

REVIEW ARTICLE

Improving the spontaneous reporting of suspected adverse drug reactions: An overview of systematic reviews

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Aim: To conduct an overview of systematic reviews examining interventions to stimulate spontaneous reporting of suspected adverse drug reactions (ADRs) by health-care professionals (HCPs) and/or patients/carers.

Methods: Systematic reviews published since 1 January 2000 were identified and the included publications categorized in relation to the 4Es (education, engineering, economics and enforcement).

Results: Almost all studies were aimed at HCPs. Educational initiatives were most often used and, in most studies, were associated with improvements in quantity and/or quality of reports, at least in the short term. Lectures/presentations and regular reminders (eg, verbal or by e-mail) were the educational methods most often identified by systematic reviews. Engineering initiatives were also generally effective, including improving the availability of reporting forms, electronic ADR reporting, modification of reporting procedures/policies or the reporting form and assistance to complete the form. Evidence for the benefit of economic incentives (eg, monetary rewards, lottery tickets, days off work, “giveaways” and educational credits) was often clouded by the potential effects of other concomitant initiatives, and any possible associated improvements often disappeared rapidly after incentives were discontinued.

Conclusion: Educational and engineering strategies appear to be the interventions most often associated with improvements in reporting rates by HCPs, at least in the short to medium term. However, the evidence for sustained impact is weak. The available data were insufficient to clearly identify the separate impact of economic strategies. Further work is also needed to examine the effects of these strategies on reporting by patients, carers and the public.

KEYWORDS

adverse drug reaction reports, overview, systematic reviews

1 | INTRODUCTION

Since the thalidomide tragedy, the spontaneous reporting of suspected adverse drug reactions (ADRs) has been a valuable

pharmacovigilance tool. Such reports are effectively anonymized case reports sent into the relevant national medicines' regulatory agencies. They are also termed individual case study reports or individual case harm reports.¹ McNaughton et al have shown that in European Union

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member states, case reports remain the single most common contributory evidence used to support safety signals leading to medicinal product withdrawal.² The UK spontaneous reporting system (the Yellow Card system) has recently updated a list of 25 issues reported in the United Kingdom over the last 7 years where ADR (Yellow Card) reports helped to identify or contributed to the assessment of important safety issues.³ Despite this and other evidence of the value of spontaneous reporting systems, under-reporting rates have been historically high, even for suspected ADRs categorized as serious. A systematic review indicated an overall median under-reporting rate across 37 studies of 94% (interquartile range 82-98%).⁴ Reasons for under-reporting by health professionals⁵ and patients⁶ have been described in detail elsewhere.

William Haddon Jr was appointed by President Lyndon B Johnson as the first US Federal Highway Safety Chief in 1966. In 1968, he proposed an aetiological (as distinct from descriptive) approach to consideration of reducing the harms (ie, trauma) caused by motor vehicle accidents.⁷ His ground-breaking Haddon Matrix paradigm has subsequently been applied to patient harms and outpatient medication safety.⁸ Budnitz and Layde identified three main strategies to improve medication safety, *education*, *engineering* and *enforcement*. These strategies (with the addition of a fourth, *economic*) were subsequently applied to the challenge of enhancing the rational use of medicines.⁹ When the Haddon Matrix structure is applied to pharmacovigilance, spontaneous reporting of suspected ADRs would be an intervention in the postevent phase.⁷ In this article, we examine the applicability of these strategies to the goal of improving spontaneous reporting of suspected ADRs.

2 | METHODS

Published systematic reviews (written only in the English language) on methods to stimulate reporting of suspected ADRs which were published between 1 January 2000 and 31 July 2022 were identified after searching PUBMED and SCOPUS. The keywords were “systematic reviews”, “adverse drug reaction reported spontaneously” and “intervention”. Other reviews (including scoping reviews) were used to identify publications outlining factors associated with under-reporting of suspected ADRs. The searches were further supplemented by relevant articles found during selected PUBMED and Google searches.

