CHAPTER 7

Detecting Medication Errors and Adverse Drug Events: A Review of Current Methodologies

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Abstract: To establish the scope of harm related to medications, and thus design harm-reduction measures, healthcare organizations are required to measure medication safety events. This chapter will investigate methodologies for detecting adverse drug events and medication errors, analyze what type of events they detect, and discuss their advantages and limitations. We conducted a scoping review, and identified studies that compared at least two detection methods directly. The review resulted in 13 studies, of which ten were conducted in hospitals, and three were from the outpatient setting. Methods used to detect medication safety events were: incident reporting, record review, computerized surveillance, direct observation, and interviews. The detection rate of adverse drug events and medication errors varied substantially depending on the method. Incident reporting detected small numbers of events, but detected events that were not identified by other methods. Record review detected more adverse drug events than incident reporting, but missed whole classes of events, such as medication administration errors and omissions. Direct observation detected most medication errors. Computerized surveillance has promising detection abilities and can be less resource and time-intensive compared with record review, after the initial implementation. Small numbers of events were detected using any one method alone, that is, none of the methods can serve as a gold standard, and each method described has its place in monitoring medication safety. The literature supports a combination of methods to be used to detect adverse drug events and medication errors. The 10 studies in this scoping review that are from hospitals, are also described and discussed in the PhD thesis of the first author(Mulac, 2022). The scoping review, however, resulted in a low number of studies (n = 3) from the outpatient setting, which highlights the research and

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knowledge gaps of detecting methods for adverse drug events in municipal health and care services.

Keywords: adverse drug events, incident reporting, medication errors, medication safety, record review

Since the turn of the millennium, worldwide medication safety initiatives have been dedicated to reducing medication errors and adverse drug events (ADEs) in healthcare (Bates & Singh, 2018). WHO's campaign established international goals for reducing medication-related harm (Donaldson et al., 2017). On the local level, technology-based interventions such as electronic health records, automated dispensing cabinets or barcode medication administration were introduced (Mulac, Mathiesen, et al., 2021). To establish the scope of the problem, and demonstrate reductions in errors and adverse event rates, organizations need reliable detection tools. Yet, there is enormous variation in how, when and even if organizations and health professionals count adverse events and measure medication-related harm (Institute of Medicine 2007).

We argue that health professionals and health authorities need a better overview of the evidence and the vast number of methods for detecting ADEs. Our review will provide information about available approaches for detecting ADEs across levels of healthcare, and a discussion of the pros and cons of each approach based on the available evidence and research literature.

Background

A variety of tools and methods are utilized to measure the extent of ADEs. Depending on what is being measured, some methods are better suited for certain types of events than others. For example, some methods detect events regardless of harm, while others detect only harmful events – ADEs (Institute of Medicine 2007). Different approaches are needed to detect errors in research versus clinical practice. Different methods, or a variation of the same method, are utilized in inpatient versus outpatient care (Hanlon et al., 2001).

Overview of Detection Methods

This chapter builds on a literature review conducted in the PhD thesis of the first author. Parts of the text below (including Figure 1, parts of Table 1, and Table 2) are also included in the PhD thesis by the first author, which was published in April 2022 at the University of Oslo (Mulac, 2022). The thesis covers inpatient setting only and not findings from the municipality setting.

Methods used to detect medication safety events can be grouped into five categories: incident reporting, direct observation, record review, computerized surveillance, and interviews.

Incident reporting is frequently adopted by organizations to detect events recognized by health professionals. Analysis of events might identify system flaws. However, incident reporting systems alone cannot be used to measure incidence. They are simply a reflection of the safety culture in a given organization. High reporting rates may indicate an organization devoted to reporting and preventing errors and ADEs, rather than reflecting a truly high ADE rate (Larson & Saine, 2013). Contrarily, health professionals might not report errors if they are afraid of repercussions, hence low reporting rates may indicate an organization with an unhealthy safety culture or one that does not recognize the value of reporting in terms of preventing future events. It is estimated that only 5%–10% of all incidents are detected through incident reporting (Dabba et al., 2019). The limitations of incident reporting as the sole method of event detection are well documented (Erstad et al., 2012; Mulac et al., 2020). Incident reports are regularly collected within healthcare organizations in the Nordic countries, and also by national reporting systems in Denmark and Finland. The Finnish national incident reporting system, HaiPRo, is used in over 200 social service and healthcare organizations (Kinnunen-Luovi et al., 2014). The Danish Patient Safety Database is an incident reporting system that collects reports on adverse events from healthcare professionals in primary healthcare and hospitals, and also allows patients to report incidents (Christiansen et al., 2021). The Norwegian Incident Reporting System was established in 2012, however it was closed down in 2017 (Mulac et al., 2020). Incident reports are still reported on a local or regional level in Norwegian hospitals.

