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DOCTORAL DISSERTATION

Adverse events in acute hospitals: Methodological aspects and results of a record review in patients with an unplanned transfer to a higher level of care

Doctoral dissertation submitted to obtain the degree of
Doctor of Biomedical Science, to be defended by

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Diepenbeek, 27 maart, 2015

If you want to get somewhere
You have to know where you want to go and how to get there.
Then never, never, never give up!

Norman Vincent Peale

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List of Abbreviations

AAT	Appropriate Antibiotic Therapy
ACHS	Australian Council on Healthcare Standards
ACOVE	Assessing Care Of Vulnerable Elders
ADL	Activities of Daily Life
AE(s)	Adverse Event(s)
ADE(s)	Adverse Drug Event(s)
ADR	Adverse Drug Reaction
ANZCA	Australian New Zealand College of Anaesthetists
APACHE II	Acute Physiology and Chronic Health Evaluation
APR-DRG	All Patient Refined Diagnosis Related Group
APR-DRG v15.0	All Patient Refined Diagnosis Related Group, version 15
ASA	American Society of Anaesthesiologists
ATC	Anatomical Therapeutic Chemical
BEDNURS	Bergen District Nursing Home
B-HDDS	the Belgian Hospital Discharge Dataset
BSI	Bloodstream Infection
CCU	Coronary Care Unit
CD	Considering Disease
CI	Confidence Interval
CMO	Chief Medical Officer
D	Drugs

d.f.	degrees of freedom
DNR	Do Not Resuscitate
DRG	Diagnosis Related Groups
DRP	Drug Related Problems
ED	Emergency Department
EWS	Early Warning (Score) System
EWR	Executive Walk Rounds
FMEA	Failure Mode & Effect Analysis
G	General hospital
GTT	Global Trigger Tool
GW	General Ward
HACCP	Hazard Analysis and Critical Control Point
HAP	Hospital Acquired Pneumonia
HFMEA™	Healthcare Failure Mode & Effect Analysis
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
IAAT	Inappropriate Antibiotic Therapy
ICU	Intensive Care Unit
ID	Independent Disease
iAMS	inpatient Anticoagulation Management System
IHM	In-Hospital Mortality
IHI	Institute of Healthcare Improvement
IHI-GTT	Institute of Healthcare Improvement – Global Trigger Tool

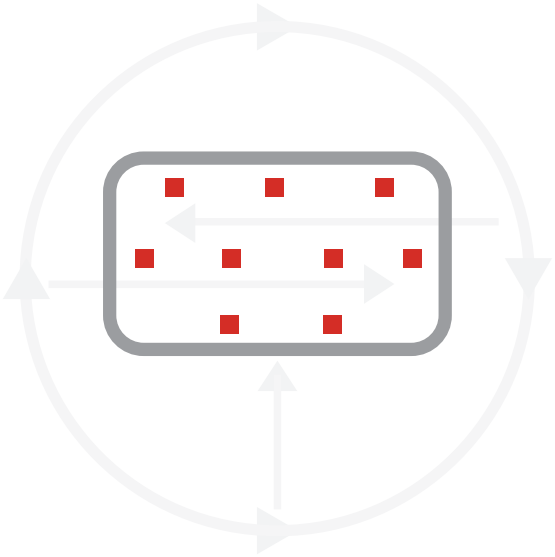
IOM	Institute of Medicine
IQR	Inter-Quartile Range
ISMP	Institute for Safe Medication Practices
LOS	Length Of Stay
LSM	Limburg Sterk Merk
MAI	Medication Appropriateness Index
MDC	Major Diagnostic Category
ME	Medication Error
Me	Median
MEDS	Mortality in Emergency Department Sepsis
MeSH	Medical Subject Headings
MET	Medical Emergency Team
MKG	Minimale Klinische gegevens
MODS	Multiple Organ Dysfunction Scale
MUG	Mobiele Urgentie Groep (Dutch for MET intervention)
N	No
NC	No Comparison
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NH	Nursing Homes
NHS	the English National Health Service
NM	Not Mentioned
NNT	Number Needed to Treat

NS	Not Significant
OR	Operating Room
OR	Odds Ratio
P	Prospective design
P	Prescriptions
pADE	preventable Adverse Drug Event
PIRx	Potentially Inappropriate prescribed medication
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSR	Patient Safety Rounds
R	Retrospective design
RASP	Rationalization of home medication by an Adjusted STOPP list in older Patients
RCA	Root Cause Analysis
ROM	Risk Of Mortality
RQ	Research Question
RR	Risk Ratio
SAB	Staphylococcus Aureus Bacteraemia
SAPS II	Simplified Acute Physiology Score II
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SOI	Severity Of Illness

SPSS	Statistical Package for Social Science
SSC	Surgical Safety Checklist
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
T	Teaching hospital
UIA	Unplanned Intensive care Admission
UK	United Kingdom
USA	United States of America
VAP	Ventilator Associated Pneumonia
Y	Yes
yr	publication year
WHO	World Health Organization

CHAPTER 1

Introduction



Chapter 1: Introduction

This chapter provides an overview of the conceptual framework of the dissertation, its main objectives and the research questions.

CONCEPTUAL FRAMEWORK

Adverse events

Since the historical report 'To err is Human' by the Institute of Medicine (IOM) in 1999 (1), patient safety receives global public attention. This report estimated that in the United States 44,000 to 98,000 hospitalized patients die each year as a result of an 'adverse event'.

Definition of an adverse event

An adverse event (AE) is defined by Wilson et al. (2) as *(1)* an unintended injury or complication, *(2)* which results in disability, death or prolongation of hospital stay, and *(3)* is caused by healthcare management (including omissions) rather than the patient's disease. A similar definition often used is: "an event that results in unintended harm to the patient by an act of commission or omission rather than by the underlying disease or condition of the patient" (3). Hofer et al. (4,5) and Wu et al. (6) emphasize that medical errors may involve commission or omission. This type of harm is frequently called 'healthcare associated injuries', as it is associated with the healthcare structures and processes, rather than with the underlying disease (7). Adverse events can show up as unwanted effects of medications, nosocomial infections, surgical complications, mistakes in diagnosis and treatment, etc. Of all patients admitted to hospitals, 3.7% to 17.7% are

inadvertently harmed by the way their healthcare is delivered (8,9). Jha et al. (10) estimate that there are 421 million hospitalizations in the world annually, and approximately 42.7 million adverse events; they provide evidence that adverse events due to healthcare represent globally a major source of morbidity and mortality. These findings highlight the importance to critically and continuously evaluate the quality and safety of healthcare and express the need to make patient safety a major concern in healthcare worldwide.

Preventability of adverse events

An adverse event results in an undesirable clinical outcome and may involve medical errors (11). However, adverse events do not always involve errors, negligence, or poor quality of care. Not preventable adverse events involve patient harm that could not have been avoided despite sufficient and appropriate procedures without evidence of errors or other problems (12). From the perspective of the legal causation theory, not preventable adverse events are not related with errors (13).

A preventable adverse event, on the other hand, is an adverse event that is due to failure to follow accepted evidence-based practice at an individual or system level. The accepted evidence-based practice is considered to be the 'current' level of expected performance for the average practitioner or system that manages the condition in question (14). Therefore a preventable adverse event leads to patient harm that could have been avoided through improved assessment or alternative actions. Common factors associated with preventable events are inadequate monitoring of patients, inadequate assessment of patients or unnoticed worsening patient conditions and omission of evidence-based diagnosis or therapy in patients without restriction code.

A review on the overall incidence and nature of in-hospital adverse events through record review suggested that the median percentage of adverse events

judged preventable was 43.5% (15). Assessing preventability can provide greater understanding of the causes of adverse events, which can be used to develop actionable improvements to the system conditions that lead to these events. Therefore, adverse events rates might be used as an approach to identify providers and cases for in-depth review of the quality of care (16). The rate of adverse events is an important indicator of patient safety performance. Safe care is one of the critical dimensions of quality of care (17); reducing the incidence of adverse events is a critical component of all efforts to improve the quality of care.

James Reason: the Swiss cheese model of system errors

Reason (18) developed the Swiss cheese model describes that nearly all adverse events involve a combination of two sets of factors:

- *Active failures* are the unsafe acts committed by professionals who are in direct contact with the patient. They take a variety of forms: slips, lapses, fumbles, mistakes, and procedural violations (19).
- *Latent conditions* are the inevitable "resident pathogens" that are present within each system. They arise from decisions made by designers, builders, procedure writers, and top level management. Vincent et al. (20) identified some of the most frequent latent work conditions:

    - Heavy workloads
    - Inadequate knowledge or experience
    - Inadequate supervision
    - A stressful environment
    - Rapid change within an organization
    - Incompatible goals (for example, conflict between finance and clinical need)

- Inadequate systems of communication
- Inadequate maintenance of equipment and buildings

Latent conditions pose the greatest threat to safety in a complex system because they are often unrecognized and have the capacity to result in multiple types of active errors.

Such 'holes' exist in all complex hazardous systems because the decision makers cannot foresee all the possible accident scenarios (21). In this philosophy, errors are seen as consequences rather than causes, based on the assumption that though we cannot change the human condition, we can change the conditions under which humans work (18). The system approach concentrates on the conditions under which individuals work and tries to build barriers to avoid errors or to mitigate their effects (18). High technology systems have many defensive layers, some barriers are engineered (e.g. alarms, physical barriers, automatic shutdowns, etc.), other rely on people, procedures and administrative controls (18). Mostly barriers protect potential victims and assets from local hazards very effectively, but there are always weaknesses.

Reasons Swiss cheese model consists of slices of Swiss cheese with many holes. The slices are the barriers; the active failure and the latent conditions are the holes. Though unlike in real cheese, these holes are continually opening, shutting, and shifting their location. The presence of holes in any one "slice" normally does not cause a bad outcome. Usually, a bad outcome only happens when the holes in many layers momentarily line up to allow a trajectory of accident opportunity-bringing hazards into damaging contact with victims (Figure 1) (18). Because failing is part of human nature and errors are to be expected, even in the best organizations and with the best defenses (18), a systematic approach is important (1) to analyze processes and detect failure modes - active and latent - and adverse events through prospective and retrospective risk management and (2) to convert these occasional setbacks into structural system changes.

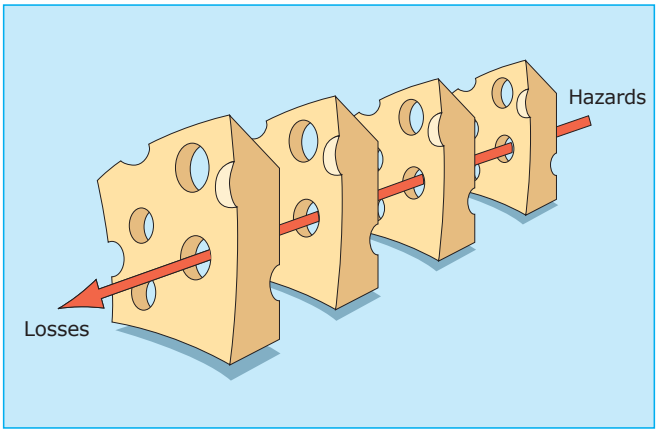


Figure 1 The Swiss cheese model (18)

Types of adverse events

Adverse events can be classified by type, such as adverse events related to

- *Diagnosis:* an adverse event arising from a delayed or wrong diagnosis
- *Procedures:* an adverse event in relation to a non-surgical procedure, such as insertion of a central venous line, nasogastric tube, cardiac catheterization, etc.
- *Surgery:* an adverse event in relation to a surgical procedure, such as a postoperative bleeding
- *Anesthesia:* an adverse event in relation to anesthesia
- *Drug therapy/intravenous fluid therapy (an adverse drug event):* an adverse event related to medication use or intravenous fluid therapy
- *Therapy, excluding drug therapy, surgery or procedural*: an adverse event arising when a correct diagnosis was made, but there was incorrect therapy or a delay in treatment
- *System issue:* an adverse event in relation to problems with hospital processes such as equipment malfunction
- *Other clinical management (including nursing care and allied healthcare)*
- *Others* (e.g. falls)

Adverse drug events

Adverse drug events (ADE) are an important group of adverse events. Adverse drug events are defined by Leape et al. (22) as 'an injury caused by a medication'. The term includes both adverse drug reactions (ADR) and preventable adverse drug events (pADE).

- An adverse drug reaction is an effect which is noxious and unintended, and which occurs at regular doses used in man for prophylaxis, diagnosis or therapy (23). The injury arises from the intrinsic properties of the medicine (24) without any error involved (25). This implies that ADRs are not preventable.
- A preventable adverse drug event can be described as a preventable medication related error with harm (8,22,26,27) the harmful effects can arise from errors at any stage in the medication process: ordering, transcribing, dispending, administering or monitoring (28). The preventable adverse drug events belong to the group of medication errors (ME).

A medication error is defined by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (29) as 'any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use'. These definition implies that a medication error does not necessary lead to an injury, whereas an adverse drug event is an injury caused by a medication (22). Bates et al. described that medication errors are common, although relatively few result in adverse drug events (30). Potential adverse drug events and trivial medication errors are two types of medication errors without injury. However, potential adverse drug events carry a potential for harm in it and need also attention.

Nebeker et al. (31) describe an overlap between adverse drug reactions and medication errors implying that there are preventable and non-preventable adverse drug reactions. In our study we used the conceptual model of Otero and Schmitt (24) which implies that adverse drug events consist of preventable adverse drug events and non-preventable adverse drug reactions (Figure 2).

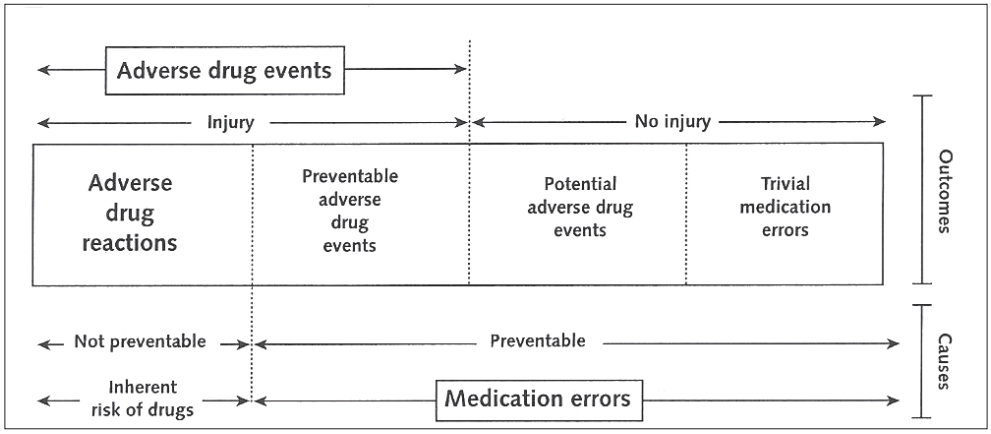


Figure 2 *Relationship between adverse drug events and adverse drug reactions from Otero and Schmitt (24)*

Drug related problems (DRPs) is another term commonly used in pharmaceutical care. It is often defined as: 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes' (32). Another approach for drug related problems is the division into three categories i.e. 'overuse', 'misuse' or 'underuse' of medicines (33). In the literature the scope of drug related problems varies between studies (34–41). Adverse drug reactions are most often included, but also drug therapy failures due to inadequate dose or non-compliance are sometimes considered, as well as inappropriate drug choice, untreated indications and drug use without indication (42). Drug therapy potentially leading to drug related problems is often called 'inappropriate prescribing' and is particularly hazardous (43–45). An important point is the clarification of and the positioning towards the concept of 'medication errors' is important. According to

the definition, a medication error concerns preventable incorrect drug use that may lead to clinical harm (and this can happen during the whole drug process of prescribing, delivering, preparing, administering and follow-up of drug therapy) (29,46,47). The focus lies on the preventable aspect and therefore a preventable drug related problem can be considered as a medication error. There is no doubt that there is no strict separation between the two concepts and in practice it is not clear when a drug related problem becomes a medication error (42).

The impact of adverse events

Adverse events are a significant issue as they can lead to substantial morbidity and mortality, consume considerable staff time, and increase healthcare costs (48). A systematic review on in-hospital adverse events (15). described that 56% of the patients involved (IQR 51.4–62.8%) experienced no or minor disability. However, a significant number of these adverse events resulted in death (5–21%); half of them could have been prevented (49–53). Next to direct harm, adverse events have a psychological and social impact on patients and their relatives and important consequences in terms of cost. Financial costs of adverse events can result from additional treatment, prolonged length of stay or costs of disability. Based on a study in 21 Dutch hospitals, the annual direct medical costs were estimated at a total of 355 million Euros for all in-hospital adverse events and 161 million Euros for preventable adverse events. The cost driver of the direct medical costs was the excess length of stay (including readmissions) (54).

An adverse event can lead to an unexpected need for a higher level of care

An in-hospital patient with an adverse event may require an unexpected higher level of care, such as an admission to intensive care. The intensive care unit

(ICU) is an essential component of most hospitals, providing high density care for critically ill patients. Admission to an intensive care can be planned: e.g. patients undergoing major surgery often require an intensive care admission postoperatively (55). It has long been recognized that admissions to the intensive care unit can be due to complications caused by patient care rather than by patient illness (56–59). This is particularly true when the intensive care admission occurs in an unexpected manner (60). Unplanned Intensive care Admission (UIA) is an existing validated clinical quality indicator (61). Baker et al. (62) defined unplanned intensive care admissions as 'all patients unexpectedly admitted to the intensive care unit from a lower level of care in the hospital'. Used as a screening tool, it can detect patients who possibly suffered from an avoidable iatrogenic complication (63). These unplanned transfers to the intensive care unit prolong hospital stay, place additional pressure on intensive care resources and increase the cost of hospitalization (64). Although intensive care beds comprise less than 10% of hospital beds, intensive care departments consume up to 22% of total hospital costs in the United States (65). A European study measured the direct costs of intensive care days at seven intensive care departments in Germany, Italy, the Netherlands, and the United Kingdom and found that direct costs per intensive care day ranged from €1168 to €2025 (66). But even more importantly, unplanned intensive care admissions have a strong impact on patients and their family. A systematic review of retrospective record review studies concluded that the percentage of surgical and medical adverse events requiring intensive care admission ranged from 1.1% to 37.2% (67). Furthermore, the preventability of the adverse events varied from 17% to 76.5% (67). A prospective study by Garry et al. (68) reported that 77% of these adverse events were considered preventable. Although all adverse events should be a concern for society, adverse events that are preventable and result in serious harm are of particular concern (69).

Adverse events in various healthcare settings

Research and knowledge on patient safety have grown rapidly and induced substantial system improvements in the acute medical healthcare setting (70). In other healthcare settings such as mental health, eldery care and general practice there is less research and evidence on patient safety issues.

In *mental healthcare,* there is a "lack of awareness of the issues as well as a shortage of research and information on the topic" (71). The examination of psychiatric adverse events in a systematic, reportable format with transparency and clarity is in its fledgling stage (72).

For nursing homes, it is only since 2013 that the Flemish nursing homes are required in the context of quality care to register 16 care related indicators (73). However, the population of many countries is ageing and more people receive care in nursing homes every year. The number of beds committed to nursing home care exceeds the number of hospital beds (74). A Dutch study investigated the incidence of three types of adverse events, namely pressure ulcers, urinary tract infections and falls in hospitals and nursing homes: 11% of in-hospital patients and 46% of patients in the nursing home developed at least one of these adverse events (75). Older patients and those with a greater number of health problems have been shown to be at increased risk for preventable adverse events (76,77).

Primary care should also not be exempt from scrutiny for medical errors. It is a potentially high risk environment because of the increasing complexity of care provided in outpatient settings and the risk created by dysfunctional interfaces between inpatient and outpatient (particularly primary) care (78). There is a perception that, even if more errors would occur in primary outpatient care than in hospitals, they are unlikely to result in significant harm to patients (79). Studies of physician recognized errors in primary care suggest, however, that errors occur frequently and that seemingly trivial mistakes can result in severe harm,

particularly for vulnerable patient populations (77,80). In Canada, retrospective record review among home care patients (81), receiving care from healthcare professionals and informal caregivers in home and community setting (82), describe an adverse event rate of 13.2 (± SD 1.6) per 100 home care cases and 32.7% of these were rated as having more than 50% probability of preventability. The most common adverse events were falls and adverse drug events (81).

A preventive approach to patient safety is essential to all patients in all healthcare settings, where the development of often preventable adverse events is a documented safety risk (15,83). This dissertation focuses mainly on acute hospitals.

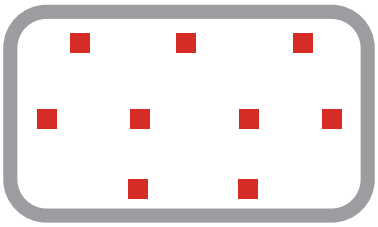


Figure 3 *In-hospital adverse events*

Risk analysis

Because an adverse event can be preventable, healthcare professionals must be aware of the occurrence of adverse events. In order to learn from their experiences they need a reliably measurement system to detect adverse events and to identify the associated (system) factors. Identification and measurement of adverse events is central to patient safety, forming a foundation for accountability, prioritizing problems to work on, generating ideas for safer care, and testing which interventions work (84). Methods can be divided into prospective risk analysis (a priori risk analysis, without the occurrence of an adverse event) or retrospective methods (after an adverse event has occurred).

Prospective risk analysis

The prospective risk analysis is a systematic assessment of the healthcare process with the common purpose to prevent adverse events, and to continuously and prospectively measure, evaluate and improve the organizational and clinical processes in healthcare. A common method, is the Healthcare Failure Mode and Effects Analysis (HFMEA™). Other prospective methods are direct prospective observation of clinical care, including Executive Walk Rounds (EWR) or Patient Safety Rounds (PSR), daily review of records, and interviews or focus groups with caregivers. However, this is not an exhaustive list.

Healthcare Failure Mode and Effects Analysis

This method was developed by the United States Department of Veterans Affairs National Center for Patient Safety with assistance from the Tenet Health System (Dallas). It is a hybrid prospective analysis model that combines concepts from the industry's FMEA model and the US Food and Drug Administration's Hazard Analysis and Critical Control Point tool (HACCP) (166) with tools and definitions from the Department of Veterans Affairs' root cause analysis (RCA) process (166).

FMEA was developed for use by the United States military and is utilized by the National Aeronautics and Space Administration (NASA) to predict and evaluate potential failures and unrecognized hazards and to pro-actively identify steps that could help reduce, eliminate and prevent failure from occurring (167). It is a widely applied error prevention method. The terms and concepts have been adjusted and the HFMEA™ method is therefore appropriate for use in healthcare settings (166).

During a HFMEA™ analysis, a process is evaluated on the occurrence, frequency and severity of failure modes (possible risks) by all involved parties. It provides insight into the safety practices that precipitate adverse events and gives opportunities for the implementation of preventive barriers. The method includes five steps: (1) defining the topic, (2) assembling the HFMEA team, (3) graphically describing the process, (4) conducting a hazard analysis and finally (5) developing actions and outcome measures.

Observation of clinical care

During the observation process an expert observes the process and checks every necessary step. Observational studies on nurses administering of medications in a large number of hospitals have shown high error rates (average 11% of doses) (85). The observation method is labor-intensive, and therefore costly. However, it yields very rich data that facilitate understanding, not only about what events occur, but also about the processes and dynamics that affect the outcome. It is a tool that can be used intermittently, as resources permit, both to identify and understand systems breakdowns and to monitor improvement after changes are implemented (86).

Safety walk rounds

Safety walk rounds were established at the University of Michigan Medical Center to improve patient safety by opening a new line of communication between the chief of staff and frontline caregivers (87). Patient safety rounds are visits by

hospital executives to the patient care areas to discuss patient safety issues with providers and enlist leadership to break down the significant barriers (88). These leadership walk rounds are a low-cost way to identify hazards of concern to front-line staff and make needed changes. They require no additional staff, equipment, or infrastructure (86). By patient safety rounds it is possible to discuss specific events or general processes that could put patients at risk for harm, executives can ask for suggestions and utilize the wisdom of the frontline professionals to improve safety. Furthermore; they demonstrate the executives' and the organization's commitment to patient safety, and they may improve provider attitudes to safety-related issues. Benefits have been documented in the improvement on the safety culture and the development and implementation of preventive strategies to solve patient safety issues (87). Thomas et al. (88) found that EWR have a positive impact on patient safety climate for nurses. Frankel et al. (89) described that PSR helps to educate leadership and frontline staff in patient safety concepts and will lead to cultural changes, as manifested in more open discussion of adverse events and an improved rate of safety-based changes. Key components for success were active medical staff leadership and the engagement of physicians and senior management in the process improvements (87).

