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SYSTEMATIC REVIEW

Adverse drug event reporting systems: a systematic review

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AIM

Adverse drug events (ADEs) are harmful and unintended consequences of medications. Their reporting is essential for drug safety monitoring and research, but it has not been standardized internationally. Our aim was to synthesize information about the type and variety of data collected within ADE reporting systems.

METHODS

We developed a systematic search strategy, applied it to four electronic databases, and completed an electronic grey literature search. Two authors reviewed titles and abstracts, and all eligible full-texts. We extracted data using a standardized form, and discussed disagreements until reaching consensus. We synthesized data by collapsing data elements, eliminating duplicate fields and identifying relationships between reporting concepts and data fields using visual analysis software.

RESULTS

We identified 108 ADE reporting systems containing 1782 unique data fields. We mapped them to 33 reporting concepts describing patient information, the ADE, concomitant and suspect drugs, and the reporter. While reporting concepts were fairly consistent, we found variability in data fields and corresponding response options. Few systems clarified the terminology used, and many used multiple drug and disease dictionaries such as the *Medical Dictionary for Regulatory Activities* (MedDRA).

CONCLUSION

We found substantial variability in the data fields used to report ADEs, limiting the comparability of ADE data collected using different reporting systems, and undermining efforts to aggregate data across cohorts. The development of a common standardized data set that can be evaluated with regard to data quality, comparability and reporting rates is likely to optimize ADE data and drug safety surveillance.

Introduction

Adverse drug events (ADEs) are harmful and unintended consequences of medication use, and a leading cause of unplanned hospital admissions and deaths [1–3]. Their detection, documentation and reporting are fundamental to pharmacovigilance activities, the science of assessing and monitoring the risk/benefit profiles of medications throughout their lifecycle [4]. Pharmacovigilance activities are essential for detecting rare but potentially dangerous ADEs, those occurring

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after prolonged exposure, and drug–drug and drug–disease interactions that may not have been observed in randomized trials conducted prior to drug licensing [5–9].

In clinical practice, fewer than 5% of ADEs are reported, even in jurisdictions where reporting is mandatory [6, 10, 11]. Without robust ADE reporting mechanisms supporting the detection of safety signals, rare ADEs may remain undetected for years, exposing the public to unanticipated risks [5]. For example, high-profile drug withdrawals such as that of the anti-inflammatory rofecoxib (Vioxx™) occurred only after millions of patients had been exposed, highlighting the need for earlier, more comprehensive data [5, 8, 9]. Despite the limitations of existing spontaneous ADE reporting systems, they remain the most common method with which pharmacovigilance centres generate safety signals [12].

National pharmacovigilance centres have developed electronic and paper-based methods to facilitate reporting. A minimum required dataset for a valid report has been proposed, which includes an identifiable patient, an ADE, a suspect medicinal product and an identifiable reporter [13, 14]. However, no other internationally-agreed upon data element standards exist for ADE reporting [15, 16]. We aim to synthesize information about the type and variety of ADE data elements collected within reporting systems internationally.

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [17].

Definitions

We define an ADE as an injury resulting from the use of a drug [18]. This definition includes adverse drug reactions (ADRs), responses to drugs which are noxious and unintended and which occur at doses normally used in humans for prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function, and includes events due to treatment failures and medication errors [3]. We define a reporting system as a set of interdependent data elements and dictionaries that captures information about actual and suspected ADEs [19].

Data sources and searches

We completed an environmental scan of websites engaged with ADE reporting through which we identified existing reporting systems. We found a range of reporting systems, from those hosted by individual hospitals to national drug regulatory authorities. We developed search concepts using the results of our environmental scan, and collaborated with a professional librarian (MDW) to develop terms and keywords. We included the concepts ADE or ADR reporting systems, health data systems, safety management and surveillance methods (Appendix 1). We adapted and applied our searches to the following databases: MEDLINE (1969–February 2014), Embase (1974–February 2014), International Pharmaceutical Abstracts (1970–February 2014) and the Association for Computing Machinery (ACM) Digital Library (1985–February 2014), and searched all databases except ACM through Ovid (Figure 1).

We completed a grey literature search using the search engine Google (www.google.ca, www.google.com and www.google.co.uk) using a combination of search terms and concepts we previously identified as we anticipated that many reporting systems would not be referenced in academic publications. We searched for websites hosting reporting platforms, and professional associations dealing with drug safety and medical information technology, information about reporting, and reporting access points. We contacted systems administrators for additional unpublished information. We limited our searches to English, French and German. Finally, we hand-searched the bibliographies of relevant articles to identify additional relevant studies and websites.