Direct observation of medication administration as a prospective method can detect the greatest numbers of medication errors. The method usually involves observation of medication administration by trained health professionals, frequently nurses and pharmacists, who compare administered medications to the prescribed medications. The additional value of this method is that it often highlights the contextual factors relating to a medication error, and reveals the causes of errors not discovered by other detection methods. Considering that observing over a long time is costly, observation is only recommended for in-depth studies or periodical monitoring. Also, the presence of observers is known to influence the health professionals being observed and consequently changes their behavior, something known as the Hawthorne effect (McCambridge et al., 2014).

Record review can be either untargeted (manual) or targeted. Manual record review involves a review of patients' complete health records, and thus is suitable for periodical review of a specific unit or institution. Targeted record review is less time consuming as it applies specific triggers/rules, such as: diagnostic codes (ICD-9 codes); symptoms (nausea, pain, new rash, vomiting); prescription of antidotes (naloxone, vitamin K); or triggers of laboratory abnormalities occurring in the presence of certain drugs (INR ≥6, serum glucose < 2.8 mmol/l) to identify records for review. Utilizing such triggers is considered to be an effective ADE detection method when applied as a two-stage review (Bates, Cullen, et al., 1995; Classen et al., 2011), such as the Harvard Medical Practice Study and the Global Trigger Tool, both of which involve a set of triggers to identify potential events (Hanskamp-Sebregts et al., 2016). The Harvard Medical Practice Study involves an extensive full chart review, and a number of questions in addition to triggers. Determining preventability is a standard, with no time limit per case. The Global Trigger Tool applies a recommended time limit per review (usually 20 minutes) for randomly selected records creating a sampling method that produces small samples over time, for example, 10 records from one population or institution, two times a month. It is not aimed at detecting every adverse event. The Global Trigger Tool is a promising, structured method for estimating and monitoring adverse event rates over time, and can be applied to the screening

of large populations, for example, national screening of all hospitals. In the first stage of this method, a health professional (e.g., a nurse) screens health records using specific criteria. In the second stage a physician validates the potential events identified in the first stage to confirm the adverse event. The Global Trigger Tool is more feasible and less time consuming than the Harvard Medical Practice Study, since it originally did not determine the preventability of the event (Griffin & Resar), although this has also been included in several studies (Hwang et al., 2014; Kennerly et al., 2013; Schildmeijer et al., 2013). By focusing on triggers within methods, the Global Trigger Tool has detected ten times more events than other ADE detection methods (Classen et al., 2011). Since its development in 2003, the Global Trigger Tool has expanded from small scale studies for quality improvement within organizations, to being used by hundreds of hospitals worldwide (Hanskamp-Sebregts et al., 2016; Hibbert et al., 2017). In the Nordic countries it has been on the rise in the last decade for monitoring adverse event rates (Doupi et al., 2015). Currently there are also initiatives to measure adverse drug events and harm using the Global Trigger tool in nursing homes in Norway (von Plessen et al., 2012).

Chart review using the trigger tool was developed as a manual method, intended for application by clinicians who review health records. With the increased introduction of electronic medical records and electronic prescribing, there may be even more effective ways to detect ADEs.

Computerized surveillance and automation provide prospective, active monitoring, and improve the efficiency of ADE detection, while decreasing the time and personnel resources. This method can monitor events in real time, and potentially limit patient harm through concurrent interventions. The implementation of computerized surveillance requires technological sophistication and an integration of comprehensive information sources from laboratories, radiology, microbiology, and pharmacies. ADE detection using computerized surveillance relies on numeric or coded medical data, including various clinical triggers, such as medication discontinuation, abnormal laboratory values, or transfer to an intensive care unit. Cases flagged by computerized surveillance are validated by dedicated surveillance personnel. The method can potentially detect greater numbers of ADEs if expanded by analyzing physician narratives or notes

using computer-based free-text searching (Bates et al., 2003). This additional adaptation facilitates detecting ADEs that would not be detected by triggers, for example, "drowsiness from morphine" (Stockwell & Kane-Gill, 2010). Text word searches add further challenges in identifying key phrases, and require adaptation to local synonyms, abbreviations, or language. These challenges can be overcome through natural language processing, pattern matching, and the development of algorithms through machine learning (Melton & Hripcsak, 2005). Additionally, computerized surveillance requires maintenance to increase the sensitivity of the rules to changing medical practice, such as the introduction of new medications or new indications for existing medications.

