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SPONTANEOUS REPORTING OF ADVERSE DRUG REACTIONS IN A TEACHING HOSPITAL: A FIVE-YEAR REVIEW

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Abstract

Spontaneous reporting remains the main way in which new and rare adverse drug reactions are first recognised, and teaching hospitals are among its most important sources of reports. This narrative review summarises published evidence on how reporting systems work, what reports from hospital programmes usually contain, how causality, severity and preventability are assessed, and why under-reporting persists. It also examines signal detection methods and the educational and organisational measures that have raised reporting rates. The review draws on published surveys, trials and guidance and presents no new data. The main limitations of the literature are incomplete reports, the lack of denominators and the absence of long-term evaluation of reporting interventions.

1. INTRODUCTION

Adverse drug reactions are a routine feature of hospital medicine. A meta-analysis of observational studies found that adverse reactions account for a notable share of hospital admissions, and a later systematic review of prospective studies reached a similar conclusion [1, 2]. Definitions matter here. The classic description of a reaction as a response that is noxious and unintended, occurring at doses normally used, separates it from overdose, error and misuse, although in daily practice the boundaries blur [3, 4]. The clinical and economic consequences include longer stays, extra costs and, in the worst cases, death [5, 6, 7]. Such burdens fall unevenly: older patients, those taking several drugs and those with impaired renal or hepatic function carry most of the risk, and so

do people in teaching hospitals who receive the most complex regimens [8, 9].

Premarketing trials cannot answer every safety question. They enrol limited numbers, exclude the elderly and those with several illnesses, and last only as long as needed to show efficacy. Reactions that occur in one patient in several thousand, that appear after months of exposure or that arise from interactions in complex regimens will normally be seen first in routine care [10, 11]. Spontaneous reporting, in which a clinician or patient sends a suspected case to a national or institutional centre, was built to catch exactly these events, and it has contributed to many of the drug withdrawals and label changes of the last half century [12, 13]. The history of drug safety shows the pattern repeatedly. A new agent enters wide use, a handful of unexpected cases are described in letters or reports, and only later do formal studies confirm a hazard. Teaching hospitals, with their dense concentration of new drugs and unusual cases, are often where the first warning appears [10, 11].

Teaching hospitals occupy a particular place in this system. They treat complicated patients, expose large numbers of trainee doctors, pharmacists and nurses to prescribing decisions, and usually host the regional pharmacovigilance centre or an adverse drug reaction monitoring unit. The quality of their reporting therefore influences both local safety and the national database. This review brings together published work on spontaneous reporting in such settings, from the structure of reporting systems to the analysis of reports, the reasons for under-reporting and the interventions that have been tried. Key findings are collected in table 1. The review draws on published sources and presents no new data. Throughout, the term reporting is used for the voluntary, clinician-initiated kind unless stated otherwise, and distinguished from active surveillance, which looks for events systematically rather than waiting for them to be noticed [14, 15]. The distinction matters because the two approaches answer different questions: reporting is cheap and can flag rare, unexpected reactions early, whereas systematic surveillance measures frequency more reliably but needs staff time, defined populations and sustained funding that few units can spare.

2. SPONTANEOUS REPORTING SYSTEMS

The international framework dates from the aftermath of the thalidomide disaster. The World Health Organization programme for international drug monitoring, which began with a small group of countries in the late 1960s, now collects reports from national centres into a shared database held at Uppsala [11, 12]. National systems differ in detail, but the principle is constant: a health professional, and in a growing number of countries a patient, completes a form describing the patient, the suspected drug, the reaction, its outcome and any concomitant treatment, and the centre reviews it, codes it and forwards it [15, 16]. Participation has grown steadily, and national centres now range from large regulatory units to small groups in university departments. The shared database has made it possible to compare experience across populations, an advantage when a reaction is rare in any one country [12].

