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SYSTEMATIC REVIEW

Strategies to Improve Adverse Drug Reaction Reporting: A Critical and Systematic Review

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Abstract
Background Underreporting is the major limitation of a voluntary adverse drug reaction (ADR) reporting system. Many studies have assessed the effectiveness of different interventions designed to reduce underreporting.
Objective We aimed to conduct a critical review of papers that assessed the effectiveness of different strategies to increase ADR reporting, regardless of the health professionals or patients included.
Data Sources Scientific papers were selected after a search of the MEDLINE-PubMed and EMBASE scientific databases up to 7 December 2010.
Study Selection We included papers in English, French or Spanish that analysed an intervention aimed at increasing the number of reported ADRs, and quantify the results of the intervention in terms of number of reports.
Data Extraction The abstracts retrieved in both computerized searches were reviewed independently by two of the authors. Initially selected papers were thoroughly read to evaluate if they met inclusion and exclusion criteria. Data in finally selected papers were independently extracted by both authors and set in pre-designed tables. A third author took the final decision in case of disagreement. For each study, we analysed study design, type of intervention, assessment period, and results of the intervention.
Results Of the 4,221 papers located that fulfilled the search criteria, 43 met the selection criteria. With the exception of one study, the interventions assessed were deemed to be effective. The vast majority of papers displayed methodological and formal limitations that lowered the grade of evidence. Multiple interventions seem to have had more impact than did single interventions. There were very few cases in which interventions were designed on the basis of inappropriate attitudes and mistaken beliefs about ADRs.
Conclusions In general, there is a need for studies of better methodological quality in this topic, so that more evidence of the effectiveness of the respective strategies can be collected for the purpose of improving ADR reporting by health professionals. It is probable that multiple interventions cause greater increases in the ADR reporting rates than single.

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1 Introduction

Adverse drug reactions (ADRs) are an important public health problem due to the high morbidity, mortality [1] and costs that they generate [2]. When a medical drug comes onto the market, very little is known about its safety profile, and spontaneous reporting of suspected ADRs by health professionals continues to be an essential element for triggering signals of drug safety.

One of the major drawbacks of spontaneous reporting of suspected ADRs is underreporting. Indeed, it is estimated that only 6 % of all ADRs are reported [3]. Underreporting delays the triggering of signals and, by extension, the making of decisions to maintain an appropriate drug benefit-to-harm balance. Any one of a series of factors may account for underreporting, including knowledge, attitudes, lack of time and respondent's motivation [4].

In order to improve ADR reporting, several interventions have been developed and evaluated in different studies. We found a bibliographic review article about the improvement of ADR reporting but it was mainly focused on the evaluation of computerized monitoring systems combined with other methods to improve the effectiveness of the computerized monitoring systems [5]. We formulated a systematic bibliographic review and discussed the effectiveness of different strategies for increasing ADR reporting.

2 Methods

2.1 Literature Search Methodology

For review purposes, a search was made of the MEDLINE-PubMed and EMBASE scientific databases up to 7 December 2010. No limits were set in terms of dates, since our interest lay in retrieving all papers describing interventions, the designated aim of which was to increase the number of ADRs reported, regardless of year of publication. Most of the surveillance systems in European countries were introduced in the 1990s [6]. References cited in the papers retrieved were used to locate further papers.

The following search terms were used in MEDLINE-PubMed: (increas* OR improv* OR motivat*) AND (ADR OR "adverse drug reaction" OR "adverse drug reactions" OR "adverse drug event" OR "adverse drug events") AND report*. MeSH terms were avoided so as to perform as sensible a search as possible. Equivalent search terms were used in the EMBASE database.

This review includes original papers published in English, French or Spanish with the goal of analysing interventions aimed at increasing the number of reported ADRs, regardless of the health professionals or patients included. Papers were excluded from our review if they failed to report quantitative results of their interventions, if they did not present sufficient data about the intervention and if the results were reported in another paper.

2.2 Data Extraction

Results retrieved from the database searches were independently screened by CGG and ELG. The papers were then reviewed independently by these authors, who decided whether or not they met the selection criteria, and also carried out data extraction; in case of disagreement, the paper was examined by a third author (AF) who then took the final decision.

