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Improving the Reporting of Adverse Drug Reactions

A Cluster-Randomized Trial Among Pharmacists in Portugal

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Abstract

Background: Adverse drug reaction (ADR) reporting systems are the basic component for comprehensive postmarketing surveillance of the risk of drug-induced adverse effects. The aim of this study was to evaluate the effectiveness of educational outreach visits aimed at improving ADR reporting by pharmacists.

Methods: The study population comprised all pharmacists working in a catchment area covered by Portugal's Northern Regional Health Authority. Using unequal randomization, four spatial-clusters were assigned to the intervention group (n = 342) and eleven to the control group (n = 1091). The intervention took the form of 1-hour long educational outreach visits tailored to training needs detected in a previous study, with a 13- to 16-month follow-up period (March–June 2004 through June 2005). This study is registered as an international standard randomized controlled trial, number ISRCTN45894687.

Results: At baseline, ADR reporting rates (per 1000 pharmacist-years) did not differ significantly between the intervention and control groups (32.28 vs 29.16). The adjusted increase in ADR reporting attributable to the intervention was 275.63 per 1000 pharmacist-years (95% CI 162.15, 389.12; relative risk [RR] = 5.87, 95% CI 1.98, 17.39). The intervention succeeded in multiplying the reporting rate of: serious ADRs, 10-fold (RR = 9.79; 95% CI 2.24, 42.66); unexpected ADRs, 4-fold (RR = 4.41; 95% CI 1.11, 17.53); high-causality ADRs, 9-fold (RR = 8.67; 95% CI 2.12, 35.42); and new drug-related ADRs, 9-fold (RR = 9.33; 95% CI 2.53, 34.40). While the greatest effect was registered during the first 4 months post-intervention, differences remained statistically significant for 8 months.

Conclusions: Educational outreach visits improve ADR reporting by pharmacists in terms of quantity and relevance.

Background

Adverse drug reactions (ADRs) are a major cause of patient morbidity, mortality and additional financial costs.[1,2] Indeed, reporting of suspected ADRs is the most important method of drug surveillance. Nevertheless, it is estimated that less than 10% of ADRs are reported,[3] greatly limiting the advantages of this surveillance method.

Pharmacists are very well placed to provide valuable postmarketing information on drug products, owing to the fact that they are a vital link between the patient and the health system before and during a course of drug therapy,[4,5] and can play an important role in monitoring adverse events in hospitals.[6,7] The pivotal role of the pharmacist in the detection, reporting and handling of ADRs has been confirmed in many countries,[8-10] with pharmacists accounting for 88% of all notifications in Canada, 40% in the Netherlands and 18% in the USA.[11] Yet, in many countries, the number of reports submitted by pharmacists is regarded as lower than expected. Despite this, we identified only three studies,[12-14] none of which were controlled, randomized trials, which involved pharmacists and sought to evaluate the effectiveness of educational interventions intended to increase spontaneous reporting.

Accordingly, research was undertaken with the aim of reducing ADR under-reporting in the Northern Health Region of Portugal. In stage I, knowledge and attitudes about under-reporting of ADRs were investigated in a case-control study.[15] In stage II of the study, a purpose-designed educational intervention was then implemented to modify such knowledge and attitudes regarding ADR reporting, and a cluster-randomized, controlled trial was used to evaluate its effectiveness. This paper reports key findings of stage II. We assessed changes in the ADR reporting rate resulting from the intervention, the quality (relevance) of reporting and the duration of the effect of the intervention.

Methods

Study Design

We conducted a cluster-randomized controlled trial. As the intervention was educational, spatial cluster-randomization was required to minimize cross contamination between groups (the likelihood of subjects in the intervention group sharing information with the control group). Each spatial-cluster consisted of one reference hospital plus the community pharmacist and any other hospital that might possibly lie in its catchment area.