Table 1: Summary of published evidence on spontaneous reporting in hospital settings

Theme|focus	Main published finding	Ref.
WHO international programme national centres	Reports from national centres pooled in a shared database to detect rare reactions across countries.	[11, 12]
Indian national programme medical colleges as centres	Medical colleges act as monitoring centres; commonly suspected classes include antimicrobials and anti-inflammatory drugs.	[17, 18]
Under-reporting sentinel comparison	Comparison of a spontaneous scheme with a sentinel system showed that most reactions never reach the scheme.	[19, 20]
Determinants of reporting attitudes and knowledge	Ignorance, complacency, fear of litigation and the belief that only serious reactions matter limit reporting.	[21, 22]

Theme|focus	Main published finding	Ref.
Educational trial physicians	Cluster-randomised educational programme raised spontaneous reporting compared with controls.	[23]
Feedback and visits hospital physicians	Regular contact with pharmacovigilance staff followed by sustained increases in reports.	[24, 25]
Naranjo algorithm ten-question score	Widely used causality score; depends on rechallenge information, and tools can disagree on the same case.	[26, 27]
Severity and preventability scales hospital use	Structured grading of severity and preventability supports feedback to prescribers.	[28, 29, 30]
Disproportionality methods large databases	Ratios and Bayesian methods screen for signals but are affected by duplicates and masking.	[31, 32, 33]
Withdrawal analyses United States	Many drug withdrawals followed spontaneous reports of serious events.	[13]

Within hospitals, local arrangements build on this. A pharmacovigilance committee, a clinical pharmacologist or a ward pharmacist receives reports, checks them for completeness and sends them on. Some centres rely on voluntary forms alone, while others add active methods such as ward rounds by a pharmacist, review of laboratory alerts or screening of antidote orders [14, 34]. The Indian national programme, which designates medical colleges as monitoring centres, is a good example of a system that places teaching hospitals at the heart of data collection [17]. Published reports from such centres show similar patterns: antimicrobials, anti-inflammatory drugs, antiepileptics and antituberculosis agents among the commonly suspected classes [18, 35]. Even so, published hospital experience shows that many reports come from a small group of enthusiastic staff, with a long tail of departments that never report at all, so participation depends on a few individuals more than on the system [18, 35].

Reports are classified in several ways. The long-standing division into type A reactions, which are dose-related and predictable from pharmacology, and type B reactions, which are idiosyncratic or immunological, remains useful for teaching and for deciding what a report might mean [4, 9]. Seriousness is defined by outcome: death, threat to life, hospitalisation, disability, congenital anomaly or other important medical event, a scheme set out in international guidance on expedited reporting [36]. Seriousness describes the event, while severity describes its intensity. A mild headache can be serious if it leads to admission, and a severe rash is not necessarily a serious one by regulatory definition. Teachers of pharmacology find these categories helpful when they ask trainees to classify each reaction in a case discussion, since the exercise forces them to think about mechanism and not merely recognition [4, 9]. Newer classifications add delayed, dose-independent and withdrawal-related categories, though the original split remains the one most students learn.

A good report is more than a drug name and a symptom. Reviewers look for the time between the first dose and onset, what happened when the drug was stopped, and whether it was restarted, along with the patient's age, other drugs, renal and hepatic function and relevant history [26, 27]. Missing items are the norm. Studies of spontaneous report forms from hospitals commonly find gaps in dechallenge information, laboratory values and outcome, which limits what can be concluded from a single case [14, 18]. Programmes that follow up with the reporter, usually by phone or ward visit, improve completeness at modest cost. Training of those who receive reports also matters. A reviewer who knows which questions to ask over the telephone can often turn a doubtful report into a useful one within minutes, whereas a form returned with a query by post may never be answered [14, 15].

A short note on terminology avoids confusion later. Adverse event describes any untoward occurrence during treatment, whether or not caused by the drug, while adverse drug reaction implies at least a reasonable possibility of a causal relationship [3, 36]. Many hospital forms ask for both, since a clinician may not be sure which applies.

Medication errors and product quality problems are usually handled through parallel channels, though in smaller hospitals one committee deals with all three. Clear definitions on the reporting form reduce the number of irrelevant submissions and help staff understand what is wanted. In smaller hospitals, the same committee may handle all three, which is acceptable provided the forms and follow-up questions are kept distinct and staff are told which route to use for which problem [16, 36].