Study selection

We included qualitative and quantitative studies, government reports, working papers and websites describing or hosting reporting systems for ADEs in humans. We excluded reporting systems that used administrative data as the sole data source, those focusing only on non-medication-related adverse events (e.g., surgical adverse events), errors or allergies, or events related to complementary and alternative medications, food supplements and over-the-counter medications. We excluded computerized physician order entry systems, electronic medical records and registries specific to one drug or disease. We excluded studies published only as abstracts, and systems for which we were unable to get information related to at least two of the following domains: data source, data fields and data dictionaries. Two study authors (MW, DP) screened all titles and abstracts for eligibility independently. If either study author felt that an abstract met the inclusion and exclusion criteria, we reviewed the full-text article. We resolved disagreements through discussion until reaching consensus.

Data extraction and quality assessment

We developed and piloted a standardized data extraction form in Microsoft Excel 2010. Two study authors (CB, CH) independently extracted data on field characteristics and properties, including whether fields were mandatory or optional, the data type (e.g., categorical or numerical), and whether data quality checks and alerts were embedded. Three study authors (MW, DP, CH) reviewed the data extraction forms for errors. Any disagreements were resolved by achieving consensus through discussion.

Data synthesis and analysis

We exported individual data fields into a visual thinking program (Inspiration, version 9.2), displaying each data field as a blob with the number of times identical fields were used (e.g., "ADE start date [11]", indicated a data field labelled "ADE start date" occurred in 11 systems). First, we sorted data fields into reporting concepts (Figures 2a–d). For example, the data fields "ADE start date", "ADE duration" and "ADE end date" were grouped into the reporting concept "ADE timeline". Second, we disaggregated fields containing multiple variables into individual fields, and eliminated duplicate and very similar fields by collapsing them. For example, "ADE start date", "start of event" and "start of reaction" were grouped under "ADE start

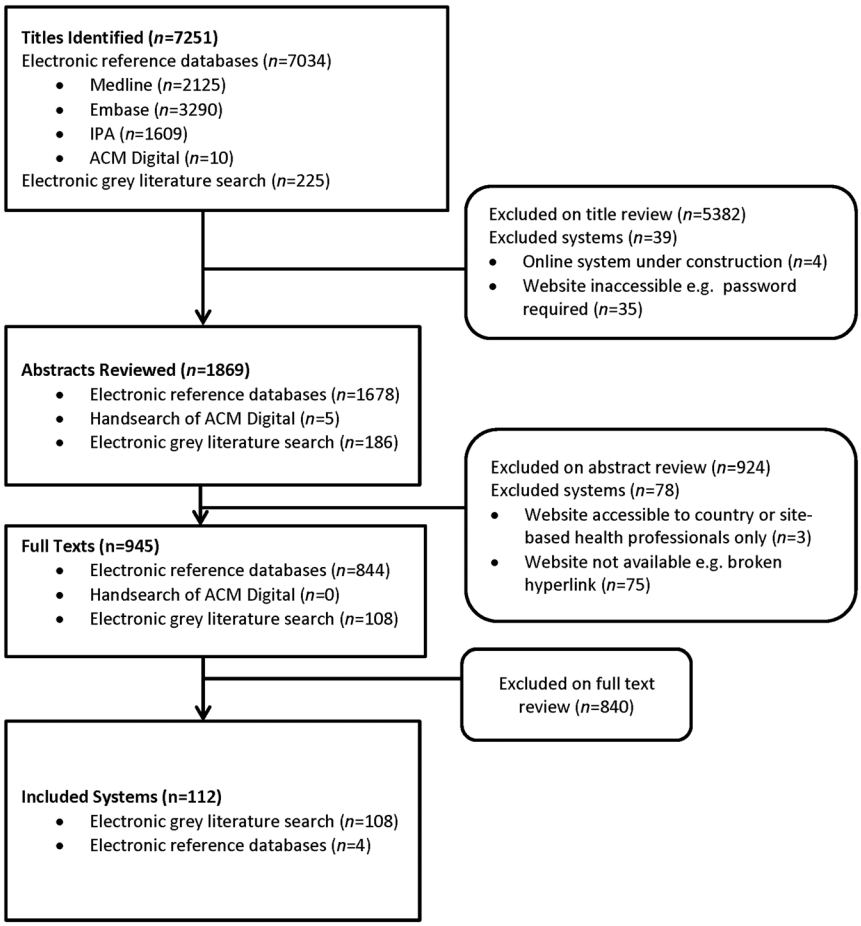

Figure 1
Flow diagram of included studies and systems

date". Third, we identified relationships and hierarchies within and between reporting concepts.

