarily participate in the study in 2008, with 235 being assigned to the FIG and 97 to the PIG. Of these two groups, a total of 308 physicians registered the LRTIs in the first audit in 2008 (92.8%) and 280 professionals carried out the intervention in 2008 and made the second registry in 2009 (84.4%). Figure 1 shows the general scheme of the study. The five groups of physicians registered a total of 5,385 LRTIs, of which 3,624 corresponded to acute bronchitis (67.3%). As shown in Table 1, antibiotic prescription was greater in the control group (76.6%) and in the pre-intervention groups (FIG: 69% and PIG: 61.3%), being lower after the intervention (43.9% versus 56.2%, respectively). By diagnoses, the greatest percentage reductions were observed in acute bronchitis in the FIG (from 62.3% to 30.2%) (Table 1).

CRP test results

The CRP test was only used by the physicians in the FIG after the intervention, with 545 determinations of a total of 1,488 contacts (36.6%). However, the numerical value was not noted or was illegible in 51 cases. Antibiotic prescription was lower among the
physicians using the CRP rapid test (43.9%) compared with the GPs who did not use the test (61.8%; \( p<0.001 \)). Prescription was also lower when the results of CRP were less than 10 mg/L, with these values being observed in 51.2% of the total number of determinations noted in the registry sheets and, in these cases, antibiotics were only prescribed in 35 contacts out of a total of 253 determinations (13.8%) (Table 2).

**Predictors of antibiotic prescription in LRTIs**

A multilevel logistic regression model of two levels was estimated including contacts with LRTIs (n: 5,385) and physicians (n: 338). In this analysis (Table 3) the use of the CRP was a very significant protective factor for antibiotic prescription. Thus, with CRP results < 10 mg/L the odds ratio (OR) for antibiotic prescription was 0.10 compared with the no use of this test (95%CI: 0.06–0.17). After adjusting for the remaining variables, no statistically significant differences were found in antibiotic prescription between the two pre-intervention and the control groups. In contrast, the post-intervention ORs were significantly lower than those of the control and pre-intervention groups. In comparison with the control group, the OR for antibiotic prescription was significant in the PIG after the intervention, being 0.42 (95%IC: 0.22-0.82). The effect of the intervention was greater with the use of the CRP, with the OR of antibiotic prescription observed in the FIG after the intervention being 0.22 (95%CI: 0.12-0.38).

Estimation results indicate that the physician effect was very significant \( (\chi^2: 574.3; \ p<0.0001) \), indicating a great random heterogeneity between the physicians in antibiotic prescription after adjusting for all the previously mentioned covariables. The random effect on the intercept differed significantly between the groups of physicians (ANOVA, \( p<0.001 \)). In addition, the random effect of the GPs was significant, differing the FIG after the intervention from the remaining groups. With respect to the constant and the
slope, both random effects were negatively correlated (-0.68), indicating that, in general, the effect of the intervention was more intense among physicians who prescribed antibiotics more frequently. Therefore, the full intervention homogenized the behaviour of the physicians. The partial intervention, on the other hand, did not present a differentiated significant random effect.

DISCUSSION

This study demonstrates that an intervention aimed to promote a more prudent use of antibiotics for LRTIs by GPs is able to reduce the prescription of antibiotics, mainly in acute bronchitis, with this reduction being much greater when these professionals are offered the possibility of performing CRP tests in their offices.