For each of the studies included in this review, the following data were extracted.

Study design Study designs were grouped into the following categories: (A) pre-post experimental design; (B) time series; (C) non-randomised controlled experimental study; (D) randomised controlled experimental study; (E) cluster-randomised controlled experimental study.

Target population Professionals to whom the intervention for increasing ADR reporting is addressed: physicians, nurses, pharmacists, young physicians/house officers, pharmacy students, section head, 'quality review staff', medical students.

Participation Number of participants in the intervention.

Type of intervention

- Educational activity: (i) session: activities carried out to inform or teach professionals about the reporting procedure and its importance, i.e oral presentation, workshops; and/or (ii) reminder: piece of information sent to the professional in order to remind them about the importance of ADR reporting, i.e. e-mail, letter, poster).
- Modification of reporting form: the original reporting form was modified, i.e the reporting card was simplified, elaboration of a new reporting form.
- Modification of procedure: the original reporting procedure was modified, i.e. by telephone, by e-mail.
- Incentive: an economical or other kind of bonus was given to the health professional when reporting an ADR, i.e educational credits, notepad, cup of coffee, money.
- Assistance or help from another professional: any help the reporter had from a trained professional (pharmacist, physician, nurse, etc.) at the moment of reporting.
- Distribution of reporting forms in order to increase availability.
- Improvement (or simply implementation) of feedback to reporters: a return of information is sent to the reporter once the ADR report is evaluated.

Period of assessment The length of the effect of the intervention, quantified in months.

Statistical analysis The type of statistical analysis performed by the authors was used as a criterion for assessing the study from a methodological standpoint. Studies were classified into the following five categories: (1) those that compared post-intervention values between groups; (2) those that compared pre- and post-intervention values within each group; (3) those that compared pre- and post-intervention values between groups; (4) those that used a

time-series analysis; and (5) those that compared pre- and post-intervention changes between groups.

Expression of results In those cases where the authors had omitted to cite increases in reporting in relative terms, we calculated the increases in reporting ('ratios') observed in the intervention group (or period) with respect to the control group, where this was possible. In order to unify units, reporting rates, whenever possible, were expressed as number of reports per month.

Data extracted directly from the results sections of the papers were used to draw up the following.

(i) A table with the characteristics of the population included in the intervention (author, year of publication, country, setting, target population, study period, study design, and risk of bias) [Table 1].

(ii) Another table listing the characteristics of the intervention undertaken: educational (a training session or reminders, brochures, etc., about the reporting of ADRs are given to the targeted health professionals); assistance or help with reporting from a trained professional; modification of the report form or reporting procedure; financial incentive (an economical or other kind of incentive is given to the health professional when reporting an ADR); distribution of report form in order to increase availability; implementation of or improvement in feedback (a feedback letter is sent to the reporter once the report is evaluated). Note that interventions could include more than one characteristic. Table 2 also shows results obtained with the interventions, expressed as increase in reporting (x-fold increase).

2.3 Study Quality

The available guidelines for assessing quality of non randomized studies [7] are not adequate for our review because some of the selected papers described designs that are not included in the scales (time series, pre-post experimental design, cluster-randomized controlled trial). For this reason, we used the study design to assess the quality of the studies. The criteria were as follows.

- *Pre-post experimental design and time-series:* We classified this as high bias risk. The lack of concurrent control group makes it impossible to eliminate potential sources of bias, such as seasonal variation or increases in reporting due to vaccination campaigns, alerts in the media, and served to minimize the effects of secular changes in behaviour [8].
- *Non-randomised controlled experimental study:* We classified this as medium bias risk because selection bias can occur due to a lack of random distribution, but the design allows controlling influences that external factors, such as vaccination campaigns or alerts in the media, could have on ADR reporting.
- *Randomised controlled experimental studies:* We classified this as low bias risk. Due to their design, this type of study is able to control the majority of potential biases except cross-contamination between groups (contamination of the controlled group by the exposition of the intervention group). Nevertheless, if cross-contamination exists, it would lead to a null effect of the intervention, and therefore the intervention effect would be underestimated.
- *Cluster-randomised controlled experimental studies:* We classified this design as low bias risk because it permits the control of almost all sources of bias, including cross-contamination between the intervention and control groups.