Focus groups or interviews

Focus groups are in-depth group interviews employing relatively homogenous groups to provide information on topics specified by the researchers (90). Interviews or focus groups with front-line people can offer an opportunity for a very rich learning environment as members within the group discuss and develop ideas. It can identify both hazards and potential solutions that otherwise remain hidden (86). Patient interviews and conservations are a particularly vital form of safety monitoring (91,92) and have been the most potent warning of recent tragedies (93).

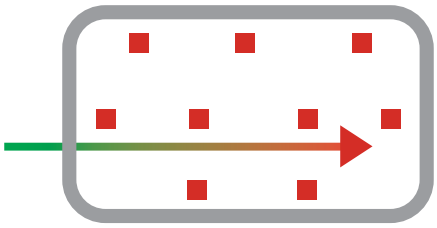


Figure 4 *Prospective risk analysis*

Retrospective risk analysis

Retrospective methods for identifying adverse events include voluntary reporting, exploring medical malpractice claims, patient complaints and satisfaction, clinical registers and administrative data analysis or retrospective record review. However, this is not an exhaustive list.

Voluntary reporting

Voluntary reporting is the least sensitive method for detecting adverse events. Studies found that only 1.5% of adverse events (94) and 6% of adverse drug events (95) identified by record review were reported by an incident reporting mechanism. Although voluntary reporting can detect a broad range of adverse events, these systems miss a vast majority of events and cannot provide stable estimates of the true underlying adverse events rates (96). A study of Levtzion-Korach et al. (97) mentioned that nurses were the main reporters, physicians accounted for only 2.5% of reporting. However, voluntary reporting systems create awareness and enhances patient safety by learning from previous failures. Therefore they have a fundamental role in all patient safety systems. Leape mentioned seven characteristics for a successful reporting system: non-punitive, confidential, independent, expert analysis, timely, system-orientated and responsive (98).

Patient complaints and satisfaction

Patients are sensitive to, and able to recognize, a range of problems in healthcare delivery (99), some of which are not identified by traditional systems of healthcare monitoring (e.g., incident reporting systems, retrospective case reviews) (97). Therefore, patient complaints provide a valuable source of insight into safety-related problems within healthcare organizations (100), strengthens the ability of healthcare organizations to detect systematic problems in care (101) and can offer an inexpensive and repeatable way to measure adverse events. In most countries it is one of the patients' rights to file a complaint with a competent and independent ombudsman. Almost all hospitals have procedures to systematically investigate patient (dis)satisfaction. There is growing international interest in harnessing patient dissatisfaction and complaints to address quality problems in healthcare (102). However, it should be mentioned that Bismark et al. (103) reported that only 0.4% of the adverse events identified by the New Zealand Quality of Healthcare Study resulted in complaints. Therefore, it is also useful to measure patient (dis)satisfaction. Qualitative research tries to find out the experiences of the patient on the basis of interviews and or group discussions. It is a time-consuming and costly method. Quantitative research in the form of surveys focused more on questioning large groups of people. The methods vary in cost, accuracy and the degree of interference with the patient. Selecting the best method or combination of methods should represent an ideal balance between the strategic goals of the organization and costs. Most hospitals use a survey at the moment of discharge.

Medical malpractice claims

Some complaints lead to medical malpractice claims. Oyebode (104) described that many negligence claims are often not regarded by medical practitioners as arising from adverse events. Nonetheless, the factors that predict that a patient will resort to litigation include a prior poor relationship with the clinician and the feeling that the patient is not being kept informed. Localio et al. (105) reported that the fraction of adverse events due to negligence that led to medical malpractice

claims is very low, namely 1.53%. In order to identify leading causes of surgical errors Somville et al. (106) retrospectively reviewed 427 surgical malpractice claims from 3,202 malpractice liability cases between 1996 and 2006 in which patients alleged error. System factors play an important role in most surgical errors, including technical errors and some non-technical errors. They concluded that malpractice claims analysis could encrypt the leading areas for intervening to reduce errors.

Analysis of clinical registers and administrative data

Clinical registers, such as the national hospital discharge dataset of all Belgian acute hospitals (the Belgian Hospital Discharge Dataset [B-HDDS]) and administrative data, such as billing data, were never intended for measuring adverse events. However, analysis of clinical registers and administrative data has several advantages and is increasingly used for detection of adverse events: these data are inexpensive, readily available, computer readable, and cover large populations (107,108). The Belgian Hospital Discharge Dataset (B-HDDS) contains patient demographics, data about the hospital stay (data and type of admission and discharge, referral data, admitting department, destination after discharge) and clinical data (primary and secondary diagnosis as described in the ICD-9-CM, diagnostic and therapeutic procedures as described in the ICD-9-CM (109). A retrospective analysis of these data for the year 2000 estimated the incidence of adverse events to be 7.12% for medical and 6.32% for surgical hospitals stays, with a high variability between hospitals, even after risk adjustment (108). However, because the nature of the data, there are some limitations. Previous studies demonstrated under (16,110) and over-reporting (111) of adverse events and a poor sensitivity for detecting individual adverse events (112,113).

Retrospective record review

Record review has historically been the first choice method to oversee care. Thomas et al. (114) indicates that identifying adverse events though record review is a complex and difficult task, requiring extensive clinical knowledge,

adequate documentation, and objectivity on the part of the researcher. Records are mostly in paper format or in an electronic format that is not readily usable for research. Transforming patient records into research data is expensive, resource intensive and requires exceptional knowledge and skills in medical context and research (115). Therefore the process of reviewing records is very time consuming (115) and costly. Woloshynowych et al. (116) also mentioned as practical disadvantages that it is time-consuming, labor intensive and expensive. Moreover, retrospective record review does not provide real-time information. It is often not longer possible to gain additional information about the events from the patients and/or professionals involved (117). However, record review is the only method for which there is a substantial number of published estimates of reliability (118). Additionally, it can provide details about both the adverse event and the circumstances, such as the patient's condition prior to and following the event (119). In addition, record review allows for evaluation of processes as well as outcomes, and can yield information about whether important processes occurred, such as communication, documentation, use of a checklist, or administration of an evidence-based therapy (86).

The catalyst of studying adverse events using record review was the Harvard Medical Practice Study. This study reviewed, in 1984, 30,121 patient records from 51 randomly chosen acute and non-psychiatric hospitals located in New York (United States of America [USA]). It estimated that 3.7% of all hospitalized patients experiences an adverse event related to medical therapy and that 27.6% of these adverse events are due to negligence (120). Modified versions of this protocol have been implemented in many studies and incidence rates of in-hospital adverse events were reported from Australia (16.6%) (2), Canada (10.6%) (121), Denmark (9.0%) (122), England (8.7%) (123), New Zealand (12.9%) (124), the Netherlands (5.7%) (50), Portugal (11.1%) (125), Spain (8.4%) (52), Sweden (12.3%) (126), Tunisia (10%) (127), Greater London area (the United Kingdom [UK]) (10.8%) (128), and the USA (region Utah and Colorado: 2.9% (129,130), region New York: 3.7% (120), region North Carolina: 25.1% (131) and the USA:

7.5% (94), 33.2% (84). The variation in the incidence of adverse events (ranging from 2.9% to 33.2%, both in the USA) may either be explained by true differences in patient safety for the different healthcare systems, or by methodological differences between studies (15). Most of these studies reported that half of the adverse events are preventable (15).

In Belgium, Verelst et al. (132) used a record review to assess the reliability of an in-depth analysis on causation, preventability, and disability by two separate review teams on five selected adverse events in acute hospitals. The selected adverse events were pressure ulcer, postoperative pulmonary embolism or deep vein thrombosis, postoperative sepsis, ventilator-associated pneumonia and postoperative wound infection. Team 1 found in 31.7% of the medical records, one of the five selected adverse event occurred. Whereas, team 2 described that 28.9% of the records, one of the five selected adverse event occurred. Another retrospective analysis of patient records on adverse drug events (ADE) found that 2.5% of the patients experience a preventable adverse drug event (133).

In reviewing patient records most studies use (a variant of) the Harvard Medical Practice Study (HMPS) trigger tool to detect triggers that could signal patient harm, and identify potential adverse events. These HMPS trigger tool consist of 18 triggers. A trigger can be a description of the harm itself or an indication that harm has occurred (such as a return to surgery) (12). The Institute of Healthcare Improvement developed the IHI Global Trigger Tool (IHI-GTT) to identify adverse events in adult inpatients throughout the hospital. The IHI-GTT contains six 'modules', or groupings of triggers: cares, medication, surgical, intensive care, perinatal and emergency department. Four of the groupings are designed to reflect adverse events that commonly occur in a particular unit. The modules 'cares' and 'medication' are designed to reflect adverse events that can occur anywhere in the hospital (134). Nevertheless, based on the type of adverse events that a study will detect, a study protocol can focus on one or a limited number of triggers. In this study we focus on the trigger 'unplanned transfer to an intensive care unit'.

Unplanned transfers to intensive care prolong hospital stay, place additional pressure on the intensive care resources and increase the cost of hospitalization (64). They have strong impact on patients and their environment. A systematic review of retrospective record review on adverse events that result in an unplanned transfer to an intensive care unit concluded that the percentage of surgical and medical adverse events requiring ICU admission ranged from 1.1% to 37.2% (67). Furthermore, the preventability of the adverse events varied from 17% to 76.5% (67). Although all adverse events should be a concern for our society, adverse events that are preventable and result in serious harm are of particular concern (69). Layde et al. (135) expressed that patient safety efforts should focus on medical injuries and prevention should focus on factors that are modifiable and most likely to bring effective change.

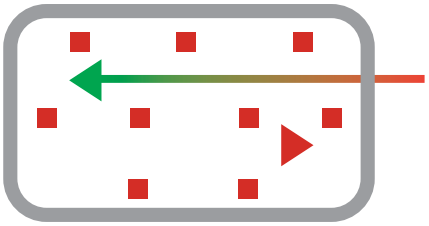


Figure 5 *Retrospective risk analysis*

The different methods described different yet complementary patient safety issues (97). Retrospective risk analysis gives a clear view of the problem (detection of adverse events) and is complementary with the prospective risk analysis which provides insight into the practices and processes that precipitate adverse events (estimation of risks). The patient safety management system of whatever healthcare organization must combine the prospective approach with retrospective analysis in order to create awareness among healthcare professionals, to obtain a comprehensive picture of the patient safety problems, to identify adverse events

and failure modes, to develop priorities for improving safety and to optimize care processes. During the PhD the prospective and retrospective approach were combined. However, the dissertation focus on the retrospective risk analysis.

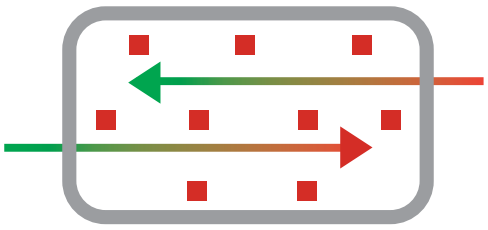


Figure 6 *Risk management includes prospective and retrospective risk analysis*

MAIN OBJECTIVES AND RESEARCH QUESTIONS

This dissertation has two parts: (1) retrospective risk analysis, (2) literature search through systematic review with meta-analysis. Two main research questions are addressed. The first research question is divided in four sub-questions and the second is further addressed in two sub-questions. This dissertation presents the results of three individual studies.

Overview of the research questions and chapters in which they are addressed

Research question	Corresponding chapter
RQ1: What are the incidence rate, preventability, harm and type of adverse events requiring a higher level of care (multidisciplinary record review)?	
- How can record review be applied in Flemish acute hospitals for the detection of this type of adverse events?	Chapter 2
- What are the incidence rate, preventability and degree of harm of adverse events requiring a higher level of care?	Chapter 3
- What are the incidence rate, preventability and degree of harm of adverse drug events requiring a higher level of care?	Chapter 4
- How is quality of the patient record keeping?	Chapter 5
RQ2: What does the literature learn us of adverse drug events?	
- What is the incidence of inappropriate antibiotics in patients with severe infection and their relationship with the outcome through a systematic review with meta-analysis?	Chapter 6
- What is the incidence of drug related problems in nursing homes: a systematic review?	Chapter 7

OUTLINE OF THE DISSERTATION

The chapters are written as separate articles and can be read independently. As a consequence, the content of the chapters may show some overlap.

Chapter 1 (introduction)

Chapter 1 sets the scene for the doctoral thesis by providing an introduction and background of the research. First, a conceptual framework is provided. The objectives and research questions are outlined.

Chapter 2 (research question 1)

The second chapter describes the protocol to investigate adverse events using a retrospective record review with a focus on patients with a need for a higher level of care. In practice, these events relate to (1) (re)admission to the intensive care unit from a general ward or (2) to an intervention by a medical emergency team due to an unanticipated change in patient's clinical condition (136).

Chapter 3 (research question 1)

The third chapter builds on chapter two and presents the incidence and preventability of adverse events that necessitate a higher level of care (137). This type of adverse events is of importance, given their medical, social and financial impact.

Chapter 4 (research question 1)

Chapter 4 chronologically follows chapters 2 and 3 since the study is based on the data of the record review. Chapter 3 describes the incidence of adverse events that necessitate a higher level of care (137). These adverse events were mostly related to medication. Therefore, chapter 4 focuses on the incidence and preventability of adverse drug events that necessitate a higher level of care.

Chapter 5 (research question 1)

Record review is far the most applied method to assess adverse events. By doing a record review, the researchers also get insight on the format, the availability and the completeness of the records. This chapter focuses on *(1)* the format, the availability and the completeness of patient records and *(2)* analyses the relation between these elements of the patient records and the occurrence of adverse events.

Chapter 6 (research question 2)

Chapter 3 and 4 describe the incidence and preventability of adverse events and adverse drug events. Antibiotics and antithrombotic agents accounted both for one-fifth of all preventable adverse drug events (138). This chapter presents a systematic review with a meta-analysis on the incidence and outcome of inappropriate in-hospital empiric antibiotics use for severe infection (139). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was applied to report this systematic review.

Chapter 7 (research question 2)

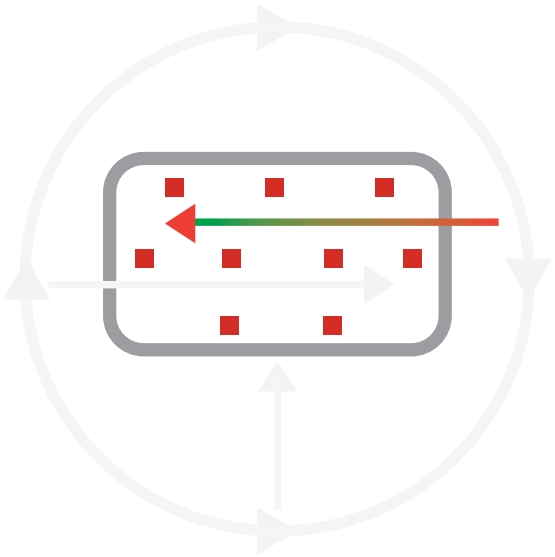
In chapter 7 medication management in residential care facilities for elderly is evaluated. This chapter presents a systematic review on the incidence of drug related problems (DRPs) in residential care facilities for elderly measure by eight instruments (ACOVE, BEDNURS, Beers' criteria, MAI, PRISCUS, RASP, START and STOPP). Due to multi-morbidity and poly-pharmacy, these patient are an important group to focus on. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was applied to report this systematic review.

Chapter 8 (discussion)

Chapter 8 contains the final discussion and presents the main conclusions, methodological considerations and recommendations for further research and practice in the field of risk management in healthcare.

CHAPTER 2

Design of a record review study on the incidence and preventability of adverse events requiring a higher level of care in Belgian hospitals



Design of a record review study on the incidence and preventability of adverse events requiring a higher level of care in Belgian hospitals

This chapter is based on

Vlayen A, **Marquet K**, Schrooten W, Vleugels A, Weekers F, Helling J, De Troy E, Claes N. Design of a retrospective record study on the occurrence of adverse events among patients admitted to intensive care units in Flemish hospitals. BMC Research Notes, 2012, 5 (1): 468-76.

This study was presented by Kristel at

- International Forum on Quality and Safety in Healthcare, BMJ, Paris, 17-20 April 2012, poster presentation
- International Student Congress of (bio)Medical Sciences (ISCOMS), Groningen, 5-8 June 2012, poster presentation
- 29ste jaarcongres, Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen, Gent, 25th November 2011, oral presentation
- 5de week voor kwaliteit en patiëntveiligheid, Federal Public Service of Health, Food Chain Safety and Environment, Brussel, 28th November 2011, poster presentation

Chapter 2: Design of a record review study on the incidence and preventability of adverse events requiring a higher level of care in Belgian hospitals

ABSTRACT

Background: Adverse events are unintended patient injuries that arise from healthcare management resulting in disability, prolonged hospital stay or death. Adverse events that require intensive care admission imply a considerable financial burden to the healthcare system. The epidemiology of adverse events in Belgian hospitals has never been systematically assessed.

Findings: A multistage retrospective review study of patients requiring a transfer to a higher level of care was conducted in six hospitals in the province of Limburg. Patient records are reviewed starting from January 2012 by a clinical team consisting of a research nurse, a physician and a clinical pharmacist. Besides the incidence and the level of causation and preventability, also the type of adverse events and their consequences (patient harm, mortality and length of stay) was assessed. Moreover, the adequacy of the patient records and quality/usefulness of the method of record review was evaluated.

Discussion: This paper describes the rationale for a retrospective review study of adverse events that necessitate a higher level of care. More specifically, we are particularly interested in increasing our understanding in the preventability and root causes of these events in order to implement improvement strategies. Attention is paid to the strengths and limitations of the study design.

INTRODUCTION

An important indicator of patient safety is the rate of adverse events in hospitals. An *Adverse event* is defined as *(1)* an unintended injury or complication, *(2)* which results in disability at discharge, death or prolongation of hospital stay, and *(3)* is caused by healthcare management (including omissions) rather the patient's disease (2,14,124,126,129). Although all medical errors should be of concern, errors that either result in serious consequences for patients or that are preventable are of particular concern. A substantial number of adverse events is detected among unintended Intensive Care Unit (ICU) admissions and readmissions. Unplanned Intensive Care Admission (UIA) is an existing clinical indicator, used in several countries on a regular basis. It was developed and implemented in Australia, in a close collaboration between the Australian and New Zealand College of Anaesthetists (ANZCA) and the Australian Council on Healthcare Standards (ACHS) and recommended as a measure of patient safety ('avoidable incidents in anaesthesia') and the effectiveness of care ('lack of planning') (61).

To estimate the incidence and preventability of adverse events requiring ICU (re) admission, we conducted a systematic review including record review studies (67). A total of 27 studies were included, of which 14 studies addressed unplanned ICU admissions due to anesthetic or surgical adverse events, eight studies investigated adverse events on general wards and five studies focused on ICU readmissions. Due to study heterogeneity, meta-analysis of the data was not appropriate. Results showed that the percentage of surgical and medical adverse events requiring ICU admission ranged from 1.1% to 37.2%. ICU readmissions varied from 0% to 18.3%. Preventability of the adverse events varied from 17% to 76.5%. Consequences of the adverse events included a mean length of ICU stay that ranged from 1.5 days to 10.4 days for the patient's first stay in ICU and mortality percentages between 0% and 58%.The large variation in study outcomes can be explained by methodological diversity. The included studies varied in sample

size, applied different methods of screening and only three out of 27 studies used a multi-center design. On the other hand, clinical diversity was high because of population mix and variation (or absence) of definitions on adverse outcomes. As a conclusion, we suggest that planning of future studies should aim to standardize terminology and measures of outcomes (standard taxonomy) and to apply more explicit study designs in order to allow for comparisons across studies.

Several nationwide studies describe the use of record review to measure the occurrence of adverse events in hospitals (2,50,120–122,124,126,129,140). 'Unplanned transfer from general to intensive care' is often used as a criterion ('trigger' or clue) to uncover adverse events and medical errors (2,120,121,126). The positive predictive value (PPV) reflecting the reliability of this screening criterion was 18.6% (126). In Belgium, retrospective analysis of the national hospital discharge dataset of all Belgian acute hospitals for the year 2000 estimated the incidence of adverse outcomes to be 7.12% for medical and 6.32% for surgical hospital stays, with a high variability between hospitals (108).

Currently, there are 194 Belgian hospitals, of which 105 acute, 66 psychiatric and 23 long-term care hospitals. Acute hospitals consist of university hospitals, general hospitals 'with university character' and other non-university hospitals. Belgium has seven university hospitals, one for each medical school that offers the entire medical education. The Flemish region of Belgium has 55 acute hospitals. The province of Limburg, which is a part of the Flemish region, has seven acute hospitals (74). This multicenter study is initialized in the province of Limburg and aims at identifying preventable adverse events that contributed to the transfer of patients to a higher level of care using the method of record review. This study is funded by 'Limburg Sterk Merk', a foundation of public use that supports healthcare and economic development projects.

It was not in the purpose of this study to detect all the adverse events in the inpatient records. An important goal was to make a clear distinction between the

causality (errors) and the consequences (patient harm) of the adverse events. Rating preventability is important in understanding the system specific aspects of healthcare processes in order to design preventive or mitigating barriers.

The objectives of this multicenter study are to:

1. Determine the incidence of adverse events requiring a transfer to a higher level of care;
2. Assess the preventability of these adverse events;
3. Assess the clinical impact of these events;
4. Evaluate the adequacy and completeness of the patient records;
5. Evaluate the use of record review as an auditing tool.

METHODS

Design and setting

A retrospective cohort study was undertaken in six acute hospitals in the province of Limburg. All acute hospitals from the province of Limburg were invited to participate in this study. Six out of seven hospitals confirmed their participation and gave permission to access their patient records.

Type of participants and record selection

To minimize selection bias, all records of the patients being transferred to a higher level of care and being discharged from or deceased in the hospital during the inclusion period (November 2011-May 2012), irrespective of the hospital admission date of the patient, were screened for the occurrence of adverse events. In practice, record selection was based on (1) (re)admission to the Intensive Care Unit from other care units in the hospital providing lower intensity care or a functional unit (e.g. operating room, radiology) or on (2) an intervention by a Medical Emergency Team (MET) due to an unanticipated change in the patient's clinical status. Considering that record selection is not based on routine hospital registration, hospitals were instructed to select the cases using a uniform selection form.

Because of their specific nature, patients admitted on neonatal or maternal ICUs were excluded. Also planned admissions to the ICU from the operation room (major elective surgery) and ICU admissions directly from the emergency department were excluded. As the included hospitals have no pediatric ICUs, only patients from the age of 16 or over were included.

Starting from January 2012, patient records were reviewed in a multistage review process by a research nurse (holder of a specialization degree in Intensive Care, Emergency care and principal researcher), a physician (holder of a specialization degree in Anesthesiology, Urgent and Emergency Medicine) and a clinical pharmacist. Record review was performed once the entire -closed and complete- record is available to the reviewers. A complete record consists of a medical (including laboratory and radiology results), nursing and pharmaceutical record. However, patient reports that were found to be incomplete or ambiguous are also included in the review process, as exactly in these cases the possibility of containing adverse events might be higher (141). The review period was accomplished when all the included records were reviewed. The period between record selection and review was relatively short and was largely dependent on (1) the length of stay from the time of transfer to a higher level of care and (2) the date of availability of the patient records. The structure of the records was not uniform in all participating hospitals.

Sample size calculation

The main (numerical) objective of this study was to estimate an overall incidence rate of adverse events (number of adverse events/patient days at risk). It was not in the aim to compare the results of the participating hospitals. The precision of this estimate was provided by a 95% confidence interval. The sample size of this study was determined in order to guarantee a sufficiently narrow confidence interval for the estimate.

From a pilot study in one hospital during two months, 66 patients with one or more adverse events leading to a higher level of care were detected for 44,165 days at risk (545 per 1,000 patient years at risk) (Figure 1). Based on these findings, a sample size of 1,000 patient years or 365,000 patient days at risk would provide a confidence interval of approximately 20% (+/- 10% around the estimate). As the total yearly

number of inpatient days (excluding palliative, neonatal, pediatric and one day-stay admissions) for the six participating hospitals was 760,057 (year 2010), the required sample size corresponds to an inclusion period of six months (136).

Different levels of clustering can be considered in this study: hospital level, ward level, pathology level, and individual patient level. Since little is known about the impact of these different levels of clustering, clustering was not considered in calculating the sample size.