Strengths and limitations of the study

The results of this study should be interpreted with caution because of a series of limitations. Firstly, this is a study in which physicians, including those assigned to the control group, have participated voluntarily and, thus, their prescription habits may not be the same as those of general use which primary care physicians globally follow. Different studies have shown that GPs who participate in audits may be more interested in research than other physicians [26]. The results of this study are based on the data reported by the GPs and even though these data were not double-checked with the actual prescription, the results obtained by the pre-intervention groups are similar or slightly lower to those obtained in observational studies carried out in our country [27-29]. Participation in a study on the rational use of antibiotics may have also influenced the GP to prescribe antibiotics more rationally in the first registry. Another limitation is that in this study possible associated comorbidities of the patients registered were not
taken into account, and this may influence the percentage and the type of antibiotic used. Likewise, not all the signs and symptoms of LRTIs were considered, although the most important as well as all those described as making bacterial aetiology more probable in the medical literature were. Neither did we consider all the non-biomedical factors which some studies have described such as the fact that one of the most powerful predictors of antibiotic prescription is inherent to the physicians themselves who prescribe more than the clinical manifestations of the patient suggest. Our study suggests that the predisposition to prescribe varies greatly among physicians. Another 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 groups. However, Cals et al. did not observe any differences in clinical outcomes between patients with LRTI treated and not treated with antibiotics [19,20]. The goal of primary care is not to minimize antibiotic prescription but rather to prescribe antimicrobial agents to patients who truly need them and avoid inappropriate prescription decisions. Although we did not measure health outcomes, the registry sheet included the referral of patients to hospital. Although this was not a clinical trial, which may also be considered as a limitation of the study, we analysed the results with multivariate multilevel analysis which allowed comparison of the GPs and determination of whether the effect of the intervention reduced not only antibiotic prescription but also the variability among physicians.

The greatest strength of this study is the large number of physicians included. In addition, less than 10% of the professionals who carried out the first registry abandoned the study. Another strength of this study is inherent to the reality of our country in that the CRP is not incorporated in the primary care offices and therefore, the effect of its use can be better established and can also be compared with the partial intervention.
Comparison with other studies

Many studies have been performed to determine the effectiveness of different types of interventions to reduce the prescription of antibiotics in respiratory tract infections. Not all interventions achieve positive results, particularly when used alone. According to a review of the Cochrane Library, only interventions taking combinations of these into account such as result feedback, interactive educational sessions and strategies aimed at patients achieve a reduction in the prescription of antibiotics in supposedly viral respiratory infections [30]. 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 multi-faceted interventions combining physician, patient and public education being the most successful in reducing antibiotic prescribing for inappropriate indications, the effectiveness of these interventions is, in fact, only modest [30].

Nonetheless, to date, few studies have been performed to determine the modification in antibiotic prescription in LRTIs with the introduction of rapid tests and in these cases the reduction in antibiotic prescription is usually more important than with other types of intervention. André et al. demonstrated that the prescription of antibiotics in paediatric offices in Sweden may be reduced from 58% among physicians not using the CRP to 36% when this technique is available [18]. In another study, GPs assigned to CRP testing safely reduced antibiotic prescription for LRTIs compared with doctors assigned to usual care (from 53% to 31%) [19]. In a recently published study carried out in Holland, patients in the CRP-assisted group used fewer antibiotics than control patients (43.4% vs. 56.6%, respectively) [20]. One advantage of our design is that it
allows the effect of the audit *per se* to be estimated separately from the availability of CRP testing. The reduction in antibiotic prescription associated with the additional availability of the test is more marked in our study than in others.

The diagnosis of pneumonia is difficult in general practice because the symptoms of the disease frequently resemble those of other LRTIs [31]. The CRP value has been found to be more valuable than any sign or symptom in differentiating pneumonia from other respiratory tract infections [11,12]. A CRP test result adds incremental information to the physicians’ information obtained from medical history and physical examination. The relation of CRP with an infiltrate on chest radiography as a reference standard shows an area under the receiver operating characteristic (ROC) curve of 0.80 [32]. The addition of CRP to a model based on signs and symptoms increases the area under the ROC curve from 0.70 to 0.90. [12]. In particular, a low CRP test result (less than 20 mg/L), which was the case in more than 50% of our patients, may be helpful in excluding antibiotic necessitating illness. In the present study, the GPs performing the determination of CRP with results less than 10 mg/L were 10-fold less likely to prescribe antibiotics than physicians who did not use the rapid test. In a Swedish study, 14% of patients with a diagnosis of nonspecific respiratory tract infection were given antibiotics when the CRP value was < 10 mg/L compared to 94% when the CRP value was > 50 mg/L [17]. On the other hand, with values > 10 mg/L, more than half of the cases were prescribed antibiotics, even with values between 10 and 20 mg/L. The antibiotic prescription rate in our study was not reduced when CRP had intermediate levels (20-99 mg/L), similar to the study by Cals *et al.* [20].

