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Adverse drug reaction reporting: A comparative analysis of five countries

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Abstract
Information on drug reactions is the main input into the ADR monitoring system. The information may come from various sources, and by various means. Generally, health professionals - particularly physicians and pharmacists - are key persons in the discovery and preliminary identification of adverse reactions resulting from use of a drug. The marketing authorization holder, who possesses information on the ingredients of a product and the processes of manufacturing, packaging, storage and distribution, is another key source. In addition, multinational corporations should also have mechanisms for collecting information on the use of their products in the countries where they are marketed. Consumers can be considered another important source of information, since they experience any adverse effects at first hand. However, it can be difficult for consumers to identify an adverse reaction, and their accuracy of reporting may be doubtful, owing to the technical nature of pharmaceuticals. ADR reporting may be either voluntary or obligatory. Spontaneous reporting by health professionals is often favored, since it is very difficult to make reporting compulsory. But in many countries, considerations of ethical responsibility and/or technical expediency have inclined governments to make reporting mandatory for the holders of marketing authorizations

Keywords: adverse drug reaction (ADR), uppsala monitoring center (UMC)

Introduction
Adverse drug reactions (ADRs) are common causes of mortality and morbidity all around the world [1, 2]. They represent an important economic burden for health systems [3, 4]. ADRs that occur in real-world medical practice cannot always be predicted by pre-marketing data since a limited number of selected patients are enrolled in clinical trials for specific indications and monitored for a limited period of time. Therefore, post-marketing surveillance is the most important tool for pharmacovigilance systems for early detection of unexpected and serious ADRs [5].

World data on ADRs are collected at the Uppsala Monitoring Center (UMC) constituted under the auspices of the World Health Organization's (WHO) Programme for International Drug Monitoring [5, 6]. All member countries send national ADR reports to the UMCs individual case safety reports (ICSR) database system, VigiBase [7, 8]. UMC continuously monitors the VigiBase for possible signals and alerts. Alerts from UMC constitute an important reference for decision-making processes of national pharmacovigilance authorities. However, ADR profiles vary from country to country owing to differences in genetics, diet and traditions of populations, and medical practices [5, 6, 9]. Additionally, pharmacovigilance legislations and the structure of the pharmacovigilance systems vary among WHO member countries [10, 11]. Because of these factors, information derived from the cumulative data may not always be relevant or applicable to individual populations. To be able to detect local signals and take accurate actions for minimization of the risk, it is important for countries to monitor and analyze their own national ADR databases continually. Such analysis can also guide actions to stimulate ADR reporting, and help to assess the effectivity of national legislations and pharmacovigilance activities.

Limitation of Premarketing Drug Safety Evaluations
Along with evaluations of drug efficacy, the detection and quantification of risks associated with drug treatment is a critical component of preclinical studies as well as the clinical phases (phases 1-3) of the drug development process before a drug is released in the market. Randomized controlled trials (RCTs), the main component of the premarketing clinical phases of drug development are the gold standard for evaluating drug efficacy but are much less effective at detecting ADRs [12]. RCTs have several limitations with regard to ADR detection. There are several issues that limit the generalizability of RCT results to clinical practice, such as limited study population size and duration of study, the selective recruitment of patients with resulting limited heterogeneity and the consideration of few predefined ADRs. The generalizability of clinical findings from RCTs to clinical practice, including that concern ADRs, has often been criticized as being inadequate and a major limitation [13-20]. The selection of patients for RCTs may also not be representative of patients who will receive the treatment and who may be more vulnerable to ADRs. It has been observed that often, less than 10% of patients in RCTs in most areas of medicine and surgery have the relevant disorder under investigation [21-26]. In addition, the inclusion criteria for RCT patients are frequently not reported, leading to significant limitations in conclusions regarding which populations are most at risk of the ADRs detected in RCTs [27]. Even in patients with the relevant disease, the severity and staging of the disease as well as comorbidities in RCTs may not reflect those found in routine clinical care and affect the extrapolation of RCT results to populations in clinical practice [28]. In particular, the frailest populations such as pediatric and geriatric patients are often underrepresented in RCTs, leading to limited premarketing drug-safety information about these patients [29-31].

Another main limitation of ADR detection and quantification using RCTs is their limited sample size [32-34]. With a small sample size, RCTs can detect ADRs that are common and that develop over short periods[29], but their relatively short follow up time compared with the length of drug use in clinical practice, particularly in the cases of interventions that require chronic treatment such as epilepsy and schizophrenia, limits the ability of RCTs to detect ADRs [35-38]. This presents an obstacle to detecting ADRs that appear at a time lag from the drug exposure, such as cancer, or those that develop after chronic use such as the long-term ADRs of oral contraceptives and hormone replacement therapy that can take years to develop [33]. In addition, rare ADRs cannot be detected by RCTs because RCTs do not contain sufficiently large populations [39].