Strengthening the partnership of patients, their relatives, and health professionals is an important approach for promoting medication safety and identifying medication-related harm (Donaldson et al., 2017). Thus interviewing patients for symptoms related to medications has also been used in identifying potential ADEs (Erstad et al., 2012). Likewise, health professionals can be interviewed to see whether any incidents have occurred. This method can, for example, be performed by trained health staff during nursing shift changes (Institute of Medicine 2007).

Several studies have evaluated the ability of different methods to detect ADEs, usually involving chart review, incident reporting, and observation (Erstad et al., 2012; Hanskamp-Sebregts et al., 2016). With the digitalization of healthcare services, the focus has shifted from measuring event rates using manual methods to automated computerized surveillance, and methods that encompass contextual and human factors in the error environment (Govindan et al., 2010; Mulac, Mathiesen, et al., 2021; Rochefort et al., 2015b). Previous studies have focused on providing evidence for one specific method, such as a medical record review (Hanskamp-Sebregts et al., 2016), or compared several specific methods in order to address their differences in detecting ADEs (Rochefort et al., 2015a). Most studies reviewing methods of ADE detection originate within a hospital setting, yet medication-related harm also occurs in primary healthcare and across municipal healthcare institutions. The literature lacks a synthesis of available methods, which could guide researchers and health professionals in choosing the most appropriate

method, depending on the purpose for measuring and the setting. Our review addresses this gap.

This scoping review will provide information about available approaches for detecting ADEs across levels of care, and categorize the available evidence for each method.

Aim

The aim of this chapter is to examine methodologies for detecting adverse drug events and medication errors, analyze what type of events they detect, and discuss their advantages and limitations.

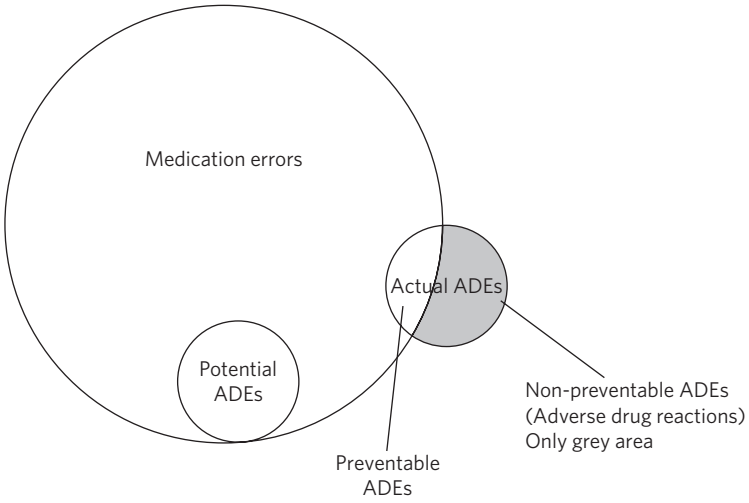
Methods

Terminology and Definitions

Box 1 Definitions of an adverse drug event and a medication error
An adverse drug event is defined as any harm caused by medication use (Nebeker et al., 2004). Medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm (NCC MERP, 2001).

In this review, we use the terms "incident", "event", "medication error" and "adverse drug event" (ADE) to describe medication safety events. These events vary in their preventability and harm. ADEs can be potential, meaning an event that has the potential to cause patient harm. Actual ADEs have reached the patient and caused some grade of harm (Bates, Boyle, et al., 1995). All potential ADEs are preventable, while actual ADEs can be preventable or non-preventable. Actual ADEs were considered preventable if they resulted from a medication error (e.g., liver damage caused by administering the wrong dose of paracetamol), or non-preventable if they did not result from a medication error (and were thus attributable to adverse drug reactions e.g., harm occurred at doses normally used in patients).

The correlation between medication errors and adverse drug events is somewhat tricky to separate, but important to distinguish. Figure 1 illustrates the terms "medication errors", "actual ADEs" (preventable/non-preventable) and "potential ADEs". Essentially, medication error does not necessarily imply harm. Only a small number of medication errors are actual ADEs, while all potential ADEs are medication errors. Which also means that, fortunately, only a small number of medication errors reach the patient and cause some grade of harm.