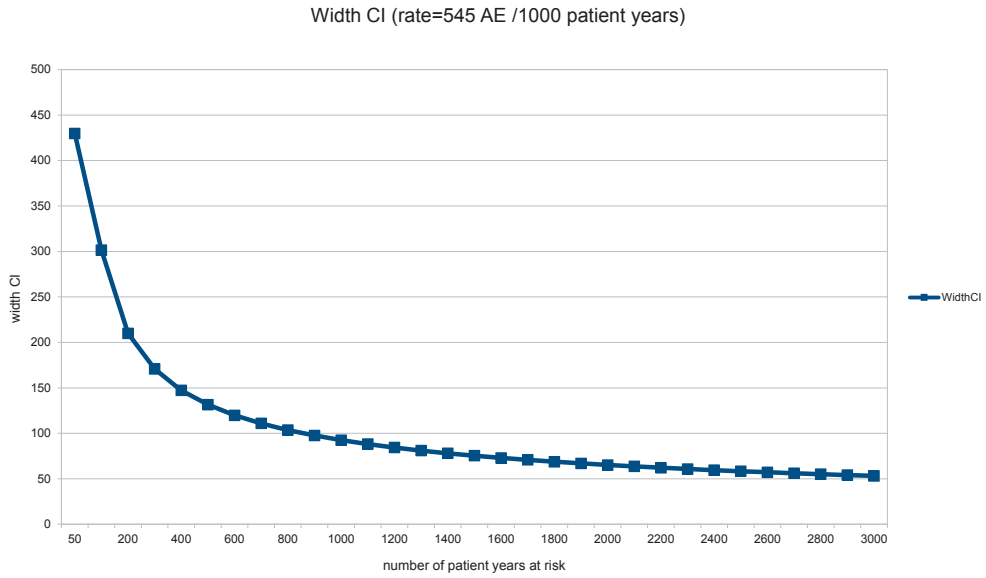


Figure 1 Sample size calculation

Outcome measures

Primary outcome measures were the number of patients transferred to a higher level of care because of an adverse event -or a combination of adverse events- per 100,000 patient days at risk, and the number of preventable adverse events in comparison with the number of adverse events. The number of patient days at

risk was calculated as the total number of hospitalization days in the participating hospitals during the study period (excluding palliative, neonatal, pediatric and day-stay admissions). Secondary outcomes were the type of event (operative, procedural, diagnostic, therapeutic, drug/ intravenous fluid or system issue), attributable causes and consequences of the events (level of patient harm, mortality and length of stay in hospital and ICU). Independent variables were presented in a non-exhaustive list in table 1.

Definitions

The definitions were adopted from previous adverse events studies. They were described in table 2.

Data collection and review process

In each hospital, the patient records were reviewed in a multistage review process (Figure 2, based on Zegers (14)).

Stage 1: Selection of records

A master list of eligible patients was generated at each hospital from the hospital administrative database by the ICU head nurses or the intensivists using a uniform selection form across hospitals. Patient records selection was based on (1) an unplanned ICU admission, (2) a MET intervention. ICU admissions were registered on the ICUs, while MET interventions were registered on the emergency departments. Only closed patient records (after discharge from the hospital or decease of the patient) were forwarded to the next stage.

Table 1 Independent variables

- Primary diagnosis for admission to the hospital
- Patient history
- Patient age (in years); year of birth
- Gender
- Number of prescribed drugs before hospital admission
- Admission day and time to ICU
- ICU admission source (location/ providers of care)
- Length of ICU stay (in days)
- Outcome in the ICU (discharge, mortality)
- Acute Physiology and Chronic Health Evaluation (APACHE) II
- Patient complexity and mortality risk are defined according to the All Patient Refined Diagnosis Related Groups, which is calculated based on patient diagnosis, procedure, and age using a scale of 1 (least complex/lowest risk) to 4 (most complex/highest risk)
- Quality and completeness of the patient records

Table 2 Definitions

Adverse event	(1) An unintended injury or complication, which results in (2) disability at discharge, death or prolongation of hospital stay, and (3) is caused by healthcare management (including omissions) rather than the patient's disease (2)
Unintended injury	Refers to any disadvantage for the patient that leads to prolonged or strengthened treatment, temporary or permanent (physical or mental) impairment or death (50)
Disability	Refers to temporary or permanent impairment of physical or mental function attributable to the adverse event (including prolonged or strengthened treatment, prolonged hospital stay, readmission, subsequent hospitalization, extra outpatient department consultations or death) (50)
Causation	Refers to injury caused by healthcare management including acts of omission (inactions) i.e. failure to diagnose or treat, and acts of commission (affirmative actions) i.e. incorrect diagnosis or treatment, or poor performance (50)
Healthcare Management	Includes the actions of individual hospital staff as well as the broader systems and care processes and includes both acts of omission (failure to diagnose or treat) and acts of commission (incorrect diagnosis or treatment, or poor performance) (121)
Preventable Adverse Event	An adverse event with enough information currently available to have avoided the event using currently accepted practices (142)
Higher Level of Care	A higher level of care may include: - An unplanned transfer to an intensive care unit - An intervention of a Medical Emergency Team
Intensive Care Units (ICUs)	Hospital units providing continuous surveillance and care to actually ill patients (Mesh definition). E.g. medical and surgical ICUs, medium care, coronary care units, pediatric ICUs and respiratory care units.
Planned ICU admissions	Admissions of patients expected to arrive on the ICU. E.g. routinely scheduled post-surgery admissions or transfers directly to the ICU from outside hospitals

Unplanned ICU admissions	All patients unexpectedly admitted to the intensive care unit from a lower level of care in the hospital during the study period. If a patient experienced more than one unplanned ICU admission during his/her hospital stay, each unplanned admission is included in the analysis (adapted from Baker, 2009) (62)
Patient harm	Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalization, or that results in death (IHI) (143)

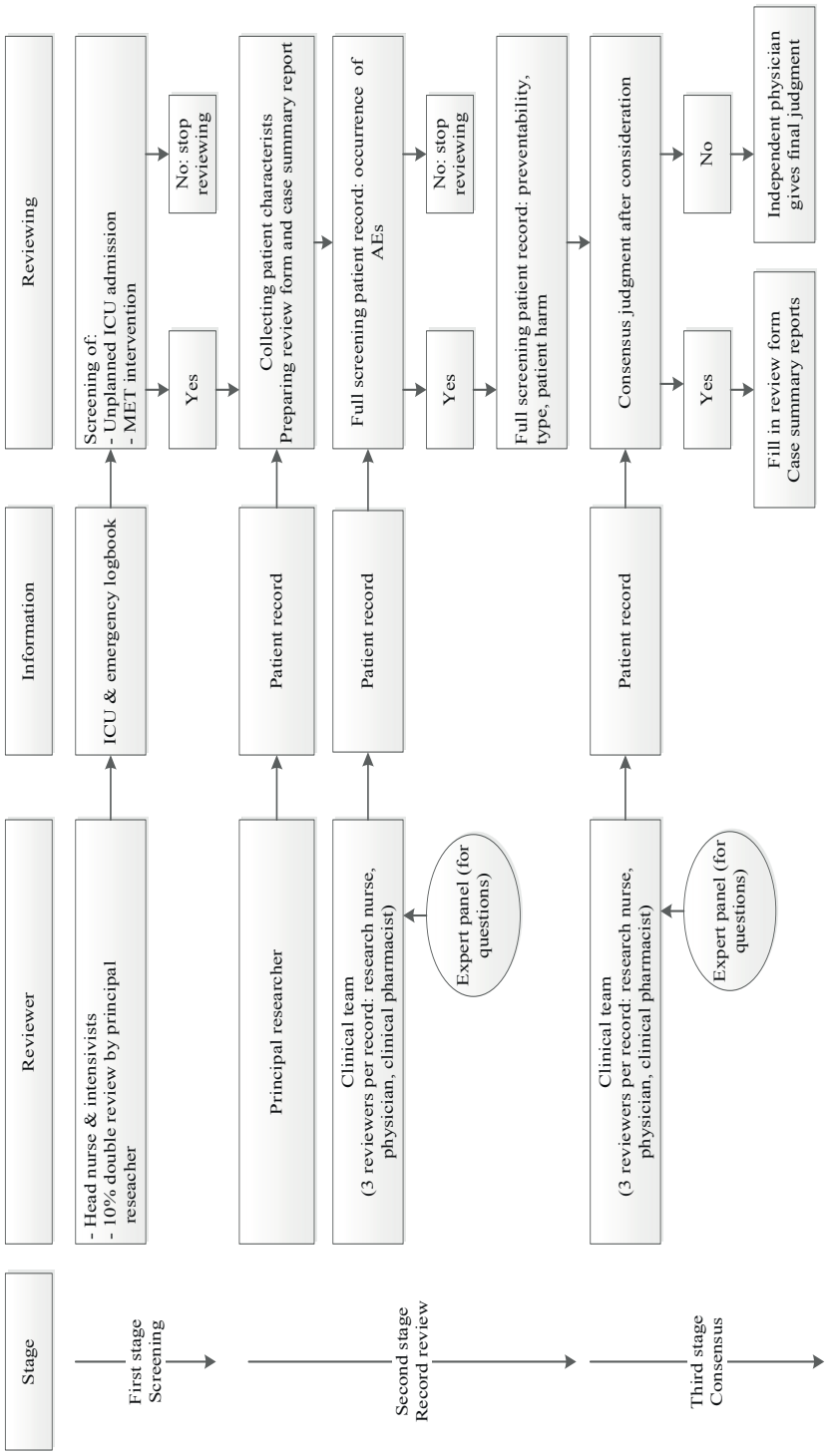


Figure 2 The review process

Stage 2: Record review for adverse events

First, the principal researcher collected from the patient records data on basic patient characteristics (gender, year of birth, reason for hospital intake, reason for transfer to ICU, number of days in the hospital prior to ICU transfer, admission day and time to ICU, number of prescribed drugs before hospital admission, ICU admission source (location, providers of care) and outcome in ICU. The principal researcher (KM) noted the data in a structured abstraction instrument, which was developed for this study.

Subsequently, each record was reviewed by the clinical team to determine if an adverse event occurred according to the definition of Wilson et al. (Table 2). The assessment of causation was performed using a scale from 1 to 6 (Table 3). Upon ratings of at least 4 (i.e. more than 50% likelihood), unintended injuries or complications were classified as adverse events.

Although each of the persons of the clinical team had a specific focus during the record review, respectively the medical record (physician), the nurse record (research nurse) and the pharmaceutical record (clinical pharmacist), assessments were made collectively.

Stage 3: Consensus judgment on occurrence, preventability and level of harm

The members of the clinical team come to consensus on the occurrence of an adverse event. Once the team concluded on the occurrence of the event, the assessment on preventability and severity ratings is performed by consensus judgment. A six-point scale was used for the assessment of the preventability. The scale is grouped into categories: no preventability, low and high evidence of preventability (Table 3). Further classification was done by type of adverse event and patient harm (severity categories) (Table 3).

During the review process

The patient records were reviewed using the structured abstraction instrument to standardize the judgments of the reviewers.

In order to evaluate the process of record review, data on the quality and completeness of the patient records, missing records and time measures of the screening processes were recorded. An important criterion was the recording of the actual reason for the transfer to a higher level of care.

An expert panel of physicians was available for second advice when needed. In case of continued disagreement, an independent physician, who did not review the patient records, but only the review forms, gave the final judgment.

Case summary reports of patients that experienced an adverse event (brief narratives of the key points of each patient's hospital stay) were written in order to facilitate an overview of the cases (128) to make a uniform re-assessment possible afterwards (after 20 à 30 cases).

Table 3 Outcome measures

Determination of the presence of an **adverse event** is based on three criteria (2,14,121): 1. an unintended (physical and/or mental) **injury** which 2. results in temporary or permanent **disability**, death or prolongation of hospital stay, and is 3. **caused** by healthcare management rather than the patient's disease
To determine whether the injury is **caused by healthcare management** or the disease process a 6-point scale will be used (2,14,121): 1. (Virtually) no evidence for management causation 2. Slight to modest evidence of management causation 3. Management causation not likely (less than 50/50, but 'close call') 4. Management causation more likely (more than 50/50, but 'close call') 5. Moderate to strong evidence of management causation 6. (Virtually) certain evidence of management causation
The **degree of preventability** of the adverse events is measured on a 6-point scale, grouped into three categories (2,14,121):
No Preventability 1. (Virtually) no evidence for preventability
Low Preventability 2. Slight to modest evidence of preventability 3. Preventability not likely (less than 50/50, but 'close call')
High preventability 4. Preventability more likely (more than 50/50, but 'close call') 5. Strong evidence of preventability 6. (Virtually) certain evidence of preventability

Classification (2,144): Adverse events can be classified by type, such as adverse events related to

- *Diagnosis*: an adverse event arising from a delayed or wrong diagnosis
- *Procedures*: an adverse event in relation to a non-surgical procedure, such as insertion of a central venous line, nasogastric tube, cardiac catheterization, etc.
- *Surgery*: an adverse event in relation to a surgical procedure
- *Anesthesia*: an adverse event in relation to anesthesia
- *Drug therapy/intravenous fluid therapy (an adverse drug event)*: an adverse event related to medication use or intravenous fluid therapy
- *Therapeutic, excluding drug therapy, surgery or procedural*: an adverse event arising when a correct diagnosis was made, but there was incorrect therapy or a delay in treatment
- *System issue*: an adverse event in relation to problems with hospital processes such as nosocomial infection or equipment malfunction
- *Other clinical management (including nursing care and allied healthcare)*
- *Others* (e.g. falls)

Confidentiality

In this study anonymity of hospitals, healthcare providers and patients was of great importance. Several measures were taken to ensure confidentiality of the data. During data collection, records were never left unattended and they are stored in a locked room or closet. Each participating hospital and each hospital admission received a unique study number. Patient identifiers were kept in a dataset separately from the primary database. During the review process in the hospitals, the data were directly entered into a protected electronic database. The reviewers have a personal password for the electronic database. The web-based database complied with the safety and privacy requirements. Patients' names were not included in the database and after completion of the data collection and analysis, patient record identifiers are destroyed. The identity of patients or healthcare professionals was not revealed in research reports (14). If a reviewer had during the review process any concern about unrecognized potential deliberate harmful

acts, illegal acts, or repetitive negligent behavior, these concerns were discussed with the ethics committee of Hasselt University.

The confidentiality agreement in which the confidentiality and the rules for disseminations of results were specified, was established between the researchers, Hasselt University and the participating hospitals. Therefore, informed consent from the patients was not necessary.

Ethical approval

Approval was obtained from the ethics committee of Hasselt University and from the ethics committee of the participant hospitals.

Statistical analysis

The incidence of unplanned ICU (re)admissions and (preventable) adverse events requiring ICU admission was calculated. Primary outcomes was measured as a rate (number of adverse events per 1,000 in-hospital patient years at risk). The number of preventable adverse events (preventability rate) was calculated as a proportion, compared with the incidence rate. Secondary outcomes (causality, severity) were presented as incidence rates for each category. A subgroup analysis was performed on patient characteristics and comorbidities, type of event, location and provider of care and type of ICU.

Testing reliability and validity

On a regular basis, the hospitals were followed up by the researchers to discuss their problems concerning the selection process of patient records. To test the validity of the process of screening by patient records analysts, 10% of all records were reviewed a second time by the principal researcher.

DISCUSSION

This paper described the methodology for a retrospective review study of adverse events that necessitate a transfer to a higher level of care.

There were several methodological limitations inherent to record review, which we are addressing within our study design. The most important limitation was that the use of the method of record review itself might lead to an underestimation of adverse events. The quality of the patient records was often poor as information is missing or incomplete. Therefore, a multidisciplinary approach, in which the team is composed of a research nurse, physician, and clinical pharmacist which had experience in this area, is a key condition and added value to conducting this record review. A strength of our multidisciplinary study design was the efficiency in which the members of the clinical team could focus on their own expertise. The nurse can concentrated on the nursing records, while the physician is focused on the medical records and the clinical pharmacist was examining the medication processes. Assessments on adverse events were always made collectively. In case of doubt or disagreement, a panel of physicians with different specialties was available for consultation. In addition, the completeness and usefulness of the patient records was assessed. Incomplete records are included in the review process, as there is a higher possibility that these cases contain adverse events (141).

Second, there was the lack of an actual gold standard for adverse event detection (136). Inevitably, the clinical team must deal with differences of record keeping within the participating hospitals. We therefore attempted to standardize our study protocol by conducting a pilot test in one hospital over a period of two months, in which the definitions, causality and severity ratings, abstraction instrument and the review processes were evaluated. Third, success of this type of research was dependent on the acceptance and participation of organizations,

professional groups, and individuals who may be at varying stages of readiness for investigation in this area. More specifically, the perceived threat to physician reputation or from medico-legal action should not be underestimated (144). Therefore, the involvement of a physician might promote the acceptance of the method. Since the clinical team is composed of external researchers, almost no workload is imposed on the hospital staff and healthcare processes are not interrupted. Moreover, ethical approval was obtained by the ethical committees of the participating hospitals and the academic institute. An agreement was signed between the researchers, participating hospitals and the academic institute in which the privacy of the participants and the confidentiality of the data is guaranteed. It was not in the purpose of this study to compare hospitals. Our multicenter study design allowed us to aggregate data and analyze patterns of these contributing factors. Results were always interpreted within the context of the current safety management systems in the participating hospitals and recommendations were formulated for the hospital management.

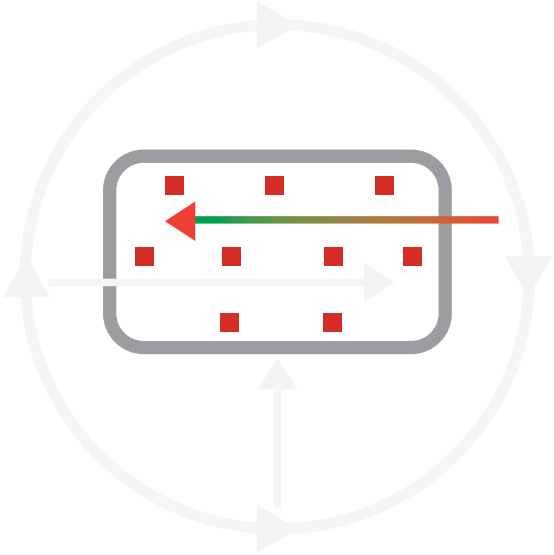
Based on this study of adverse event detection, several additional studies can be launched. It would be interesting to link the results of this study to the hospitals administrative databases to trace whether adverse events can be properly flagged. In a later time period, a cost study can be undertaken to assess the costs of care for patients with an adverse event. Insights from this study can provide information for the hospital management and policy makers to implement cost reducing interventions. In conclusion, review of the records and further analysis of the adverse events may trigger important system changes within the hospitals.

AUTHORS' CONTRIBUTIONS

AV prepared and conceived the study protocol and the design of the study, collected and analyzed the literature and wrote the manuscript. KM prepared and conceived the study protocol and the design of the study, prepared and contributed to the manuscript and conducted the pilot study and is the responsible researcher for the record review study. WS contributed to manuscript, the design and conception of the study and performed the power analysis. AVL and JH contributed to the manuscript, the design and conception of the study. FW and ED have been involved in revising the article critically for important intellectual content. NC contributed to manuscript, the design and conception of the study and is the general coordinator. All authors read and approved the final manuscript.

CHAPTER 3

One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals



One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals

This study was accepted for publication as

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- Medische directie Ziekenhuis Oost Limburg, 24 september 2014
- Uhasselt research conference, georganiseerd door Uhasselt en Federale Overheid Dienst Volksgezondheid, Veiligheid van de voedselketen en Leefmilieu, Brussel, 17 oktober 2014
- Stuurgroep kwaliteit en patiëntveiligheid Ziekenhuis Oost Limburg, 25 november 2014
- Symposium Kwaliteit en patiëntveiligheid: Voorkomen is veel beter dan genezen. Georganiseerd door Sint-Franciscus Ziekenhuis, 25 november 2014

Chapter 3: One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals

ABSTRACT

The objectives of this study are to determine the incidence and preventability of adverse events (AEs) requiring an unplanned higher level of care, defined as an unplanned transfer to the intensive care unit or an in-hospital medical emergency team intervention, and to assess the type and the level of harm of each AE.

Design & setting: A three-stage retrospective review process of screening, record review and consensus judgment was performed in six Belgian acute hospitals.

Interventions: During a six month period the records of all patients with an unplanned need for a higher level of care were assessed by a trained clinical team consisting of a research nurse, a physician and a clinical pharmacist.

Results: AEs were found in 465 (56%) of the 830 reviewed patient records. Of these, 215 (46%) were highly preventable. The overall incidence rate of patients being transferred to a higher level of care involving an AE was 117.6 (95% CI 106.9–128.3) per 100,000 patient days at risk, of which 54.4 (95% CI 47.15–61.65) per 100,000 patient days at risk involving a highly preventable AE. This means that 25.9% of all unplanned transfers to a higher level of care were associated with a highly preventable AE. The AEs were mainly associated with drug therapy (25.6%), surgery (23.7%), diagnosis (12.4%) and system issues (12.4%). The level of harm varied from temporary harm (55.7%) to long term or permanent impairment (19.1%) and death (25.2%).

Though the direct causality is often hard to prove, it is reasonable to consider these AEs as a contributing factor.

Conclusion: AEs were found in 56% of the reviewed records, of which almost half were considered highly preventable. This means that one fourth of all unplanned transfers to a higher level of care were associated with a highly preventable AE.

INTRODUCTION

Adverse events (AEs) are a world-wide concern for healthcare professionals, policy-makers and patients. An adverse event is (1) an unintended injury or complication, which results in (2) disability at discharge, death or prolongation of hospital stay, and (3) is caused by healthcare management (including omissions) rather than the patient's disease (2). Record reviews have shown that 2.9% to 33.2% of patients in acute hospitals experience one or more AEs (2,8,50,114,121,122,124,125,128,131,145–149). Several studies (2,8,121,125,126) have used the Harvard Medical Practice trigger tool to uncover AEs. A review on the overall incidence and nature of in-hospital AEs through record review suggested that AEs affect 9.2% of the patients during hospital admission, of which almost half were assessed as being preventable (15). In Belgium, a retrospective analysis of patient records on adverse drug events (ADE) found 2.5% of the patients having a preventable ADE (133). A retrospective analysis of the national hospital discharge dataset of all Belgian acute hospitals for the year 2000 estimated a prevalence of in-hospital AEs accounting for 7.1% of the medical stays and 6.3% for surgical hospital stays, with a high variability between hospitals (108).

A patient with an AE may require an Unplanned Intensive care Admission (UIA). UIA is a validated clinical quality indicator (61) and is defined as 'all patients unexpectedly admitted to the Intensive Care Unit (ICU) from a lower level of care in the hospital' (62). The indicator was developed by the Australian and New Zealand College of Anaesthetists and the Australian Council on Healthcare Standards and has been recommended as a measure of patient safety (avoidable incidents in anaesthesia) and effectiveness of care (lack of planning) (61,150). Used as a screening tool, it can detect patients who possibly suffered from an avoidable iatrogenic complication (63). Posa et al. (151) reported that 1% to 9% of all ICU admissions were unplanned. These unplanned transfers to ICU prolong

hospital stay, place additional pressure on ICU resources and increase the cost of hospitalization (64). More importantly, they have a strong impact on the patient and family. In the IHI-GTT UIA is one of the triggers to uncover AEs (152). The positive predictive value (PPV) of this trigger was estimated at 18.6% (number of AEs/number of selected patients with this trigger) (126). A systematic review concluded that the percentage of surgical and medical AEs requiring ICU admission ranged from 1.1% to 37.2% (67). Furthermore, the preventability of the AEs varied from 17% to 76.5% (67). However, not every critical patient requiring an unplanned transfer to a higher level of care reaches the ICU. Therefore, it is also important to include patients with a Medical Emergency Team (MET) intervention to detect AEs with an unplanned need for a higher level of care.

Although all AEs should be of concern for society, AEs that are preventable and result in serious harm are of particular concern (69). Garry et al. (68) reported that 77% of the adverse events preceding ICU admission were considered preventable. Layde et al. (135) expressed that patient safety efforts should focus on medical injuries and prevention should focus on factors that are modifiable and most likely to bring effective change. Therefore, the objectives of this multicenter study are to determine the incidence, the preventability, the type and the level of harm of AEs that require an unplanned transfer to a higher level of care.