2.4 Additional Analysis

We calculated the median of the reporting increase in the interventions that were classified to have greater evidence by its design (studies that included a concurrent control). These values were used to compare the improvement in the reporting increase of single interventions to the multiple ones.

3 Results

3.1 Selection of Papers

Based on searches of the computerised MEDLINE-PubMed and EMBASE databases, a total of 4,221 papers were identified. After reading the title and abstract (if available), 57 studies were selected [9–65]. Following the initial search and a horizontal review of the papers selected, eight more studies [66–73] were selected. One of the potentially eligible papers was excluded for language reasons [54], another because the results were reported in another paper [73], and a further nine for not reporting interventions aimed at increasing the number of reported ADRs [47–53, 57, 72]. Another two papers were excluded because of an incomplete intervention description [63, 64]. In addition, a further nine studies were excluded because they failed to furnish quantitative results in terms of the number of adverse reactions reported before and after the intervention [28, 33, 34, 39, 57, 60, 66, 69, 70] (Fig. 1). Consequently, a total of 43 papers were finally included in the review.

Tables 1 and 2 show the papers that fulfilled all the inclusion criteria. A breakdown by geographical distribution showed that 60 % of studies had been conducted in the USA (26/43) [9–12, 14, 15, 17–26, 32, 36, 41, 56, 59, 61, 62, 67, 68, 71], and 37 % (16/43) [13, 16, 27, 29–31, 35, 37, 38, 40, 42–46, 55] in Europe.

Table 1 Characteristics of the population included in the intervention

Author, year of publication, country	Setting[a]	Target population[b]	Study period (months)[c]	Study design[d]	Risk of bias
Miwa and Randall [9], 1986, USA	1	2, 3	6	A	High
Kilarski et al. [67], 1986, USA	1	1, 2, 3	12	A	High
Michel and Knodel [10], 1986, USA	1	1, 2, 3	3	A	High
Kimelblatt et al. [12], 1988, USA	1	2, 3	36	A	High
Winstanley et al. [13], 1989, England	1	1, 2, 3	36	A	High
Vorce-West et al. [14], 1989, USA	1	1	3	A	High
Fincham [71], 1989, USA	(1) 1, (2) 2	1, 3	26	A	High
Smith Rogers [59], 1989, USA	1, 2	1	9	A	High
Scott et al. [15], 1990, USA	1,2	1	36	A	High
Feely et al. [16], 1990, Ireland	1	(1) 3, (2) 4	(1) 1.5, (2) 1.5	A	High
Gilroy et al. [17], 1990, USA	1	1, 4	12	A	High
Chatas and Vinson [18] 1990, USA	1	1, 2, 3	12	A	High
Prosser and Kamysz [19], 1990, USA	1	2, 7	11	A	High
Nazario et al. [20], 1994, Puerto Rico (USA)	1	1, 2, 3, 7, 8	24	A	High
Yee et al. [21], 1995, USA	1	1, 2, 3	15	A	High
Szymusiak-Mutnick and Ross [22], 1995, USA	1	1, 2, 3	12	A	High
Saltiel et al. [23], 1995, USA	1	1	19	A	High
Orsini et al. [24], 1995, USA	1	1, 2, 3	24	A	High
Sivaram et al. [25], 1996, USA	1	1	48	A	High
McGettigan et al. [27], 1997, Ireland	1	1	12	A	High
Sharkey et al. [61], 1999, USA	1, 2	3	24	A	High
Colodny and Spillane [62], 1999, USA	1	3	12	A	High
Ryan et al. [32], 2002, USA	2	1, 2, 3	12	A	High
Perkerson et al. [36], 2004, USA	1	2, 3	10	A	High
Lee et al. [68], 2004, USA	1	1, 2	6	A	High
Sullivan and Spooner [41], 2008, USA	1	5	12	A	High
Ortega et al. [42], 2008, Spain	1	1, 2, 3	36	A	High
Tabali et al. [44], 2009, Germany	2	1	20	A	High
Valente [56], 2010, USA	1	2	17	A	High
Yen et al. [65], 2010, Taiwan	1	1, 2, 3	39	A	High
Castel et al. [35], 2003, Spain	1, 2	1	(1) 154, (2) 48	B	High
Pedrós et al. [46], 2009, Spain	1	1	36	B	High
Schlienger et al. [29], 1999, Switzerland	1	1, 2	24	C	Medium
Cantú and Tyler [11], 1988, USA	1	1, 2, 3		C	Medium
Welsh et al. [26], 1996, USA	1	4	15	C	Medium
Clarkson et al. [30], 2001, England	1	1, 3	12	C	Medium
Bäckström et al. [31], 2002, Sweden	1	2	12	C	Medium
Bracchi et al. [37], 2005, England	2, 3	1, 3	12	C	Medium
Bäckström and Mjörndal [38], 2006, Sweden	1	1	6	C	Medium
Gony et al. [55], 2010, France	1	1, 2	31	C	Medium
Johansson et al. [45], 2009, Sweden	2	6	12	D	Low
Figueiras et al. [40], 2006, Portugal	1, 2	1	20	E	Low
Herdeiro et al. [43], 2008, Portugal	1, 3	3	13–16	E	Low