Figur 1. The Relationship Between Medication Errors and Adverse Drug Events. Adapted from Bates (1995). ADEs- adverse drug events. Duplicated from Mulac (2022)

Research Question, Literature Search and Study Selection

We conducted a scoping review (Arksey & O'Malley, 2005; Levac et al., 2010) to examine methodologies for detecting ADEs and medication errors, analyze what type of events they detect, and evaluate their efficacy. To answer the research question, we identified keywords and MeSH terms describing the fundamental concepts of medication errors, adverse drug events, and detection. We conducted the search in PubMed and EMBASE and included keywords: "adverse drug events", "medication errors", "medication safety" combined with operator OR. The above terms

were searched in combination with keywords: "detection", "measuring", "surveillance" with operator AND. One reviewer screened all titles and abstracts. Full text articles were retrieved and reviewed independently by two reviewers. Study inclusion was discussed to reach consensus. We manually searched the references of included studies for additional articles of relevance.

We included articles from inpatient and outpatient settings published until October 2021. A key inclusion criterion of studies was that they had used and compared at least two methods. The search was restricted to studies published in English. Studies that evaluated event detection of one single trigger criterion, "disease", "drug", "drug class" or "route of administration" were not included.

Where possible we extracted the positive predictive value (PPV) of the methods used. PPV is applied with studies involving triggers to express the ability of methods to detect adverse events, and is calculated by dividing the number of true positive triggers related to confirming AEs by the total number of positive triggers.

Results

Study Characteristics

The literature search identified 172 citations, which were reviewed for title and abstract. Of these we retrieved and reviewed 53 articles in full. We excluded 42 articles because they did not contain sufficient information regarding ADEs, did not compare at least two detecting methods, or because they involved individual triggers or medications. We additionally identified two articles from manually searching the references of included articles. Our analysis of 13 articles published from 1998 to 2018 is summarized in Table 1. Three studies (Field et al., 2004; Olsen et al., 2007; Weissman et al., 2008) involved outpatients, while the remaining studies involved inpatients. Two studies focused on pediatric patients (Ferranti et al., 2008; Maaskant et al., 2018), and one study focused on older persons (Field et al., 2004). We categorized the articles based on the types of methods used, types of medication safety events that were detected, and the efficacy of methods to detect events.

Table 1. Characteristics of the Reviewed Studies

Reference	Study design, setting and population	Event type detected	Results
(Ferranti et al., 2008)	Prospective over 14 months, pediatric inpatients of one hospital, 4711 patients	ADEs, medication errors	Computerized surveillance detected 78 ADEs, Voluntary reporting detected 93 ADEs,
(Field et al., 2004)	Cohort study over 12 months for older persons in the ambulatory setting, 31,757 per month	ADEs, preventable ADEs	In total 1,523 (100%) ADE identified of which 421 (28%) preventable ADEs. Per method: Provider reports: 11% of ADEs and 6% of preventable ADEs Hospitalizations: 11% of ADEs and 14% of preventable ADEs Emergency department visits: 13% of ADEs and 17% of preventable ADEs Computer-generated signals: 31% of ADEs and 37% of preventable ADEs Electronic notes: 39% of ADEs and 29% of preventable ADEs Incident reports: 4% of ADEs and 2% of preventable ADEs.
(Flynn et al., 2002)	Retrospective and prospective, 85,197 doses from 36 hospitals	Medication errors	2556 doses were compared for three methods: 457 medication errors detected (100%): Direct observation: 300 (66%) medication errors Chart review: 17 (3,7%) medication errors Incident reporting: 1 (0,2%) medication error
(Franklin et al., 2009)	Prospective and retrospective, surgical ward of one hospital during two 4-week periods, 207	Medication (prescribing) errors	In total: 135 (100%) prescribing errors detected Ward pharmacist alone: 48 (35%) prescribing errors Record review: 86 (69%) prescribing errors Ward pharmacist and record review: 7 (5%) prescribing errors Spontaneous reporting: 1 (1%) prescribing errors Trigger tool: No errors detected
(Franklin et al., 2010)	Retrospective pilot study, surgical ward of one hospital for two 4-week periods, 207 patients	ADEs, ADRs, medication errors	Trigger tool: 7 ADEs detected, 5 non-preventable ADEs (ADRs) and 2 medication errors Health record review: 5 medication errors