3. ASSESSING CAUSALITY, SEVERITY AND PREVENTABILITY

Once a report arrives, someone has to decide how likely it is that the drug caused the reaction. Informal clinical judgement is variable, so structured tools have been developed. Among the many published tools, the Naranjo algorithm is probably the most familiar. It scores answers to ten questions about timing, dechallenge, rechallenge, alternative causes, drug levels and previous experience, and places the case on a scale from doubtful to definite [26]. The WHO-Uppsala Monitoring Centre categories, running from certain to unlikely, rely on a more descriptive approach and are widely used by national centres [12, 16]. Both give reasonable agreement among trained users, though neither is perfect. In practice, many hospital units combine tools, using Naranjo scoring as the routine step and reserving the WHO-UMC wording for the report they send onward. This duplicates some effort, but it keeps the local record comparable with the national one [12, 16, 26].

Concerns about the Naranjo scale are well known. It was written for a particular context and gives heavy weight to rechallenge, which is seldom ethical or possible, while comparisons of published algorithms show that different tools can place the same case in different categories of likelihood [26, 27]. The Liverpool tool was developed to address some of these issues, with a decision-tree structure and explicit handling of drug-drug interactions, and has shown good inter-rater reliability in the publication that introduced it [27]. Whichever tool is chosen, consistency within a centre matters more than the choice itself, because the aim is to compare cases over time. The reliability of any such tool depends on the reviewer. Studies of agreement between pharmacists and physicians show that even with a structured scale, individual judgements differ on borderline cases, particularly when the information supplied is thin, so a second assessor or a committee decision is a sensible safeguard [14, 27].

Severity and preventability are assessed separately. Severity is commonly graded on an ordinal scale, such as the five grades of the Common Terminology Criteria for Adverse Events, which run from mild through moderate, severe and life-threatening to death [28]. Published preventability criteria ask whether the drug was inappropriate for the condition, whether dose, route or frequency was wrong, whether necessary monitoring was missed, whether there was a documented history of allergy or a known interaction, and whether the reaction was treated, and methods of this kind are reviewed in the literature on detecting and classifying adverse drug events [29]. Applying them, a meta-analysis estimated that a substantial minority of reactions in hospitalised patients are potentially preventable, depending on the definition used [30]. The scale and criteria are not unique to any hospital, which is helpful, because published series from different centres can be compared on the same terms. Ratings should be recorded at the time of the report and revisited if new information arrives, as a reaction first scored as possible can become probable once a dechallenge result is known [28, 29].

Preventability matters to teaching hospitals because it points directly to action. Reactions that stem from known interactions, unadjusted doses in renal impairment or repeat exposure to a documented allergen can be reduced by prescribing alerts, formulary controls and teaching [8, 34]. Studies of older outpatients show a similar picture, with errors at the stages of prescribing and monitoring accounting for many preventable events [8]. A local reporting programme that records preventability, not just the reaction, produces information that can be fed back to prescribers in the form of concrete advice about which patients need extra care. Cost is a

further reason to pay attention. Hospital studies from several countries found that adverse reactions lengthen stay and raise expenditure, and that preventable ones account for a good part of the excess [5, 6, 7]. A pharmacovigilance unit that can show a reduction in avoidable events is therefore making an economic argument as well as a clinical one.

4. WHY REPORTS ARE MISSING

Under-reporting is the central weakness of spontaneous systems. A comparison of a spontaneous reporting scheme with a sentinel system estimated that only a small fraction of reactions ever reached the scheme [19]. Other work in general practice reached comparable conclusions, with only a small share of recognised reactions reported [20]. These estimates mean that the number of reports received cannot be read as an incidence. They also mean that a drug with few reports is not necessarily safe, a point that the clinician reading a spontaneous-report summary should keep in mind. The actual percentage differs widely between studies, as it depends on how reports were counted and how reactions were identified. Even so, no study has found a population in which most reactions were reported, and that is the important message for teaching hospitals planning a programme [19, 21].