Quality assessments

There is no agreed-upon metric for evaluating the quality of ADE reporting systems. Therefore, we adapted two quality assessment tools that were developed by consensus opinion: the 'minimum required dataset' developed by the World Health Organization (WHO) [20] and a scale by Bandekar *et al.* (Appendix 2) [21]. We calculated quality assessment scores by tabulating the number of data fields present in each reporting system. In addition, we rated each system for the maximum achievable ADR report score (i.e. Grade 0 to Grade 5), assuming each data field was completed using the Documentation Grading System for ADR reports developed by the WHO (Table 1) [22, 23]. Two authors performed quality assessments independently. Any disagreements were resolved by achieving consensus through discussion.

Results

Main results

We identified 7034 titles by searching electronic reference databases, and 225 systems by searching grey literature (Figure 1). Four titles found in the bibliographic databases, and 104 in the grey literature met inclusion criteria. All reporting systems were being used at the time of our review, and collected data for drug regulatory purposes (Appendices 3 and 4). We identified 11 systems used for international, and 97 used for national level reporting: 22 were based in Africa, 16 in Asia, 3 in Australasia, 28 in Europe, 13 in South America and 15 in North America. Pharmaceutical companies (n = 8) and hospitals (n = 5) hosted other systems. Health professionals and industry personnel could access all systems; however, patients could report in only 20. Thirty-four systems accepted both electronic and paper-based reports, while 27 used only electronic, and 51 only paper-based reporting methods. Some electronic systems ensured that the minimum required data defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) were collected by making those fields mandatory. The most common data dictionary used was the *Medical Dictionary for Regulatory Activities* (MedDRA), a standardized dictionary of medical terminology developed by the ICH.

Quality assessments

Figure 3 shows that none of the reporting systems achieved maximum scores on either quality assessment tool used (Figure 3;