(Jha et al., 1998)	Prospective cohort, 21,964 patient days on 9 medical and surgical wards for 8 months	ADEs, preventable ADEs	In total: 617 ADEs and 86 potential ADEs detected Computer-monitor strategy: 2 potential ADEs; 275 ADEs of which 70 preventable Chart review: 23 potential ADEs; 398 ADEs of which 109 preventable Voluntary reporting (stimulated): 61 potential ADEs; 23 ADEs of which 9 preventable ADEs
(Kilbridge et al., 2006)	Prospective cohort over 8 months at two hospitals (one university and one community hospital) 33,206 patients 146,416 patient days	ADEs	Automated surveillance: University hospital: 520 ADEs detected Community hospital: 283 ADEs detected Voluntary reporting: University hospital: 144 ADEs detected Community hospital: 23 ADEs detected
(Maaskant et al., 2018)	Cross-sectional study, 369 patients, 4 pediatric wards at one hospital for 2 months	Medication errors, harmful medication errors (ADEs)	Multifaceted method: 242 medication errors detected, of which 33 harmful medication errors (ADEs) Record review: 27 harmful medication errors (ADEs) Incident reports: 5 harmful medication errors (ADEs) Direct observations and pharmacy logs: No ADEs detected Trigger tool: No harmful medication errors (ADEs) detected When trigger tool was modified (added pain, nausea/vomiting symptoms) 19 ADEs were detected.
(O'Leary et al., 2013)	Retrospective, 250 randomly selected patients	AEs, ADEs	In total: 66 (100%) ADEs detected Traditional trigger tool: 44 (67%) ADEs detected Enterprise data warehouse screening: 46 (70%) ADES detected
(Olsen et al., 2007)	Prospective, 288 patients discharged from one hospital	AEs, ADEs, medication errors	Active pharmacist surveillance: 30 medication errors Record review: 14 medication errors Incident reporting: No medication errors detected
(Tinoco et al., 2011)	Retrospective, 2137 patient admissions, surgical services of one hospital for 14 months	AEs, ADEs	In total: 195 ADEs (100%) Computerized surveillance: 102 ADEs detected (52%) Manual chart review: 96 ADEs detected (51%)

(*Continued*)

Table 1. (Continued)

Reference	Study design, setting and population	Event type detected	Results
(Weissman et al., 2008)	Random sample survey, 988 patients discharged from 16 hospitals	AEs, ADEs	Medical records review: 32 ADEs detected Patient interview: 135 ADEs detected
(Yun et al., 2012)	Retrospective, 30 wards, one hospital, for 14 moths	ADEs	In total: 1539 ADEs Spontaneous reporting: 1055 (66%) ADEs detected Ward rounds with chart review: 309 (20%) ADEs detected Clinical data repository: 229(14%) ADEs detected

AE = adverse event, ADE = adverse drug event, ADR = adverse drug reaction Built on Table 1 in Mulac (2022).

Method Characteristics

All studies have directly compared at least two methods. Ten studies used incident reports to measure the baseline. Incident reporting was voluntary spontaneous reporting within institutions for the majority of studies. One study used stimulated, confidential reporting (Jha et al., 1998) whereby the nursing and pharmacy staff were asked about possible events to report. The majority of studies used record reviews (n = 11), which involved a non-targeted and/or targeted review that utilizes triggers. The included studies varied considerably in the information sources used and the type and number of triggers. Computerized surveillance (i.e., automated detection method) was used in five studies (Ferranti et al., 2008; Field et al., 2004; Jha et al., 1998; Kilbridge et al., 2006; O'Leary et al., 2013). Using targeted triggers was common for all computerized detection methods, however the application of the triggers and the data sources used varied greatly. Two studies involved prospective pharmacist surveillance of prescription records (Franklin et al., 2009; Olsen et al., 2007), and two studies involved direct observation (Flynn et al., 2002; Maaskant et al., 2018).

ADEs and/or Medication Errors Detected

Some studies distinguished between preventable and non-preventable ADEs (Ferranti et al., 2008; Field et al., 2004; Franklin et al., 2010; Jha

et al., 1998; Maaskant et al., 2018; Olsen et al., 2007). Four studies detected adverse events in general and detected ADEs as a subgroup within these (O'Leary et al., 2013; Olsen et al., 2007; Tinoco et al., 2011; Weissman et al., 2008). Two studies detected medication errors alone (Flynn et al., 2002; Franklin et al., 2009).