The reasons clinicians give are consistent across countries. Inman captured them in the mnemonic of the seven deadly sins of non-reporting, which includes complacency, fear of litigation, guilt over having caused harm, ambition to publish a series, ignorance of the system, diffidence about reporting a case that might be wrong, and lethargy [22]. A systematic review of determinants reached a more structured conclusion: knowledge and attitudes both matter, with the belief that only serious reactions need reporting, that a known reaction is not worth a form, and that a single case contributes nothing being especially common [21]. Most of these causes can be addressed, at least in principle, through simpler forms, regular feedback and reassurance that reporting is non-punitive. The harder ones, such as the feeling that one more case adds nothing, need a cultural shift that comes slowly [21, 22].

Studies of Indian and other medical students and prescribers show that awareness of pharmacovigilance is limited and that many have never completed a report form, even when they have seen reactions in practice [17, 35]. Pharmacists show higher willingness in some settings, and their attitudes toward reporting strongly predict whether they actually do so [37]. Nurses, who often observe reactions first, are underused as reporters in many hospitals. Time pressure is a practical barrier that all groups mention. A form that takes fifteen minutes to complete will be abandoned in a busy outpatient clinic. Qualitative accounts suggest that junior doctors leave reporting to seniors, seniors assume pharmacy will do it, and pharmacy waits for a prescriber to raise a query. Clarifying who is responsible for each step, and writing it into hospital policy, removes a lot of this diffusion of duty [35, 37].

A more nuanced view comes from analyses of what is reported. Clinicians tend to report reactions that are serious, unusual or involve new drugs, and to skip those they regard as expected [19, 20, 21]. This selective pattern introduces bias that is hard to correct. Reporting is also stimulated by publicity, by regulatory warnings and by media attention, which produce bursts of reports that reflect awareness rather than a change in risk. Interpreting a rise in reports therefore requires some knowledge of what else happened in the same period [13, 33]. Bias of this kind has consequences for signal work, because a drug that gets a great deal of attention may seem less safe than an older competitor which attracts few reports, although the underlying risk is the same. Cautious interpretation is the safeguard against this effect [13, 33].

Patients themselves are a growing source of reports in several countries. Direct patient reporting has been shown to add information about the experience of a reaction, such as its effect on daily life, that clinician reports often leave out. Hospitals that publicise the route, through leaflets at discharge or notices in outpatient areas, can add this stream at limited cost. Concerns that patient reports are less reliable have not been borne out in general, though they usually need more follow-up to establish the drug, the dose and

the sequence of events [14, 15]. Patient reports have to be handled carefully with respect to privacy, and clear procedures for contacting the patient's own doctor are a sensible precaution before any clinical details are passed on.

5. FROM REPORTS TO SIGNALS

A signal in pharmacovigilance is information suggesting a new potentially causal association between a drug and an event, or a new aspect of a known one, that justifies further investigation [38]. Case-by-case review by an experienced assessor remains the backbone of signal detection in both national centres and hospital units. Clustering of reports, a positive rechallenge, an unusual time course or a reaction known to be biologically plausible all raise suspicion [39, 40]. For rare and serious events such as hepatic failure or severe cutaneous reactions, a handful of well-documented cases can be enough to trigger action. Hospital units contribute mainly at this stage, by identifying the unusual case, writing it up carefully and sending it forward with enough detail to be useful. A well-documented report with a clear time course and a positive dechallenge carries far more weight than several vague ones [38, 39].

Large databases use statistical screening on top of this. Disproportionality methods compare the proportion of reports for a particular drug-event pair with the proportion for all other drugs. The proportional reporting ratio, the reporting odds ratio and the Bayesian confidence propagation neural network each give a measure of how far a combination departs from expectation [31, 32, 41]. Comparisons of the measures show broadly similar results for strong signals but differences in sensitivity and in the number of false alarms [39, 41]. These methods suit the national or international level, where there are enough reports to give stable estimates. The numbers are usually presented with confidence intervals and thresholds, such as a minimum number of cases and a lower bound above one, so that isolated reports do not trigger an alert. Different centres choose different thresholds, which influences how many pairs reach review [31, 32].