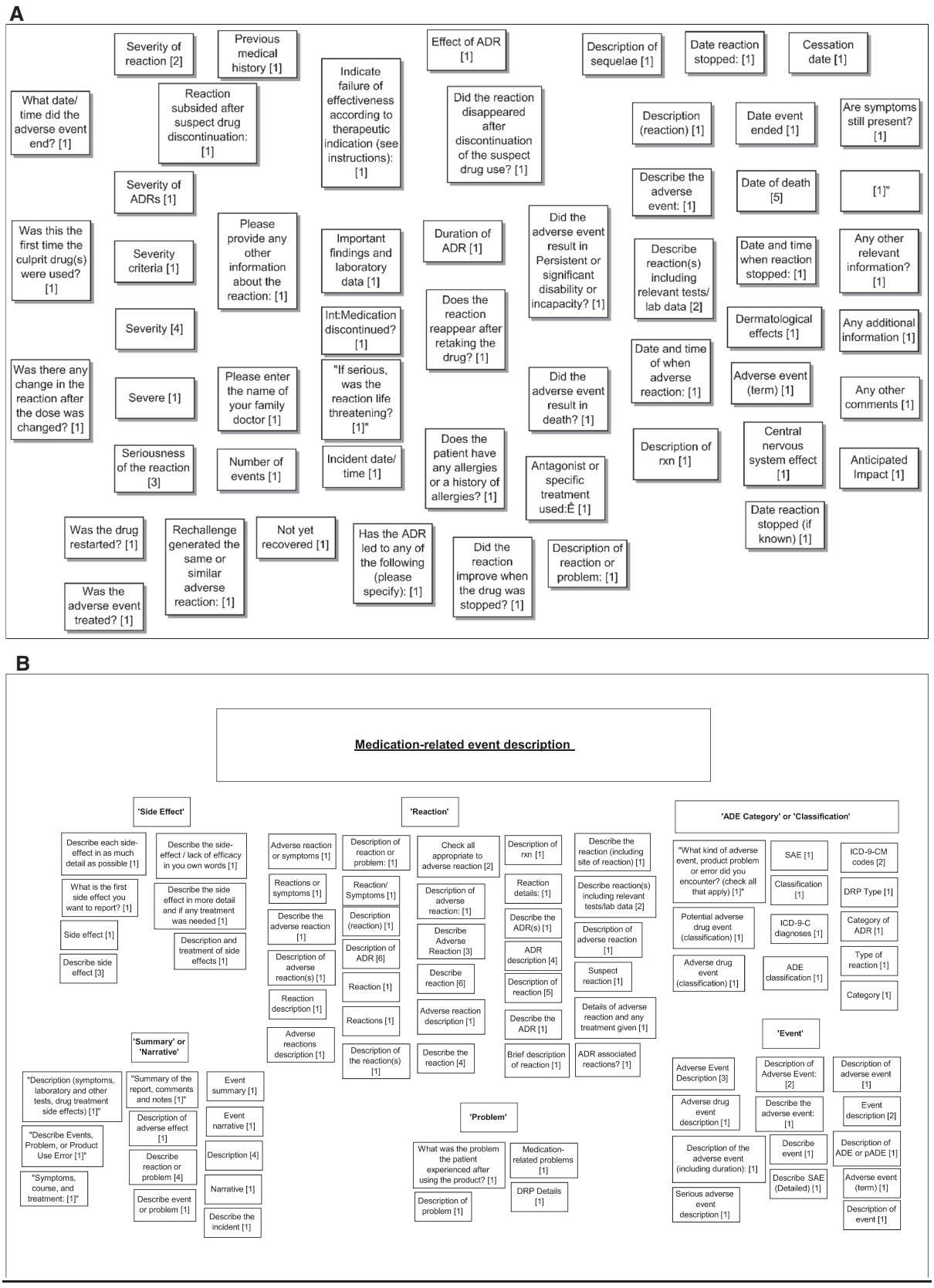

Figure 2

Iterations of data fields and reporting concepts sorted using visual thinking software: (a) Example of raw data prior to being sorted. (b) STEP 1: Example of sorting into reporting concepts. (c) STEP 2: Elimination of duplicate fields. (d) STEP 3: Identification of relationships between concepts

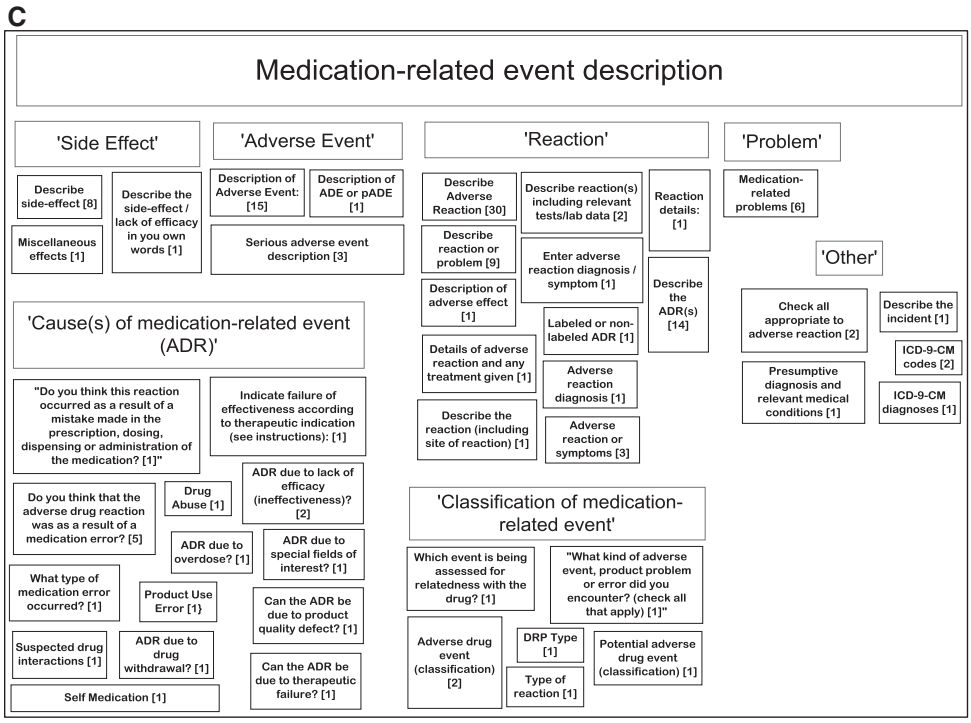

Figure 2
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Table 1

World Health Organization documentation grading system for adverse reaction reports

Grade	Documentation grade interpretation	Number of reporting systems
No grade	Systems that did not meet the Adverse Reaction minimum criteria	6
Grade 0	Adverse Reaction minimum criteria met: patient, reporter, name of suspected product(s) and description of adverse reaction(s)	5
Grade 1	Information required for Grade 0 plus: Patient age and sex	10
Grade 2	Information required for Grade 1 plus: Date of onset of reaction AND treatment dates for the suspected health product(s)	2
Grade 3	Information required for Grade 2 plus: Patient outcome	1
Grade 4	Information required for Grade 3 plus: Suspect product dosage	6
Grade 5	Information required for Grade 4 plus: Route of administration of the suspected product.	78

Documentation grade is a value assigned based on the quality of information achievable in adverse reaction reports.