ADR adverse drug reaction

[a] Where the intervention took place: (1) hospital; (2) primary care; (3) community pharmacy

[b] Professionals to whom the intervention for increasing ADR reporting was addressed: (1) physicians; (2) nurses; (3) pharmacists; (4) young physicians/house officers; (5) pharmacy students; (6) section head; (7) 'quality review staff'; (8) medical students

[c] Number of months from the beginning of the intervention to the result analysis: (1), (2): corresponding to various interventions in a single study

[d] Methods used: (A) pre-post experimental design; (B) time series; (C) non-randomised controlled experimental study; (D) randomised controlled experimental study; (E) cluster-randomised controlled experimental study

Table 2 Characteristics of interventions implemented

Author	Educational		Assistance	Modified reporting		Incentive	Report form	Feedback	Increase in reporting (x-fold increase)
	Session	Reminder		Form	Procedure				
Miwa and Randall [9]	X	X		X					*26.5
Kilarski et al. [67]		X	X		X				10.0
Michel and Knodel [10]	X	X			X				–
Kimelblatt et al. [12]	X	X	X				X		*136.0
Winstanley et al. [13]	X	X		X	X		X		8.0
Vorce-West et al. [14]					X			X	–
Fincham [71]	(1) X, (2)X	(1) X, (2) X	(1) X		(1) X, (2) X				*4.2
Smith Rogers [59]	X	X			X				4.0
Scott et al. [15]	X	X		X	X		X	X	17.0
Feely et al. [16]					(1) X	(2) X			(1) *27.0, (2) 50.0
Gilroy et al. [17]	X	X	X		X	X	X	X	*43.8
Chatas and Vinson [18]	X	X	X	X			X	X	*180.0
Prosser and Kamysz [19]	X			X			X		–
Nazario et al. [20]	X			X					1st year:* 5.2; 2nd year: 8.5
Yee et al. [21]	X	X	X	X	X	X		X	2.5
Szymusiak-Mutnick and Ross [22]	X	X		X			X		*1.7
Saltiel et al. [23]	X			X			X		2.0
Orsini et al. [24]	X	X	X	X	X			X	3.0
Sivaram et al. [25]	X								*64.3
McGettigan et al. [27]		X					X		5.0
Sharkey et al. [61]	X					X			2.4*
Colodny and Spillane [62]	X	X		X	X	X	X	X	1.5
Ryan et al. [32]	X	X	X						–
Perkerson et al. [36]		X	X			X			4.4
Lee et al. [68]	X	X			X	X			*4.3
Sullivan and Spooner [41]	X								8.0
Ortega et al. [42]	X				X				
Tabali et al. [44]	X	X	X			X			2.5
Valente [56]	X	X							≈10.0
Yen et al. [65]					X				3.6
Castel et al. [35]		(1) X					(1) X, (2) X		(1) *1.3, (2) *1.7
Pedrós et al. [46]	X	X				X			*5.4
Cantú and Tyler [11]		X		X	X			X	–