Most cluster-randomized trials allocate approximately equal numbers of clusters to experimental and control groups. While this is the most statistically efficient randomization ratio, it may nevertheless not be the most economically efficient.[16] Where there is a substantial cost difference between the intervention group and the control group, it may be more economically efficient to randomize fewer clusters to the intervention than to the control group.[16] The 15 clusters were therefore distributed by means of unequal randomization,[17] with an approximate intervention to control group ratio of 1 : 3. Using a computer-generated procedure, four clusters were assigned to the intervention and 11 to the control group.

Study Population and Settings

The Northern Region of Portugal, which covers an area of 20 000 square kilometres, has 3.7 million inhabitants, 14% of whom are aged >65 years. It has 104 outpatient centres, 25 hospitals (5 of which are specialty hospitals) and 761 community pharmacies. In Portugal, pharmacists are permitted to report directly to health authorities, independently of physicians.

The study population was made up of pharmacists employed in hospital and community pharmacies across the designated catchment area of Portugal's Northern Region Health Authority. All pharmacists working at the regional pharmacosurveillance centre or attached to specialty hospitals were excluded (see figure 1); the reason for exclud-

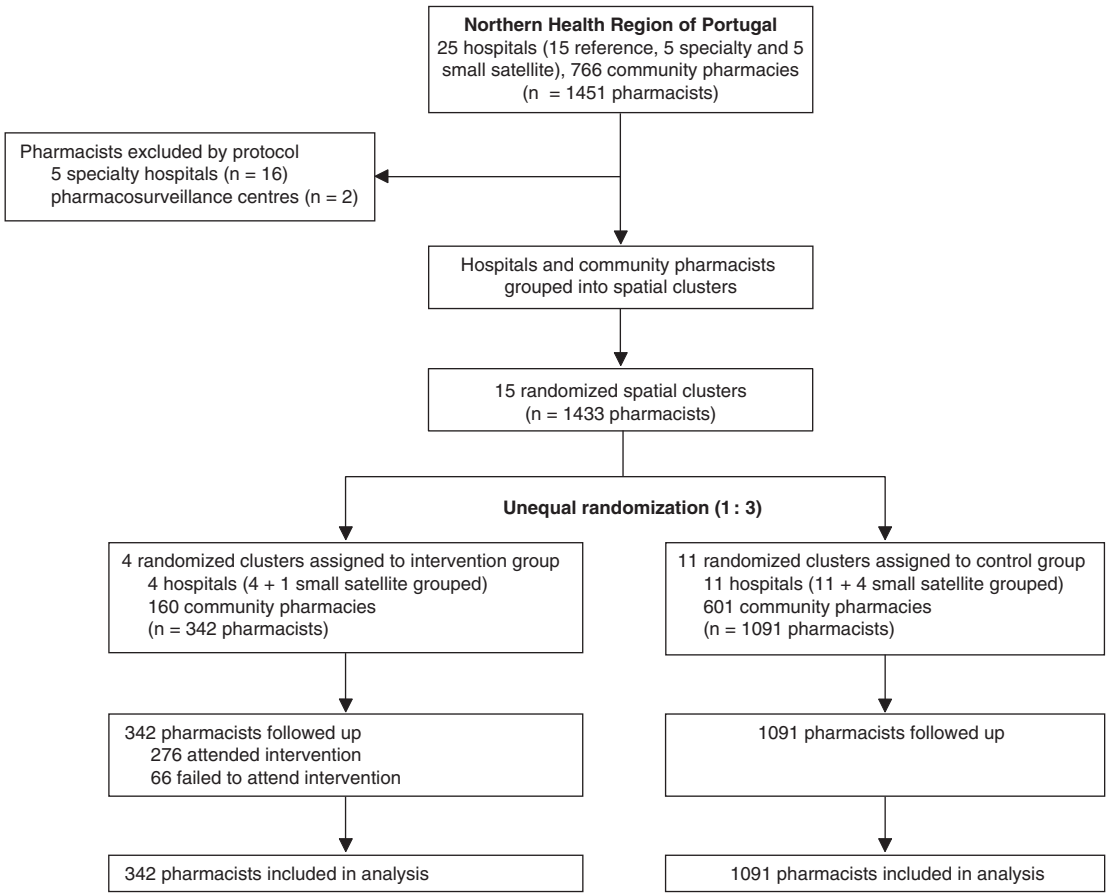

Fig. 1. Study population selection protocol.

ing specialty hospitals was that the risk of contamination between the control and intervention groups would be increased by having the entire region as a catchment area.