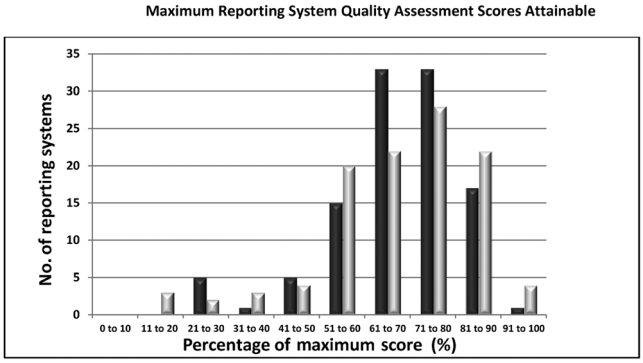

Figure 3

Quality assessment scores of reporting systems using QA scales proposed by WHO – UMC and Bandekar

Appendices 3 and 4) [20, 21]. For example, most systems collected 50–70% of data fields required within each quality assessment tool. Table 1 presents the maximum achievable score that could be obtained using each reporting system according to the WHO Documentation Grading System for ADRs, assuming complete data entry [22, 23]. A maximum ADE report score (i.e. Grade 5) could be achieved in 72% of systems.

Reporting elements

We found 1728 unique data fields that were used to capture information that we grouped into reporting concepts (Table 2). Data fields either captured a single variable such as 'dosage', or multiple variables within one field 'dosage, frequency and route of administration'.

Patient information

We identified three reporting concepts used to describe patient information: patient identifiers, demographics and medical history. Most systems provide free-text data entry options for patient identifiers (n = 94). To avoid report duplication, some systems generated unique identifiers. Generally, systems did not require patients' contact details as pharmacovigilance centres would follow up with reporters for further information. Demographic information included age, date of birth, gender, height, weight and ethnicity. However, 15 systems did not request information related to age, and nine did not request information related to gender, precluding the use of these variables for age- or gender-specific analyses [23, 24]. Ethnicity was present in 24 systems, and usually captured information in categorical format. Information on medical history, including ADE risk factors such as hepatic or renal dysfunction, was collected in 60 systems in free-text formats [23, 24].

ADE description

We identified six reporting concepts used to describe ADEs: timeline, management, classification, severity/seriousness, causality and outcome**.** We found 98 systems that collected data on ADE onset, duration or resolution. Forty-four systems requested data about the clinical management of the ADE, mostly using free-text data entry field options for this with optional completion. Figure 4 presents the range of information collected under this concept. ADE classification was present in 29 systems, allowing reporters to classify events into those related to dosing, errors, drug interactions, treatment failures, and non-adherence (Figure 2d). In 103 systems, reporters could use free text to describe the ADE with up to 4000 characters. Fields collecting data on severity or seriousness were present in 72 systems. In 28 systems data on ADE severity and seriousness were collected using dropdown menus reflecting outcome, for example 'permanent disability', 'prolonged hospitalization', 'persistent or significant disability', 'congenital malformation', 'life-threatening' and 'death'. In these systems it was unclear how life-threatening ADEs with excellent outcomes (e.g., anaphylaxis resulting in airway compromise but no permanent disability) might be documented. Many systems requested information related to the causality of the ADE, such as whether rechallenge (n = 45) or dechallenge occurred (n = 51), and whether dechallenge resulted in improvement. Table 3 provides an example of the wide range of information collected within one of these fields. Only one system requested information about

Table 2

Reporting concepts and data fields encountered in 108 identified reporting systems for the domains suspect/concomitant drugs and ADE description

Suspect/Concomitant drugs		**ADE description**	
Reporting concept	**Data fields bullet points indicate data values**	**Reporting concept**	**Data fields bullet points indicate data values**
Medication/ Drug name	Prescribed medications: • Drug dictionary or Free-text Complementary and alternative medications: • Free text Over-the-counter medications: •Free text Generic name/ Brand name: •Drug dictionary or free-text Active ingredient: • Drug dictionary or Free-text Medication source: • Pharmacy or other Manufacturer: • Free-text Manufacturing date: • dd/mm/yyyy or Free-text Batch/Lot number: • Free-text Expiration date: • dd/mm/yyyy or Free-text	**Timeline**	Onset date/Detection date/Report date: • dd/mm/yyyy or Free-text Duration of ADE: • Free-text
		Management	Was the ADE treated? Was further treatment required? • What treatment was administered? • Treatment date(s)
		Classification (Confirmed or Suspected)	Patient self-management Non-adherence Allergy Drug interaction Untreated indication Sub-therapeutic dose(s) Supra-therapeutic dose(s) Treatment failure Drug overdose Intentional misuse Medication error: •Prescribing/Dispensing/ Administration/Dosing/ Product quality defect/ Other
Clinical indication	Symptoms •ICD-10 or Free-text	**Seriousness/Severity**	How would you rate the seriousness or severity of the ADE? • Life-threatening or Other
Dose	Dose prescribed/Dose taken/ Dose administered •Units e.g. mg •Free-text	**Causality**	Risk factors: (ICD-10 or Free-text) Rechallenge: (Yes/No/Unknown) Dechallenge: (Yes/No/Unknown) Alternative diagnosis: •ICD-10 or Free-text