3 | RESULTS

3.1 | Educational strategies

Educational interventions have traditionally been the most common approach to improving reporting. One of the first initiatives (published in 1990) was when the US Food and Drug Administration commissioned an educational programme for physicians in Rhode Island.¹⁰ The programme included direct mailings, presentations to physicians, advertisements and articles in local medical journals. Information

about the importance of reporting and the mechanisms was also included. After 2 years, ADR reports had increased more than 17-fold from a very low baseline (eg, 31 reports per year in 1981) when increased reporting had not occurred elsewhere in the United States. There was also an associated increase in reports of severe suspected ADRs. A survey conducted after 2 years identified a significant increase in knowledge and in positive attitudes toward the reporting system.¹⁰

We identified six published systematic reviews, five of which included studies of educational interventions over the 20-year period 2000-2020.¹¹⁻¹⁵ The sixth systematic review examined the use of engineering interventions (eg, information systems) and is discussed in the next section.¹⁶ A timeline of publication dates and number of studies included is shown in Figure 1. There were 101 separate publications included in the six systematic reviews combined. Educational interventions were the predominant (or only) approach in 57 of these studies and engineering strategies were the predominant intervention(s) in 35 studies. Economic interventions figured in nine studies, although often combined with other types of strategy classed as educational or engineering. A full list of educational interventions involved in all studies listed in the systematic reviews (as well as the interventions categorised into the other three strategies) is shown in Table 1.

In the first of the five systematic reviews examining the effects of education, Molokhia et al selected articles published in English between January 1997 and August 2007. They identified six quantitative studies where educational interventions had been employed to stimulate reporting of suspected ADRs.¹¹ Four reports studied physicians, one nurses and one medical students. Although all included studies claimed an increase in quantity or quality of reporting, study quality was considered variable and only two of the studies (one of them involving only medical students) were randomized controlled trials (RCTs). The second RCT involved 13-16 months of follow-up of reporting by physicians and revealed a 10-fold increase in reporting rates from a low baseline rate in the intervention group of 7.6 (95% confidence interval [CI] 4.0-12.6 ADR reports per 1000 patient years). The effect was also attenuated over time.¹⁷ Molokhia et al concluded that based on these studies, educational interventions combined with reminders can improve hospital-based ADR reporting in the short to medium term.¹¹

Pagotto et al published a systematic review in 2013 and identified 16 eligible papers written in English, Spanish or Portuguese to March 2013.¹² The earliest included study was that by Scott et al,¹⁰ which has been discussed above. Three of these had previously been included in the first systematic review by Molokhia et al.¹¹ Ten of the included studies (63%) were conducted in Europe, and medical staff were the target group in 12 (75%). All the included studies demonstrated the benefits of the interventions, which consisted of lectures, educational outreach and visits, telephone interviews, questionnaires, distribution of educational materials and reminders. The interventions were associated with increased reporting rates and, in some studies, in the quality of the reports. However, a quality assessment of the studies themselves (eg, assessment of risk of bias) was not conducted.¹²