Table 2 continued

Author	Educational		Assistance	Modified reporting		Incentive	Report form	Feedback	Increase in reporting (x-fold increase)
	Session	Reminder		Form	Procedure				
Welsh et al. [26]	X								*2.6
Schlienger et al. [29]	X		X						9.0
Clarkson et al. [30]	X	X					X		*2.4
Bäckström et al. [31]	X								10.0
Bracchi et al. [37]	X					X			*2.6
Bäckström and Mjörndal [38]						X		X	1.6 NS
Gony et al. [55]	X		X		X				*198.5
Johansson et al. [45]		X							*1
Figueiras et al. [40]	X	X							10.0
Herdeiro et al. [43]	X	X							5.9

(1), (2): corresponding to various interventions in a single study

Session: Activities carried out to inform or teach professionals about the reporting procedure and its importance: oral presentation, workshops, etc.

Reminder: Piece of information sent to the professional in order to remind them the importance of ADR reporting: e-mail, letter, poster, etc.

Assistance: Any help the reporter had from a trained professional (pharmacist, physician, nurse, etc) at the moment of reporting

Form: The original reporting form was modified: reporting card was simplified, new reporting form, etc.

Procedure: The original reporting procedure was modified: telephone, e-mail, etc.

Incentive: An economic or other kind of bonus is given to the health professional when reporting an ADR: educational credits, notepad, cup of coffee, money, etc.

Report form: distribution of reporting forms in order to make them easily available to health professionals

Feedback: A return of information is sent to the reporter once the report is evaluated

* Authors calculated increases expressed in x-fold, except where unavailability of data prevented this

NS non significant

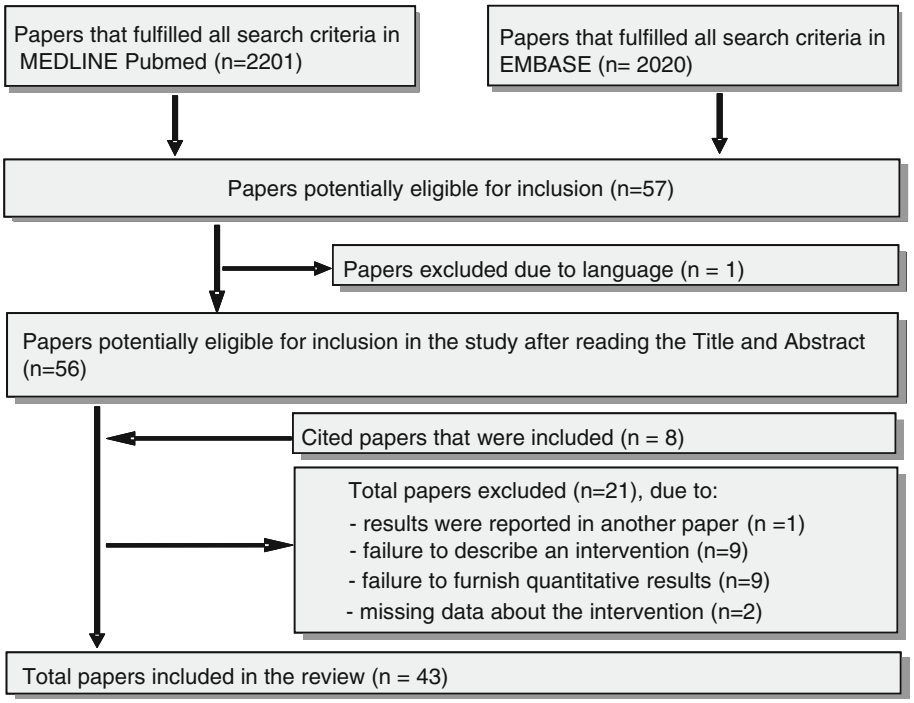

Fig. 1 Identification of studies and inclusion/exclusion criteria

3.2 Setting

Results from 44 settings reported in 43 papers were considered. One paper described results from two different settings [71].