(continues)

Table 2

(Continued)

Suspect/Concomitant drugs		ADE description	
Reporting concept	**Data fields bullet points indicate data values**	**Reporting concept**	**Data fields bullet points indicate data values**
Dosing interval	Frequency • Dosage e.g. od, qh • Units e.g. mg	**Outcome**	**Resolution:** Has the adverse event stopped? (Yes/No/Unknown) **Outcome/Sequelae:** Permanent disability Exacerbation of pre-existing condition New medical condition Congenital abnormality ED visit or hospitalization Prolonged hospitalization Death due to ADE or other cause Other
Duration	Start date: • dd/mm/yyyy or Free-text Stop date: • dd/mm/yyyy or Free-text Unknown date: •dd/mm/yyyy •Free-text		
Route of administration	Oral/Intravenous Intramuscular/Topical/Other		

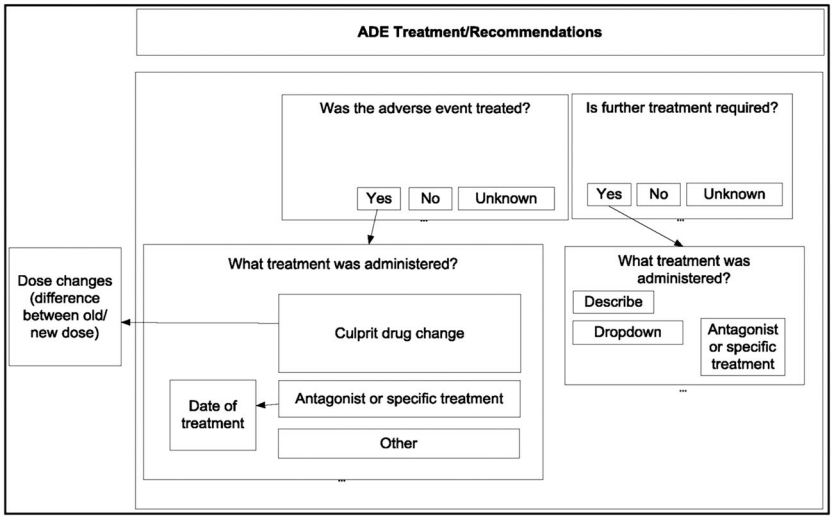

Figure 4

Example of relationships and hierarchies within one reporting concept

Table 3

Range of data elements collecting information about rechallenge to the suspect drug

No.	Rechallenge data elements
1	Adverse event or reaction reappeared on rechallenge
2	Check reaction at rechallenge?
3	Did adverse reaction re-appear upon re-use?
4	Did re-exposure to the suspect cause the same or a similar reaction?
5	Did the ADR reappear after the drug was restarted?
6	Did the ADR reappear after readministering the suspect drug?
7	Did the adverse reaction reappear, when the drugs was readministered?
8	Did the event reappear after re-administering the medication?
9	Did the problem reappear after introduction of the suspected drug again?
10	Did the reaction appear after reintroducing the suspected product?
11	Did the reaction reappear after drug was stopped?
12	Did the reaction reappear after reintroduction
13	Did the reaction reappear after reintroduction of the drug?
14	Did the reaction reappear after suspect drug was restarted?
15	Did the reaction reappear after the drug was reintroduced?
16	Did the reaction reappear if product was re-introduced?
17	Does the reaction reappear after retaking the drug?
18	Event appeared on rechallenge
19	Event reappeared after the drug is reintroduced?
20	Event reappeared on use
21	If [a rechallenge happened] did the undesirable effect recur?
22	If [there has been improvement after the medication was discontinued] was/were the medication(s) readministered?(=rechallenge)
22	If the medication was readministered, the undesirable effect reappear?
23	Int: Was the medication re-administered?
24	No rechallenge performed
25	One or more side effects after re-exposure occurred?
26	Problem returned after person started taking or using the product again?
27	Reaction appeared after reintroduction (rechallenge)
28	Reaction reappear after restart of suspected drug
29	Reaction reappeared after reintroducing drug
30	Reaction reappeared after reintroduction
31	Reappearance of event with readministration
32	Reappearance of the reaction after re-introduction of the medication?
33	Rechallenge
34	Rechallenge generated the same or similar adverse reaction
35	Rechallenge not done
36	Rechallenge to the product?