The low quality of ADR reporting in RCTs and the known publication bias associated with the pharmaceutical industry are other obstacles to ADR detection, quantification, and dissemination [40]. On one hand, RCTs often have few or no predefined ADR screening protocols and cannot detect ADRs that are genuinely unexpected and for which no screening tests may therefore be carried out. This is a limitation inherent to the RCT design and such new ADRs can only be detected serendipitously. On the other hand, the quality of published RCT reports have been heavily criticized for a lack of transparency in their published ADRs reports [41]. A review of 113 RCTs published in high impact factor journals found that 15% of studies did not provide numerical data on the frequency of ADRs, 27% provided no information on the severity of ADRs, and 48% did not report the number of patients drop-outs due to ADRs [42]. There are several cases of such suspected low-quality ADR reporting in the literature. A review of 25 non-steroidal anti-inflammatory drug (NSAID) RCTs with a total of 2566 patients, found that not one of the trials explicitly reported any renal ADRs, potentially suggesting underreporting [31]. Although renal damage is not common, it is unlikely that not a single patient experienced renal ADRs. In RCTs, warfarin had much lower reported ADR rates than in clinical practice, contributing to concerns about the validity of RCT ADR data that consequently led to under-prescribing of warfarin in patients who could most benefit from warfarin therapy[43-45]. The low-quality ADR reporting in RCTs has prompted concerted efforts to improve ADR reporting, as through the Consolidated Standards of Reporting Trials (CONSORT) guidelines [46]. Nevertheless, the quality of published ADR reporting from RCTs has remained low [42].

Classification of Adverse Drug Reactions

Adverse drug reactions are frequently classified as 'type A' and 'type B' reactions. An extended version of this classification system is shown here:

Type A Reactions Type A (augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent. Examples include respiratory depression with opioids or bleeding with warfarin. Type A reactions also include those that are not directly related to the desired pharmacological action of the drug, for example dry mouth that is associated with tricyclic antidepressants.

Type B Reactions Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug. These are less common, and so may only be discovered for the first time after a drug has already been made available for general use. Examples include anaphylaxis with penicillin or skin rashes with antibiotics.

Type C Reactions Type C, or 'continuing' reactions, persist for a relatively long time. An example is osteonecrosis of the jaw with bisphosphonates.

Type D Reactions Type D, or 'delayed' reactions, become apparent sometime after the use of a medicine. The timing of these may make them more difficult to detect. An example is leucopoenia, which can occur up to six weeks after a dose of lomustine.

Type E Reactions Type E, or 'end-of-use' reactions, are associated with the withdrawal of a medicine. An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines [47].

Costs of Adverse Drug Reactions

The impact and the management of ADRs is complex and in the USA, may cost up to 30.1 billion dollars annually. ADRs may increase costs due to increased hospitalization, prolongation of hospital stay and additional clinical investigations in more serious cases. In addition, ADRs may trigger prescription cascades when new medications are prescribed for conditions that are a consequence of another medication, which is often an unrecognized ADR. Examples include the use of antipsychotics in Parkinson's disease patients treated with dopaminergic drugs or the use of anticholinergic drugs for urinary retention in Alzheimer's disease patients treated with cholinesterase inhibitors [48]. This increases the costs of pharmacotherapy as well as compounding the risk of further ADRs.

Out of incident ADRs that resulted in hospitalization, the cost per preventable ADR was estimated to be higher than for non-preventable ADRs [49]. Another study conducted in inpatient setting found the cost to be $US 2262 per ADR [50]. The costs of ADRs in inpatient setting varies within different hospital wards, costing $US 13,994 in a non-intensive care unit (ICU), but $US 19,685 in ICU [51]. In addition, drug surveillance studies have been able to identify the following ADRs as those having the greatest economic burden in hospital setting: fever, bleeding, diarrhea and cardiac arrhythmia, in decreasing order [50]. NSAIDs, antibacterial agents, anticoagulant agents and antineoplastic agents are a major cause of ADR-related costs [52]. Both the extended duration of hospital stay as well as the outpatient care as a result of ADRs constitute the source of financial burden [53]. The main costs of ADRs in a hospital are wages, disposable goods and medications [54]. Aside from the direct financial costs, there are also several indirect costs for patients and their care givers that are incurred by ADRs, such as missed days from work and/or morbidity such as anxiety due to the ADR episode [55].

A Comparative Analysis

New Zealand

The Centre for Adverse Drug Reactions Monitoring (CARM) programme monitors adverse drug reactions in New Zealand (Table 1). New Zealand has arguably the highest rate of adverse reaction reports in the world, ''both in terms of reports per 1000 doctors and reports per million population'' [56]. Pharmacists (community and hospital), however, play only a minor role in ADR reporting, with only 2.3% of reports, compared to 65% by community doctors and 17% by hospital doctors[56]. It has been estimated by CARM that only 5% of all reactions are being reported.