On having incorporated two levels – contacts with LRTIs and GPs - our model has allowed estimation of the predisposition to prescribe antibiotics of each physician. There was a high degree of heterogeneity among general practitioners with respect to
the trend to prescribe antibiotics, which was reduced when CRP testing was provided. Nevertheless, the partial intervention based on the discussion of results, courses for GPs and leaflets for patients did not apparently reduce the intrinsic heterogeneity of the prescription habits of the physicians.

**Implications for future research**

After having determined physician behaviour regarding antibiotic prescription for LRTIs it is necessary to know whether these results can be maintained in the future with observation of the behaviour of the same physicians several years after the introduction of the CRP rapid tests. This should also be reproduced in other geographical areas with different healthcare systems and different antibiotic prescription behaviours. On the other hand, qualitative investigation is required to determine why physicians do not reduce their antibiotic prescription behaviour with intermediate CRP concentrations. Future studies will also better define the CRP cut-off points to be used to safely withhold antibiotic therapy. Only in this way will we be able to carry out strategies to change the attitudes of GPs and encourage rational use of antibiotics in these infections.

**Summary**

The results of the present study demonstrate that a reduction may be achieved in the prescription of antibiotics, particularly in acute bronchitis, with the implementation of a simple methodology aimed at encouraging the prudent use of antibiotics in LRTIs, including feedback and discussion of baseline antibiotic prescription, training courses in the diagnosis of
treatment of LRTIs, discussion of guidelines and patient information leaflets. Moreover, this reduction may be greater with the availability of CRP tests in the consultation offices. We believe that the pragmatic nature of our study enhances the generalizability of the results to other countries where these rapid tests are not routinely used.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared

REFERENCES


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<th>Year 2009</th>
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<td>Full</td>
<td>Subtotal</td>
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<td>Acute bronchitis</td>
<td>254/532</td>
<td>801/1,285</td>
<td>1,055/1,817</td>
<td>240/338</td>
<td>173/424</td>
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<td></td>
<td>(47.7)</td>
<td>(62.3)</td>
<td>(58.1)</td>
<td>(71.0)</td>
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<td>Acute exacerbations of CB/COPD</td>
<td>176/217</td>
<td>371/451</td>
<td>547/668</td>
<td>119/143</td>
<td>129/162</td>
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<td></td>
<td>(81.1)</td>
<td>(82.3)</td>
<td>(81.9)</td>
<td>(83.2)</td>
<td>(79.6)</td>
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<td>Pneumonia</td>
<td>89/97</td>
<td>116/132</td>
<td>205/229</td>
<td>40/40</td>
<td>70/76</td>
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<td></td>
<td>(91.8)</td>
<td>(87.9)</td>
<td>(89.6)</td>
<td>(100.0)</td>
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<td>Total</td>
<td>510/846</td>
<td>1,288/1,868</td>
<td>1,792/2,714</td>
<td>399/521</td>
<td>372/662</td>
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<tr>
<td></td>
<td>(61.3)</td>
<td>(69.0)</td>
<td>(66.2)</td>
<td>(76.6)</td>
<td>(56.2)</td>
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CB/COPD: chronic bronchitis or chronic obstructive pulmonary disease
TABLE 2. Antibiotic prescription in lower respiratory tract infections according to the C-reactive protein value obtained

<table>
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<th>Use of C-reactive protein</th>
<th>Antibiotic prescription.</th>
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<td>n (%)</td>
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<td>No use of C-reactive protein</td>
<td>2,992/4,840 (61.8)</td>
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<td>Use of C-reactive protein</td>
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<tr>
<td>- 0 – 10 mg/L</td>
<td>35/253 (13.8)</td>
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<tr>
<td>- 11 – 20 mg/L</td>
<td>16/28 (57.1)</td>
</tr>
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<td>- &gt; 20 mg/L</td>
<td>168/213 (78.9)</td>
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<tr>
<td>- Figure not written or illegible</td>
<td>20/51 (51.0)</td>
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<tr>
<td>- Total</td>
<td>239/545 (43.9)</td>
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TABLE 3. Odds ratio for antibiotic prescription in lower respiratory tract infections