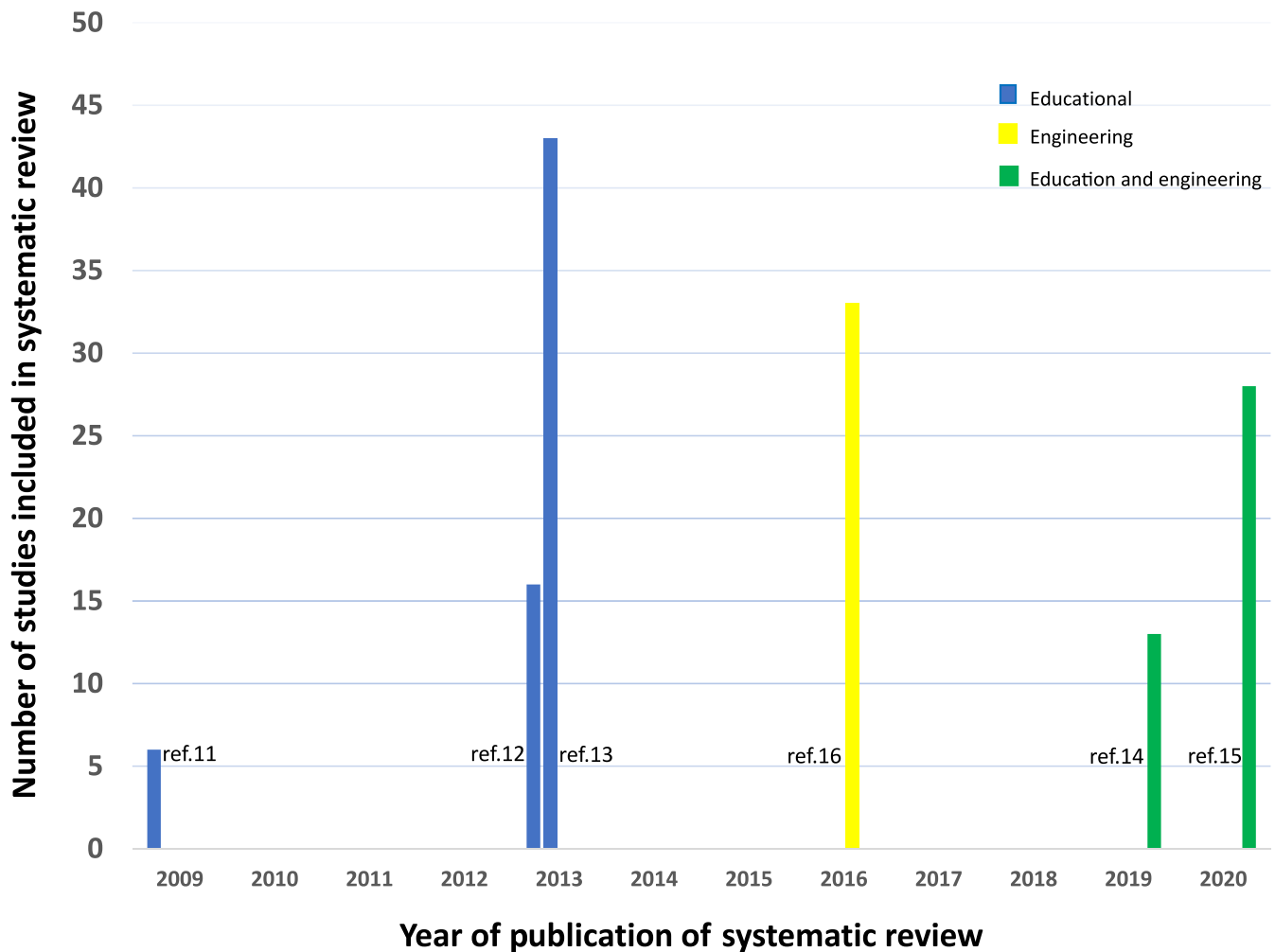


FIGURE 1 Publication years of systematic reviews on improving adverse drug reaction reporting, number of relevant studies included and the predominant interventions studied.

Gonzalez-Gonzalez et al published a critical and systematic review of strategies to improve ADR reporting.¹³ They discovered 43 articles written in English, French or Spanish which met their criteria, and their publication dates covered a 24-year period (from 1986 to 2010). However, they included just 10 of the 16 papers used by Pagotto et al in their systematic review published that same year.¹² Only nine of the 43 included studies had been included in either of the two systematic reviews published earlier. Doctors were the target population in 12 papers (28%), but other studies focussed on nurses, pharmacists, other members of the healthcare team, and medical and pharmacy students. Educational initiatives were the most common intervention, and in addition to those types of intervention listed by Molokhia et al and Pagotto et al feedback was separately listed and was given to the reporter after evaluation of the submitted reports in nine studies. All but one of the 43 papers included in this systematic review claimed that the interventions used were effective. However, only three of the included studies were considered to have a low risk of bias.¹⁷⁻¹⁹

The fourth systematic review, by Li et al,¹⁴ included studies published in English over a 10-year period (2010-2020) examining the impact of a range of interventions (not just educational) on reporting

of suspected ADRs. They found 13 articles meeting their criteria, four of which had appeared in one or more of the previously published systematic reviews. The educational interventions were also like those identified in the two previous systematic reviews and only three of the studies (all spatial cluster randomized controlled in design) were considered to have a low risk of bias.²⁰⁻²² All studies were associated with an increase in reporting rate, and for those which used traditional educational methods as intervention, the point estimate increase in ADR reporting rate was 4.42-fold (95% CI 0.66-8.19).¹⁴