The Intensive Medicines Monitoring Program (IMMP) is a prescription event pharmacovigilance system supplementary to CARM. This system commenced in 1977 to monitor the ADRs of selected new drugs. IMMP aims for cohorts of around 10 000 patients for any new drug, with long-term prospective observational data collection. Pharmacy dispensing software has the ability to flag and print reports for IMMP medicines. Pharmacists send these printouts to IMMP periodically. Prescribers receive questionnaires to report any adverse events that have occurred since the most recent prescription. If a prescription for a particular patient ceases to appear at the centre, the prescriber is asked for specific reasons for stopping the medication [57].

Table 1: ADR reporting in New Zealand

Reporters	organization	Reportable events	Reporting systems	Reporting analysis and feedback mechanism
Doctors, pharmacists, nurses	CARM (Centre for Adverse Drug Reactions Monitoring)	Any suspect reactions of clinical concern to all medicines, vaccines, OTC medicines, herbal, traditional and alternative remedies, and events to IMMP medicines	Yellow reporting form (available via Prescribers' Update, New Ethicals Catalogue and online from the CARM website)	CARM undertakes regular analysis of the database to determine significant patterns of adverse reactions, resulting in the suggestion to change prescribing advice
		Adverse reactions and interactions that are serious and adverse reaction of current concern	Electronic/online reporting via CARM website)	Individual patients receive warning or danger alerts against their 'unique National Health Index number' for severe or life-threatening reactions
Doctors, pharmacists, nurses	IMMP (The Intensive Medicines Monitoring Program)	All adverse reactions to new medications and all events to IMMP medications	Prescription Event Monitoring (PEM) form (IMMP Prescription Form) and Electronic/online reporting, via CARM website)	Undertakes ''prospective, observational, cohort studies on selected new medicines''
				The results are reported to the Ministry of Health and health professionals IMMP supplements the ADR database

Canada

ADR reporting is considered one of the essential components of post-marketing surveillance in Canada. The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) monitors the ADR reporting scheme for drug products. Physicians, pharmacists and other health professionals can report all suspected ADRs using the ADR reporting form to CADRMP, and this is followed by systematic analyses. The Laboratory Centre for Disease Control monitors adverse reactions to vaccines for disease control (Table 2) [58]. Pharmacists have been included in the Canadian ADR reporting programme since its inception [59]. During 1998, pharmacists contributed to 37.6% of national ADR reports, followed by 27.1% from physicians. Further, a British Columbian study indicated that 74% of all reports came from pharmacists (38.8% hospital pharmacists and 34.8% community pharmacists) [60].

Table 2: ADR reporting in Canada

Reporters	organization	Reportable events	Reporting systems	Reporting analysis and feedback mechanism
Physicians, pharmacists and other health professionals	Canadian Adverse Drug Reaction Monitoring Program (CADRMP)	All suspected ADRs which are unexpected, regardless of their severity; serious, whether expected or not; reactions to recently marketed drugs	Using the ADR reporting form to report suspected adverse reaction due to drug products marketed in Canada (vaccines excluded). The form is available from national and regional ADR centres and is included in the Compendium of Pharmaceuticals and Specialties (CPS)	Systemic review of all reports by a team of experts
Physicians, pharmacists and other health professionals	Laboratory Centre for Disease Control	All suspected ADRs for Vaccines	Using vaccine-associated adverse event form. This form is included in the CPS	

The Netherlands

A spontaneous ADR reporting scheme started in the Netherlands in 1963, and pharmacists have been involved in this reporting scheme since its inception (Table 3). ADR reports are submitted by GPs, specialists and pharmacists to the Netherlands Pharmacovigilance Centre, Lareb, which reports to the Netherlands Medicine Evaluation Board [61]. Nearly 40% of reports to date have been submitted by pharmacists. ADR reporting is not mandatory in the Netherlands, and pharmacists can report independently. A recent study of 200 randomly sampled community pharmacists (response rate 73%) confirmed that community pharmacists in the Netherlands have a positive attitude towards suspected ADR reporting, are knowledgeable about ADR reporting and consider this a professional responsibility [61]. The study also highlighted feedback from Lareb as an important motivating factor, while 18% of Dutch respondents mentioned 'incentive' as a motivating factor to report, compared to one-third of the pharmacists in the UK [62].