Hospital programmes seldom have enough data for disproportionality analysis, and the methods are not a substitute for clinical review even where they do. Warnings about data mining stress that results are affected by duplicate reports, by the masking of one signal by another, by co-reported drugs and by the way events are coded [33, 39]. A statistical signal is therefore only a prompt. Teaching hospital units tend to use the methods in a supporting role, searching the national or WHO database for patterns that match what they have seen on the wards, and sharing their own case series with the national centre [15, 40]. Regulators and CIOMS have published practical guidance on how signals should be prioritised, verified and communicated, including the roles of clinical review, literature searching and consultation of other data sources [40]. Hospital teams that follow similar steps on a smaller scale find that the discipline of writing down the reasoning improves consistency.

History offers useful examples of how reporting works in practice. A review of drug withdrawals in the United States between 1969 and 2002 found that many were triggered by spontaneous reports of serious events such as liver injury and cardiac arrhythmia [13]. The point is not that every signal leads to withdrawal, but that case reports, once reviewed and combined with epidemiology, can change prescribing quickly. Equally, many signals turn out to be noise or to reflect confounding by indication, which is why verification with pharmacoepidemiological studies is normally the next step [38, 40]. Time to detection has also been studied, and early signals commonly rest on a very small number of reports, which highlights the value of high-quality information from every contributing centre [13, 38].

Findings across the topics above are summarised in table 1, and the distribution of entries by theme is shown in fig. 1. Several themes recur. Systems differ in structure but share the same basic chain from clinician to centre to database. Assessment tools give structured but imperfect judgement. Under-reporting is large, consistent across settings and driven by attitudes as much as by

lack of time. Analytical methods help at scale but cannot replace review of individual cases [33, 39]. Reading across the table, a hospital team can see where its own programme sits and which elements it lacks, whether a clear causality procedure, a feedback routine or a link to the national database [16, 17, 40].

6. IMPROVING REPORTING IN HOSPITALS

Education is the most frequently tried approach. A cluster-randomised trial in Portugal gave physicians a series of educational sessions on pharmacovigilance and reported a large increase in spontaneous reports in the intervention group compared with controls, an effect that persisted over the period of observation [23]. Observational studies from Spain and Italy found that regular contact between pharmacovigilance staff and hospital physicians, through visits, feedback and simple stimulus materials, was followed by sustained rises in reporting [24, 25]. Not every educational effort works, and the quality of the session appears to matter more than its length. Effect size varied between studies, and few followed participants for more than a year or two, so it is unclear how long the gains last without reinforcement. Reminders and repeat sessions look sensible, though trial evidence for them is limited [23, 24].

Several features recur in successful programmes. Reporting is made easy, with short forms, electronic submission and a named person to contact. Feedback is quick: reporters receive an acknowledgement and, later, some indication of what happened to the case. Senior staff set an example, and reporting is built into the routines of ward rounds and drug-safety meetings. Where pharmacists or trainee doctors are tasked with identifying reactions and helping to complete forms, the load on busy consultants falls and the volume of reports rises [14, 25]. None of these elements is expensive, but each depends on someone being responsible. Hospital leadership is a further factor. Where the chief pharmacist or medical superintendent signs off on a safety committee and reports back to staff, reporting tends to be sustained. Without sponsorship, programmes frequently depend on one enthusiast and collapse when that person moves [14, 25]. Recognition for the people who do this work, through acknowledgement at safety meetings, costs little and helps.