Efficiency of Detection Methods

Targeted record reviews detected more ADEs than incident reporting (Jha et al., 1998; Olsen et al., 2007). However, this was not the case for all populations or event types. In a multicenter study on medication errors, targeted record review detected 3,7%, while direct observation detected 66% of medication errors (Flynn et al., 2002). In another study on pediatric patients, 33 harmful medication errors were detected as a baseline by a multifaceted method, while the trigger tool did not detect any harmful medication errors (ADEs) (Maaskant et al., 2018). When the trigger tool was extended for two additional symptoms (pain and nausea/vomiting), the tool detected 19 harmful medication errors. It is likely that the trigger tool was not properly adapted to the specific setting and pediatric population. In another study that evaluated prescribing errors in a surgical hospital ward, the trigger tool method detected only 2% of prescribing errors, while manual record review detected 83%, and pharmacist surveillance detected 24% of prescribing errors (Franklin et al., 2009). Targeted record review alone is, according to Franklin et al., not the method of choice to measure medication safety during prescribing (Franklin et al., 2009). Interviewing patients after discharge detected four times more ADEs than record review, and more serious events that were not documented in the medical record (Weissman et al., 2008). Computerized surveillance detected ADEs at a rate 3.6 times greater than incident reporting at a university hospital, and 12.3 times greater at a community hospital (Kilbridge et al., 2006). Similar results were found in the study by Jha et al., that detected ADEs with computerized strategies at a rate 12 times higher than incident reporting (Jha et al., 1998). When compared with record review, computerized surveillance detected similar numbers of ADEs

(O'Leary et al., 2013; Tinoco et al., 2011). In a study focusing on medication errors in pediatric patients, Ferranti et al. found that computerized surveillance did not detect drug omissions, meaning the detection was entirely reliant on incident reporting to detect this type of events (Ferranti et al., 2008).

There was generally a poor overlap between events detected with more than one source. Although incident reporting detected small numbers of events, these were not detected by other methods (Maaskant et al., 2018; Olsen et al., 2007). This applies for other methods as well. Tinoco et al. found that overlap between events detected by record review and computerized surveillance was 3% (Tinoco et al., 2011). Field et al. found that only 5% of ADEs were detected with more than one source when comparing multiple detection methods (Field et al., 2004).

PPV was calculated in three studies that used signals generating ways to establish the cost and productivity of the methods for detecting ADEs. In one study that evaluated ADEs in older patients in the ambulatory setting, the PPV for computer-generated signals was 7%, while it was highest for provider reports (54%) (Field et al., 2004). In the same study nearly three-fourths of the computer-generated signals were eliminated after prompting a record review. The overall PPV was low in a study that evaluated harm from medication errors, and the signals generated with a trigger tool led to reviewing the charts of 61% of patients while ADEs were identified in 3.4% of patients (Franklin et al., 2010).

There were substantial differences in time and resources required for utilizing the different methods. Jha et al. evaluated the time needed to conduct the different methods. Chart review was most time consuming requiring 55 person-hours per week, computer strategy required 11 person-hours per week, and voluntary reporting required five person-hours per week (Jha et al., 1998). Record review was also found to be resource intensive in other studies (Flynn et al., 2002; Franklin et al., 2010; Weissman et al., 2008). The main advantages and limitations of the reviewed methods are presented in Table 2.

Table 2. Advantages and Limitations of Detection Methods for Adverse Drug Events (ADEs) and Medication Errors. Duplicated from Mulac (2022)

Method	Advantages	Limitations
Incident reporting (voluntary and stimulated)	Detect events not detected by other methods Require minimal training of health professionals to report an event Identifies system failures, potential ADEs (non-harmful medication errors), omissions, medication administration errors that are not detected by trigger tools (targeted record review) Can identify ADE trends with sufficient data Stimulated reporting is likely to detect more events than voluntary	Detect small number of ADEs Underreporting Reporting bias: Healthcare providers report the most severe events Health professionals must be aware of an event to report Higher reporting rates do not indicate higher rate of ADEs, but a culture devoted to reporting
Record review: manual (untargeted) or triggers (targeted)	Utilizes readily available data Well adopted and commonly used Targeted review less time-consuming than manual review Detects more ADEs than incident reporting Effective to detect ADEs when applied as a two-stage review	Dependent on training and experience of reviewers Interrater reliability issues between reviewers Time and resource intensive: Best suited for periodical review Involve reviewing patients' complete written or electronic records Not effective in detecting latent errors, non-harmful medication errors Dependent on the rules/triggers to be adjusted to specific setting Many false positive signals Sensitivity and specificity of the trigger tools for ADE detection dependent on how the rules are applied and used in the given setting
Automated monitoring (computerized)	Can monitor ADEs in real time and thus potentially prevent harm Integrates multiple data sources Inexpensive after initial implementation, but needs maintenance to increase trigger sensitivity Identifies events associated with known areas of risk (high-risk medications) and harmful events	Applies for setting with full electronic records Costly to implement, requires software Integrating multiple data sources takes time (years) Vulnerable to programming errors Not effective in detecting latent errors, non-harmful