Table 3: ADR reporting in The Netherlands

Reporters	Organization	Reportable events	Reporting systems	Reporting analysis and feedback mechanism
GPs, specialists, Pharmacists	Lareb (Netherlands Pharmacovigilance Foundation)	Any suspected adverse reaction and the Following: ▪ all side-effects and reactions caused by new ▪ prescription medicines ▪ serious side effects ▪ effects which result in hospital admission, ▪ work incapacity or death ▪ suspected interactions with other medications ▪ side effects of vaccines, self-administered ▪ medication or alternative therapies	Reporting form printed inside the Dutch equivalent Of the National Formulary	Systemic review of all reports by a team of experts

Sweden

In Sweden, ADRs are reported from National Healthcare and hospitals by prescribers, via seven regional adverse drug reaction centres to the Medical Products Agency (MPA) [63]. The MPA further transfers the ADRs concerning centrally approved medicinal products to the European Agency for the Evaluation of Medicinal Products (EMEA) (Table 4) [63].

In Sweden, it is mandatory for prescribers to report all serious or unexpected adverse reactions to the regulatory authority. For new products, all suspected adverse reactions, excluding those included in the summary of product characteristics, are to be reported [63-65]. However, well known and non-serious ADRs to older medicinal products generally do not need to be reported [63]. Backstorm *et al*. identified a serious drawback of this system in that all adverse reactions, including serious and fatal reactions, are not reported [63-65]. Pharmacists in Sweden are not authorized to report suspected ADRs directly to the regulatory authority [66].

Table 4: ADR reporting in Sweden

Reporters	organization	Reportable events	Reporting systems	Reporting analysis and feedback mechanism
Mandatory for prescribers; other ources Industry and industry publications, government bodies, WHO	Medical Products Agency (MPA)	All serious or unexpected adverse reactions which appear to increase in frequency shall be reported. For new products, all suspected adverse reactionsexcluding those included in the summary of product characteristics are to be reported	The MPA form can be used with advantage and supplemented with relevant extracts from case analyses, patient records, laboratory results. Reports can be sent directly to MPA or the regional pharmacovigilance centres of the MPA	MPA undertakes risk/ benefit analysis, information and alerts, withdrawals etc. MPA further transfers the ADRs concerning centrally approved medicinal products to the European Agency for the Evaluation of Medicinal Products (EMEA). EMEA provides information to health care professionals

Singapore

The Pharmacovigilance Unit (PV Unit) at the Centre for Pharmaceutical Administration, Singapore, is responsible for ADR report monitoring, and has been in operation since 1993 (Table 5). Physicians, dentists and pharmacists report all ADRs related to pharmaceutical medicines using the ADR reporting form (Centre for Pharmaceutical Administration, 2003) [67]. The PV unit compiles nationwide ADR reports and collaborates with other national centres (for example, the WHO Collaborating Centre).

Table 5: ADR reporting in Singapore

Reporters	organization	Reportable events	Reporting systems	Reporting analysis and feedback mechanism
Physicians, dentists, pharmacists	Pharmacovigilance (PV) Unit, the Centre for Pharmaceutical Administration	All ADRs related to pharmaceutical medicines (as defined by the WHO). Also, accepts reports associated with Chinese proprietary medicines and herbal remedies	Using the ADR reporting form via telephone, mail, fax, email and lectronically through the internet. Form can also be found in the MIMS Singapore	All reports are individually analysed with particular attention to the serious ADRs. The reporter is informed if he/she ‘‘ticked the box on the form to request information about other reports associated with the suspected drug’’

Discussion

ADR reporting is seen as an important part of post marketing surveillance and drug safety internationally. Many developed countries have adopted ADR reporting systems, managed by national ADR/pharmacovigilance reporting centres. Most of these reporting systems are voluntary, primarily relying on the vigilance of healthcare professionals. Voluntary reporting involves consumers in the US, and to a minor extent in Australia.

Pharmacists are in an ideal situation to detect and report ADRs through daily contact with patients and initiatives such as medication reviews. Controlled trials confirm that pharmacists' participation in clinical care helps to reduce ADRs for patients [68, 69].

However, in most countries, physicians are the main contributors to ADR databases, except in the Netherlands and Canada, where community pharmacists play the major role in ADR reporting, considering this a professional responsibility [60, 70]. It should be noted though that systems in these countries do not facilitate reporting by consumers. Further, it has been noted that doctors in the Netherlands found ADR reporting to be complex and the system time-consuming and bureaucratic [71].

Factors that may positively impact on community pharmacists' participation in ADR reporting are clear guidelines as what to report, promotion of ADR reporting as a professional responsibility to ensure quality use of medicines, professional training, incentives for reporting and feedback. There is currently little research to substantiate these concepts.

Lastly, effective analysis of reported data requires patient-related outcome measures. A more elaborate patient follow-up system, depending on pharmacist's input, could provide comprehensive patient outcome data, including economic, clinical and quality of life impact.

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