The fifth systematic review and meta-analysis by Paudyal et al included 28 trials (published with no language restrictions) during an almost 20-year period (January 2000 until August 2019) that examined the effects of interventions on either the quality or quantity (or both) of spontaneous ADR reporting.¹⁵ Eighteen of the 28 studies had been included in one or more of the previously published systematic reviews. Seven of the included studies were RCTs, all of which examined educational interventions. The authors noted that even in these RCTs insufficient information had been given to permit a judgement of the presence of high or low risk of bias. However, they concluded that economic and face-to-face educational interventions

TABLE 1 Examples of interventions for improving spontaneous reporting of suspected ADRs utilized in publications included in systematic reviews, classified using the 4Es approach.

Strategy	Examples of interventions	Reference no. of systematic review
Education	Lectures/presentations	11-15
	Regular reminders (eg, verbal or by e-mail)	11-15
	Workshops/group sessions	12-15
	Interviews (eg, by telephone)	12-15
	Provision of educational materials/newsletters/bulletins	11-13,15
	Feedback to reporters	13-15
	Questionnaires	11-13
	Group dynamics (discussion/debate)	12
	Engineering	Improving availability of forms
Electronic ADR reporting		14-16
Modification of procedure/policies		13-15
Modification of reporting form		13,14
Assistance to complete form		13,14
Economic	Rewards (eg, monetary, lottery tickets, days off work, "giveaways", educational credits and markers of esteem)	12-15
	Financial penalties	
Enforcement	Mandatory reporting	Not included in any systematic review (but see Section 3.4)

Abbreviation: ADR, adverse drug reaction.

(as well as other types of intervention, as discussed later) improved the quality and quantity of ADR reporting by HCPs compared with non-face-to-face interventions. They also conducted a meta-analysis of five of the RCTs to estimate the pooled risk ratio for the effectiveness of predominantly educational interventions on suspected ADR reporting rates. This indicated a (statistically significant) 3.5-fold overall increase (RR 3.53; 95% CI 1.77-7.06) in the reporting rate of ADRs in the intervention group compared with the control group.¹⁵ Forest plots also showed that serious reports and unexpected ADRs were reported more frequently in these five studies, indicating a likely improvement in quality of reporting.¹⁵

We recognize that publication bias can mean that statistically significant reports are more likely to appear in the literature. A study of randomized controlled clinical trials in general estimated that significant results are almost three times more likely to be published.²³

Nevertheless, the considerable weight of evidence concerning educational interventions in the studies included in these five systematic reviews (including seven RCTs) has led the authors of the relevant systematic reviews to make positive conclusions about the value of educational interventions in improving reporting of suspected ADRs by HCPs.

Khalili et al conducted a scoping review (not a systematic review so not analysed together with the six systematic reviews) to identify existing gaps in the evidence base and areas that could be improved.²⁴ They concluded that although educational interventions appeared to be effective, many of the studies were short term so questions about sustainability of impact remain. Like some of the previous authors of the systematic reviews, they also suggested the need for studies with greater methodological rigour.

Only one of the five systematic reviews²⁵ included any studies on the impact of education on patient reporting of suspected ADRs. That study was a Scottish community pharmacy Yellow Card promotional campaign conducted in January-February 2011 and targeted at patients. It was not associated with an increase in suspected ADR reporting by patients during the 6-week campaign or over the subsequent 12-month follow-up period.²⁵ A more recent report from 12 countries of Europe reported an increase in patient reporting. Public awareness campaigns, engagement with patient groups on specific safety issues and provision of targeted publications in relation to medicines safety and ADR reporting in Ireland were stated to be associated with increased patient reporting, although no statistical analysis was provided in relation to any of the increases reported.²⁶

3.2 | Engineering strategies

Engineering issues can be relevant to environmental barriers to reporting. Reporting can only occur efficiently if the appropriate infrastructure, processes and clear guidelines are in place to allow such reporting. Hussain et al noted that respondents felt an important barrier to ADR reporting was the lack of a proper reporting system.²⁷ Even when a suitable reporting system is present, ready access to it when required and ease of use are important factors.