METHODOLOGY

A multistage retrospective record review study on incidence and preventability of AEs requiring an unplanned transfer to a higher level of care was performed in one province of Belgium. All seven acute hospitals from the province of Limburg were invited to participate in this study. Six out of seven hospitals confirmed their participation, including two teaching hospitals (74). Cardiac surgery, neurosurgery, hematology are medical specialties which are provided only in these two hospitals. In total these six hospitals account for 2,939 hospitals beds (range 213-1,003) and 134 ICU beds (range 8-52) spread over medical, surgical, mixed ICU and Coronary Care Units. Three hospitals also had a stroke unit; one hospital had a step-down unit.

During a six month observation period in each of the participating hospitals the following cases were reviewed: (1) an unplanned (re)admission to the ICU or (2) an intervention by a Medical Emergency Team (MET) due to an unanticipated change in the patient's clinical status during the index hospital admission. The index hospital admission is the admission during which the patient meets the inclusion criteria and therefore is sampled in the study. A hospital readmission within 72 hours from the index admission was regarded as the same admission. Planned admissions to the ICU (such as planned postoperative admission after major surgery) and ICU admissions directly from the emergency department were excluded. Because of their specific nature, neonatal and maternal ICU were excluded.

Sample size calculation

Prior to this study, a two month pilot study was conducted to test the research protocol, train the clinical team and obtain an initial estimate of the incidence rate

in order to do a sample size calculation. Based on these findings, a sample size of 1,000 patient years or 365,000 patient days at risk would provide a confidence interval of approximately 20% (+/- 10% around the estimate). As the total yearly number of inpatient days (excluding palliative, neonatal, pediatric and one day-stay admissions) for the six participating hospitals was 760,057 (year 2010), the required sample size corresponds to an inclusion period of six months (136). The data obtained in the pilot study were not included in this study.

Data collection

A three-stage retrospective review process of screening, record review and consensus judgment was used. The review process was deducted from the protocol of the Harvard Medical Practice Study I (8), which was already used by several nationwide studies (2,8,50,121,122,124–126). Definitions were adopted from previous AE studies (2,14,62,121,142) and were described in detail in the research protocol (136), in the table 1 and in the supplement digital content.

In the first stage, all patients who required an unplanned transfer to a higher level of care between November 7th 2011 and May 6th 2012 were selected on the hospital sites by the ICU head nurses or the intensivists. To guarantee a uniform selection across the hospitals a half-day training on case selection was organized explaining the standardized selection form, the study protocol, the definitions and the review forms. The elementary selection process consists of the selection of (1) all MET interventions and (2) UIAs by exclusion of the planned ICU admissions (such as planned postoperative admission after major surgery) and the ICU admissions directly from the emergency department. The UIAs and MET interventions were identified via the ICU or emergency logbook. In case of doubt, the record was forwarded for review in the second stage. There were in total 4,693 exclusions, these were mostly ICU admissions directly from the emergency department (50.9%) and planned admissions to the ICU (41.4%). In order to test the validity

of the screening process, 470 excluded patients (a random sample of 10%) of the 4,693 excluded patients were reviewed by the principal investigator. Five percent of these controls (n= 23 of the 470 controls) were considered incorrectly classified and were subsequently included in the study. This degree of misclassification was similar between the hospitals.

In the second stage, a case note for each patient was made by the principal investigator. Patient characteristics (gender, year of birth, type of hospital admission, number of days in hospital prior to ICU transfer, number of prescribed medication before hospital admission, Acute Physiology and Chronic Health Evaluation (APACHE) II (153) at the moment of transfer were collected using Open Clinica (154). The anaesthesist estimated the American Society of Anaesthesiologists (ASA) physical status at the time of the hospital admission (155–157).

Subsequently, the record review was done to determine whether an AE requiring an unplanned transfer to a higher level of care had occurred. The review was done in the six hospitals by the same, experienced and independent clinical team consisting of a research nurse (specialized in Intensive Care, Emergency care and Healthcare management, with 11 years' experience), a physician (specialized in Anesthesiology and Emergency Medicine, with 16 years' experience) and a clinical pharmacist (with 7 years' experience). The three members of the clinical team were employed by the university to ensure an independent review process.

The clinical team used the definition of Wilson et al. which states that an AE is *(1)* an unintended injury or complication, which results in *(2)* disability at discharge, death or prolongation of hospital stay, and *(3)* is caused by healthcare management (including omissions) rather than the patient's disease *(2)*. For each case the relevance of these three criteria was explicitly written out in the case note and the assessment of causation was done using a scale from 1 to 6 (2,14,121). Upon ratings of at least 4 (i.e. more than 50% likelihood), unintended injuries or complications were classified as AEs (Table 1). It was not the purpose of this study

to detect all the AEs in the inpatient records. The team only considered AEs in which there was a clear association with the required higher level of care.

During the third stage of the review preventability of the detected AEs was assessed using a six-point scale (Table 1). Based on this scale, preventability was grouped in three categories: no (score 1), low (score 2, 3) and high (score 4-6) preventability (2,14,121). Rating preventability is important in understanding the system specific aspects of health care processes in order to design preventive or mitigating barriers (136). Further classification was done by type of AE and the consequences of the events. The AEs were divided into types, such as drug therapy (an AE arising when a correct diagnosis was made, but there was incorrect medication therapy or delay in the medication treatment), surgery (related to a surgical procedure, such as a postoperative bleeding), diagnosis (a delayed or wrong diagnosis), system issues (in relation to problems with hospital processes, such as a nosocomial infection), procedural (in relation to a non-surgical, medical procedure, such as a dissection during cardiac catheterization), therapeutic, excluding drug therapy, surgery or procedural (an AE arising when a correct diagnosis was made, but there was incorrect therapy or a delay in the treatment), adverse drug reactions (an effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy (23)), anesthesia, other clinical management (including nursing care and allied healthcare) and others (e.g. falls) (2,144). The outcome was assessed as the level of harm at the moment of discharge from the hospital. It was divided into three categories: (1) temporary harm with a complete recovery expected within 12 months, (2) permanent impairment or resulted in permanent institutional or nursing care and (3) all-cause mortality during hospitalization. Furthermore, the length of stay (LOS) in ICU, a redo or additional surgery, the destination after hospital discharge and readmissions in the same hospital or death during a follow-up period of one, three and six months were registered. Evidently, the outcome is also influenced by the underlying disease and comorbidities and other confounding factors as reason for hospital admission. Therefore during this retrospective cohort study the causality between the outcome and the AE was not

discussed. The clinical team referred to evidence-based guidelines to define adverse event and to assess the preventability. During the whole review process an expert panel of physicians was available for advice.

Records that were found to be incomplete were also included as particularly in these cases the possibility of containing AEs might be higher (141). In 118 (13.6%) of the patient records some parts of the information was missing. Of these, 80 were included as they were considered to contain enough information to be evaluated. However 38 (4.4%) records were excluded as the research team considered them too incomplete to evaluate.

Table 1 Overview of the basic definitions (136)

Adverse event	*(1)* An unintended injury or complication, which results in *(2)* disability at discharge, death or prolongation of hospital stay, and *(3)* is caused by healthcare management (including omissions) rather than the patient's disease (2).
Causation	Refers to injury caused by health care management including acts of omission (inactions) i.e. failure to diagnose or treat, and acts of commission (affirmative actions) i.e. incorrect diagnosis or treatment, or poor performance (50). To determine whether the injury is caused by health care management or the disease process a 6-point scale will be used (2,14,121). 1. (Virtually) no evidence for management causation 2. Slight to modest evidence of management causation 3. Management causation not likely (less than 50/50, but 'close call') 4. Management causation more likely (more than 50/50, but 'close call') 5. Moderate to strong evidence of management causation 6. (Virtually) certain evidence of management causation
Preventable Adverse Event	An injury that is caused by medical intervention or management (rather than the disease process) and either prolonged hospital stay or caused disability at discharge, where there was enough information currently available to have avoided the event using currently accepted practices (142). The degree of preventability of the adverse events is measured on a 6-point scale, grouped into three categories (2,14,121) -*No Preventability* 1. (Virtually) no evidence for management causation -*Low Preventability* 2. Slight to modest evidence of management causation 3. Management causation not likely (less than 50/50, but 'close call') -*High preventability* 4. Management causation more likely (more than 50/50, but 'close call') 5. Moderate to strong evidence of management causation 6. (Virtually) certain evidence of management causation

Ethical approval & confidentiality

Ethical approval was received from the Institutional Review Board of Hasselt University and each of the participating hospitals. The study was registered at Clinicaltrial.gov (NCT02044718). Researchers signed a confidentiality agreement with the hospitals, which was approved by the Belgian Privacy Commission (158).

Statistical analyses

The patient characteristics were expressed as the means ± standard deviation (SD) or as number and percentages. Incidence per 100,000 patient days and their 95% confidence interval (CI) were calculated. The PPV as the proportion of true positive results and thus reflecting the reliability of this screening criterion was calculated. All statistical calculations were performed using Statistical Package for Social Science (SPSS Inc., Chicago, IL), version 20.0 and STATA 10.0 SE (StataCorp LP, Texas).

RESULTS

Patient characteristics

During the six-month observation period 395,338 patient hospitalization days (all patient days excluding intensive care, palliative, neonatal, pediatric and one day-stay admissions), 5,446 admissions to the ICUs and 255 MET interventions were registered in the six participating hospitals. Seven hundred and fifty-three (13.8%) of the transfers to intensive care were unplanned; 183 (24.3%) of these were readmissions to the ICU. One hundred and fifteen patients received a MET intervention without transfer to intensive care. Combined, 868 patients with an unplanned need for higher level of care were included in the record review (Figure 1), of which 515 (59.3%) were included by the two teaching hospitals. Of this initial cohort, 38 records (4.4%) were found too incomplete for the review and were excluded. Therefore, 830 patient records were reviewed. Their demographic and clinical characteristics are shown in table 2 and in supplement table 2.

Incidence of AEs requiring a higher level of care

One or more AEs were detected in 465 patient records (56% of the reviewed records), 457 (98%) patients had one AE and eight (2%) patients had more than one AE. In total 473 AEs were found (Figure 1). In the six-month measurement period, there were 395,338 patient days (1083 years) at risk (all patient days excluding intensive care, palliative, neonatal, pediatric and one day-stay admissions) in the six participating hospitals. The overall incidence rate of patients transferred to a higher level of care involving an AE(s) was 117.6 (95% CI 106.9–128.3) per 100,000 patient days at risk. The PPV was 56.0% (95%CI 52.6-59.4) for unplanned transfer to a higher level of care (465 patients with an AE(s) per 830 UIA and/or MET intervention with a record review). Selecting only the patients with an UIA, the PPV was 57.7% (95%CI 54.0-61.4) being 415 patients with an AE(s) per 719 UIA with a record review.

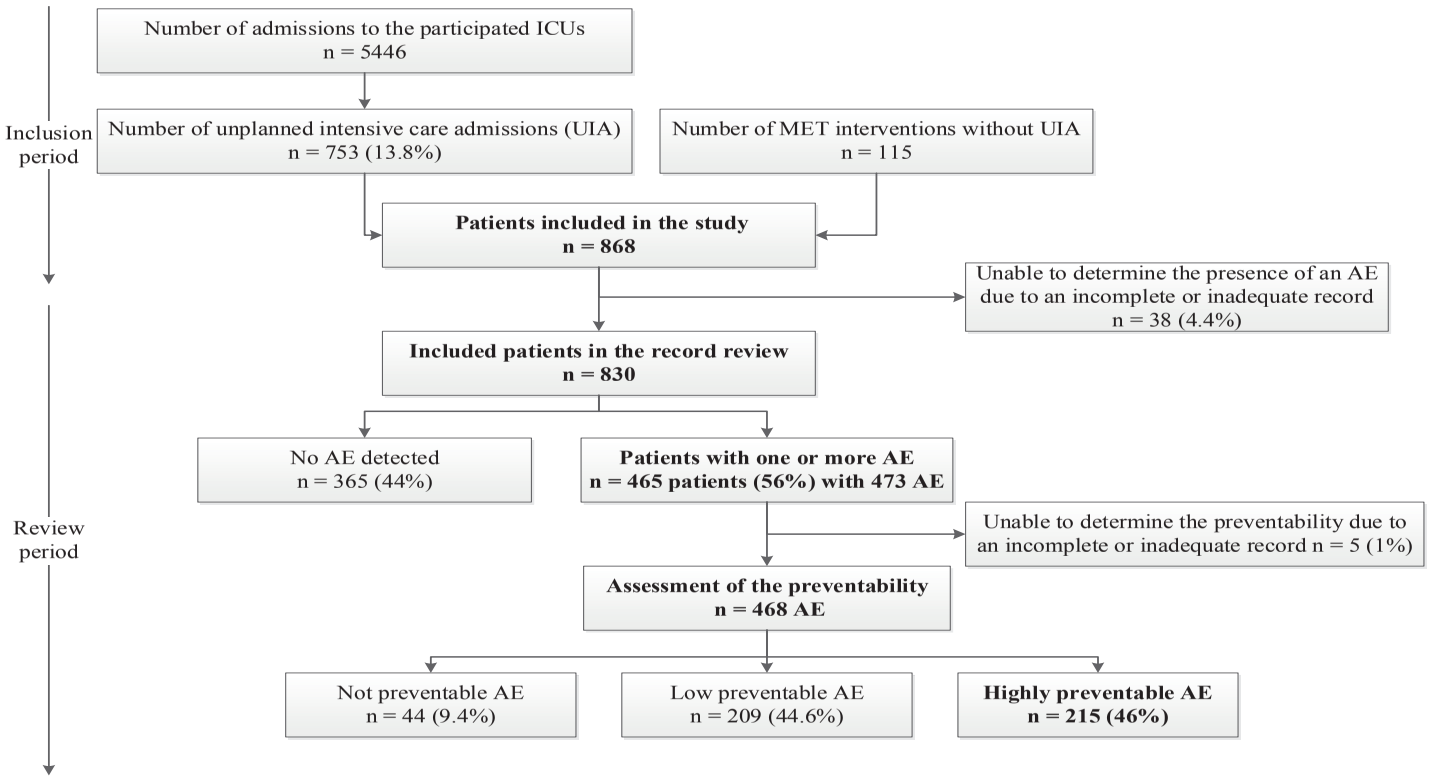

Figure 1 Overview of the inclusion and review process

AE: Adverse Event - ICU: Intensive Care Unit - MET: Medical Emergency Team - UIA: Unplanned Intensive care Admissions

Table 2 Characteristics, medical history and type of admission of the included patients (n= 830)

Variable	Number (%)
Age category	
- 21-40	45 (5.4)
- 41-65	218 (26.3)
- 66-79	328 (39.5)
- ≥80	239 (28.8)
Male	421 (50.7)
Comorbidities: ASA classification at the moment of hospital admission	
- I: Normal healthy patient	60 (7.2)
- II: Patient with mild systematic disease	171 (20.6)
- III: Patient with severe systematic disease	231 (27.8)
- IV: Patient with severe systematic disease that is a constant threat to life	368 (44.3)
ADL functional limitations	545 (65.7)
Previous hospital admission ≤ 3 months	380 (45.8)
Cognitive impairment	77 (9.3)
APACHE II at ICU admission, mean ±SD	17.8 ±8.7
Number of medications on admission, mean ±SD	7.4 ± 4.7
Polypharmacy on admission (≥5 different prescription medications)	588 (70.8)
Admission to the hospital	
- Emergency admission	538 (64.8)
- Elective admission	233 (28.1)
- Admission after consultation	36 (4.3)
- Transfer from another hospital	23 (2.8)
Classification based on APR-DRG v15	
- Surgical patient	415 (50.5)
- Extreme (class IV) Severity Index (SOI)	389 (47.4)
- Extreme (class IV) Risk of Mortality (ROM)	360 (43.4)
Top 3 of verified admission diagnosis	
- ICD-9-codes 390-459: diseases of the circulatory system	226 (27.7)
- ICD-9-codes 460-519: diseases of the respiratory system	120 (14.7)
- ICD-9-codes 520-579: diseases of the digestive system	106 (13.0)

ADL: Activities of Daily Living
APACHE II: Acute Physiology and Chronic Health Evaluation
APR-DRG v15.0: All Patient Refined Diagnosis Related Group, version 15
ASA: American Society of Anaesthesiologists
ICD-9: International Classification of Diseases, 9th revision
ICU: Intensive Care Unit
ROM: Risk Of Mortality
SD: Standard Deviation
SOI: Severity Of Illness

Preventability of the AEs

The reviewers considered 215 of the 473 AEs (46%) to be highly preventable AEs; 209 (44.6%) and 44 (9.4%) AEs were considered low or not preventable respectively (Figure 1). This means that 215 (25.9%) of all unplanned transfers to a higher level of care were related to a highly preventable AE. The overall incidence rate of highly preventable AEs requiring a higher level of care was 54.4 (95% CI 47.15–61.65) per 100,000 patients days at risk.

Type of the AEs

The AEs were mainly associated with drug therapy (n= 134, 25.6%), surgery (n= 124, 23.7%), diagnosis (n= 65, 12.4%), system issues (n= 65, 12.4%) and procedural (n= 49, 9.4%) (Table 3). The drug related adverse events were mainly associated with antibiotics and antithrombotic agents.

Outcomes

All the observed AEs required a higher level of care. This has important implications for the patients and their relatives. The severity of the harm, however, varied. A redo or additional surgery was necessary for 110 patients with an AE(s) (23.7%). Upon discharge 301 of the 465 patients with an AE went back to the original home situation (64.7%), 47 (10.1%) patients required a different type of care than before the admission (transfer to another (university) hospital, rehabilitation center, nursing home). Overall, 259 (55.7%) of the 465 patients with an AE(s) resulted in temporary harm with a complete recovery expected within 12 months, while 89 patients with an AE(s) (19.1%) suffered long term or permanent impairment or needed permanent institutional or nursing care. The all-cause mortality rate of the patients with an AE was 25.2% (117 of 465 patients). Nevertheless in

the group of patients without the detection of an AE, also 28.7% of the patients died. The majority of these patients had multiple comorbidities and polypharmacy. Within one, three and six months respectively 68 (19.6%), 105 (30.1%) and 131 (37.6%) of the 348 surviving patients with an AE had a readmission in the same hospital. In this study the causality of the mortality was not discussed. However, in the total group of 830 patients with an unplanned transfer to higher level of care 243 died, 98.4% of these deceased patients had no pre-existing DNR order; 117 of the 243 deceased patients (48.1%) had an AE of which 62 (51.7%) were highly preventable. Therefore 25.5% (62 of 243) of the deceased patients suffered from a highly preventable AE.

The mean ICU LOS of patients with a highly preventable AE was 6.20 ± 7.3 days and had a median ICU LOS of 3.5 days (Q1-Q3: 2-8 days), as 25% of these patients had LOS in ICU longer than 8 days. The total ICU LOS of patients who had an UIA and a highly preventable AE was 1,166 days (5.64% of the total LOS ICU).

Table 3 Overview of the types of adverse events

AE classification	AEs n, (%)	Highly preventable AEs n, (%)
Drug therapy: an AE arising when a correct diagnosis was made but there was incorrect medication therapy or a delay in the medication treatment (preventable adverse drug events)	134 (25.6)	134 (100)
Surgery: an AE related to a surgical procedure	124 (23.7)	34 (27.6)
Diagnostic: an AE arising from a delayed or wrong diagnosis	65 (12.4)	58 (89.2)
System issue: an AE in relation to problems with hospital processes such as nosocomial infection or equipment malfunction	65 (12.4)	8 (12.3)
Procedural: an AE in relation to a procedure such as insertion of a central venous line, nasogastric tube, cardiac catheterization, etc.	49 (9.4)	7 (14.3)
Therapeutic (other than drug therapy/surgery/ medical procedure): an AE arising when a correct diagnosis was made but there was incorrect therapy or a delay in the treatment	30 (5.7)	24 (80.0)
Drug/fluid: side effects, allergic reactions, anaphylaxis (adverse drug reactions)	26 (5.0)	0
Anesthesia: an AE related to the given anesthesia	14 (2.7)	4 (28.6)
Other clinical management: including nursing care and allied healthcare	10 (1.9)	6 (60.0)
Other (e.g. fall)	6 (1.1)	2 (33.3)

AE: adverse event

DISCUSSION

The overall incidence of AEs requiring an unplanned higher level of care was 117.6 per 100,000 patient days at risk. A higher level of care was defined as: (1) an unplanned (re)admission to the ICU or (2) an intervention by a Medical Emergency Team (MET) due to an unanticipated change in the patient's clinical status. In 56% of the patients with an unplanned need for a higher level of care an AE was found. This study methodology, using unplanned transfer to a higher level of care as a trigger, has a much higher AE detection rate compared to previous record review studies (2,8,50,114,121,122,124,128,145–148). The PPV, which reflects the reliability of the screening criteria, was 56% for unplanned transfer to a higher level of care (UIA and MET interventions). Selecting only the patients with an UIA, the PPV was 57.7%. A previous retrospective record review based on the use of 18 screening criteria of the HMPS trigger tool described a PPV for UIA of 18.6% (126). Explanations for the higher proportion can be found in the different methodology. Firstly, in our study the clinical team consisted of a research nurse, a physician, a clinical pharmacist and was supported by a panel of experts. In addition, the composition of the team was the same for the six hospitals to ensure a uniform decision process. Based on this multidisciplinary approach, the assessment of the AEs differs from the assessment by one discipline, which is a strength of our methodology. Secondly, the selection of patients differed. In previous research 18 triggers were used and 648 patients were selected, whereas in our study only patients based on the trigger 'unplanned transfer to a higher level of care' were selected. Therefore, the PPV for UIA of our study is calculated on a much higher sample size. Based on the PPV and the fact that record review is a costly and time-consuming method (28), focusing on unplanned transfer to a higher level of care to detect the most serious AEs is more efficient compared to reviewing random records.

One in four unplanned transfers to a higher level of care were related to a highly preventable AE. A systematic review of retrospective record studies found the proportion of highly preventable AEs in patients with an UIA between 17 and 77%. The wide variation was due to the methodological heterogeneity and clinical diversity due to population mix and the use of different definitions on outcomes. In order to provide full detail on the study methodology, the research protocol of this study was published earlier (136).

Preventing AEs is a complex process with organizational factors, such as safety policy, hospital resources, safety protocols, training and supervision. The six participating hospitals all had a safety management system with an incident report system with retrospective analysis, evidence-based protocols, regular measurement of safety culture and training opportunities. The hospitals had electronic patient records to some extent, however none of them had a hospital-wide electronic patient record that facilitates the exchange of patient information between all caregivers. In the hospitals with electronic drug ordering, there was no or a very preliminary decision support system to prevent adverse drug events. Three hospitals had a stroke unit and only one participating hospital had a step-down unit. These organizational factors most likely have an impact on the results.

The observed AEs were mainly associated with drug therapy (25.6%), surgery (23.7%), diagnosis (12.4%), system issues (12.4%) and procedures (9.4%). The classification of AEs in earlier studies was not uniform, which makes comparison difficult. However, categories such as incorrect (drug) therapy, surgical, procedural, diagnosis were the main categories in earlier studies on AEs requiring ICU admission (67) and in-hospital AEs (2,8,50,121,124,129). The proportion of all-cause mortality the group of patients with an AE was 25.2%. Nevertheless in the group of patients without the detection of an AE, also 28.7% of the patients died. The majority of these patients had multiple comorbidities and polypharmacy. Therefore in our research the causality between AE and mortality was not specifically investigated. However, 25.5% of the deceased patients had

a highly preventable AE. These observations are consistent with a systematic review (67) on AEs in patients with an UIA with mortality percentages between 0 and 58%. The patients in our study had a mean age of 70. Almost all of them suffered from multiple comorbidities and had polypharmacy. This group of frail patients was found to have high risk of in-hospital AEs resulting in a transfer to a higher level of care. This has an important impact on patient outcome. Further, it puts additional burden on ICU resources and increases the cost of hospitalization. Healthcare professionals have to bear in mind the vulnerability in this group of patients. Specific improvement projects should aim for a better follow-up system for these patients in order to avoid the occurrence of AEs.