A total of 82 % of interventions (36/44) were implemented in a single setting, i.e., 73 % (32/44) at hospitals and 9 % (4/44) at primary-care facilities. The remaining 18 % were implemented jointly in two settings.

Similarly, three papers [30–32] had more specific intervention settings, in the form of a paediatric hospital, a geriatric clinic and a neurology clinic, respectively (already included in the above analysis). Moreover, interest in pharmacovigilance interventions implemented in settings other than hospitals was observed to increase with the passage of time.

3.3 Target Population

Results from 44 target populations were reported in the 43 papers considered. One paper described results from two different populations [16].

A total of 25 % (11/44) of interventions exclusively targeted physicians. Some interventions focused on house officers and others focused on pharmacy students and, in one instance, on a 'section head'.

In all, 52 % (23/44) of interventions targetted more than one type of health professional, and 25 % of all interventions (11/44) jointly targeted physicians, pharmacists, and nursing staff. Target population was not stated in one of the studies [61].

3.4 Study Period

Of the 43 papers included in the review, two showed results from two different study periods [16, 35], which meant that 45 result sets were considered.

The intervention period was specified in all studies but one [11] (98 %: 44/45). In 47 % of interventions, the study period was longer than 1 year (21/45), and in 33 % it lasted from 7 to 12 months (15/45).

3.5 Study Design

The vast majority of the papers reviewed made no mention of the type of study undertaken. Indeed, this was classified in only six cases (14 %; 6/43) and consisted of a prospective trial [26], a prospective comparative open cross-over study [29], a cluster-randomised controlled trial [40, 43] and two time-series analyses [35, 46].

3.6 Participation

Study participation, defined as the number of participants in the intervention, was reported in only 19 % (8/43) of papers [31, 35, 37, 40, 43–45, 56].

3.7 Intervention

Taking into account that an intervention could include several components or characteristics, among the 43 papers selected, the authors of three [16, 35, 71] undertook two

different interventions each; our review was therefore deemed to cover 46 interventions.

A total of 78 % (36/46) of interventions included more than one type of activity for motivating staff to report ADRs.

Overall, 87 % of interventions (40/46) included an educational activity, such as presentations, report reviews, problem-based learning and clinical cases.

In 52 % of interventions (24/46), the authors modified the reporting process, by amending the reporting form in 50 % of cases (12/24) and changing the reporting procedure in 75 % (18/24). In regard to the latter, seven interventions switched to telephone and two to electronic ADR reporting procedures.

It should be noted that (i) 24 % of interventions (11/46) included a financial incentive; (ii) 28 % (13/46) of interventions included the assistance of another specialised professions with the ADR reporting, another factor of special relevance; (iii) 28 % (13/46) of interventions included the distribution of reporting forms; and (iv) only 17 % (8/46) of interventions included or improved feedback to reporters.

3.8 Type of ADR-Reporting Incentive

Financial incentives were varied in nature, being either direct (three papers [16, 17, 44]) or indirect—which could include incentives such as fees received by physicians for meeting annual targets ("which, on average, were less than 1 % of the physician's salary" [46]), special contribution award programmes [61], or educational credits [37, 68] or vouchers exchangeable for gifts [21, 36, 62] (coffee, dessert, scratch pad or a pen).

3.9 Reporting Increase

With the exception of one [45], the interventions assessed were deemed to be effective. One intervention also described the increase in reporting as non-significant [38].

Figure 2 shows the distribution of the reporting increases in the selected papers.

3.10 Additional Analysis

In the group of studies with more evidence (studies with a concurrent control), the increase of ADR reporting following a single and a multiple intervention was 2.6 and 5.9, respectively.