Molokiah et al and Gonzalez-Gonzalez et al included studies in their systematic review that showed how changes in the reporting form (eg, simplification) or reporting procedure, or improving the availability of report forms were associated with significant increases in reporting.^{11,13} For example time series analysis indicated that a large increase in reporting occurred after an ADR report form was included in prescription pads.²⁸ However, improving availability alone may not be sufficient. Over a 3-month period, improving the availability of ADR report forms and reminders about reporting ADRs led to an approximately 5-fold increase in reports (from a low baseline of 24 reports per 3 months), but the rate declined rapidly when verbal reminders were withdrawn, despite continued and ready availability of forms.²⁹

Since lack of time has been identified as a barrier by HCPs, systems that can facilitate the reporting process have been developed,

including electronic ADR reporting systems. Electronic ADR reporting was listed as an intervention in five of the 13 studies included in the systematic review by Li et al¹⁴ and all showed significant increases in reporting. A point estimate increase of ADR reporting of 13.69-fold (95% CI 5.29-32.68) was reported. Six of the 13 studies included in this systematic review had been included in one or more of the previously published systematic reviews.

Information systems are valuable in supporting decision-making. A systematic review and meta-analysis of the role of information systems in improving reporting included studies of HCPs in hospitals. Most of the interventions were web-based or involved electronic health record systems.¹⁶ Seven of the studies contained data on the number of ADR reports, which was pooled in a meta-analysis. This revealed that these engineering interventions were associated with a doubling of ADR reports. The study which saw the largest proportional effect (5.4-fold increase) was a Danish initiative in which a dedicated adverse drug event manager used electronic health records to complete an ADR report whenever physicians working on one of five wards in a single hospital required assistance.³⁰ However, the baseline reporting rate in the active hospital before this initiative was low (2.5 reports/month), no confidence intervals for the proportional change in reporting were given, and the costs and cost-effectiveness of such an intervention were not discussed in the publication.

Mobile apps to support reporting have been developed,^{31,32} but the evidence for their possible benefits in improving reporting is at an early stage. Nevertheless, reports from patients were significantly more frequent with the VigiBip[®] app than with classical reporting methods.³²

3.3 | Economic strategies

In the context of interventions, “economics” refers to the incentivization of wanted behaviour by offering rewards. In most studies, rewards have been financial in nature. Feely et al gave a small fee (equivalent to approximately £2.71/€2.99/US\$3.5) to junior doctors who completed an ADR report and gave the card to a designated registrar (middle grade doctor).³³ They observed an almost 50-fold increase in reporting over the 6-week intervention period (although from a very low baseline rate). However, they were unable to distinguish any positive benefit of being able to report to an individual colleague from any effect of the fee. Nevertheless, the number of reports fell substantially within 6 weeks of withdrawal of the fee, indicating that the presence of such a reward was likely to have been important.

In the study by Bracchi et al, the assessment of any positive impact of awarding continuing medical education credits to the general practitioners (GPs) who reported was complicated by the fact that educational interventions were also used.³⁴ Two studies involving hospital physicians and other HCPs also included the introduction of an electronic reporting system in addition to the award of continuing education credits for completing a training module³⁵ or a fee³⁶ so the separate effect of the incentive could not be ascertained. An initiative

to improve spontaneous ADR reporting by hospital physicians in Spain also involved a range of other interventions so the impact of the financial remuneration given (5% to 7% of the physician's salary) could not be separately determined.³⁷ A financial incentive (a fee) was included as part of a multifaceted strategy by Fang et al so, again, any effect of the fee could not be separately ascertained.³⁸ Increased reporting was also observed when US\$5 was given to house staff physicians in a tertiary hospital in Vermont but assistance was also given by pharmacists to complete the reporting form.³⁹

One small study appeared to use an incentive as the only intervention. The modest award of two lottery tickets worth around €5 per report to hospital physicians and GPs in a county in northern Sweden was associated with a 59% increase in reported suspected ADRs in the intervention group over the 12-month study period compared with the previous 12 months (from 39 to 62) with no change in the corresponding number in the control group (50 and 50 reports over the same period, respectively).⁴⁰ However, the small number of total reports coupled with the small percentage increases meant that the percentage increase in total ADR (or in serious ADR) reports appeared not to achieve statistical significance. The same authors also conducted a larger survey of attitudes which revealed that 301 respondents (78%) believed that a financial reward to individual reporters was not a proper way to increase the number of reported ADRs.⁴⁰ The authors highlight the potential ethical and moral issues associated with the use of such an inducement. It has been argued that reporting suspected ADRs is part of an HCP's fundamental professional duties so should not need to be separately incentivized.