Besides the methodological strengths, the study also has limitations. Firstly, there is the lack of an actual gold standard for AE detection (28). Therefore the judgment of presence of AEs is difficult and always susceptible to subjectivity. A retrospective record review is currently the best method available to assess incidence of AEs. An important limitation is that the method of record review itself might lead to an underestimation of AEs (136). A conservative approach was chosen to detect AEs: if any doubt existed, the event was not classified as an AE. Therefore the results presented might be an underestimation of the actual figure. Secondly, the quality of the records was often suboptimal, which could also lead to an underestimation. We tried to prevent both limitations by working with an experienced multidisciplinary team consisting of a research nurse, a physician and a clinical pharmacist. In addition, there was an expert panel available when necessary. Thirdly, the registration of the MET interventions in the participating hospitals might not have been complete. Fourthly, for feasibility purposes, the hospitals of the province of Limburg were selected in this study. The included hospitals can be considered comparable to other hospitals in Belgium. Two out of the six hospitals were teaching hospitals. It was not the objective of this study to provide results which can be generalized to all settings worldwide. However, this study can certainly trigger further research in other countries. To create transparency in the methods and improve comparability, we published the study protocol (136).

Our findings on the impact of AEs should create a greater awareness of the occurrence of AEs and should lead to the optimization of healthcare procedures and multidisciplinary care management in order to achieve better prevention. Record review and analysis of the (preventable) AEs may trigger important system changes within hospitals. Based on this study, several quality improving interventions, such as Inpatient Anticoagulation Management System with seven key areas [(1) protocols and guidelines, (2) implementation of a trigger tool method, (3) implementation of a new computer order entry system, (4) education of health care providers, (5) patient education, (6) care transitions and (7) outcomes and risk management], early warning systems with Situation Background Assessment Recommendation (SBAR) communication and review of in-hospital reanimations have already been implemented in some of the participating hospitals. Further study is planned to assess the costs of care for the patients that were identified in this study. Insights from such a study can provide information for healthcare professionals, hospital management and policy makers on how improvement actions can substantially reduce healthcare costs.

One of the challenges in safety improvement in healthcare is the measurement of AEs. Retrospective record review is one of the methods to measure the incidence of AEs. Since this is a labor intensive and therefore costly method, the use is mostly restricted within the context of a study. This study used the trigger 'unplanned transfer to a higher level of care' and estimated the PPV at 56% (95% CI 52.6 – 59.4). This means an AE was related to the unplanned transfer to a higher level of care in 56% of the cases. The number of unplanned transfers to a higher level of care itself is relatively easy to measure and could be proposed as a proxy indicator for the number of AEs related to unplanned transfers, at least within similar settings as the hospitals involved in this study. Based on the finding of this study, the number of unplanned transfers to a higher level of care relative to the number of patient days will be proposed as a safety indicator for Belgian hospitals.

CONCLUSION

In this retrospective record review study, adverse events leading to unplanned transfers to higher level of care are common. One fourth of unplanned transfers are associated to highly preventable adverse event highlighting the need for dedicated quality improvement programs.

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CONTRIBUTING OF AUTHORS

KM prepared the study, conducted the pilot and the multicenter study, analyzed and interpreted the data. KM is the manuscript's guarantor. KM, MD & GK were the members of the clinical team. WS performed the sample size calculation and give advice in working with Open Clinica, SPSS and STATA. NC, ED, FW, MV, AnV, WS, ArV made critical revisions to the paper for important intellectual content. ArV was the initiator of the project. All authors read and approved the final manuscript.

SUPPLEMENT DIGITAL CONTENT

Table 1 Overview of the used definitions

Adverse event	*(1)* An unintended injury or complication, which results in *(2)* disability at discharge, death or prolongation of hospital stay, and *(3)* is caused by healthcare management (including omissions) rather than the patient's disease (2).
Unintended injury	Refers to any disadvantage for the patient that leads to prolonged or strengthened treatment, temporary or permanent (physical or mental) impairment or death (50).
Disability	Refers to temporary or permanent impairment of physical or mental function attributable to the adverse event (including prolonged or strengthened treatment, prolonged hospital stay, readmission, subsequent hospitalization, extra outpatient department consultations or death) (2). The disability can be divided into categories - Temporary disability included AEs from which complete recovery occurred within 12 months; - Long term/permanent disability included AEs which caused permanent impairment or which resulted in permanent institutional or nursing care; - All-cause mortality during hospitalization (2).
Causation	Refers to injury caused by health care management including acts of omission (inactions) i.e. failure to diagnose or treat, and acts of commission (affirmative actions) i.e. incorrect diagnosis or treatment, or poor performance (50). To determine whether the injury is caused by health care management or the disease process a 6-point scale will be used (2,14,121). - (Virtually) no evidence for management causation - Slight to modest evidence of management causation - Management causation not likely (less than 50/50, but 'close call') - Management causation more likely (more than 50/50, but 'close call') - Moderate to strong evidence of management causation - (Virtually) certain evidence of management causation

Health Care Management	Includes the actions of individual hospital staff as well as the broader systems and care processes and includes both acts of omission (failure to diagnose or treat) and acts of commission (incorrect diagnosis or treatment, or poor performance) (121).
Preventable Adverse Event	An injury that is caused by medical intervention or management (rather than the disease process) and either prolonged hospital stay or caused disability at discharge, where there was enough information currently available to have avoided the event using currently accepted practices (142). The degree of preventability of the adverse events is measured on a 6-point scale, grouped into three categories (2,14,121).
	No preventability 1. (Virtually) no evidence for preventability
	Low preventability 2. Slight to modest evidence of preventability 3. Preventability not likely (less than 50/50, but 'close call')
	High preventability 4. Preventability more likely (more than 50/50, but 'close call') 5. Strong evidence of preventability 6. (Virtually) certain evidence of preventability
An unplanned higher level of care	A higher level of care may include: An unplanned transfer to an Intensive Care Unit, An intervention of a Medical Emergency Team.
Intensive Care Units (ICUs)	Hospital units providing continuous surveillance and care to actually ill patients (Mesh definition). E.g. medical and surgical ICUs, for example medium care, coronary Care Units, pediatric ICUs and respiratory care units.
Planned ICU admissions	Admissions of patients expected to arrive on the ICU, e.g. routinely scheduled post-surgery admissions or transfers directly to the ICU from outside hospitals.
Unplanned ICU admissions	All patients unexpectedly admitted to the intensive care unit from a lower level of care in the hospital during the study period (adapted from Baker, 2009) (62).

Medical Emergency team (MET)	The MET team consists of a physician and two specially trained nurses from the emergency department and is available 24/7. In case of deterioration during hospitalization, the MET team provides a rapid response, assesses and stabilizes the patient, e.g. resuscitation, administers medication, etc. The aim is to prevent further deterioration and to decide if enhanced levels of care are appropriate.
Patient harm	Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalization, or that results in death (IHI) (143).

Table 2 Overview of all the ICD-9 verified reasons for hospital admission

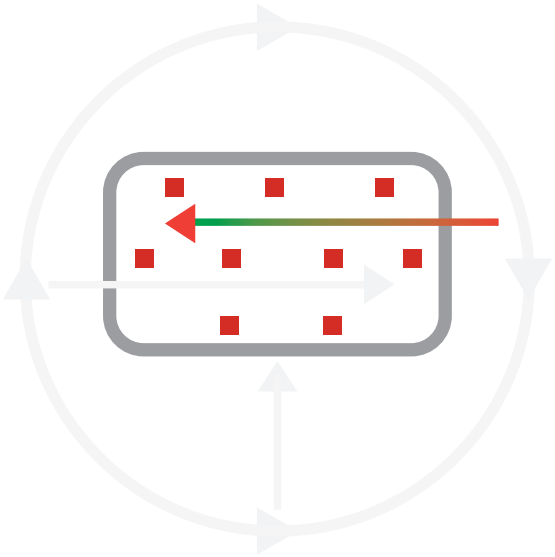
List of ICD-9-codes	Frequency	Percent	Valid Percent	Cumulative Percent
List of ICD-9 codes 011-139 : infectious and parasitic diseases	10	1,2	1,2	1,2
List of ICD-9 codes 140-239 : neoplasms	76	9,2	9,3	10,5
List of ICD-9 codes 240-279: endocrine, nutritional and metabolic diseases, and immunity disorders	25	3,0	3,1	13,6
List of ICD-9 codes 280-289: diseases of the blood and blood-forming organs	5	0,6	0,6	14,2
List of ICD-9 codes 290-319: mental disorders	12	1,4	1,5	15,7
List of ICD-9 codes 320-359: disease of nervous system	15	1,8	1,8	17,5
List of ICD-9 codes 360-389: diseases of the sense organs	11	1,3	1,3	18,8
List of ICD-9 codes 390-459: diseases of the circulatory system	226	27,2	27,7	46,5
List of ICD-9 codes 460-519: disease of the respiratory system	120	14,5	14,7	61,2
List of ICD-9 codes 520-579: diseases of the digestive system	106	12,8	13,0	74,2
List of ICD-9 codes 580-629: diseases of the genitourinary system	27	3,3	3,3	77,5
List of ICD-9 codes 630-679: complications of pregnancy, childbirth, and the puerperium	14	1,7	1,7	79,2
List of ICD-9 codes 680-709: diseases of the skin and subcutaneous tissue	2	0,2	0,2	79,4
List of ICD-9 codes 710-739: diseases of the musculoskeletal system and connective tissue	34	4,1	4,2	83,6

List of ICD-9 codes 780-799: symptoms, signs, and ill-defined conditions	16	1,9	2,0	85,6
List of ICD-9 codes 800-999: injury and poisoning	93	11,2	11,4	96,9
List of ICD-9 codes E and V codes: external causes of injury and supplemental classification	25	3,0	3,1	100,0
Total	817	98,4	100,0	
Missing	13	1.6		
Total	830	100,0		

ICD-9: International Classification of Diseases, 9th revision, Clinical Modification

CHAPTER 4

A multicenter record review of in-hospital adverse drugs events requiring a higher level of care



A multicenter record review of in-hospital adverse drugs events requiring a higher level of care

This study was submitted as

Marquet K, Claes N, De Troy E, Kox G, Droogmans M, Vleugels A. A multicenter record review on in-hospital Adverse Drugs Events requiring a higher level of care. Submitted.

This study was presented at

- The European Society Clinical Pharmacology Annual Symposia: Patient Safety: Research, Bridging the gaps. Copenhagen, Denmark, 22nd-24th October 2014.

Chapter 4: A multicenter record review of in-hospital adverse drugs events requiring a higher level of care

ABSTRACT

Purpose: Adverse drug events (ADEs) are a world-wide concern, particularly when leading to a higher level of care. This study defines a higher level of care as an unplanned (re)admission to an Intensive Care Unit (ICU) or an intervention by a Medical Emergency Team. The objectives are to determine the incidence and preventability of ADEs leading to a higher level of care, to assess the types of drug involved and the levels of harm induced and to identify the risk factors.

Methods: A three-stage retrospective review was performed in six Belgian hospitals. Patient records were assessed by a trained clinical team consisting of a nurse, a physician and a clinical pharmacist. Descriptive statistics, univariate and multiple logistic regressions were used.

Results: In this study 830 patients were detected for whom a higher level of care had been needed. In 160 (19.3%) cases an ADE had occurred; 134 (83.8%) of these were categorized as preventable. The overall incidence rate of patients transferred to a higher level of care because of a pADE was 33.9 (95% CI: 28.5-39.3) per 100,000 patient days at risk. Antibiotics and antithrombotic agents accounted both for one-fifth of all pADEs. Multivariate analysis indicated ASA score as a risk factor for pADEs.

Conclusions: The high number of pADE with patient harm shows that there is a need for structural improvement of pharmacotherapeutical care. Detection of these pADEs can be the basis for the implementation of these improvements.

INTRODUCTION

Patient safety has become a major concern and identifying risks and hazards that cause or have the potential to cause healthcare associated injury or harm is an important challenge (7). Detection of these unintended injury or complication, defined as adverse events (AE), can be the basis for the implementation of improvements. A review on the overall incidence and nature of in-hospital AEs through record review suggested that AEs affect 9.2% of the patients during their stay; surgery and medication-related events constituted the majority (15). An injury resulting from medical intervention related to a drug (1,27), or an injury caused by a medication (22) is defined as an adverse drug event (ADE). The incidence of in-hospital ADEs has been described as 6.5 to 29 per 100 admissions (27,159–161).

Detection and analysis of ADE must focus on preventable ADE (pADEs). The proportion of pADE varied from 14%-75% (25,27,159–164). pADEs are most often related with antibiotics (159), non-steroidal anti-inflammatory drugs (NSAID) (159,165), inappropriate fluid management (60), anticoagulant treatment (165) in combination with NSAIDs (166) and cardiovascular drugs (165) such as antihypertensives (159) and diuretics (159). Previous research described that ADEs result in considerable increase of the length of hospital stay (LOS) of 6.2 days (95% CI 3.6 - 8.8) and average additional cost of €2,507 (95% CI 1,520 – 3,773) (166). Most ADEs were not fatal, however in 4.9% (161) to 12% (27) they were life-threatening or were described as serious in 30% (27) to 33% (161). ADEs could result in the unplanned need for a higher level of care, such as Intensive Care Unit (ICU). Intensive care prolongs length of hospital stay, places additional pressure on ICU resources and increases the costs (64). A prospective study (68) describes that 17% of the adverse events (AEs) which lead to an ICU admission are drug related. However, an overall incidence rate of ADEs which lead to a need for a higher level of care hasn’t been described.

Although all AEs should be of concern, AEs that are preventable and result in serious harm are of particular concern (69). The identification of these (p)ADEs is therefore a substantial component of patient safety policy. The most common methods for detecting ADEs are voluntary reporting, record review, computerized monitoring, and exploring claims data. Although record review is costly and time-consuming, this approach is the most valuable (28). Therefore, the objectives of this study were to determine the incidence and preventability of in-hospital ADEs requiring a transfer to a higher level of care, the type of drugs involved, the risk factors concerned and the level of harm induced by using a retrospective record review.

METHODS

A multistage retrospective patient record review study on in-hospital ADEs requiring a higher level of care was performed in six Belgian hospitals.

Definitions

ADEs are defined by Leape et al. (22) as an injury caused by medication. Using this definition, the term includes both adverse drug reactions (ADR) and preventable adverse drug events (pADE). ADR is an effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy (23). ADR give harm directly caused by the drug at normal doses (167). The injury arises from the intrinsic properties of the medicine (24) or injury with no error involved (25), which implicated that ADRs are not preventable. A pADE can be described as a preventable medication related error with harm (8,22,26,27); the harmful effects can arise from errors at any medication use stage including ordering, transcribing, dispending, administering or monitoring (28). Nebeker et al. (31) describe that there is an overlap between ADRs and medication errors and implicated that there are preventable and non-preventable ADRs. However, during this study we used the conceptualization model of Otero and Schmitt (24) which imply that ADEs consist of pADEs and non-preventable ADRs.

A higher level of care was defined as (1) an unplanned (re)admission to the ICU or (2) an intervention by a Medical Emergency Team (MET) due to an unanticipated change in the patient's clinical status during the hospital admission. A hospital readmission within 72 hours was regarded as the same admission. Planned admissions to the ICU from the operation room (major surgery) and ICU admissions directly from the emergency department were excluded. Because of their specific nature, the neonatal and maternal ICU were excluded.

Setting

All hospitals from one province were invited to participate in the study. Six of the seven acute hospitals confirmed their participation and gave permission to access patient records, of which two teaching hospitals (74). In total these six hospitals account for 2,939 hospitals beds (range 213-1,003) and 134 ICU beds (range 8-52) were included, divided over medical, surgical, mixed ICU and Coronary Care Units.

Data collection

A three-stage retrospective review process of screening, record review and consensus judgment was used (136). The research protocol was prior to this multicenter study tested during a two month pilot study.

In the first stage, all patients who required a higher level of care were screened during six months from 7th November 2011 until 6th May 2012 by the head nurses or the intensivists of ICU. These people had a half-day training program on case selection using a standardized selection form. UIAs and MET interventions were identified via ICU or emergency logbook. In case of doubt, the record was forwarded for review in the second stage. There were in total 4,693 exclusions, these were mostly ICU admissions directly from the emergency department (50.9%), planned admissions to the ICU (41.4%). In order to test the validity of the screening process, 470 excluded patients (a random sample of 10%) of the 4,693 excluded patients were reviewed by the principal investigator. Five percent of these controls (n= 23) were considered incorrect classified and were subsequently included in the study. This degree of misclassification was similar between the hospitals.

In the second stage, a case note of each patient was made and patient characteristics (such as gender, year of birth, type of hospital admission, number of prescribed

medication before hospital admission) were collected by the principal investigator using Open Clinica (154). The anaesthetist estimated the American Society of Anaesthesiologists (ASA) physical status at the time of the hospital admission (155,156). Subsequently, the record review was done in the six hospitals by the same, experienced and independent clinical team consisting of a research nurse (specialized in Intensive Care and Emergency care, Master in Healthcare management), a physician (specialized in Anesthesiology and Emergency Medicine) and a clinical pharmacist. The clinical team referred to various evidence-based guidelines to decide if the patient who requiring an unplanned transfer to a higher level of care had an ADE. The assessment of causation was done using a scale from 1 to 6 (Table 1) (2,14,121). Upon ratings of at least 4 (i.e. more than 50% likelihood), unintended injuries or complications were classified as ADEs. While starting from the focus an unplanned need for a higher level of care, it was not the purpose of this study to detect all the ADEs in the inpatient records. The team only considered ADEs showing a clear association with the requiring higher level of care.

The third stage started once the clinical team had concluded on an ADE. The review was continued with an assessment of preventability using a six-point scale (Table 1) (2,14,121). Rating preventability is important in understanding the system specific aspects of health care processes in order to design preventive barriers (136). Next, the drug, the type and the outcome were described. To classify the drugs the Anatomical Therapeutic Chemical (ATC) classification system was used. In this system, the active substances are ordering into five different levels according to the organ or system (first level), their therapeutic (second level), pharmacological (third level), chemical properties (fourth level) and chemical substance (fifth level) (168). The analysis went up to the second level (ATC2). The pADEs were divided into type of errors, such as inappropriate posology (refers to inappropriate dose, such as a dose not adapted to the pathology, the blood levels of the patient), omission of the drug (the act of omitting of necessary drug therapy), inappropriate drug choice, known contraindication or others. The outcome was assessed at the moment of discharge from the hospital, which was divided into

three categories: (1) temporary harm with a complete recovery occurring within 12 months, (2) permanent impairment or resulted in permanent institutional or nursing care and (3) all-cause mortality. Evidently, the outcome is also influenced by confounding factors as reason for hospital admission, comorbidities. Therefore during these retrospective cohort study the causality between the outcome and the AE was not discussed. During the whole review process an expert panel of physicians was available for advice.

Table 1 Definitions

Adverse drug event	An injury resulting from medical intervention related to a drug (1,27). An injury caused by a medication (22), including both adverse drug reactions and preventable adverse drug events
Adverse drug reaction	An effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy (23)
Preventable adverse drug event	A preventable medication related error with harm (8,22,26,27); the harmful effects can arise from errors regarding any medication use stage including ordering, transcribing, dispensing, administering or monitoring (28). The degree of preventability of the adverse events is measured on a 6-point scale (2,14,121) - (Virtually) no evidence for preventability - Slight to modest evidence of preventability - Preventability not likely (less than 50/50, but 'close call') - Preventability more likely (more than 50/50, but 'close call') - Strong evidence of preventability - (Virtually) certain evidence of preventability
Causation	Refers to injury caused by health care management including acts of omission (inactions) i.e. failure to diagnose or treat, and acts of commission (affirmative actions) i.e. incorrect diagnosis or treatment, or poor performance (50). To determine whether the injury is caused by health care management or the disease process a 6-point scale will be used (2,14,121) - (Virtually) no evidence for management causation - Slight to modest evidence of management causation - Management causation not likely (less than 50/50, but 'close call') - Management causation more likely (more than 50/50, but 'close call') - Moderate to strong evidence of management causation - (Virtually) certain evidence of management causation
Health Care Management	Includes the actions of individual hospital staff as well as the broader systems and care processes and includes both acts of omission (failure to diagnose or treat) and acts of commission (incorrect diagnosis or treatment, or poor performance) (121)

Unplanned higher level of care	A higher level of care may include: - An unplanned transfer to an intensive care unit - An intervention of a Medical Emergency Team
Unplanned ICU admissions	All patients unexpectedly admitted to the intensive care unit from a lower level of care in the hospital during the study period. If a patient experienced more than one unplanned ICU admission during his/her hospital stay, each unplanned admission is included in the analysis (adapted from Baker, 2009) (62)
Medical Emergency team	The MET team consist of specialize healthcare professionals, namely a physician and two specially trained nurses from the emergency department and is available 24/7. If deterioration during hospitalization, the MET team provide a rapid response, assess and stabilize the patient, e.g. resuscitation, administer medication, etc. The aim is to prevent further deteriorating and to decide if enhanced levels of care are appropriate
Outcome measuring as disability	Refers to temporary or permanent impairment of physical or mental function attributable to the adverse event (including prolonged or strengthened treatment, prolonged hospital stay, readmission, subsequent hospitalization, extra outpatient department consultations or death) (2). The disability can be divided into three categories: - Temporary disability included AEs from which complete recovery occurred within 12 months; - Long term/permanent disability included AEs which caused permanent impairment or which resulted in permanent institutional or nursing care; - All-cause mortality during hospitalization (2)

Ethical approval & confidentiality

Ethical approval was received from the Institutional Review Boards of Hasselt University and each of the participating hospitals. The study was registered at Clinicaltrial.gov (NCT02044718). The researchers signed a confidentiality agreement with the hospitals, which was approved of by the Belgian Privacy Commission (158). To protect patient's identity from disclosure each inclusion received a unique study number. Patient identifiers were kept in a dataset separately from the primary database. The reviewers had a personal password to access the electronic databases. The identities of patients or physicians were not revealed in any research reports.

Statistical analyses

The primary outcome of the study was the frequency of ADEs. The secondary outcomes were the preventability, the associated risk factors and the level of harm. Continuous variables were presented as the mean ± standard deviation (SD) and categorical variables as number and percentages. Incidents per 100,000 patient days, odds ratios and their 95% confidence interval (CI) were calculated. To evaluate the risk factors univariate and multiple logistic regressions were used. All statistical calculations were performed using Statistical Package for Social Science (SPSS Inc., Chicago, IL), version 20.0 and STATA 10.0 SE (StataCorp LP, Texas).

RESULTS

Patient characteristics

During the six months 868 patients with a higher level of care were included in the six hospitals. Of the initial cohort of 868 patients, 38 (4.4%) records were found too incomplete, therefore 830 records were further reviewed. The demographic and clinical characteristics of these subjects are shown in table 2. Four hundred thirty-nine patients (50.6%) were men; the mean age was 70.1 (±14.5) years. The average number of prescribed medication before hospitalization was 7.5 (±4.6); 390 patients (44.9%) had a severe life-threatening systematic disease (ASA 4).

Incidence and preventability

One hundred and sixty patients (19.3%) had an ADE, of which 134 (83.8%) patients suffered a pADE and 26 (16.2%) patients had an ADR (Figure 1). The 134 pADEs were related to inappropriate posology (47.0%), omission (34.3%), inappropriate drug choice (8.2%), known contraindication (6.0%), and others such as incorrect timing, known side-effects and medication interactions (4.5%). The overall incidence rate of patients transferred to a higher level of care because of an ADE and a pADEs was 40.5 (95% CI: 34.2-46.7) and 33.9 (95% CI: 28.5 - 39.3) per 100,000 patient days at risk respectively (Table 3).