Intervention Group

The educational intervention was designed, taking into account knowledge and attitudes reported by the case-control study,[15] to address the under-reporting of ADRs among health professionals. The type of intervention used[18] was a combination of active (group-session slide presentation) and passive approaches (distribution of press material leaflets). The initial presentation addressed the matter of pharmacosurveillance and the definition of ADRs. This was then followed by a discussion of examples of international studies on the effect of ADRs on mortality, morbidity, hospital admissions and costs; the methods used in pharmacosurveillance; spontaneous reporting, and under-reporting of ADRs in particular. During the presentation a series of animated pictures were shown, depicting health professionals talking amongst themselves about the possible factors that affect under-reporting, namely: (i) complacency (the belief that very serious ADRs are well documented by the time a drug is marketed); (ii) diffidence (the belief that an ADR would only be reported if it were certain that it was related to the use of a particular drug); (iii) ignorance (the belief that it is only necessary for serious or unexpected ADRs to be reported); and, lastly, (iv) lack of time to consider the diagnosis of an ADR. These

attitudes were categorized on the basis of Inman's classification.[19] The presentation ended with an explanation outlining all the possible ways of contacting the Northern Pharmacovigilance Unit. The leaflet, which had the same external dimensions and colour as the report form, was drawn up to act as a reminder of the presentation, containing its main messages and key image.

The intervention took place from March 2004 through June 2004, targeting the same four spatial-clusters as used in a similar published study involving physicians.[20] Presentations were given by one of the researchers (Maria Herdeiro, a pharmacy postgraduate). The intervention lasted about 1 hour (approximately 30 minutes of presentation and another 30 minutes of discussion or debate). Intervention groups ranged from 1 community to 15 hospital pharmacists, although the groups normally had from 1 to 5 pharmacists in all.

Control Group

Control clusters did not receive the educational intervention; however, in common with the intervention group, the control clusters received the briefing and standard training given by Portugal's Northern Pharmacosurveillance Unit.

Follow-Up and Outcome Measures

The follow-up period began immediately after the intervention and ended in June 2005. During follow-up, five dependent variables were generated for each pharmacist and each month of follow-up: (i) indicator of reporting quantity (total number of reports); (ii) number of serious ADRs (one that results in death, is life-threatening, is a congenital anomaly, requires hospital admission or prolongation of stay in hospital, or results in persistent or great disability, incapacity or both);[21,22] (iii) number of ADRs with attribution of definitive or probable causality ('high-causality' ADRs as assessed by 'global introspection' or differential clinical diagnosis);[23-26] (iv) number of unexpected, unlabeled ADRs (unknown ADRs that are not described in the summary of product characteristics);[25] and (v) number of ADRs including medications that have been on the market for <5 years.[25] All these data came from the Northern Pharmacosurveillance Unit (part of the Portuguese Health Authority) and were certified in accordance with WHO guidelines. The Pharmacosurveillance Unit expert (Jorge Polónia) responsible for codifying adverse reactions was blinded as regards the study group to which the reporting pharmacist belonged.

Statistical Analysis

The pre-intervention monthly reporting rate among Portuguese pharmacists was estimated as approximately 0.0025 per month. We calculated that with four clusters in the intervention group and 11 in the control group (mean of 100 pharmacists), the study could have a power of over 80% (two-sided $p < 0.05$) to identify a 6-fold increase in reporting (equivalent to an absolute change in reporting of 150 reports per 1000 pharmacist-years) if 13 measures of the response variable were taken for each pharmacist, with a correlation among these of 0.01.[27-29] This assumed an over-dispersion in the response variable of 10% and an intracluster correlation coefficient of 0.005.