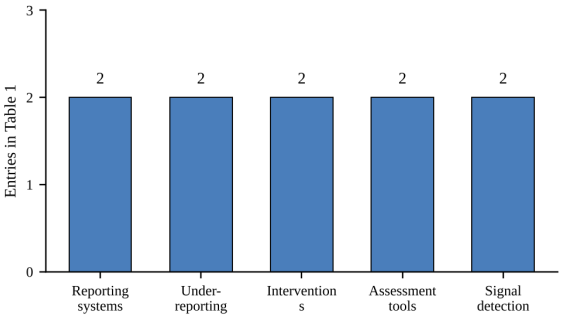


Fig. 1: Number of entries in table 1 by theme group

Alerts built into electronic records are a newer tool. Triggers such as the use of antidotes, abrupt stopping of a drug, or abnormal laboratory values can prompt a pharmacist to look for a reaction, increasing detection beyond what voluntary reporting finds [14, 34]. Such active surveillance does not replace spontaneous reporting, but it can fill gaps for events clinicians would not otherwise report. It also helps estimate how many cases the voluntary scheme is missing. The effort required, however, is considerable, and the specificity of triggers is moderate, so each hospital has to decide how much to invest. Cost and workload studies of such triggers are scarce, so decisions are often made on judgement. A pilot on one or two wards, with a defined set of triggers and a review of how many lead to genuine reports, is a practical way to find out whether the effort is justified in a given hospital [14, 34].

Medical, pharmacy and nursing curricula are a second route. Undergraduate teaching about reporting, including practical exercises with real forms, builds familiarity before habits are set [17, 35]. Hospitals can add case-based discussions at morbidity meetings and drug-safety journal clubs. Programmes in which students take part in ward-level monitoring have the double advantage of generating reports and training future prescribers, though the quality of student-initiated reports needs to be checked by an experienced assessor before they go on to the national centre [15, 18]. Simulation of reaction recognition, using cases built from published reports, has been used in some

courses and is well received by students, although controlled evaluation is lacking [15, 35].

7. LIMITATIONS AND FUTURE DIRECTIONS

Spontaneous reporting has well-recognised limits, and they apply fully to hospital programmes. Reports lack denominators, so incidence cannot be calculated. Under-reporting and selective reporting distort the pattern. Reports come with variable quality, and the causal assessment depends on the information supplied [14, 21, 33]. Published descriptions of single-hospital programmes inherit these limits, and are often further restricted by short observation periods and small numbers. Comparisons between hospitals are difficult because definitions of a reaction, reporting culture and case mix differ, as does the intensity of local stimulation. Teaching hospitals also differ from the community from which they draw patients, so reaction patterns seen in a tertiary setting may not apply to primary care [8, 9]. Regional differences in the structure of health services further complicate any attempt to generalise from one centre to another.

The literature on interventions is also modest. Most studies are before-and-after or time-series designs with limited follow-up, and only a few trials exist [23, 24, 25]. Few have tested whether higher reporting leads to better detection of true signals or to safer prescribing, which is the real purpose of the system. Evidence on patient reporting, electronic triggers and the contribution of nurses is thinner still. Without these data, resources may be spent on raising counts that do not translate into safety gains. Publication bias is probable, as programmes that succeed are more likely to be written up than those that fail, which may give an optimistic view of what education can achieve [14, 23]. Longer follow-up and independent replication would strengthen the conclusions that can be drawn.

8. CONCLUSION

Spontaneous reporting in teaching hospitals is useful, inexpensive and flawed. It has detected many serious reactions that trials could not, and hospitals that report well add valuable cases to national databases [11, 12, 13]. Its weaknesses are equally clear: most reactions go unreported, reports are often incomplete, and the numbers say little about incidence [19, 20, 21]. Structured assessment tools bring order to causality, severity and preventability, but they cannot rescue a report that lacks basic information [26, 27, 28]. For a hospital team, the sensible reading of any report count is as a measure of attention more than of risk [21, 33].

Practical progress depends mainly on people and routines. Education, easy forms, rapid feedback and a named pharmacovigilance contact have all been linked to higher reporting, with the strongest evidence for educational programmes [23, 24, 25]. The research agenda is plain: harmonised data, longer evaluation and a clearer link between reporting and safer prescribing. Until then, hospitals will do best by keeping the system simple, protecting reporters from blame and returning findings to the clinicians who supplied them [22, 40]. Small, steady efforts of this kind are more likely to last than one-off campaigns [25].

9. ABBREVIATIONS

ADR-Adverse drug reaction, WHO-World Health Organization, UMC-Uppsala Monitoring Centre, PRR-Proportional reporting ratio, ROR-Reporting odds ratio, BCPNN-Bayesian confidence propagation neural network, CIOMS-Council for International Organizations of Medical Sciences, ICH-International Council for Harmonisation, PvPI-Pharmacovigilance Programme of India

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All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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