(continues)

Table 3

(Continued)

No.	Rechallenge data elements
37	Rechallenged?
38	Reintroduction of product
39	Result on reintroduction of the drug
40	The reaction reoccurred if the drug was used again?
41	Was product re-used after detection of adverse reaction (re-challenge)?
42	Was the patient re-exposed to the drug?
43	Was there an adverse event on drug re-administration?
44	Was there one or more side effects after re-exposure?
45	Which adverse event recurred on drug re-administration?

the potential for alternative diagnoses. Causality was generally based on the reporter's opinion and captured using free-text format, or the WHO Uppsala Monitoring Centre causality scale (i.e. 'certain', 'probable', 'possible', 'unlikely', 'unclassified' or 'unaccessible' (n = 10)) [23]. Four systems allowed reporters to submit supporting data such as the results of laboratory tests or clinical investigations.

Suspect and concomitant drugs

We identified six reporting concepts used to capture information on suspect and concomitant drug(s): medication name, indication, dose, route of administration, dosing interval and duration. All systems required information on suspect medications, whether prescribed or not, including over-the-counter and complementary and alternative medications. Forty-nine systems requested information on both suspect and concomitant drugs, while 63 did not request any information on concomitant drugs. In four systems, reporters could categorize drugs as 'suspect', 'concomitant' or 'interacting'. Generic and brand names could be reported within electronic systems using predictive entry using built-in drug dictionaries [25, 26]. Three systems required reporters to list the active ingredients implicated in the ADE [27–29]. Information on clinical indication for the drug(s) was present in 93 systems. This could be used to identify off-label use, and was collected in free-text format (n = 76) or using dropdown menus of dictionaries of clinical conditions (e.g. MedDRA (n = 17)). Dosing information was collected in 77 systems. Reporters could provide details on the dose prescribed (n = 15), taken and/or received (n = 4). Response options were usually standardized and prepopulated with multiple dosing options such as '500 mg' within electronic systems. Information on dosing interval was usually categorical, and present in 40 systems. Route of administration was present in 85 systems, and reporters could choose from standardized prepopulated response options within electronic systems. Drug therapy duration could be calculated using 'start date' and 'end date' or 'therapy dates'.

Reporter information

Reporter and report details were two concepts identified under reporter information. Primarily free-text data elements were used to capture reporter details including name, profession and contact information. Sixty-eight systems required reporters to indicate whether they were health professionals. Three systems requested information on the name of the prescribing physician. Reporters were required to record details about the reporting institution, including its name, address and telephone number.

Discussion

Our objective was to synthesize concepts and data elements used within existing ADE reporting systems. In contrast to previous publications that reviewed subsets of national pharmacovigilance systems [12, 16, 21, 30–33], our study is the first to systematically synthesize data elements used to report ADEs internationally. Most systems we reviewed were used by national drug regulators, and hosted on the websites of pharmacovigilance organizations. We found a high degree of variability and a lack of standardization between systems. Numerous terms, phrases and questions were used to request data on the same or similar variables, and definitions were not standardized. For example, the terms 'adverse event', 'adverse reaction', 'incident' and 'medication-related problem' were all used interchangeably, without explicit definitions to ensure consistency of use. Lack of standardization between systems is likely to limit the comparability of the data being generated using different systems, and may undermine efforts to pool and analyse data across cohorts for improved signal detection of rare and emerging signals.

Within the systems reviewed, we frequently encountered the use of composite data elements. In contrast to single data elements targeting one concept (e.g., 'dose'), the use of composite elements contained multiple elements (e.g., 'dose, frequency and route used'), making it difficult for reporters to prioritize constructs, and possibly more likely to omit critical information. This may contribute to errors and higher non-

response rates in reporting [34, 35]. In addition, composite data make it difficult to parse out information on individual data elements, limiting the ability to aggregate and analyse data across systems. In many instances, reporting systems collected data on the same concept (e.g., dechallenge), but used incompatible dropdown menus or tick-box response options, reflecting broader or narrower meanings. For example, in one setting the term 'adverse drug reaction' included drug–drug interactions, but in another, it excluded it. Consequently, when data are combined for analysis, and their context or system-specific data field label is lost, data may be inappropriately aggregated and could be misinterpreted.