Statistical analysis was carried out on an intention-to-treat basis.[30] Generalized linear mixed models (GLMMs), using penalized quasi-likelihood, were applied to the statistical analysis.[31] This method allows for longitudinal data analysis adjusted for the baseline values of the dependent variable. To construct the models, we took the number of ADR reports as the dependent variable (as this was a count outcome, a Poisson-GLMM was used), with individual observations (per month per pharmacist) as level one, pharmacists as level two and spatial-clusters as level three; random effects were considered, both among pharmacists and among spatial-clusters. Models were adjusted for those sociodemographic and personal variables in respect of which the groups became unbalanced after random distribution (workplace: hospital pharmacy vs community pharmacy). Since the Poisson assumption (that the mean and variance of the dependent variable are equal) was not met in our data, the models

were adjusted taking the over-dispersion parameter into account.[31]

The effect of educational intervention was measured on the basis of the interaction between the period (0 for the baseline period, 1 for other months) and group variables (1 for intervention group, 0 for control group). The duration of the effect was measured by reference to the interaction between the 4-month (values of: 0 for baseline period; 1 for the first 4-month period post-intervention; and 2, 3 and 4 for the ensuing periods, respectively) and group variables. Results are expressed as relative risks (RRs) and their 95% confidence intervals (CIs), indicating by how much the reporting probability was increased by the educational intervention. The estimated absolute change, adjusted for baseline and work setting, was calculated by multivariate-adjusted risk differences using link identity in generalized estimating equation models. These analyses were performed using S-Plus 6.2 (Insightful Corp. Seattle, WA, USA).

Results

Participation and Subjects

Of the total number of pharmacists involved in the trial (1451), 18 were excluded (two for being members of the Northern Pharmacosurveillance Unit, and 16 for working in specialty hospitals). The remaining 1433 subjects comprised 342 who belonged to the intervention group and 1091 who belonged to the control group. Intervention was received by 276 pharmacists (see figure 1). Post-intervention follow-up duration was 13 months for 9 (2.6%), 14 months for 200 (58.5%) and 16 months for 133 (38.9%).

Table I shows the baseline characteristics of the intervention and control groups. Distribution by gender, age and workplace proved similar in both groups. Baseline reporting values are compared in table II, expressed as reports per 1000 pharmacist-years pre- and post-intervention. Compared with the control group, the reporting rate for the intervention group was slightly lower for high-causality, serious and new drug-related ADRs, and slightly higher for total and unexpected ADRs. Possible baseline differences between groups do not bias the results because the Poisson-GLMM adjusts for such differences.

Table I. Pharmacists' personal and professional characteristics in each study group[a]

Characteristic	Intervention group (n = 342)	Control group (n = 1091)
Sex		
male	70 (20.5)	221 (20.3)
female	272 (79.5)	870 (79.7)
Age[b]		
mean (SD)	38.2 (11.7)	37.5 (11.3)
median (percentile 25, 75)	35 (30, 43)	34 (29, 42.8)
Workplace		
pharmacy	315 (92.1)	1013 (92.9)
hospital	27 (7.9)	78 (7.1)

a Values are expressed as number (%) unless otherwise indicated.

b Age data available for 49.9% of subjects in the intervention group and 15.8% in the control group.

Total Reports

Comparing total ADR reporting, the intervention group increased the reporting rate per 1000 pharmacist-years from 32.28 at baseline to 326.28 in the post-intervention period, a rise of 910%, while the control group increased from 29.16 to 47.64, an increase of 63.2% ($p = 0.13$, see table III, model 1, period variable: RR = 1.63). The adjusted increase in the total ADR reporting rate attributable to the intervention was 275.63 per 1000 pharmacist-years (95% CI 162.15, 389.12), which amounted to a 5.87-fold increase in reporting (95% CI 1.98, 17.39; $p = 0.001$) [see table III, model 1].

From figure 2, it can be seen that in the first 4 months' post-intervention (measured from the start of the intervention period), spontaneous reporting increased >20-fold (RR = 20.21; $p < 0.0001$, table III, model 2) and, although it decreased thereafter, it nevertheless remained approximately 3.0-fold higher than that of the control group. This meant that the intervention led to a 5.49-fold increase (95% CI 2.37, 12.75) in the number of pharmacists reporting ADRs.