<table>
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<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.012</td>
<td>1.007 - 1.017</td>
<td>0.000</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.103</td>
<td>0.928 - 1.309</td>
<td>0.265</td>
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<td>COPD</td>
<td>2.883</td>
<td>2.275 - 3.653</td>
<td>0.000</td>
</tr>
<tr>
<td>Fever</td>
<td>4.667</td>
<td>3.813 - 5.712</td>
<td>0.000</td>
</tr>
<tr>
<td>Cough</td>
<td>1.058</td>
<td>0.809 - 1.384</td>
<td>0.679</td>
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<tr>
<td>Increase in dyspnoea</td>
<td>1.390</td>
<td>1.152 - 1.677</td>
<td>0.001</td>
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<tr>
<td>Increase in sputum</td>
<td>2.369</td>
<td>1.962 - 2.860</td>
<td>0.000</td>
</tr>
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<td>Purulent sputum</td>
<td>10.068</td>
<td>8.079 - 12.521</td>
<td>0.000</td>
</tr>
<tr>
<td>Demand for antibiotics</td>
<td>3.02</td>
<td>1.668 - 5.468</td>
<td>0.000</td>
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<td>Request for a X-ray</td>
<td>1.602</td>
<td>1.142 - 2.247</td>
<td>0.006</td>
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<td>X-ray positive for consolidation</td>
<td>8.07</td>
<td>4.232 - 15.387</td>
<td>0.000</td>
</tr>
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<td>CRP &lt; 10 mg/l</td>
<td>0.103</td>
<td>0.061 - 0.173</td>
<td>0.000</td>
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<td>CRP 10-20 mg/l</td>
<td>1.488</td>
<td>0.542 - 4.08</td>
<td>0.440</td>
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<td>CRP &gt; 20 mg/l</td>
<td>4.6</td>
<td>2.781 - 7.606</td>
<td>0.000</td>
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<td>CRP missing or illegible</td>
<td>0.396</td>
<td>0.182 - 0.859</td>
<td>0.019</td>
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<tr>
<td>Partial intervention group, preintervention</td>
<td>0.574</td>
<td>0.298 - 1.104</td>
<td>0.096</td>
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<td>Partial intervention group postintervention</td>
<td>0.424</td>
<td>0.219 - 0.821</td>
<td>0.011</td>
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<td>0.811</td>
<td>0.461 - 1.426</td>
<td>0.466</td>
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<tr>
<td>Full intervention group, postintervention</td>
<td>0.217</td>
<td>0.123 - 0.382</td>
<td>0.000</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein

*aCompared with no use of CRP

*bCompared with control group
FIGURE 1. General scheme of the study

FULL INTERVENTION GROUP
- 235 General practitioners were invited to participate in the study
- 224 General practitioners accepted to participate in the study
- 214 General practitioners completed the registries in the first year, 2008
- 14 Physicians did not complete the intervention
- 210 General practitioners undertook the intervention and completed all the registries in the second year, 2009

INTERVENTION PERFORMED:
- Follow-up meeting with presentation of the results of the first registry
- Training courses on the diagnosis and treatment of lower respiratory tract infections
- Discussion of guidelines
- Hand-out of brochures for patients
- Workshop on rapid tests and provision of CRP rapid test

PARTIAL INTERVENTION GROUP
- 97 General practitioners were invited to participate in the study
- 87 General practitioners accepted to participate in the study
- 74 General practitioners completed the registries in the first year, 2008
- 14 Physicians did not complete the intervention
- 70 General practitioners undertook the intervention and completed all the registries in the second year, 2009

INTERVENTION PERFORMED:
- Follow-up meeting with presentation of the results of the first registry
- Training courses on the diagnosis and treatment of lower respiratory tract infections
- Discussion of guidelines
- Hand-out of brochures for patients

CONTROL GROUP
- 59 General practitioners were invited to participate in the study
- 58 General practitioners completed all the registries in 2009
- 1 Physician did not fill out the registries

No intervention performed