4 Discussion

The results of this review indicate that interventions to improve ADR reporting are effective and it is most likely

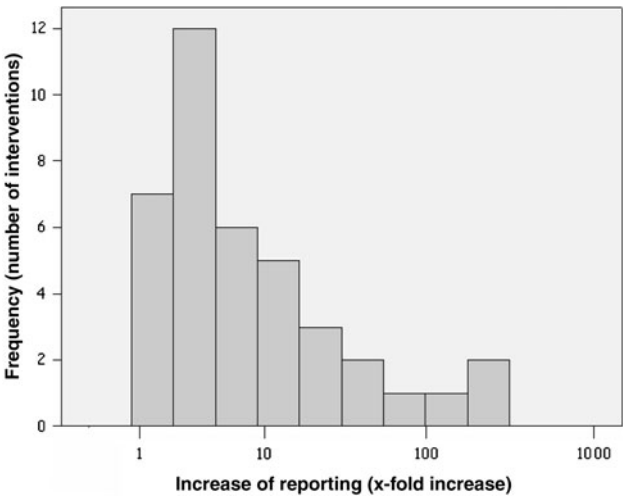

Fig. 2 Distribution of the reporting increase in the studies

that multiple interventions have a greater impact than single. There were very few cases in which interventions were designed on the basis of inappropriate attitudes and mistaken beliefs about ADRs. Our results also indicated that most of the studies displayed important design limitations, something that limits the grade of their evidence.

4.1 Discussion of Internal Validity of Studies

Most of the studies made no mention of the design used to conduct the study, and in some cases, the authors even identified the study design erroneously [44], despite this being one of the principal requirements for publication [74, 75]. Our review found that 75 % of studies compared a single group before and after the intervention (pre-post design). These designs call for a cautious interpretation of the results because differences between 'pre' and 'post' measures may be due to external factors unrelated to the intervention, such as health system alerts, items in the news media or vaccination campaigns [8].

For the purpose of assessing the effectiveness of an intervention intended to increase ADR reporting, the highest grade of evidence would be afforded by a randomised concurrently controlled design with pre-post measures and control of cross-contamination between groups. The control group would serve to eliminate (or minimise) the influence of external factors, since these affect both groups; and pre-post measures would enable baseline characteristics to be adjusted for where the groups were not equivalent. From a statistical point of view, moreover, these designs afford higher statistical power as a result of applying repeated measures techniques, and require the application of mixed linear models for longitudinal data [76]. As few as 12 studies used a concurrent control group, and of these, only 25 % (3/12) [40, 43, 45]

used randomised allocation. Failure to randomise allocation could lead to overestimation of the effect of the intervention. When interventions are of an educational type, there is a risk of cross-contamination of the control group. To minimise this eventuality, three studies [30, 37, 55] used a control group that had similar baseline characteristics to, but was geographically distant from, the intervention group. To this same end, two studies used a cluster-randomised distribution [40, 43].

Only two studies in our review made use of time-series analysis [35, 46]. Such studies lack a concurrent control group and so have the same limitations as pre-post studies. Furthermore, they are aggregate data studies, thereby giving rise to the possibility of incurring so-called 'ecological fallacies' and, by extension, to the need to show caution when drawing inferences at an individual level.

Many of the interventions reported in the papers lack relevant data (choice of participants, participation, description of the intervention) for accurate description, something that hinders the reproducibility of results. Only two studies [40, 43] indicated that educational interventions were designed on the basis of ADR-related attitudes and behaviour previously detected in the same population, even though many authors contend that such knowledge contributes to the success of educational interventions in health professionals [77]. The prior undertaking of a pilot study to assess the intervention was mentioned in only seven papers [10, 12, 14, 30, 32, 55, 71], despite the fact that it can be very useful for an intervention to be qualitatively evaluated beforehand, and even for possible limitations to be identified [78].

In most cases, the inclusion criteria in the studies reviewed were fairly wide. The sole restriction imposed in most of the studies was in the form of the definition of the target group itself, comprising physicians, nurses and pharmacists. The studies reviewed were conducted in very different settings (geographical, health-related, cultural and socioeconomic), so that the characteristics of the health professionals and health-care models were very different. In addition, interventions—albeit identical—are extremely difficult to reproduce in terms of effectiveness, since there are factors that are difficult to measure, such as the communication skills of the professional in charge. All this must be taken into account when it comes to applying the results of the studies to settings others than those in which they were originally undertaken.