(*Continued*)

Table 2. (Continued)

Method	Advantages	Limitations
Direct observation	Prospective method Preferred approach for detection of medication errors and potential ADEs Provides data otherwise unavailable such as near misses, latent failures, contextual and human factors of the error environment Provides clues to error causes	Not suitable for detection of ADEs Require experience and training of observers (data collectors) in observation technique and appropriate medication knowledge Costly, recommended for periodical monitoring Observers' presence may affect the observed (Hawthorne effect)
Interviews (Patients, healthcare professionals)	Detect more incidents than record review or incident reporting Could be combined with discharge/medication review/reconciliation to optimize resource and time use Unique perspective (interviewing patients)	Only patients that are conscious and healthy enough can participate Time from the ADE occurred to interview affects detect rates, especially in discharged patients

Discussion

A comparison of different methods reveals that they vary in the number and type of events they can detect. This is best illustrated in a study performed in 36 hospitals and skilled-nursing facilities that compared three methods for medication error detection, and found that direct observation was more efficient and accurate than reviewing charts and incident reports. It is a well-established fact that chart reviews and incident reporting underestimate the true rates of medication errors (Meyer-Massetti et al., 2011; Westbrook et al., 2015), while the method that detects the highest number of medication errors is direct observation (Barker & Allan, 1995). Nevertheless, observation was least effective for detecting ADEs (Maaskant et al., 2018) when compared to other methods.

While known as a low-cost method that provides rich data within or across healthcare systems or nationwide, incident reporting detected the least number of ADEs, and is thus not suited to establish ADE rates.

Chart review has been the most effective method for ADE detection in the majority of studies, however, this requires a trained and experienced reviewer, and is resource intensive. The role of computerized surveillance in detecting ADEs is important, since it integrates comprehensive

information sources, and it can identify ADEs missed by clinicians more quickly and inexpensively than other methods. More importantly, there was a poor overlap between ADEs detected with record reviews, computerized surveillance, and incident reporting. The results of our literature review are consistent with prior studies, and confirm the need for complementary detection methods as a standard for measuring ADEs and medication errors.

Why Do Different Methods Detect Different Events?

Incident reporting is a valuable low-cost monitoring tool that detects all types of events, but in very small numbers. The incidents that were, however, detected with incident reporting overlapped minimally with ADEs detected by other methods, which argues the case for utilizing this method to detect additional events. This specifically concerns potential ADEs, and non-harmful medication administration errors that are not routinely detected through record review (Jha et al., 1998).Manual record review is more effective in detecting ADEs than incident reporting, but is too costly to be used routinely. Targeted chart review detects significantly more events than incident reporting, but has, for instance, not detected whole classes of incidents, for example, medication administration errors, prescribing errors, and omissions (Franklin et al., 2009; Franklin et al., 2010; Maaskant et al., 2018). The computerized method detected ADEs overlooked by a targeted chart review and incident reporting. The potential of the computerized method has not been fully exploited, and studies suggest that computerized surveillance would detect more events if integrated with information from physician notes (Tinoco et al., 2011). One study (Nwulu et al., 2013) reviewing triggers involving INR values over 6, found that the average time to intervention (for example a vitamin K-administration, a blood transfusion or both) after a trigger was generated was 6 hours. Through "real time" ADE detection the ability of the computerized method to potentially prevent harm must be recognized, and it may have a role in reducing the time to critical intervention. We believe that the capability of computerized surveillance to limit harm from ADEs should be further exploited.