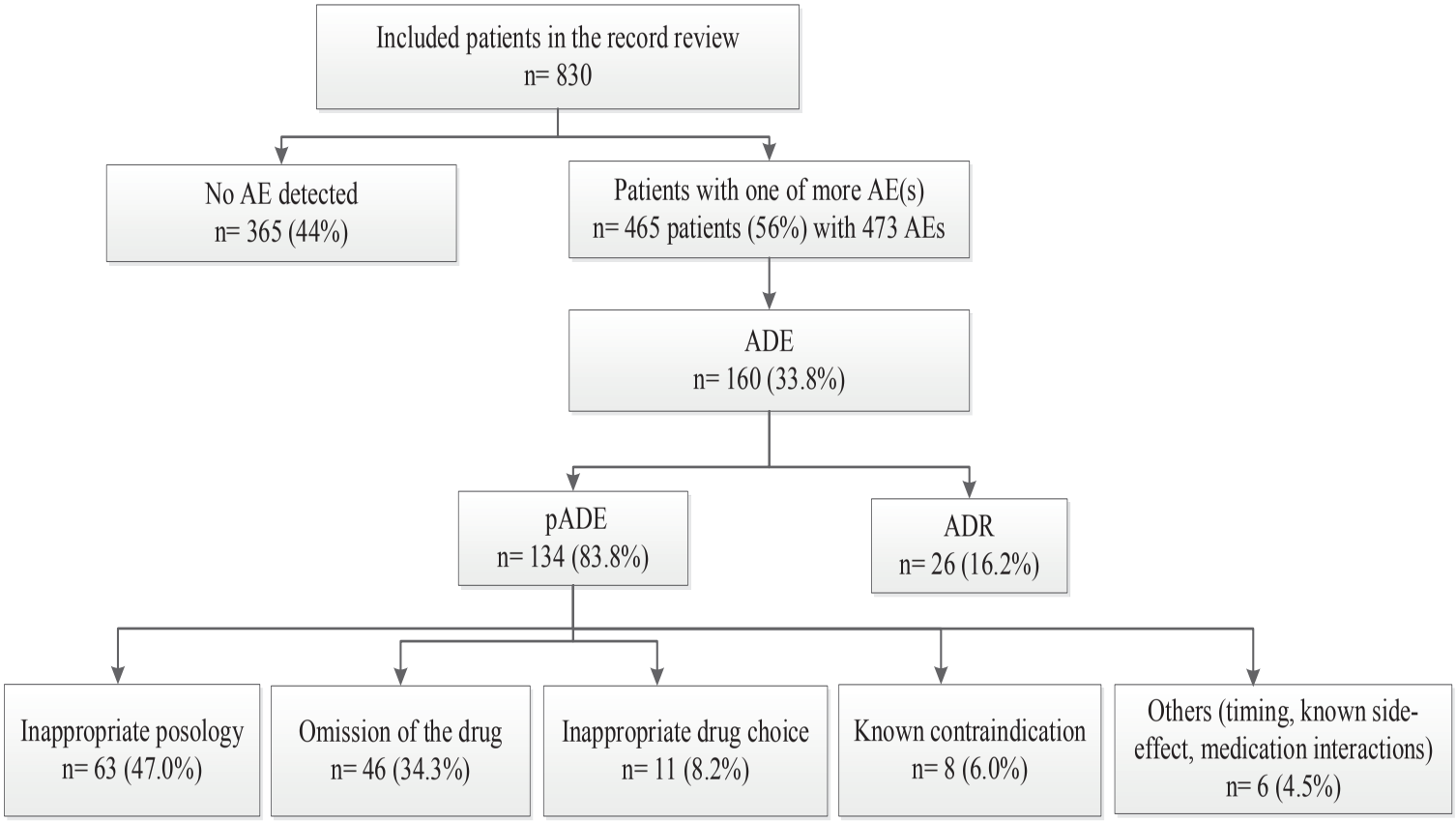


Figure 1 Overview of the incidence and type ADE

ADE: Adverse Drug Event - ADR: Adverse Drug Reaction - AE: Adverse Event - pADE: preventable Adverse Drug Event

Table 2 Characteristics, medical history and APR-DRG classification of included patients (n= 830)

Variable	Number (%)
Age, Median years (±SD)	70.1 ± 14.5
Male	439 (50.6)
ASA class IV: severe systematic disease that is a constant threat to life	390 (44.9)
ADL functional limitations	578 (66.6)
Previous hospital admission ≤ 3 months	402 (46.3)
Cognitive impairment	82 (9.4)
Number of medications on admission, median amount (±SD)	7.5 (4.7)
Polypharmacy on admission (use of 5 or more different prescription medications)	622 (71.7)
Classification based on APR-DRG v15	
- Medical patient	435 (50.8)
- Extreme (class IV) severity index (SOI)	412 (48.1)
- Extreme (class IV) Risk of mortality (ROM)	379 (43.7)
- Top 3 of verified admission diagnosis	
ICD-9-codes 390-459: diseases of the circulatory system	241 (28.3)
ICD-9-codes 460-519: diseases of the respiratory system	129 (15.1)
ICD-9-codes 520-579: diseases of the digestive system	108 (12.7)

ADL: Activities of Daily Living
APR-DRG v15.0: All Patient Refined Diagnosis Related Group, version 15
ASA: American Society of Anaesthesiologists
ICD-9: International Classification of Diseases, 9th revision
ROM: Risk Of Mortality
SD: Standard Deviation
SOI: Severity Of Illness

Table 3 Numbers of ADEs and overall incidence rate per 100,000 patient days at risk

ADE	Number (%)	Incidence per 100,000 patient days at risk	95% CI
pADE	134 (83.8)	33.9	28.5-39.3
ADR	26 (16.2)	6.6	4.1-9.1
Total	160	40.5	34.2-46.7

ADE: Adverse Drug Event
ADR: Adverse Drug Reaction
CI: Confidence Interval
pADE: preventable Adverse Drug Event

Types of drugs related to ADEs

Antibiotics and antithrombotic agents accounted each for one-fifth of all ADEs. Blood substitutes, perfusion solutions and diuretics accounted for 8.8 and 8.1% of ADEs (Table 4). pADEs were more common with antibiotics (n= 34, 25.4%) and antithrombotic agents (n=31, 23.1%), whereas antineoplastic agents were the most frequent in case of ADR (n= 6, 23.1%). Of the 160 ADEs, 120 were caused by drugs that were started in the hospital and 40 ADEs were caused by home medication. The number of medications prescribed before hospitalization was significantly (respectively p= 0.03 and p= 0.004) higher in the groups patients with ADEs (8.2 ± 4.2) and pADEs (8.5 ± 4.2) than the groups without ADEs (7.3 ± 4.7) or pADEs (7.3 ± 4.7).

Table 4 Frequency of top 10 ADEs according to Anatomical Therapeutic Chemical (ATC 2) drug classes

ATC2 classes	ADE, n (%)	pADE, n (%)	ADR, n (%)
J01 Antibacterial for systemic use	36 (22.5)	34 (25.4)	2 (7.7)
B01 Antithrombotic agents	35 (21.9)	31 (23.1)	4 (15.4)
B05 Blood substitutes & perfusion solutions	14 (8.8)	12 (9.0)	2 (7.7)
C03 Diuretics	13 (8.1)	11 (8.2)	2 (7.7)
L01 Antineoplastic agents	8 (5.0)	2 (1.5)	6 (23.1)
N02 Analgesics	6 (3.8)	5 (3.7)	1 (3.8)
C01 Cardiac therapy	6 (3.8)	5 (3.7)	1 (3.8)
C07 Beta Blocking Agents	6 (3.8)	4 (3.0)	2 (7.7)
A10 Drug used in diabetes	5 (3.1)	5 (3.7)	0
V08 Contrast media	5 (3.1)	1 (0.7)	4 (15.4)
Others ATC 2 classes, not in the top 10	26 (16.2)	24 (17.9)	2 (7.7)
Total	160 (100)	134 (100)	26 (100)

ADE: Adverse Drug Event
ADR: Adverse Drug Reaction
ATC: Anatomical Therapeutic Chemical
pADE: preventable Adverse Drug Event

Risk factors for ADEs

Based on univariate analysis, the number of medications prescribed before admission (OR 1.06, 95% CI 1.02-1.10, p= 0.005), ASA score (OR 1.38, 95% CI 1.12-1.71, p= 0.03) and age (OR 1.02, 95% CI 1.01-1.04, p= 0.005) were associated with pADEs (Table 5).

Table 5 Risk factors associated with ADEs and pADEs using univariate analysis

Risk factors	ADE		pADE	
	Crude OR (95% CI)	P value[a]	Crude OR (95% CI)	P value[a]
Age	1.01 (0.99-1.02)	NS	1.02 (1.01-1.04)	0.005
Male [b]	1.24 (0.88-1.75)	NS	1.16 (0.80-1.68)	NS
Number of prescribed medications before admission	1.04 (1.00-1.08)	0.033	1.06 (1.02-1.10)	0.005
ASA score	1.22 (1.01-1.47)	0.036	1.38 (1.12-1.71)	0.03

[a] *Univariate analysis*
[b] *Reference category: female*
ADE: Adverse Drug Event
ASA: American Society of Anaesthesiologists
CI: Confidence Interval
OR: Odds Ratio
pADE: preventable Adverse Drug Event

The multivariable backward logistic regression analysis (OR 1.275, 95% CI 1.01-1.60, p= 0.038) adjusted for significant univariate predictor ASA score, which was confirmed by the multivariable forward logistic regression analysis. Other factors were not significant in the multivariable regression analysis.

Outcome

All the ADEs in the study require a higher level of care; the level of harm, however, was variable. Overall, 86 ADEs (53.8%) resulted in temporary harm with a complete recovery within 12 months, while 29 ADEs (18.1%) caused permanent impairment or were in need for permanent institutional or nursing care. The all-cause mortality rate of the patients with an ADE was 28.1%. Because of many confounders and the study design, the causality between ADEs and harm, such as mortality, wasn't tested.

DISCUSSION

This study focused on patients who required a higher level of care, defined as an UIA or an intervention of the MET team, to detect serious (p)ADEs. 33.8% of the detected AEs were drug related or in 19.3% of these patients with a need for a higher level of care an ADE was detected. This is comparable with previous research that described that 17% (68) to 33% (69) of the AEs which lead to an ICU admission are drug related. The overall incidence rate of patients transferred to a higher level of care because of an ADE was in our study 40.5 per 100,000 patient days at risk.

Of these ADEs 83.8% were preventable. This proportion of pADE was higher than expected from the literature on in-hospital ADEs (14% - 75%) (27,159–164). A retrospective cohort study by Hug et al. (160) was a similar design and described that 75% of the ADEs were preventable. There are several possible methodological explanations for this difference. Firstly, in three of the earlier studies the detection method was a combination of record review and voluntary reporting (27,161,164). The reported preventability among the voluntarily reported ADEs may be lower from the ADEs detected with a record review. Secondly, in this study the clinical team consisted of a research nurse, a physician and a clinical pharmacist. Based on this multidisciplinary approach, the assessment of the ADEs will be more rigorous than the assessment by one discipline (27,160,161) or two disciplines (159,162). The records in previous studies were assessed by a physician (159–161), a pharmacist (159,162) a nurse (27) or a multidisciplinary team (164).

The proportion of preventable ADEs (83.8% pADEs/ADEs) is higher than the proportion of preventable AEs in general detected in an earlier record review in the same patient population (46% highly preventable AEs/AEs) (137). Maybe ADE’s are to a larger degree preventable than AE’s in general. However, we cannot exclude that a specific focus on drugs makes the judgment of the preventability probably less ambiguous.

The overall incidence rate of patients transferred to a higher level of care because of a pADE was 33.9 per 100,000 patient days at risk. These pADEs were more common with antibiotics, antithrombotic agents, blood substitutes and perfusion solutions, whereas antineoplastic agents were the most frequent in cases of ADR leading to a higher level of care. These results fit with earlier research (60,159,165,166). Using a univariate analysis, the ASA score, older age and number of medications used before admission were positively associated with pADEs. These data are comparable with the results from Aljadhey et al. (159).

Twenty-nine (18.1%) patients had permanent impairment or were transferred to permanent institutional or nursing care; forty-five (28.1%) patients died during hospitalization after the occurrence of the ADE. Previous studies described ADEs as serious in 30% to 33 % and as life-threatening in 4.9% to 12% (27,161). Our study focused on patients with a need for a higher level of care, whereby the most serious ADEs show up; harm can be expected to be higher in this study. For the reasons explained above causality between the ADE and the harm cannot be assessed validly.

This study has several methodological strengths. Firstly, the methodology of the three-stage retrospective review process (screening, record review and consensus judgment) was tested preliminarily in a pilot that was conducted for two months in one hospital. Based on this pilot, the methodology was optimized. Secondly, a major strength of our methodology was the multi-professional approach with a clinical team consisting of a research nurse, a physician and a clinical pharmacist and the panel of experts. To ensure a uniform decision process the team remained the same over time and in all six hospitals. Previous studies most often assess the records with one or two disciplines. Thirdly, record review is a costly and time-consuming method (28), although by focusing on the most serious cases its efficiency can substantially be increased.

Besides its strengths, the study has several limitations. Firstly, there is no actual gold standard for ADE detection (136). The judgment of the presence of AEs

remains therefore difficult and subjective. Retrospective patient record review is currently considered the best method available to assess incidence of AEs (29). However, an important limitation is in the observation that the method itself might lead to an underestimation of AEs (136) and ADEs. Secondly, the quality of the records was often suboptimal, which could lead to an underestimation. We tried to prevent both limitations by working with a multi-professional team consisting of a research nurse, a physician and a clinical pharmacist, each of them with experience in this area and focusing on their own clinical expertise whereas at the end the assessment was always made collectively. In addition, there was an expert panel available when necessary. Thirdly, by classification medication according to the ATC until the second level, risk medication groups could be identified. However, the second level of the ATC group is probably too broad when attempting to focus on a specific strategy for a specific drug within the same classification group. Fourthly, in our retrospective record review it was impossible to detect in which stage (prescribing, transcribing, dispensing, administering and monitoring) of the medication use process the ADE occurred. Therefore prospective studies, observation of medication dispensing or administration, analyses of self-reports and hospital incident reporting systems are also needed. As long as a gold standard is lacking, it is important to systematically use the full range of methods to identify ADEs (169).

In recent years efforts to prevent ADEs have increased. However, more resources are needed for training, research and implementation of the prevention practices. Our findings can be a basis to increase both the awareness for preventable ADEs, also in older people, and the yield of their detection. They can help in optimizing healthcare procedures and multi-professional patient management in order to make preventable ADEs actually more preventable in the future. Review of the records and analysis of the (preventable) ADEs may trigger important system changes within hospitals. However, further research is needed to detect in which stage of the medication process the in-hospital ADEs occur and to evaluate quality projects to prevent in-hospital ADE. As a consequence of this study participating hospitals

have already started the implementation of quality improving interventions, such as an Inpatient Anticoagulation Management System.

CONCLUSION

Twenty percent of unplanned transfers to a higher level of care is related to an ADE. A high number of these ADEs are preventable. Antibiotics and antithrombotic agents account each for one-fifth of all pADEs. The high number of pADEs in this specific population show that there is a need for structural improvement of pharmacotherapeutical care in these hospitals. Detection and identification of pADEs are a necessary basis for the implementation of these improvement actions.

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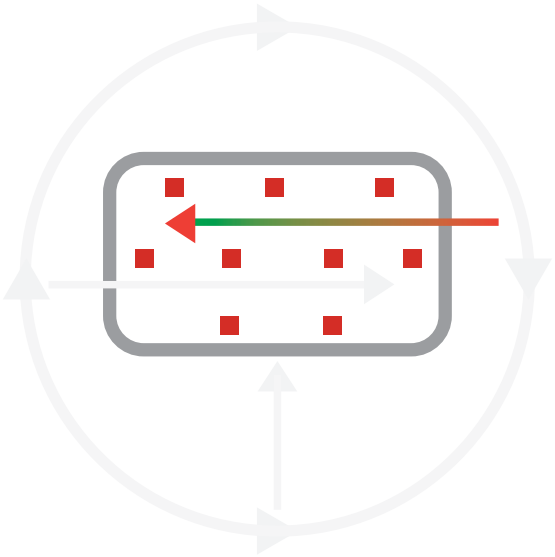
CONTRIBUTING OF AUTHORS

KM prepared and conceived the study protocol and the design of the study, collected and analyzed the literature concerned and conducted the study. KM, MD

& GK were the members of the clinical team. NC, ED, AV made critical revisions to the paper for important intellectual content. All authors read and approved the final manuscript.

CHAPTER 5

The quality of patient records and its relationship to the quality of care: a record review study



The quality of patient records and its relationship to the quality of care: a record review study

This study is in preparation

Marquet K, Claes N, Weekers F, Vleugels A. The quality of patient records and its relationship to the quality of care. In preparation.

This study will be presented at

- International Forum on Quality and Safety in Healthcare, BMJ, London, the England, 22nd-24th April 2015.

Chapter 5: The quality of patient records and its relationship to the quality of care: a record review study

ABSTRACT

The objectives of this study were *(1)* to assess the format, availability and completeness of patient records and *(2)* to analyze their relation to the occurrence of adverse events (AEs) in patients with unplanned transfers to a higher level of care.

Methods: During a six-month period we assessed in six acute Belgian hospitals the records of all patients who were unplanned transferred to a higher level of care. We focused on format, availability and completeness by auditing the matching to basic standards. To study the relationship between the quality of records and AEs we matched these data with data on AEs from an earlier study on the same patient population. Univariate and multivariate logistic regression were used.

Results: 868 records were reviewed. For 26.4% of the records one or more parts of the record (the medical part, the nursing part or the medication list) were not available. Only 0.3% and 3.3% of the medical and nursing parts were complete. Medication lists were complete in 61.5%. There were fewer highly preventable AEs with a partly unavailable record [OR 0.58, (95% CI 0.39-0.86), p: 0.007]. The absence of a validated discharge letter was associated with more highly preventable AEs [OR 0.65 (95% CI 0.46–0.92), p: 0.01].

Conclusions: Physicians and nurses fail to register continuously and accurately the delivered care. The incidence of highly preventable AEs is underestimated when the record is partially unavailable during the record review; the absence of a validated discharge letter is a predictor for highly preventable AEs. Standardization

by using evidence-based standards and an integrated digital format are necessary to support the healthcare professionals in improving patient record keeping and making healthcare safer.

INTRODUCTION

Patient safety receives global public attention. Good note-keeping in the patient record is essential for the delivery of safe care. The patient record must enable efficient and accurate communication of clinical information between multidisciplinary staff and facilitate continuity of care (170). Previous research showed that structured records have beneficial effects on performance and patient outcomes (171). A lack or poor quality of the information in patient records may be a cause of poor quality of care (141). Therefore the quality of patient records can be a predicting factor for adverse events (AEs), which is defined as 'an unintended injury or complication which results in disability, prolongation of hospital stay or death and is caused by healthcare management rather than the patient's disease' (2).

Retrospective record review has shown that 2.9% to 33.2% of patients in acute hospitals experience one or more AEs (2,50,84,114,121,122,124,125,128,131,145–148,172,173). When selecting patients with an unexpected flow of the care process, such as an unplanned transfer to a higher level of care - Intensive Care Unit (ICU) or an intervention by the Medical Emergency Team (MET) - the rate of AEs is even higher. Multidisciplinary record review in this patient group reveals that 56% of these patients experience an AE, of which 46% were highly preventable (137).

Routine monitoring and reviews of patient records are therefore an important aspect of clinical audits and an underutilized tool for quality improvement (174). An audit of patient records may be done for several reasons. The patient record audit is most often used as part of an ongoing process of quality improvement. Evidence exists that a continuous audit of patient records, combined with discussions about improvements, is a way to improve the quality of the records and to change the behavior of healthcare professionals (175–177). Another benefit of auditing patient records is that it allows comparisons over time and between wards or hospitals (178). Patient records audits are also recognized as a valuable

method for evaluating the effects of quality management (179) as they identify professional strengths and the weaknesses that need to be addressed.

The objectives of this study were *(1)* to audit the patient's records on their format, availability and completeness and *(2)* to analyze the relation between these features and the occurrence of AEs.

METHODOLOGY

An audit of the patient record of patients with an unplanned transfer to a higher level of care was performed in six Belgian acute hospitals. A higher level of care was defined as (1) an unplanned (re)admission to the ICU or (2) an intervention by a MET team due to an unanticipated change in the patient's clinical condition during the hospital admission. These patients were selected since an unplanned transfer to a higher level of care can be used as a trigger to detect poor quality of care (141). Planned admissions to the ICU (such as planned postoperative admission after major surgery) and ICU admissions directly from the emergency department were therefore excluded. Because of their specific nature, neonatal and maternal ICU were excluded. The inclusion period ran over 6 months from November 7th, 2011 through May, 6th 2012 (137).

Data collection

For the selected patients, the complete records were requested from the participating hospitals. The patient record consists of a medical and a nursing part and a medication list. For all three components the format, the availability and the completeness were assessed. The details of the patient selection procedure are described in detail elsewhere (137). The audit of the records was organized in three stages.

First a survey on the format of the (parts of) patient records was done. The format of the patient records could be digital, on paper or a combination of both. In a second stage the availability of three parts (medical, nursing part and medication list) of the patient record for the researchers was evaluated at the moment that they got access the patient record. In cases where the digital part of the medical record was limited to an overview of existing documents in a hospital results

server without free space to enter admission data, progress notes and other free data, the researchers also asked for manual documents with these information. In a third stage the completeness was assessed by checking the presence of essential elements in the patient records during admission, hospital stay and at discharge. In the medical part of the record we looked for (1) patient identification, (2) registrations on admission of elements such as allergies, medical history, medication used at home, the initial clinical findings through physical examination, (3) diagnostic procedures, treatment, observation and follow-up during hospital stay with clinical progress notes, reports of diagnostic and/or therapeutic interventions and (4) a validated (digitally finalized and signed) discharge letter. The selection of these items was based on the English National Health Service (NHS) guidelines (180) and the prescriptions of Belgian law (KB 3 May 1999) (181). In the nursing part we looked for (1) patient identification, (2) registration on admission of allergies, report of medical history, (3) registration of nursing care, vital signs and follow-up with nursing progress notes and (4) physician orders. The medication list was evaluated based on the presence of medication(s) name, dose per administration, route and frequency of administration and the fact whether it was validated by the physician. The data were collected in Open Clinica (154) using a structured abstraction instrument that was developed specifically for this study.

For the comparison of these audit results with the occurrence of AEs, data (136) from a multidisciplinary record review on AEs in the same group of 868 patients were used. Nevertheless, for the assessment of the occurrence of AEs, 38 records (4.4%) were excluded as the research team considered the records too incomplete. Using the definition from Wilson et al. (2) at least one AE was found in 465 patients (56% of 830); 215 AEs (46%) were highly preventable (137). The data of the 830 patients included in both studies, were compared.

Ethical approval & confidentiality

Ethical approval was received from University Hasselt and from each participating hospital. The study was registered at Clinicaltrial.gov (NCT02044718). The researchers signed a confidentiality agreement with the hospitals, which was approved by the Belgian Privacy Commission (158).

Statistical analyses

Descriptive statistics are expressed as frequencies. To evaluate the relation between the availability of the record, completeness of the patient information and the occurrence of AEs uni- and multivariate logistic regressions were performed. We calculated 95% confidence intervals and results were considered statistically significant if the confidence interval did not include unity. Statistical calculations were performed using Statistical Package for Social Science (SPSS Inc., Chicago, IL), version 20.0.

RESULTS

The six-month observation of the six participating hospitals led to 395,338 patient hospitalization days, 753 unplanned admissions to the ICUs and 115 MET interventions without transfer to ICU (Figure 1) (137). A total of 868 patients were included in the audit of patient records. For the comparison of these audit results with the occurrence of AEs, data of the 830 patients included in both studies, were compared. Their demographic and clinical characteristics are shown in table 1.

Table 1 Characteristics, medical history and type of admission of the patients (n= 830)

Variable	Number (%)
Age category	
- 21-40	45 (5.4)
- 41-65	218 (26.3)
- 66-79	328 (39.5)
- ≥80	239 (28.8)
Male	421 (50.7)
Comorbidities: ASA classification	
- I: Normal healthy patient	60 (7.2)
- II: Patient with mild systematic disease	171 (20.6)
- III: Patient with severe systematic disease	231 (27.8)
- IV: Patient with severe systematic disease that is a constant threat to life	368 (44.3)
Admission to the hospital	538 (64.8)
- Emergency admission	233 (28.1)
- Elective admission	36 (4.3)
- Admission after consultation	23 (2.8)
- Transfer from another hospital	
Classification based on APR-DRG v15	
- Surgical patient	415 (50.5)
- Extreme (class IV) Severity Index	389 (47.4)
- Extreme (class IV) Risk of Mortality	360 (43.4)
- Top 3 of verified admission diagnosis	
ICD-9-codes 390-459: diseases of the circulatory system	226 (27.7)
ICD-9-codes 460-519: diseases of the respiratory system	120 (14.7)
ICD-9-codes 520-579: diseases of the digestive system	106 (13.0)

APR-DRG v15.0 All Patient Refined Diagnosis Related Group, version 15
ASA: American Society of Anaesthesiologists
ICD-9: International Classification of Diseases, 9th revision

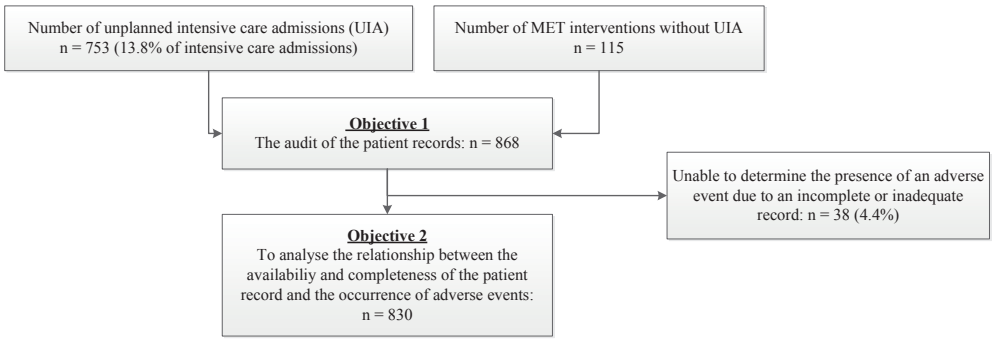


Figure 1: The inclusion process

MET: Medical Emergency Team
UIA: Unplanned Intensive care Admission

Format of the patient records

Digital record keeping was, at least partially, in place in the six participating hospitals. The medical part of the records was digital in all cases. However, for 195 (22.5%) records the digital information was limited to an overview of existing documents (such as lab tests, operative reports, discharge letters, etc.) but without free space to enter admission data, progress notes and other free data. In these records this type of unstructured information was sometimes available in manual documents. For 141 records (16.2%), the medical part contained only information from the hospital results server. 115 nursing records (13.2%) were a combination of digital data and paper forms. All other nursing records were only on paper. The medication list was digital in 526 cases (60.6%). Two hospitals did not yet start the digitalization of the medication list. The software tools used for the digital record keeping varied between the hospitals and sometimes even between disciplines in the same hospital. The three parts of the patient records were seldom integrated; records integration between the emergency department and the general wards was highly deficient (Figure 2).