Finally, the majority of studies do not show data about the number of professionals who were engaged in the interventions. This fact made it impossible to (i) know the reporting rate per professional-time unit, therefore we could not calculate the initial reporting rate and its influence in the observed relative reporting increases; and (ii) calculate the absolute increases in the reporting rate, which are of great importance in pharmacovigilance.

4.2 Discussion of Results

Our results show that, in general, the interventions for improving ADR reporting are effective and that the magnitudes of the observed effect are very high (greater than fivefold in 46.5 % of the studies). The impact of interventions was observed to be greater in the first papers published on the subject, possibly due to a lower initial reporting rate or worse methodological design and analysis of results. We also observed that reporting increased when combined with the support of professional, possibly because this helped break the barrier of fear or ignorance about reporting. In view of the fact that most of the studies applied more than one type of intervention, it was impossible to pinpoint the individual influence of each intervention in the final result.

Important effect magnitudes were reported by most of the studies. These results are in contrast to those yielded by interventions for improving the behaviour of physicians, in which increases of 20 % were deemed to be moderately important [79]. One factor that may account for such important improvements in ADR reporting is the absence of important barriers. Part of this effect might also be due to possible self-selection biases (arising in cases where interventions are voluntary and are attended by the most motivated professionals). We also observed that interventions not only increased overall reporting rates, but also enhanced the relevance of such rates (construed as an increase in serious, unexpected, high-causality and new-drug-related ADR reporting) [21, 37, 40, 43, 44, 46].

Many studies have established that, in terms of improving professional practice, multiple are more effective than single interventions [80]. This could be because professionals respond differently to different types of interventions, or that there may be synergies among the effects of various simultaneous interventions. There is evidence to show that, when it comes to bringing about changes in professional practice, interventions that boost the active participation of professionals (i.e. workshops) can be more effective than passive didactic sessions [79].

Another vital factor is the duration of the effect of the intervention. Some studies analysed this aspect, with the maximum duration of the effect being 3 years [46]. From this it can be concluded that, as was to be expected, the longer the period from the date of the intervention, the more the latter's effect is progressively reduced. In this regard, Molokhia et al. [5] concluded that, in view of the fact that most interventions have a limited effect over time, the use of electronic health data combined with other methods can enhance the efficiency of ADR detection.

4.3 Limitations of our Review

As in the case of any systematic review, ours could suffer from the limitation of publication bias. The high degree of heterogeneity of both the methodology and the results rendered meta-analysis impossible. Identification of the design was a complex task and, due to incomplete descriptions of the methodology used, there is the possibility that the design of some studies may have been misclassified. Similarly, we estimated the increases in reporting in cases where the authors had failed to do so: these increases were not adjusted for confounding variables, since the data were either unavailable or could be interpreted in various ways. In many cases, deficiencies in the design and description of the interventions made it difficult for us to tabulate the characteristics of the studies.

Study design was used as the single quality criterium because, when scales to value the quality of non-randomized studies were applied, (i) many of the designs were not included; and (ii) when those scales are applied to studies that assess the effect of an intervention to increase ADR reporting, many of the items take the same value for all the studies.

A sub-analysis was carried out with the studies that showed greater evidence. Nevertheless, these results should be interpreted very cautiously because (i) there are few studies in each category; (ii) the weight of each of the studies in the whole is not taken into consideration; (iii) the majority of papers do not have intra-study variability data (confidence intervals); (iv) the inter-study variability is very high; (v) study follow-up period varies considerably between papers; (vi) the reporting increases we have calculated are not adjusted for confounding variables.

5 Conclusions

We feel that, even though the reporting rate of ADRs is already high, there is still room for improvement. As the point of departure for enabling readers to evaluate the applicability of results to their own setting, it is vital that studies that assess the effectiveness of interventions for improving reporting give a detailed description of the methodology, study setting, intervention undertaken and type of health-care system. To assess the effectiveness of interventions for increasing ADR reporting, the design with the highest grade of evidence would be a concurrent randomised controlled design with pre and post measures and control of cross-contamination between groups. In addition, it would also be of interest if the results could be accompanied by the cost of each increase in ADR reported.

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