Detecting ADEs in the Outpatient Setting

Our literature search yielded three outpatient studies: two conducted on discharged patients and one involving outpatients in the ambulatory setting. No studies involving nursing homes or long-term facilities were evaluated in this review, however, evidence from studies on outpatients suggests similar advantages and challenges with incident reporting, manual chart reviews and targeted chart reviews (Field et al., 2004; Hanlon et al., 2001). Studies that have assessed the trigger tools criterion for ADE detection in nursing homes (Boyce et al., 2014) (Handler & Hanlon, 2010; Kapoor et al., 2019) used data sources (laboratory, medication charts, pharmacy orders) similar to those used in studies from inpatient settings. There is less research on ADE detection in this setting, and more specifically, there is limited research on comparing ADE detection rates, using at least two methods, in nursing homes that could provide more information on the efficiency of ADE detection methods in this particular setting (Field et al., 2004; Honigman et al., 2001). The lack of competence and unexperienced staff have been raised as issues associated with medication errors in nursing homes (Bengtsson et al., 2021). Nurses, due to staff shortage, often delegate medication administration tasks to unlicensed staff, who are usually not familiar with the reporting systems and are less prone to reporting mistakes and errors (Leape, 2002). Elderly nursing home residents are more vulnerable to medication errors due to their age-related pharmacological changes and associated polypharmacy. Also, studies have shown that elderly are more frequently subjected to medication errors than other populations (Fialová & Onder, 2009; Mulac, Taxis, et al., 2021). Therefore, we should address the knowledge gaps on detecting and reporting medication errors and ADEs in outpatient settings in future studies.

Strengths

Studies describing computerized surveillance originate from the later 1990s, or even earlier in the USA, while the method has not been introduced on a large scale in European countries. Despite some of these studies having been conducted around 20 years ago (Field et al., 2004; Jha

et al., 1998; Kilbridge et al., 2006), we do not consider them to be outdated in light of todays' technological advances. The implementation of electronic medication administration records is in its infancy stage in the Nordic countries, while this technology was implemented in single frontier hospitals in the USA two decades ago. Therefore, we can value on the experience derived from these early established systems.

Evaluating ADE detection rates in studies comparing at least two methods suggests that ADEs might be more common than previously indicated in studies that used only one method for detecting events (Franklin et al., 2009; Jha et al., 1998).

Limitations

Because of the differences in the type and number of triggers across studies, it is difficult to discuss the exact detection value of the different methods applied to review health records. ADE rates are easier to compare between studies that apply similar triggers, such as comparing studies that have used the broadly recognized Global Trigger Tool (von Plessen et al., 2012). This however also involves challenges, as even this method must be adapted to local settings to increase efficiency and specificity, as well as to changes in medical practice over time (Field et al., 2004).

Box 2 ADEs and Medication Errors: Detection Methods Summary

- Healthcare organizations use different methods to detect adverse drug events: incident reporting, direct observation, record review, computerized surveillance, and interviews.
- The detection rate of adverse drug events and medication errors vary substantially according to the method used.
- The different methods detect different types of events, e.g., trigger tool strategies missed whole classes of events (medication administration errors, prescribing errors, omissions).
- Incident reporting detects only a small number of events.
- There is poor overlap in events detected by more than one method.

Box 2 (*Continued*)

- A complementary multi-method approach is a gold standard in monitoring and detecting adverse drug events.
- Computerized surveillance offers future potential benefits in detecting real time events and following up with concurrent intervention to limit patient harm.
- Research efforts should focus on developing effective adverse drug event and medication error detection methods for outpatient settings, and as well as seamless transitioning between hospitals and nursing homes.

Conclusion

This review of the pros and cons of current ADEs and medication error detection methodologies can assist and inspire stakeholders to choose the most appropriate methods relevant to their local, regional or national setting. We have discussed how the detection methods vary in their detection rates, cost, time, and resources required. We have exemplified the event types the different methods detect, the ability to detect preventable events, and their ability to limit harm.The low number of studies from the outpatient setting highlights the research and knowledge gaps of detecting methods for adverse drug events in municipal health and care services.

Few medication errors and adverse events are detected using any one method alone, that means that none of the methods can serve as a gold standard, and each method described has its place in monitoring medication safety. The literature supports a combination of methods to be used to detect the diversity of ADEs and medication errors.

One single method cannot detect and measure all medication errors and adverse events. Our discussion of how the current methodologies can detect and measure medication errors – their advantages and limitations – will hopefully expand the toolbox of stakeholders when they set out to learn from the past, and prevent future adverse drug events and medication errors.

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