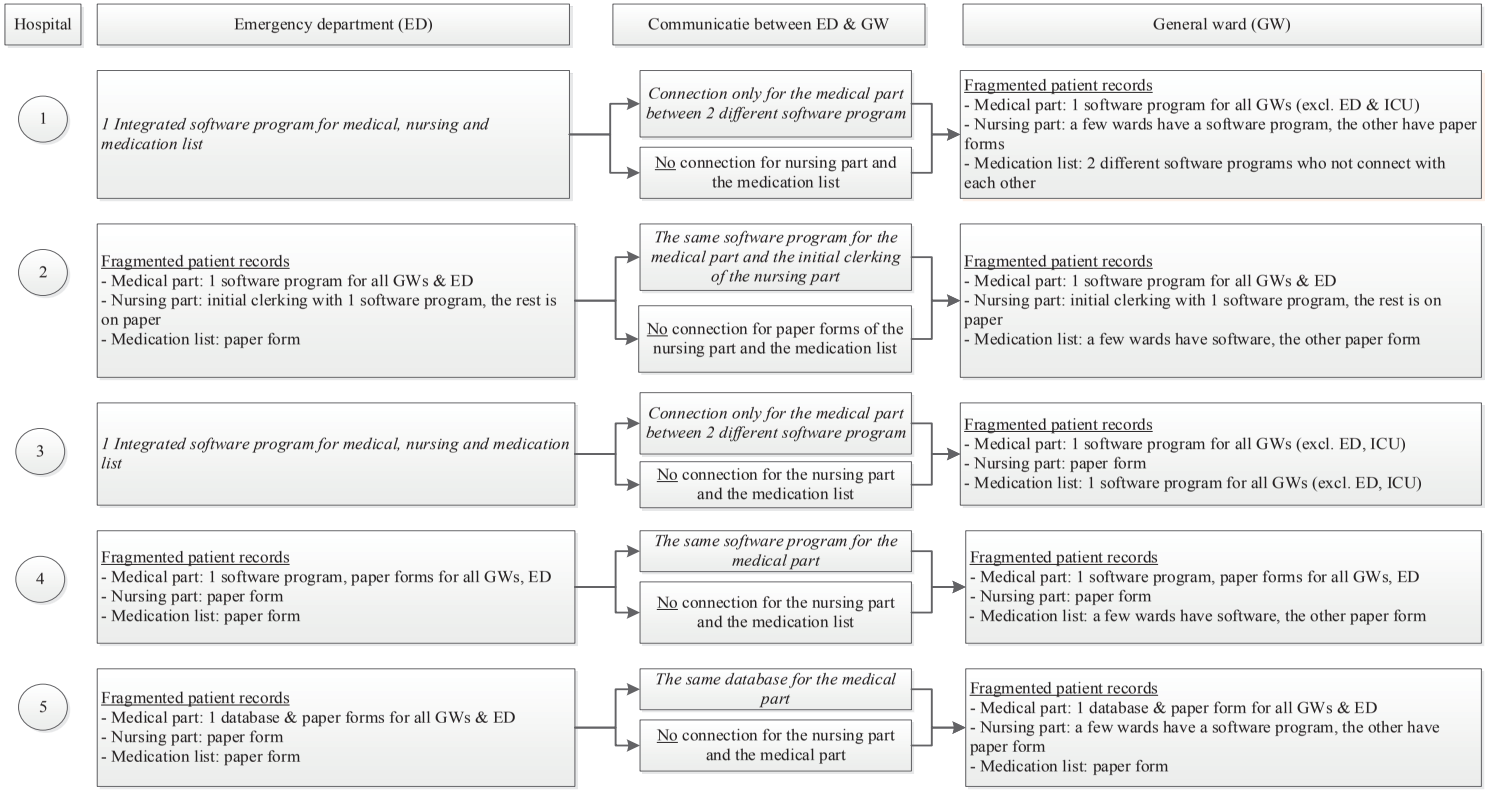


Figure 2 Overview of the format and the connections of the patient record

Availability of patient records

Records were requested for the initial 868 patients. In 118 records (13.6%) (parts of) the nursing records were missing (Table 2). Because of the separate digitalization of the medication lists in some hospitals, the medication lists (as part of the nursing records) were missing in 66 cases (7.6%). In all cases the medical part was digital and available for the researchers. However, as mentioned above, its content was often limited. In total, 26.4% of the records was not fully available for the researchers.

Table 2 Percentage missing record components and the relationship between availability of the record and the occurrence of adverse events

Record components	% missing	OR (95% CI) for AEs	OR (95%CI) for highly preventable AEs
Medical part	16.2	1.31 (0.88 - 1.94)	0.57 (0.35 - 0.93)*
Nursing part	13.6	1.27 (0.81 - 1.98)	0.71 (0.41 - 1.21)
Medication list	7.6	2.17 (1.10 - 4.28)*	0.72 (0.34 - 1.52)
Patient record	26.4	1.13 (0.82 - 1.55)	0.58 (0.39 - 0.86)*

** p <0.05*

Completeness of patient records

Table 3 and 4 describe the presence of the basic standards in the medical and nursing part. In the medical part patient identification was complete in 857 records (98.7%). The presence of the items registration of clinical information on admission, treatment and follow-up during hospitalization, documentation of surgical treatment (if applicable) and discharge notes was 1.0%, 1.7%, 48.4% and 75.7%, respectively. For only 0.3% of the records the medical information was complete for all audited items.

In the nursing part, patient identification was complete in 691 records (79.6%). For the other items, the completeness of the information ranged from 15.6 to 72.4%. Allergies (74.8%) and report of medical history (80.8%) were reported more frequently than in the medical part (respectively 19.2 % and 34.8%). At least one check of heart rate and blood pressure every 24 hours was registered for 550 patients (63.4%). All included patients had at some time a need for a higher level of care during their stay. However, in only 251 patients (28.9%) the frequency of registration of the vital signs increased when patient's condition deteriorated; 328 patients (37.8%) had nursing progress notes which described the deterioration. Only in 3.3% (n= 29) of the records were the nursing parts complete for all standards.

Table 3 Completeness of the medical part of the patient records

The medical part of the patient record includes the following items	n (valid %)
Identification	
The patient's name, identification number is on every page	*857 (98.7)*
Registration of clinical information on admission	
Allergies (also not known allergies)	*167 (19.2)*
Name and phone number of relevant contact	*133 (15.3)*
Reason for the hospital admission	*302 (34.8)*
Report of medical history (relevant past medical, surgical and mental health history)	*302 (34.8)*
Report of physical examination	*281 (32.4)*
Medication on admission	*147 (16.9)*
All these quality criteria were met with	8 (1.0)
Treatment and follow-up during hospitalization	
Treatment during the hospitalization	*68 (7.8)*
Dated, timed (24-hour clock), legible and signed entry	*433 (49.9)*
An entry with a maximum interval of four days for acute medical care	*251 (28.9)*
All these quality criteria were met with	14 (1.7)
Surgical treatment, applicable for the surgical patients (n= 370)	
Anesthetic record	*279 (75.4)*
Operative record	*230 (62.2)*
All these quality criteria were met with	179 (48.4)
Discharge	
Validated (digital finalized and signed) discharge letter	657 (75.7)
All these quality criteria were met with	3 (0.3)

Table 4 Completeness of the nursing part of the patient records

The nursing part of the patient records includes the following items	n (valid %)
Available	750 (86.4)
Identification	
The patient's name, identification number is on every page	691 (79.6)
Registration of information on admission	
Allergies (also not known allergies)	*649 (74.8)*
Report of medical history (relevant past medical, surgical and mental health history)	*701 (80.8)*
All these quality criteria were met with	628 (72.4)
Care and follow-up during hospitalization	
Provided nursing care	*744 (85.7)*
Vital signs (at least one check of heart rate and blood pressure every 24 hours)	*550 (63.4)*
The amount of checks of the vital signs increasing in situations of deterioration	*344 (28.9)*
Nursing progress notes	*328 (37.8)*
All these quality criteria were met with	183 (21.1)
Physician orders	
Undersigned physician orders for the nurses	*136 (15.6)*
All these quality criteria met with	29 (3.3)

The results on the completeness of the medication list are presented in table 5. The items related to medication intake, such as dose, route, frequency, were frequently available in the patient records (range between 89.9% and 92.7%). The medication lists were authorized by physicians in 539 cases (62.1%).

Table 5 Completeness of the medication lists

The medication list includes the following items	n (valid %)
Available	802 (92.4)
The patient's name, identification number is on every page	767 (88.4)
Full medication name (may be generic name or brand name)	805 (92.7)
Medication dose	780 (89.9)
Medication frequency	784 (90.3)
Route (medication administration description)	798 (91.9)
Manual or digital authorized by the physician	539 (62.1)
All these quality criteria were met with	534 (61.5)

The relationship between the availability and completeness of the record and the occurrence of AEs

Availability

We found less highly preventable AEs with a partly unavailable patient record (OR 0.58, 95% CI 0.39-0.86, p: 0.007). Secondly, the absence or partial absence of the medical information was also associated with less highly preventable AEs (OR 0.57, 95% CI 0.35-0.93, p: 0.02). The multivariable logistic regression analysis confirmed this significant correlation (p: 0.02). Finally, the unavailability of the medication list was associated with more AEs (OR 2.17, 95% CI 1.10-4.28, p: 0.02), which was confirmed by multivariable logistic regression analysis (p: 0.04).

Completeness

As to the completeness of the patient record we found more highly preventable AEs when there was no validated discharge letter (OR 0.65, 95% CI 0.46–0.92, p: 0.01). The multivariable logistic regression analysis adjusted for significant univariate predictor validated discharge letter (p: 0.03).

DISCUSSION

The objectives of this study were twofold: *(1)* to assess format, availability and completeness of the records and *(2)* to analyze the relation between the quality of patient records and the occurrence of AEs in patients with an unplanned need for a higher level of care. Firstly, the audited records had digital data, data on paper or a combination of both; 26.4% of records were not totally available and only 0.3% and 3.3% of the medical and nursing parts were complete. Secondly, there was an underestimation of highly preventable AEs with a partly unavailable record. However, the absence of a validated discharge letter was associated with more highly preventable AEs. So the quality of the patient records in our study can be qualified as poor and it has effect on the detection of AEs.

The percentage of missing nursing (13.6%) and medical components (16.2%) is higher in our study than in similar research in the Netherlands (141). However, the percentage of missing medication lists (7.6%) is lower than in that study. Only 0.3% and 3.3% of the medical and nursing parts of the patient records were complete for all selected items. The completeness for the items of the medical information ranged between 1.0% (registration of information on admission) and 98.7% (identification). The item 'validated discharge letter' scored high. However, for one fourth of the patients a validated discharge letter was absent; this figure is higher than previous research in the Netherlands (141) in which 86.9% of the records were found to have a discharge letter. In contrast, an audit of record keeping in maxillofacial surgery in Nigeria (182) using the CRABEL Scoring system (devised by Crawford, Beresford and Lafferty and named after the authors (183)) found that the worst aspect of the notes was the discharge summary with a mean score of 29%.

Only 28.9% of the patient's progress notes were found on a regular basis. The items related to the medication intake, such as dose, frequency and route were

registered with a range of 89.9% to 92.7%. These better figures are probably related to the almost general presence and the degree of digitalization of the medication list. However, the authorization of the medication list by physician signature was lacking in almost 40% of the cases.

The second objective was to analyze the relation between the availability and completeness of the patient records and the occurrence of AEs. It could be expected that an unavailable patient record during the record review could lead to an underestimation of AEs based on incomplete information. Previous research (141) confirmed this assumption. In our study, we found less highly preventable AEs if the patient record was (partly) unavailable. It suggests that the completeness of records, measured by auditing the presence of the basic standards, could lead to an underestimation of AEs. In our study, more highly preventable AEs were found if there was no validated discharge letter. This observation may suggest that the absence of a discharge letter in these cases reflects a general slovenliness in the care process and/or that after the occurrence of a highly preventable AE physicians are less prone to add a discharge letter to the patient record. In the latter case their attitude hinders future improvement actions based on learning from past AEs. In the worst case it can also lead to new AEs after discharge because the general practitioner does not get all the essential information. Further research on this issue is certainly needed.

There are several explanations why no more significant relations were found. Firstly, the chance for an AE may be higher in situations where the patient records are found incomplete or ambiguous (141). In this respect the quality of patient record keeping can be a predicting factor for AEs. On the other hand, the absence of the basic items in the patient record components can lead to underestimation of AEs in record review studies. These two conflicting mechanisms can explain why we didn’t find a significant correlation for other items. Secondly, quality of a patient records is not only about absence or presence of data (‘completeness’) but also about their legibility, accuracy and meaningfulness. In our study we focus

on only one aspect of quality, namely completeness. Thirdly, the most incomplete patient records (n= 38, 4.4%) were excluded as the research team considered them too incomplete to allow a correct review process of the occurrence of AEs.

Our study shows some limitations. Firstly, the fact that the relation between the availability or completeness of the records and the occurrence of AEs was impossible for the 38 most incomplete records will have influenced the results. Secondly, as mentioned above only the completeness was measured, so the study gives no insights about the accuracy and other quality aspects of the records. Further research should also include these dimensions of records quality.

In our study we looked only for the most basic components of the patient records, which means that anything less than a perfect score may be interpreted as inadequate and incomplete. Standard note keeping is an important aspect of patient management, and the importance of availability and completeness of patients' records cannot be overemphasized. It is an integral part of good medical practice. The elements that we found missing were not available for the researchers. However, they were consequently also not unavailable for the healthcare professionals caring for that patient. The lack of completeness that we observed in many aspects of the patient record shows that physicians and nurses fail to document continuously and accurately the delivery of care and the clinical status of the patient. Probably the time-consuming nature of documentation and an apathy for 'administrative work' are reasons for this under registration. However, further research is necessary to explore the actual reasons and improve the current systems and processes.

A patient record consist of a medical, a nursing part and a medication list. These parts are inter-related; they are, however, not systematically integrated. The existence of different parts leads to duplication of information. The preference should be an integrated patient record with a standardized layout for all healthcare workers. All records relating to the same patient should be kept in a single patient

record rather than be distributed over several hospital departments or sites which we observed in this study (184). Physicians, paramedical and nursing staff should be trained in proper maintenance of patient records.

Unequivocal, efficient and accessible record keeping guidelines for the documentation of patient information may lead to better communication between healthcare providers and will contribute to better patient outcomes and safer healthcare (141). Standard note keeping is an important aspect of patient management, and the importance of completeness of patients' records cannot be overemphasized, especially for the purpose of auditing, research, and medico-legal reasons. It is also an integral part of good medical practice. However, our findings on the format, availability and completeness of patient records should create greater awareness that we need and can optimize the multidisciplinary care management in order to prevent preventable AEs. Insights from studies like ours can provide information for healthcare professionals, hospital management and policy makers on how improvement actions can be made. The drive to improve the quality and safety of medical practices and hospital services and the increasing pressure on the costs of care ask more than ever for more concern about the structure and content of patient records (185). Evidence-based standards and a digital format for good patient record keeping are necessary for standardization of recording patient information (141). We suggest that improved quality of patient records may be stimulated through the use of a standardized format for records in all wards of the same hospital and adoption of guidelines for patient record keeping.

CONCLUSION

Standard medical note keeping is an important aspect of patient management and a fundamental part of efficient patient care. However, physicians and nurses fail to document continuously and accurately the delivery of care. The incidence of highly preventable AEs is underestimated when records are (partly) unavailable. The absence of a validated discharge letter appears to be an indicator of poor quality of care. Standardization by using evidence-based standards and digital integrated format is necessary to support the healthcare professionals in improving the patient record keeping and making the healthcare process safer.

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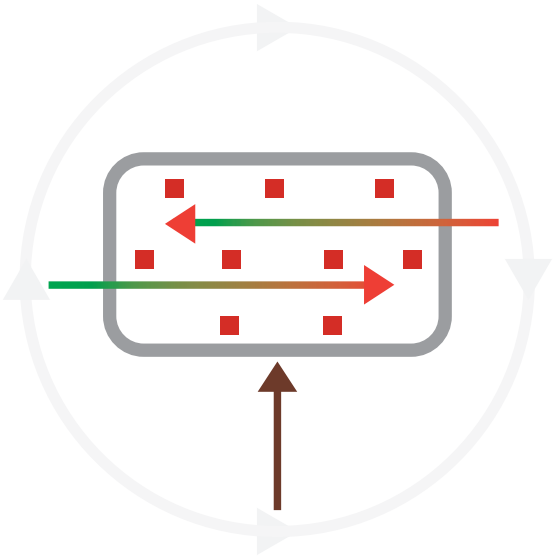
CONTRIBUTING OF AUTHORS

KM prepared and conceived the study protocol and the design of the study, collected and analyzed the literature and conducted the study. NC, FW, AV made critical revisions to the paper for important intellectual content. All authors read and approved the final manuscript.

CHAPTER 6

Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review with a meta-analysis



Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review with a meta-analysis

This study was submitted as

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Chapter 6: Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review with a meta-analysis

ABSTRACT

Introduction: To study aims to explore the incidence of in-hospital inappropriate empiric antibiotic use in patients with severe infection and to identify its relationship with patient outcomes.

Methods: MEDLINE (from 2004 to 2014) was systematically searched using predefined inclusion criteria. Reference lists of retrieved papers were screened for additional relevant studies. The systematic review included original articles reporting a quantitative measure of the association between the use of (in) appropriate empiric antibiotics in patients with severe in-hospital infections and their outcomes. Meta-analysis, using a random-effects model, was conducted to quantify the effect on mortality using risk ratios (RR).

Results: Twenty-seven individual papers fulfilled the inclusion criteria. The percentage of inappropriate empiric antibiotic use ranged from 14.1% to 78.9% (Q1-Q3: 28.1-57.8%); 13 of 27 studies (48.1%) described an incidence of 50% or more. A meta-analysis for 30-day mortality and in-hospital mortality showed a RR of 0.71 (95% CI 0.62-0.82) and 0.67 (95% CI 0.56-0.80), respectively. Studies with outcome parameter 28-day and 60-day mortality reported also significantly ($p \leq 0.02$) higher mortality rates in patients receiving inappropriate antibiotics. Two studies assessed the total costs, which were significantly higher in both studies ($p \leq 0.01$).

Conclusions: This systematic review with meta-analysis provides evidence that inappropriate use of empiric antibiotics increases 30-day and in-hospital mortality in patients with a severe infection.

INTRODUCTION

Infections are among the top three leading causes of death worldwide (186). Septicaemia and pneumonia combined are the sixth most common causes of death in the United States (187). Bloodstream infections (BSI) are associated with substantial morbidity, mortality, and health care costs (188). Sepsis is one of the leading causes of death in the critically ill, with a mortality rate of 28-55% (189). Antibiotics are the mainstay of treatment for these serious infections (190). Antibiotic treatment for moderate to severe infections has to start early and is, in the absents of evidence on the causative pathogen or its sensitivity to antibiotics, often guided by empirical evidence (191).

Estimates of the potential benefit of appropriate empirical antibiotic treatment (AAT) vary widely (192–196). Studies on the effect of inappropriate empiric antibiotic therapy (IAAT) on patient outcomes have yielded variable results (191,197). Nevertheless it is common wisdom that IAAT may lead to progressive deterioration and the development of complications or mortality (198–203).

Considering the high incidence of infections and the not well-established relationship between empiric (I)AAT and clinical outcome (204–207), synthesizing the best available evidence is necessary. Therefore, this systematic review with meta-analysis was conducted to synthesize the best available evidence regarding *(1)* the definition, *(2)* the incidence and *(3)* the outcome of empiric IAAT.

METHODS

Data sources and search strategy

Quantitative studies on the association between the use of empiric (I)AAT in patients with a severe infection and their outcomes in public or private general hospital settings were searched in MEDLINE. Studies published in the last ten years (August 20th 2004 and August 20th 2014) were selected as critical illness management changes continuously and earlier studies may be less relevant for current practice. The following Medical Subject Headings (MeSH) search terms and free-text keywords were used, either individually or in combination: 'antibiotic', 'infection', 'appropriate', 'inappropriate', 'adequate', 'inadequate', 'outcome', 'mortality', 'survival rate', 'cost' and 'length of stay'. Only studies published in English, Dutch, German or French were included. Reference lists of retrieved papers were hand searched for additional relevant studies. A detailed description of the search strategy is included in the supplement digital content.

Eligibility criteria

Study design. Potentially included studies designs included: randomized controlled trials, non-randomized controlled trials, controlled before-after studies, interrupted time series and repeated measures studies. Only studies reporting a quantitative evaluation regarding the association between the use of AAT or IAAT in patients with a severe infection and their outcomes within the hospital setting were included. The studies use (I)AAT as the independent variable and outcome (measured as mortality, hospital length of stay (LOS) and costs) as the dependent variable. Studies that recruited less than 75 patients were excluded because the research team assumes that these studies bear the risk to be underpowered.

Patients. The included patients were adults (age ≥18 years) with a severe infection. For this review pneumonia, BSI or bacteraemia, sepsis, severe sepsis or septic shock were considered as severe infections. Studies specifically focused on meningitis, endocarditis or infections in burn and transplant patients were excluded as the literature (199,203,208,209) showed that treatment effects are expected to largely deviate from any common effect.

Intervention. The intervention of interest concerned empiric AAT versus IAAT. Empiric antibiotic therapy is defined as all non-definitive therapy and refers to antibiotics given prior to the result of the final culture and the antibiotics sensitivity tests (210). Studies that didn't specify the used definition of AAT or IAAT were excluded. Studies comparing two or more types of antibiotics rather than (in) appropriateness were excluded.

Outcome. The outcome was assessed in terms of mortality, hospital LOS and costs.

Study appraisal

Two reviewers (KM, AL), independently performed the initial scan of titles and abstracts of all retrieved citations, using standardized screening forms. Both reviewers documented the reasons for exclusion. Full-text copies of all potentially relevant studies were obtained and further checked for inclusion. Any discrepancies between reviewers were resolved by discussion. Continuing disagreements were settled by a third reviewer (NC). Additional sources that had been cross-referenced from the Medline search results were included if they met the criteria above. The quality of the papers was evaluated using the Downs and Black quality assessment method, which is a list of 27 criteria to evaluate both randomized and nonrandomized trials (211). This scale assesses study reporting, external validity, internal validity, power of nonrandomized studies and has been ranked in the top six quality assessment scales suitable for use in systematic reviews (212,213).

As had been done in other reviews using the Downs and Black scale (214–216), the tool was modified slightly for use in this particular review. Specifically, the scoring for question 27 dealing with statistical power was simplified to a choice of awarding either 1 point or 0 points, depending on whether there was sufficient power to detect a clinically important effect. The criterion was that to detect a 10% difference, assuming power of .90 and alpha of .05. The Downs and Black scores were grouped into the following 4 quality levels: excellent (26 to 28), good (20 to 25), fair (15 to 19) and poor (less than 14) (216). Only papers with a quality level of good or excellent were retained.