Table II. Adverse drug reaction (ADR) reporting rate per 1000 pharmacist-years. Description by ADR type and period[a]

ADR type	Group	Pre- intervention period	Overall post-intervention period	4-month post-intervention period			
				1st	2nd	3rd	4th[b]
Total	Intervention	32.3 (14)	326.3 (138)	570.0 (65)	315.6 (36)	244.9 (28)	114.6 (9)
	Control	29.2 (44)	47.6 (58)	24.7 (9)	57.7 (21)	66.0 (24)	31.1 (4)
Serious	Intervention	11.5 (5)	156.0 (66)	201.7 (23)	201.7 (23)	105.0 (12)	101.9 (8)
	Control	15.2 (23)	19.7 (24)	5.5 (2)	27.5 (10)	33.1 (12)	0 (0)
Unexpected	Intervention	11.5 (5)	85.1 (36)	157.9 (18)	87.7 (10)	22.0 (8)	0 (0)
	Control	9.2 (14)	15.6 (19)	11.0 (4)	19.2 (7)	16.5 (6)	25.4 (2)
High-causality	Intervention	11.5 (5)	193.8 (82)	306.9 (35)	175.4 (20)	175.0 (20)	89.0 (7)
	Control	13.9 (21)	25.4 (31)	13.8 (5)	16.4 (6)	46.8 (17)	23.3 (3)
New drug-related	Intervention	13.8 (6)	135.6 (57)	210.5 (24)	149.2 (17)	87.7 (10)	76.4 (6)
	Control	17.3 (26)	18.0 (22)	11.0 (4)	19.2 (7)	24.7 (9)	15.5 (2)

a Numbers in parenthesis after each rate indicate the number of ADRs.

b In the fourth 4-month period, follow-up of all subjects was not complete.

Reporting Quality

The effects of the intervention in terms of reporting quality (relevance) can be seen in table III, which shows reporting rates, adjusted for baseline values and workplace, for serious ADRs (10-fold [RR = 9.79; p = 0.002]), unexpected ADRs (4-fold [RR = 4.41; p = 0.04]), high-causality ADRs (9-fold [RR = 8.67; p = 0.002]), and new drug-related ADRs (9-fold [RR = 9.33; $p < 0.001$]).

Analysis by Subgroup

Lastly, when the sample was stratified by workplace, the intervention was observed to have increased the likelihood of reporting by 5.96-fold ($p < 0.01$) among community pharmacists but to have had no effect on hospital pharmacists (p = 0.99).

Discussion

Monitoring and reporting of ADRs is a vital component of overseeing the drug-use process, and is something in which pharmacists can play an important role. The results of this trial indicate that ADR reporting is stimulated by a 1-hour long educational intervention. In terms of quantity, despite the fact that the maximum value was attained in the first 4-month period and declined thereafter, there was nevertheless an overall 6-fold improvement in ADR reporting during the year following the intervention. In terms of relevance, this too was evident in the reporting of serious, unexpected, high-causality and new drug-related ADRs. In addition, the results of this trial demonstrated that the number of pharmacists' reports increased 5.9-fold.

Comparing our results with those of other studies proved difficult, because few studies addressing the effectiveness of educational interventions on pharmacists could be found. First, unlike pharmacists in other countries, such as Finland, Sweden[32] or, until recently, the UK,[33] pharmacists in Portugal report directly, and entirely independently, to the relevant health authority. Second, in contrast with other studies[12-14] in which there was an interaction among health professionals, our intervention was not designed with this intention. Instead, our intervention was aimed at modifying the knowledge and attitudes of pharmacists; attitudes and knowledge that had been previously investigated in the case-control study.