Time series analysis was used to measure the effects of financial incentives on spontaneous reporting of ADRs by hospital medical staff in an observational study in a tertiary care university hospital in Henan Province of China.⁴¹ The study was included in two of the systematic reviews.^{14,15} A bonus of 20 renminbi (RMB) (around €2.5) was given for each ADR report, and a fine of 50 RMB (€6.3) imposed for any withheld ADR report (missed suspected ADRs were identified during routine retrospective review of the medical charts by dedicated pharmacists). There was an 9.55-fold increase in reporting associated with the financial intervention (the first intervention period in the study), although this was from a low baseline monthly reporting rate of 3.56 ± 3.60 /month. However, no associated qualitative improvement, as measured by the number of serious reports submitted, was seen. In the study, it is not possible to separate the impact of the financial reward from the possible change in behaviour caused by the risk of a fine for not reporting.

Economic drivers are not only financial. Indicators of esteem have also been used. Thus, the UK Medicines and Healthcare products Regulatory Agency awarded the Dunlop Prize in 2015 to Hunt and Flossman for their reporting of the association of interferon beta with thrombotic microangiopathy.^{42,43} A recognition of high reporters (nomination for employee of the month) was part of the incentives used in another positive study, although a day off work (which could be considered as a form of financial reward) was also part of the incentive.⁴⁴

3.4 | Enforcement strategies

No enforcement strategies (eg, mandatory reporting) featured in any of the 101 papers included in the six systematic reviews. However, in some countries governments have sought to use enforcement to encourage ADR reporting. On 25 May 1984, the French government decreed that all prescribing physicians, midwives or dentists should report all unexpected or toxic drug reactions to their regional monitoring centre.⁴⁵ Reporting “serious” or “unlabelled” ADRs to the French Regional Centres subsequently became a mandatory legal requirement (underpinned by article R-5144-19) for any prescriber, physician, dentist or midwife in France in 1995.⁴⁶ We are not aware of any data showing the impact of these requirements on reporting rates and are not aware of any countries which have followed France in making reporting of certain ADRs mandatory for individual prescribers. However, an international comparison of reporting by countries to Vigibase[®] indicated that France (with 174 reports/million inhabitants/year) had an average rate after the law had come into force (13th highest out of 36 high-income countries between 2000 and 2009⁴⁷).

As a result of the 2014 Protecting Canadians from Unsafe Drugs Act (Vanessa's law), several amendments were made to Canada's Food and Drugs Act. As from 16 December 2019, serious ADRs and medical device incidents were required to be reported, in writing, to Health Canada within 30 calendar days from the date of their first documentation within a hospital. However, the mandatory reporting requirement applies to the hospital rather than to the individual HCPs working there.⁴⁸ Concern has been expressed that because of their frequency and the subjectivity involved, Canadian hospitals will face difficulties reporting all serious ADRs.⁴⁹ It will be important to evaluate the impact of this new requirement on the reporting of serious ADRs from the hospital sector in Canada.

4 | DISCUSSION

Although interventions (particularly educational and engineering) have been associated with increased reporting rates of suspected ADRs, the generalizability of the studies included in the systematic reviews is limited. Paudyal et al highlighted the need for educational and other interventions to be developed and evaluated in low- and middle-income countries and further work should also be targeted at patient reporting.¹⁵ The Uppsala Monitoring Centre has developed educational resources in pharmacovigilance aimed at HCPs, using a micro-learning approach to overcome technological problems such as narrow internet bandwidth. The resources are based on small learning units connected to specific learning objectives and was positively received by learners internationally.⁵⁰ In their literature review of pharmacovigilance education, Reumerman et al concluded that “there is an urgent need to improve and innovate current pharmacovigilance education for undergraduate healthcare students”.⁵¹