We found important variables to be missing in many systems. For example, half of the reviewed systems did not contain data elements to document ADE severity. Yet, research undertaken by our group in parallel with this study indicates that reporters' uncertainty about which level of ADE severity to report (e.g., all ADEs *vs*. only severe events) may be a deterrent to reporting [36]. Thus, it is possible that omission of crucial data elements within some systems impacts reporting rates and the types of events recorded.

Good quality data can be defined as the characteristics that enable data to fulfil its intended use, e.g. accuracy, relevance, accessibility and interpretability [37]. Applied to ADE reporting, the intended use of data is to generate safety signals for monitoring and research activities to enable estimates of risks and benefits. Failure to standardize data fields across systems can undermine data quality when data are aggregated for analysis. Using terms such as 'adverse event', 'adverse reaction' and 'medication-related problem' as semantically equivalent, although they may have different meanings, can undermine our efforts to understand the epidemiology of ADEs. For example, 'adverse reaction' may include events varying in severity while 'adverse event' may capture only events severe enough to require hospitalization. Therefore, threats to data quality include lack of standardization of data fields and their response options, across systems from which data are aggregated, inconsistent terminology, incomplete reports, coding errors in systems using coders to translate free-text reports into categorical data, and underreporting [37–39]. Unfortunately, we found no quality assessment scales that assess these attributes, and no studies which addressed data accuracy or completeness, or reporting rates within spontaneous ADE reporting systems**.** Instead, existing scales focused on the presence or absence of individual fields used to collect data, but not their quality [20–22]. None of the systems reported use of quality assurance procedures to identify and correct errors at the development phase of databases, or on an ongoing basis [40, 41]. Applicable quality dimensions to define, measure and manage data quality, and improve the reliability and validity have yet to be implemented [42]. We believe that content validity of the data being generated within each system must be understood to ensure that the resulting data accurately capture what system developers intended to collect, to ensure their correct interpretation and appropriate use. However, content validity can only be assured if systems administrators understand how the reporters at the front-line who diagnose and report ADEs will interpret and utilize data fields within the system. These fundamental questions can be answered in prospective evaluation studies, and may help to elucidate whether, how and what ADE data should be used. Schuurman and Balka have suggested that 'demand for data is outstripping our ability to ensure data integrity, and sometimes analysis is performed on data that are not appropriate for the purposes they are used for' [43]. Such data errors can negate the sensitivity and specificity of the resulting datasets used to inform drug benefit/risk profiles and hence drug alerts, warnings and recalls.

Our study is not without limitations. While our search was exhaustive, multiple terms have been used in the past to describe and index ADE reporting systems. It is possible that the terms we used missed relevant systems. Existing quality scales used to rate ADE reporting systems are limited in scope, and fail to assess the crucial elements of data quality that should impact on their use. Instead, quality scales emphasized the presence or absence of data elements [20–22]. Finally, underreporting of ADEs remains an unresolved problem [44], and undermines our ability to generate robust frequency estimates and comparisons of ADE rates [23]. We were unable to explore whether system factors such as the use of mandatory fields, or the structure of reporting forms influenced reporting frequency.

Conclusion

We found a large degree of variability between ADE reporting systems. Lack of standardization between systems likely undermines the comparability of the ADE data being generated, and limits meaningful data aggregation across cohorts. In light of the small portion of ADEs that are documented internationally, we were particularly interested in identifying means through which reporting could be integrated into clinical care and generate a report that would be meaningful for drug regulators. As we conducted analysis of all the fields present in forms and systems used to gather information about ADEs, we were struck by the extent to which data sought on forms often were present to support regulatory rather than clinical care needs. Attempts to capture data required for regulatory purposes (e.g., the lot number of a drug) often served as deterrents to clinicians.

Future research should investigate the use of specific data fields and data dictionaries for ADE reporting, and evaluate their impact on data quality, completeness, accuracy and reporting rates, while keeping in mind that these factors may be influenced by work organization (e.g., poor access to computers or forms, multiple conflicting demands), and information technology system design. The results of these studies should inform the development and implementation of standardized ADE reporting systems internationally. Failure to address these issues will undermine drug safety monitoring and research.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and have stated that they have no conflicts of interest.

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Appendix S1 Search strategies for adverse drug event (ADE) reporting systems

Appendix S2 Combined WHO 'Minimum Recommended Dataset' for ADE reporting and the assessment criteria for spontaneous ADR reporting forms developed by Bandeker for quality assessment of reporting systems used for quality assessment data extraction

Appendix S3 Characteristics of publicly funded reporting systems

Appendix S4 Characteristics of privately funded reporting systems