In view of the lack of studies on continuing education among pharmacists specifically, we relied on the same principles as those used in other continuing medical education strategies to explain the great magnitude of the effect of intervention observed by us.[34-36] These principles were namely:

- the nature of the target audience of the intervention (i.e. pharmacists), a factor that might also account for the highly effective nature of intervention reported by other authors who addressed this same topic via uncontrolled studies;[12-14]

- the fact that the intervention was designed to be as interactive as possible,[35] not only with regard to the presentation, but also with regard to the discussion and leaflet;
- the fact that the intervention was designed on the basis of the gaps detected in a previous study,[15] which helped to ensure that the message was clear and more specific;[34] and finally
- the fact that the body sponsoring the intervention was academic.[37]

If the absolute increase observed in the intervention group were to be applied to the entire Northern Region of Portugal, pharmacist-based reporting could be increased from 12 to 127 reports per million of the population. Combining this with the rate achieved with a similar intervention involving physicians,[20] the rate of reporting of ADRs in the Northern Region of Portugal would rise to almost 300 reports per million of the population per year, putting it on a par with the countries having the highest reporting rates in the world.[11] This means that, with a 1-hour long intervention involving physicians and pharmacists, the Northern Region of Portugal would be transformed, for at least 1 year, from an area having a low or very low reporting rate to one having a high reporting rate.[11] Since the pharmacist reporting rate is low in most countries,[11] the results of our trial may well indicate that many settings could benefit from an intervention like ours, and we feel that this type of intervention could also increase reporting in settings with higher reporting rates, since even in the UK, the rate of under-reporting is very high.[38]

Table III. Effect of intervention on adverse drug reaction (ADR) reporting by pharmacists. Evaluation of the effect of the report form and duration of the effect

Models		Results	
model description with dependent variable	independent variables	RR (95% CI)	p-value
Model 1. Effect of intervention on total number of ADR reports	Period[a]	1.63 (0.87, 3.06)	0.13
	Group	1.52 (0.35, 6.68)	0.58
	Period × group	5.87 (1.98, 17.39)	0.001
Model 2. Effect of time elapsed (in 4-mo periods) since intervention on total number of ADR reports	1st 4-mo period	0.85 (0.27, 2.69)	0.78
	2nd 4-mo period	1.98 (0.86, 4.56)	0.11
	3rd 4-mo period	2.26 (1.02, 5.03)	0.05
	4th 4-mo period	1.06 (0.20, 5.51)	0.95
	Group	1.54 (0.35, 6.75)	0.58
	Group × 1st 4-mo period	20.21 (4.60, 88.87)	<0.0001
	Group × 2nd 4-mo period	4.80 (1.31, 17.57)	0.02
	Group × 3rd 4-mo period	3.27 (0.88, 12.05)	0.08
	Group × 4th 4-mo period	2.77 (0.33, 23.35)	0.35
Model 3. Effect of intervention on reports of serious ADRs[a]	Period	1.30 (0.59, 2.84)	0.51
	Group	1.08 (0.18, 6.37)	0.93
	Period × group	9.79 (2.24, 42.66)	0.002
Model 4. Effect of intervention on reports of high-causality ADRs[a]	Period	1.82 (0.87, 3.81)	0.11
	Group	1.15 (0.20, 6.47)	0.88
	Period × group	8.67 (2.12, 35.42)	0.002
Model 5. Effect of intervention on reports of unexpected ADRs[a]	Period	1.68 (0.74, 3.80)	0.22
	Group	1.24 (0.37, 4.18)	0.73
	Period × group	4.41 (1.11, 17.53)	0.04
Model 6. Effect of intervention on reports of new drug-related ADRs[a]	Period	1.05 (0.50, 2.16)	0.90
	Group	0.80 (0.26, 2.51)	0.71
	Period × group	9.33 (2.53, 34.40)	<0.001

a RR for period is the adjusted RR of ADR reporting between pre-intervention and post-intervention period in the control group. It assesses secular trends and possible contamination of the control group by the intervention group. RR for group is the adjusted RR of baseline ADR reporting between the intervention group and the control group. RR for intervention (period × group) measures the adjusted RR of ADR reporting for the intervention itself, as an interaction between the group variable and the period variable. RR adjusted for workplace (hospital/community pharmacist).

RR = relative risk.