In relation to engineering approaches, it has been argued that incident reporting systems in health improvement should be built to have wide accessibility and ease of use, to allow timely data analysis

and have a feedback loop so that employees are aware action is being taken based on their reports.⁵² This approach could equally apply to the design of systems for reporting suspected ADRs by HCPs. Several of the first engineering interventions in ADR reporting described earlier (eg, improving availability of forms, modification of procedure/policies and reporting forms, and assistance to complete forms) have met some of these requirements. However, the impact of electronic information systems is particularly encouraging^{14,16} and digital technologies have the potential to make an increasingly important contribution in the future.

Patient reporting of suspected ADRs is an increasingly important source of safety information and it is plausible that the above approaches could also encourage reporting by patients. However, one systematic review on factors affecting reporting concluded that many patients were not aware of reporting systems and others were confused about reporting.⁶ A recent survey of 1600 people living in Wales showed that only 18.4% of respondents said they knew how to report a side effect to the UK Yellow Card scheme.⁵³ Immediately after watching a short educational video, 71% of respondents in this study said they know how to report a side effect to the Yellow Card scheme, but it is likely that reinforcement of this knowledge may be required in the medium to long term.

Measurement of the impact of economic interventions on HCP reporting rates is more difficult because they are often bundled together with other interventions (usually educational) in a multifaceted approach. However, Li et al calculated that multifaceted strategies resulted in a point estimate increase in ADR reporting of 9.26-fold (95% CI –2.21-17.11)¹⁴ so future interventions may well benefit from such a multifaceted approach.

The value of enforcement strategies, when they were applied, remains unproven. However, in healthcare improvement more generally, one of the features of an effective reporting culture is the elimination of the fear of punishment when reporting.⁵² The situation of under-reporting is a different scenario, but “fear of appearing ridiculous for reporting merely suspected ADRs” was identified as an important factor in under-reporting in a systematic review of the problem.⁵

The possible limitation of the interventions discussed in this overview is that even if they are evidence-based, their impact may nevertheless be short-lived and decline quickly when the intervention is no longer applied. This may particularly apply to economic incentives, but the effects of educational interventions may not be long-lived either. For example, the effect of an educational intervention using distance learning and educational credits for GPs had attenuated in the year following the 12-month study.³⁴ It is therefore important to work to identify effective interventions that are also sustainable in the medium to long term within available ongoing resources.

Leatherman and Berwick have identified the establishment of adverse event reporting and a “just culture” as necessary interventions for reducing avoidable harm and thus achieving global healthcare improvement, albeit in the context of medical error rather than ADRs occurring in the context of prescribing.⁵⁴ The introduction of a national reporting indicator as a benchmark of ADR reporting, with regular feedback, was associated with increased reporting rates by

GPs in Wales over at least a 4-year period, indicating that such quality improvement benchmarks could be a useful tool in maintaining improvement.⁵⁵

Spontaneous reporting systems for suspected ADRs are a vital tool in healthcare improvement and, despite their limitations, provide valuable signals in drug safety.⁵⁶ Further work is needed to explore how all HCPs can be encouraged to spontaneously report suspected ADRs.

5 | CONCLUSION

Despite concerns about methodology in some studies and the potential issue of publication bias, we believe the weight of data contained in the more than 100 studies included in five meta-analyses over the last 20 years strongly supports the positive value of educational interventions involving HCPs, at least in the short term. However, further information on the most effective types of education and how the beneficial effects can be sustained in the longer term would be valuable. Educational interventions were bundled together in the studies and we are not aware of any studies comparing the relative impact of any one of them with any other educational strategy. Studies have also indicated that engineering interventions have also been associated with increased reporting. Economic incentives may have some effect, at least in the short term. We are not aware of any evidence of an impact of enforcement strategies on ADR reporting.

AUTHOR CONTRIBUTIONS

P.A.R. wrote the first draft of the manuscript and R.B. contributed by reviewing and editing. Both authors agreed to the final version prior to submission.

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CONFLICT OF INTEREST STATEMENT

Neither author has any conflict of interest to declare in relation to this work.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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