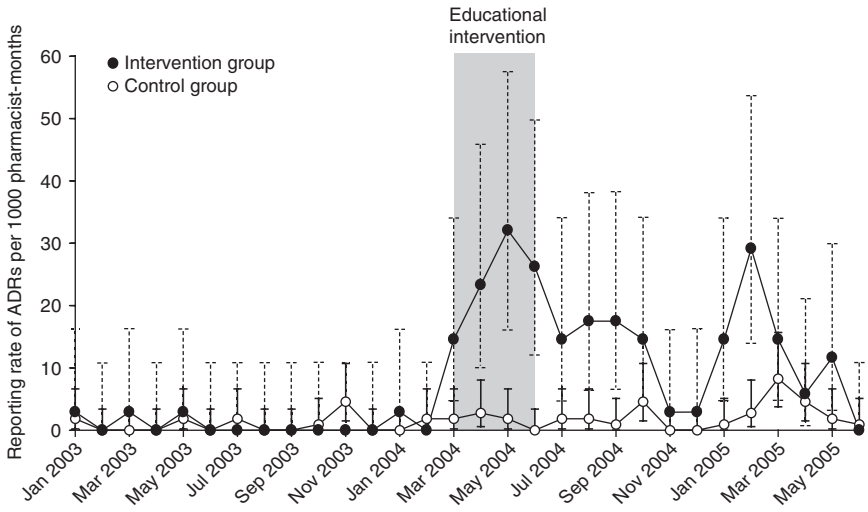

Fig. 2. Trends in reporting rates of adverse drug reactions by month (January 2003 through June 2005) and study group, per 1000 pharmacist-months. T bars represent upper and lower 95% confidence intervals.

The design of this trial had some strengths, such as (i) use of a control group, which is important for the purpose of negating other potential sources of bias and confounding, such as seasonal variation in reporting;[39] (ii) randomization, which minimizes the potential for selection bias; and (iii) cluster-based distribution, which reduces the risk of cross-contamination between groups but raises the risk that groups may become unbalanced by baseline values, particularly in cases with a small number of clusters,[40] as in our trial.

Important limitations also must be considered in interpreting the results of our study. First, a limitation of educational intervention-based studies is that the effect of the intervention may wane over time.[41,42] According to our study, the effect of our intervention could last up to 8 months. In the third 4-month period, the reporting rate in the intervention group was >3-fold higher than that in the control group, although it failed to prove statistically significant ($p = 0.08$), possibly due to standard training given throughout the region by the Northern Portugal Pharmacosurveillance Unit. Second, we had no data on those pharmacists that died or became professionally inactive during follow-up. In the analysis, these pharmacists were counted as non-reporters. We believe that the proportion of these pharmacists is probably very similar in the two groups and does not distort the reporting rate ratios. Third, the same ADR could be reported by more than one health professional, nevertheless the members of the Northern Pharmacosurveillance Unit identify the cases in which duplicate reporting has occurred, and the occurrence of this is very rare (during the study period it only occurs eight times).

Finally, a further limitation of our study may lie in the fact that the educational interventions among pharmacists and physicians were simultaneously implemented in the same spatial-clusters, meaning that intervention in one profession might have influenced the other. However, in our case, we feel that any interaction between pharmacists and physicians is almost non-existent, because community pharmacists and primary-care physicians work in different locations. Where professional contact does exist between physicians and pharmacists, it is in hospitals. Nevertheless, only 7% of pharmacists in the sample actually work in hospitals, and the effect of the intervention among hospital pharmacists was not statistically significant, possibly because their knowledge and attitudes about ADR reporting were already adequate before the intervention.[15]

Conclusion

The role of the pharmacist in the pharmacosurveillance system was originally poorly defined in some countries. Over the years, pharmacists in many countries have been incorporated into the system as independent reporters [11] because of the high quality of their reporting.[4] In the current period of crisis that the drug surveillance system is undergoing, with repeated withdrawals of medications from the market,[43-45] the role of the pharmacist would seem to be fundamental when it comes to collaborating in raising the alert to suspected ADRs. In this respect, this study suggests that educational interventions can considerably increase the quantity and relevance of ADR reporting.

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