Data extraction

Data extraction was completed independently by two reviewers (KM, AL), using a standardized data collection form. Following data were extracted and reported (1) data on study setting and patient population as possible confounding factors, (2) definition and incidence of the independent variable [(I)AAT], (3) definition and measurement of the dependent variables (in terms of mortality, hospital LOS and costs among patients given AAT versus IAAT). In case of disagreement between the two reviewers, a third reviewer extracted the data (NC).

Study characteristics. For every included study descriptive data on the study setting, (i.e. study design, geographic location of the study, baseline characteristics, study years, sample size) and patient characteristics (i.e. source of infection, severity scale) were collected.

Definition and measuring incidence of (I)AAT. We reviewed how empiric (I) AAT was defined and measured. We assessed which evidenced-based elements, such as therapy dose, route, timing, etc. were evaluated. Empiric antibiotic therapy is defined as all non-definitive therapy and refers to antibiotics given prior to the result of the final culture and the antibiotic sensitivity tests (210).

Measurement of the dependent variable. The outcome was measured as mortality, LOS and costs for patients given empirical (I)AAT. The time span of mortality assessment was also registered.

Data analysis

Data were analyzed using R (a language and environment for statistical computing) (217). All reported P values were two-sided; $P<0.05$ was considered to indicate statistical significance. A random-effects meta-analysis using the DerSimonian-Laird estimator obtained risk ratios (RRs) and 95% per cent confidence intervals (CIs) for mortality rate reductions (218). Heterogeneity of the study results was assessed using the Cochran Q test and the Higgins I^2 test. Following thresholds were used to quantify heterogeneity: $P< 0.10$ in Cochran's Q test and for I^2 25% for low, $25\% < I2 < 50\%$ for moderate, and $I2 \geq 50\%$ for high. Funnel plots assessed publication bias. Sensitivity analysis identified heterogeneous studies that influenced the meta-analysis. Meta-regression was used to examine the impact of study characteristics on study effect size and heterogeneity.

RESULTS

Results of the search

The initial database search identified 1097 unique citations. Review of the reference lists of included studies identified 11 additional studies. After critical assessment of these 1108 publications, 32 individual trials (193,197,204,206,207,219–245) fulfilled the inclusion criteria and were considered for further analysis (Figure 1). After quality assessment of the individual studies, 27 studies (193,197,204,206,207,220,221,223–235,237–239,241–244) were included in the systematic review.

Study characteristics

Characteristics of the 27 included studies are presented in table 1. The studies were conducted in Asia (n= 9) (193,197,206,228,231,237–239,242), North America (n= 8) (207,220,221,223,224,229,232,241), Europe (n= 6) (204,225,233,235,243,244), the Middle East (n= 2) (230,234) and two studies were multinational (226,227). Eight studies (29.6%) were multicenter trials (range 2-60) (197,221,225–227,235,237,243). Twenty studies (74.1%) were conducted in university or teaching hospitals (193,204,206,207,220,223,224,227–229,231–233,235,238,239,241–244), three studies (11.1%) combined university and general hospitals (197,225,226), two studies (7.4%) were performed in general hospitals (234,237) and two studies (7.4%) did not mention the nature of the site (221,230). Twenty-three studies (85.2%) reported on retrospective analysis (193,197,204,206,207,220,221,224,226–233,235,238,239,241,243,244).

Included studies covered a total of 15306 patients, with an average of 567 patients per study (range 76–5715). The severe infection was BSI or bacteremia

in 15 studies (55.5%) (193,197,204,206,207,220,223,224,226,233,234,237, 239,242,243), pneumonia in 6 studies (22.2%) (221,228,231,235,238,244), sepsis in 3 studies (225,229,232); 2 studies described severe sepsis or septic shock (227,241). Severity of illness was reported in 23 studies (85.2%) using a variety of severity indexes including the Acute Physiology and Chronic Health Evaluation (APACHE) II (153), Charlson index (246), the Sequential Organ Failure Assessment (SOFA) (247), Simplified Acute Physiology Score (SAPS) II (248), Multiple Organ Dysfunction Scale (MODS) (249), Pitt Bacteremia score (250) and the McCabe's classification (251). A significant difference (p: 0.04) in illness severity between the two groups was found in two studies (233,237). However, nine studies (204,220,225,227,237–239,241,242) did not compare the severity of illness between patients with IAAT versus AAT.

Data on definition and measurement of (I)AAT

Data on the definition and the incidence of (I)AAT were presented in table 2. A spectrum of definitions exists in the literature concerned. Fifteen (55.6%) studies included a definition of AAT, four studies (14.8%) mentioned a definition of IAAT and eight studies (29.6%) defined both. Thirty-two of the 34 definitions (94.1%) mentioned the element 'matching with the in vitro susceptibility' or 'intermediate or full in vitro resistance'. Other frequently mentioned definitions items were the timing of administration (n= 24, 70.6%), the correct dose (n= 8, 23.5%) and the correct indication for the antibiotics (n= 6, 17.6%).

The percentage of empiric IAAT showed an enormous range from 14.1% to 78.9% (Me: 49.3%, IQR 28.1-57.8%). The magnitude of this range can partially be explained by the differences in the definitions, settings, diseases and infectious agents. Because of this considerable heterogeneity, it may be misleading to quote an average value for the incidence. However, 13 of these 27 studies (48.1%) described an incidence of IAAT of 50% or more.

Measurement of the dependent variable

Outcome was measured as mortality, LOS and costs. A meta-analysis was conducted to quantify the effect of appropriateness in empiric antibiotics on mortality. The number of studies that assess the total LOS (235,242), LOS after infection onset (223,232) and the costs (224,235) were very small. Therefore these results are only presented in a descriptive manner.

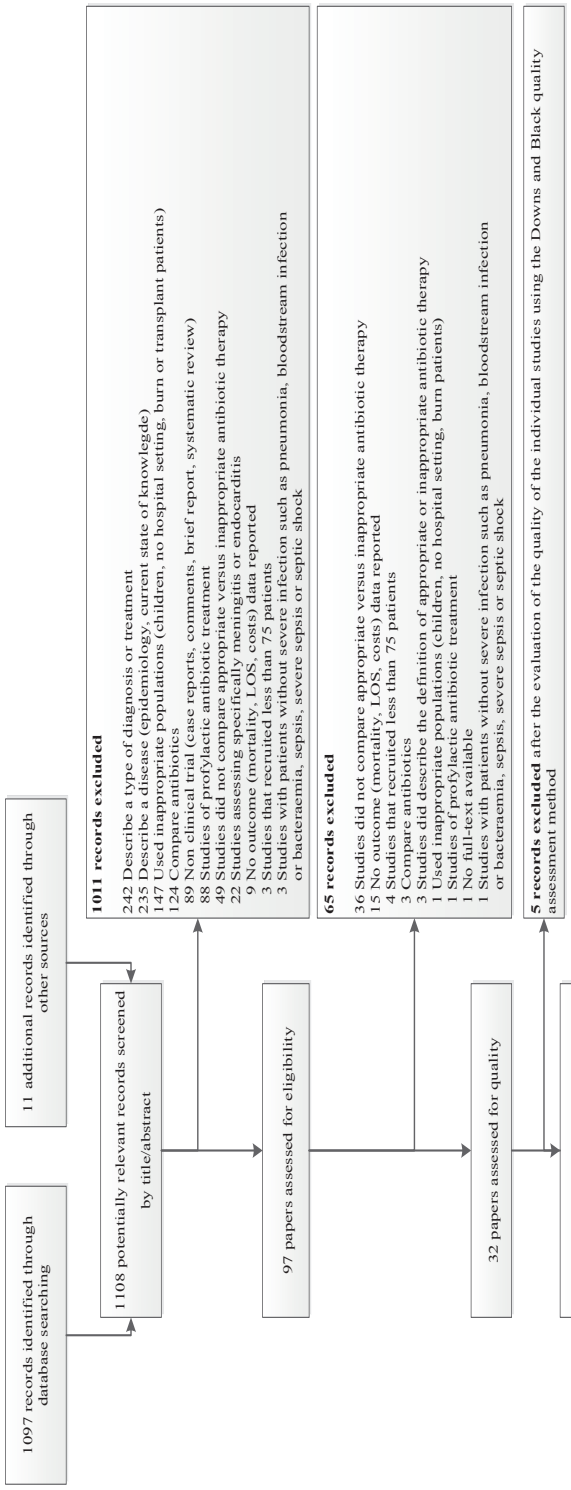

Figure 1 PRISMA diagram for study selection

Table 1 Characteristics of 27 included studies in the systematic review

Author(s), yr (reference)	Study yr(s)	Location	Design	Center No	Center Type	No. of patients	Outcome	Main type of infection	Severity index scale & significance difference
Kim et al. (206)*	1998-2001	Korea	R	1	U	127	M – 30	MRSA bacteremia	McCabe's classification, Jackson: NS
Kang et al. (197)*	1998-2002	Korea	R	2	U,G	286	M – 30	Antibiotic-resistant Gram-negative Bacilli BSI	APACHE II: NS
Rodriguez-Bano et al. (225)*	2003	Spain	P	59	U,G	209	M – 30	Sepsis	Charlson index: NC
Ammerlaan et al. (226)*	2007	West European countries	R	60	T,G	334	M – 30	SAB	Modified Charlson index: NS
Erbay et al. (204)*	2005-2008	Turkey	R	1	U	103	M – 30	Acinetobacter baumannii bacteremia	APACHE II: NC
Paul et al. (230)*	1999-2007	Israel	R	1	NM	510	M – 30	MRSA bacteremia	NM
Joung et al. (231)*	2000-2006	Korea	R	1	U	116	M – 30	Pneumonia (HAP) Acinetobacter baumannii	APACHE II: NS
Suppli et al. (233)*	2002-2005	Denmark	R	1	T	196	M – 30	Enterococcal BSI	Charlson index: NS, except score 0 (p 0.04)
Reisfeld et al. (234)*	2005-2007	Israel	R	1	G	378	M – 30	Gram-negative bacteremia	NM

Frakking et al. (243)*	2008-2010	The Netherlands	R	8	U	232	M – 30	ESBL bacteremia	Pitt Bacteremia score: NS
Micek et al. (220)*	1997-2002	USA	R	1	U	305	M - IHM	Pseudomonas Aeruginosa BSI	SAPS II: NC
Scarsi et al. (207)*	2001-2003	USA	R	1	U	884	M - IHM	Gram-negative BSI	Charlson index: NS
Marschall et al. (223)*	2006-2007	USA	P	1	T	250	M - IHM LOS	Gram-negative bacteremia	Charlson index, McCabe's classification: NS
Shorr et al. (224)*	2002-2004	USA	R	1	U	291	M - IHM LOS C	MRSA infection	NM
Kumar et al. (227)*	1996-2005	Canada, USA Saudi Arabia	R	22	U	5715	M - IHM	Septic shock	APACHE II: NC
Tseng et al. (228)*	2005-2007	Taiwan	R	1	T	163	M - IHM	Pneumonia	Charlson index: NC
Micek et al. (229)*	2002-2007	USA	R	1	U	760	M - IHM	Gram-negative sepsis	APACHE II, Charlson index: NS
Wilke et al. (235)*	2007	Germany	R	5	T	221	M - IHM LOS C	Pneumonia (VAP, HAP)	NM
Lye et al. (237)*	2007-2009	Singapore	R	2	G	675	M - IHM	Gram-negative Bacteremia	APACHE II < 0.001; Charlson index: NS
Labelle et al. (241)*	2002-2007	USA	R	1	T	436	M - IHM	Septic shock	APACHE II, Charlson index: NC
Tumbarello et al. (244)*	2008-2010	Italy	R	1	U	110	M - IHM	Pseudomonas Aeruginosa pneumonia	SAPS II, SOFA: NS
Chen et al. (239)	2006-2011	China	R	1	T	118	M – IHM	SAB	APACHE II: NC

Luna et al. (221)	1999-2003	Argentina	P	6	NM	76	M – 28	Pneumonia (VAP)	APACHE II: NS
Chen et al. (242)	2008-2009	Taiwan	P	1	U	937	M - 28, LOS	BSI	MEDS, Charlson index: NC
Tseng et al. (238)	2007-2008	Taiwan	R	1	U	163	M – 60	Pneumonia (VAP)	APACHE II, Charlson index, SOFA: NC
Kim et al. (193)	1998-2001	South-Korea	R	1	U	238	M – 12w	SAB	McCabe's classification, Jackson: NS
Shorr et al. (232)	2002-2007	USA	R	1	U	760	LOS	Gram-negative sepsis	APACHE II, Charlson index: NS

**: 21 included studies in meta-analysis*
APACHE II: Acute Physiology and Chronic Health Evaluation
BSI: Bloodstream Infection
C: Costs
G: General hospital
HAP: Hospital Associated Pneumonia
IHM: In-Hospital Mortality
LOS: Length Of Stay
M: Mortality (number expressed the time span of mortality assessment)
MEDS: Mortality in Emergency Department Sepsis
NC: No Comparison
NM: Not Mentioned
NS: Not Significant
P: Prospective
R: Retrospective
SAB: Staphylococcus Aureus Bacteraemia
SAPS: II Simplified Acute Physiology Score
SOFA: Sequential Organ Failure Assessment
T: Teaching hospital
VAP: Ventilator Associated Pneumonia
U: University hospital

Table 2 Definition and incidence of (in)appropriate antibiotic therapy in the reviewed studies

Author(s), yr (reference)	Appropriate empiric antibiotic therapy											Inappropriate empiric antibiotic therapy							
	Aspects of appropriate antibiotic therapy											Aspects of inappropriate antibiotic therapy							
	Definition	According to the culture	Timing	Dose	According to guidelines	Route	Indication	Duration	No known contra indication	Frequency	**Number of items**	**Definition**	Intermediate or full in vitro resistance	Timing	Omission	Indication	Route	**Number of items**	**% IAAT**
Kim et al. (206)*	**Y**	Y	Y	N	N	Y	N	N	N	N	**3**	**N**							**76.38**
Kang et al. (197)*	**N**											**Y**	Y	Y	Y	N	N	**3**	**52.80**
Rodriguez-Bano et al. (225)*	**Y**	Y	Y	Y	N	Y	N	N	N	N	**4**	**N**							**78.95**
Ammerlaan et al. (226)*	**Y**	Y	Y	N	N	Y	N	N	N	N	**3**	**Y**	Y	Y	Y	Y	Y	**5**	**28.14**
Erbay et al. (204)*	**Y**	Y	Y	Y	Y	Y	N	N	N	N	**5**	**N**							**58.25**
Paul et al. (230)*	**Y**	Y	Y	N	N	N	N	N	N	N	**2**	**N**							**67.06**
Joung et al. (231)*	**Y**	Y	Y	Y	N	Y	N	N	N	N	**4**	**Y**	Y	Y	N	N	N	**2**	**57.76**
Suppli et al. (233)*	**Y**	Y	Y	Y	Y	N	Y	Y	Y	N	**7**	**N**							**25.51**
Reisfeld et al. (234)*	**Y**	Y	N	Y	N	N	N	N	N	Y	**3**	**N**							**39.95**
Frakking et al. (243)*	**Y**	Y	Y	N	N	N	N	Y	N	N	**3**	**N**							**63.36**
Micek et al. (220)*	**N**											**Y**	Y	N	Y	N	N	**2**	**24.59**

Scarsi et al. (207)*	**Y**	Y	Y	Y	Y	N	N	N	N	N	**4**	**Y**	Y	Y	N	N	N	**2**	**14.14**
Marschall et al. (223)*	**Y**	Y	Y	N	N	N	N	N	N	N	**2**	**Y**	Y	N	Y	N	N	**2**	**31.6**
Shorr et al. (224)*	**Y**	Y	Y	N	N	N	N	N	N	N	**2**	**N**							**76.98**
Kumar et al. (227)*	**Y**	Y	Y	N	N	N	N	N	N	N	**2**	**Y**	Y	Y	N	N	N	**2**	**19.88**
Tseng et al. (228)*	**Y**	Y	N	N	N	N	Y	N	N	N	**2**	**Y**	Y	N	N	Y	N	**2**	**49.26**
Micek et al. (229)*	**Y**	Y	Y	N	N	N	Y	Y	N	N	**4**	**N**							**31.32**
Wilke et al. (235)*	**Y**	N	N	N	Y	N	N	N	N	N	**1**	**N**							**51.58**
Lye et al. (237)*	**Y**	Y	N	Y	Y	N	N	N	N	N	**3**	**N**							**43.56**
Labelle et al. (241)*	**Y**	Y	Y	N	N	N	N	N	N	N	**2**	**N**							**51.88**
Tumbarello et al.(244)*	**N**											**Y**	Y	N	N	N	N	**1**	**50.91**
Chen et al. (239)	**Y**	Y	Y	N	N	N	N	N	N	N	**2**								**38.98**
Luna et al.(221)	**Y**	Y	N	N	Y	N	N	N	N	N	**2**	**Y**	Y	Y	N	N	N	**2**	**68.42**
Chen et al. (242)	**Y**	Y	Y	Y	Y	Y	N	N	N	N	**5**	**N**							**27.21**
Tseng et al. (238)	**Y**	N	N	N	N	N	N	N	N	N	**1**	**N**							**56.44**
Kim et al. (193)	**Y**	Y	Y	N	N	Y	N	N	N	N	**3**	**N**							**49.16**
Shorr et al. (232)	**N**											**Y**	Y	Y	Y	N	N	**3**	**31.30**
Total	**23**	**21**	**17**	**8**	**7**	**7**	**4**	**3**	**1**	**1**		**11**	**11**	**7**	**5**	**2**	**1**		

IAAT: Inappropriate Antibiotic Therapy
Y: Yes
N: No
**: included in the meta-analysis*

Mortality

In total, 26 studies (193,197,204,206,207,220,221,223–231,233–235,237, 238,241–244) reported mortality as an outcome variable in patients with severe infection treated with (I)AAT. However, the time span of mortality assessment varied from 28 (221,242) – 30 (197,204,206,225,226,230,231,233,234,243) - 60 (238) days to 12 weeks (193). Eleven studies (207,220,223,224,227–229, 235,237,241,244) assessed in-hospital mortality. Given methodological considerations meta-analysis on the effect of AAT on 30-day mortality (n= 10) and in-hospital mortality (n= 11) was conducted separately (Table 3). Five of the ten studies (197,204,230,231,233) reporting on 30-day mortality, showed a significant lower mortality rate for patients treated with AAT compared to those treated with IAAT. Meta-analysis for 30-day mortality revealed a RR of 0.71 (95% CI 0.62-0.82; P<0.0001) in favor of AAT, without significant heterogeneity (Cochran's Q= 11.37, 9 d.f., P=0.252; I^2=20.8 (0-61%) (Figure 2). Of the 11 trials (207,220,223,224,227–229,235,237,241,244) included in the meta-analysis on in-hospital mortality, 8 trials (220,227–229,235,237,241,244) yielded significant lower mortality ratios in patients receiving AAT. Meta-analysis for in-hospital mortality revealed that the RR for mortality with AAT was 0.67 (95% CI 0.56-0.80; P<0.0001). However, there was significant heterogeneity (Cochran's Q= 74.45, 10 d.f., P<0.0001; I^2=86.6 (77.8-91.9%) (Figure 3). Funnel plots displayed an asymmetrical pattern for in-hospital mortality, but not for 30-day mortality studies. The results of the sensitivity analysis suggest that 3 studies contribute to residual heterogeneity; removing them from the meta-analysis would reduce variability between studies. However, because this did not affect the results, these studies were retained. Meta-regression revealed that study quality (Down & Black score) (p=0.003), inclusion of a definition of appropriate AB usage (p=0.0194), and studies reporting outcome for sepsis (p=0.0001) significantly influenced the meta-analysis on in-hospital mortality.

Table 3 Summary of mortality data included in the meta-analysis

Author(s), yr (reference)	Time of mortality assessment	AAT mortality rate (%)	IAAT mortality rate (%)	P-value
Kim et al. (206)	30	36.67	41.24	0.36
Kang et al. (197)	30	27.41	38.41	0.049*
Rodriguez-Bano et al. (225)	30	18.18	24.24	0.3
Ammerlaan et al. (226)	30	25.00	21.27	NS
Erbay et al. (204)	30	39.53	65.00	0.011*
Paul et al. (230)	30	33.33	49.12	0.001*
Joung et al. (231)	30	22.45	49.25	<0.0001*
Suppli et al. (233)	30	20.55	40.00	0.009*
Reisfeld et al. (234)	30	33.48	46.36	OR 1.4 (0.86-2.29) (NS)
Frakking et al. (243)	30	18.82	20.41	NS
Micek et al. (220)	IHM	17.83	30.67	0.018*
Scarsi et al. (207)	IHM	16.07	13.60	0.48
Marschall et al. (223)	IHM	14.03	13.92	1.0
Shorr et al. (224)	IHM	11.94	19.64	0.15
Kumar et al. (227)	IHM	48.00	89.70	<0.0001*
Tseng et al. (228)	IHM	35.44	50.00	OR 2.17 (1.4-3.38) 0.001*
Micek et al. (229)	IHM	36.40	51.68	<0.001*
Wilke et al. (235)	IHM	14.02	26.32	0.021*
Lye et al. (237)	IHM	19.16	26.19	OR 0.67 (0.46-0.96) 0.03*
Labelle et al. (241)	IHM	51.38	68.30	<0.001*
Tumbarello et al.(244)	IHM	24.07	64.29	<0.001*

AAT: Appropriate Antibiotic Therapy
IAAT: Inappropriate Antibiotic Therapy
IHM: In-Hospital Mortality
NS: Not Significant
OR: Odds Ratio

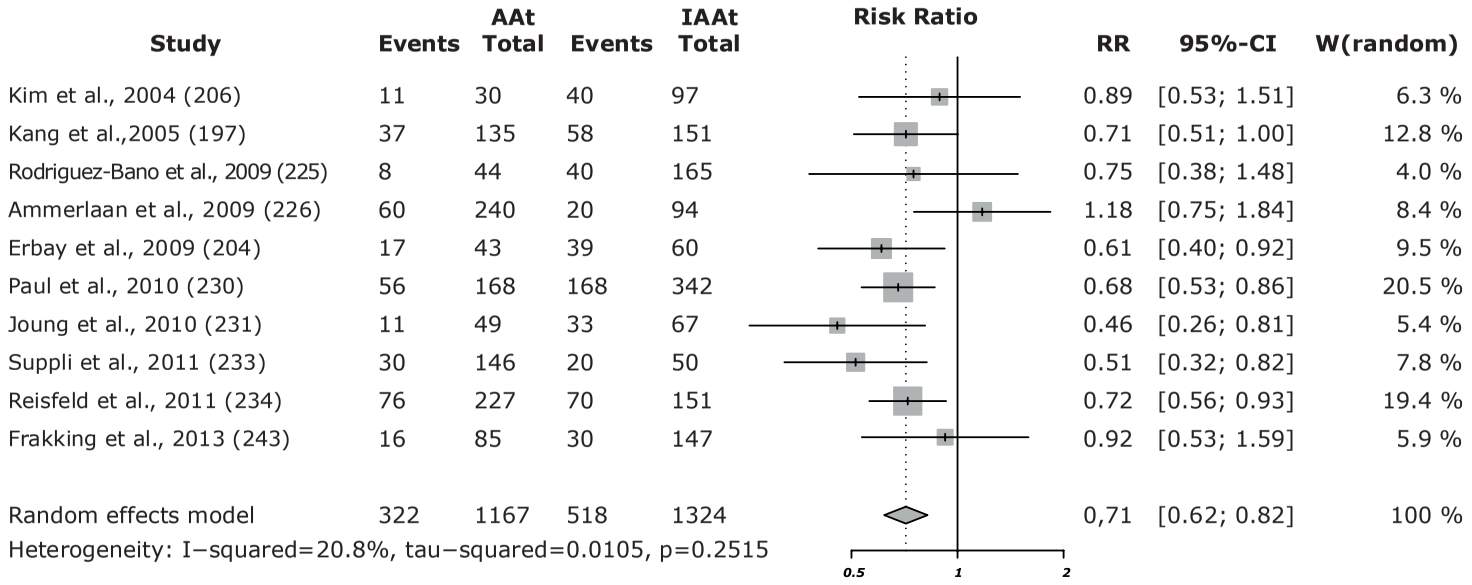

Figure 2 *Forest plot showing the effectiveness of appropriateness empirical antibiotics in severe infections on 30-day mortality*

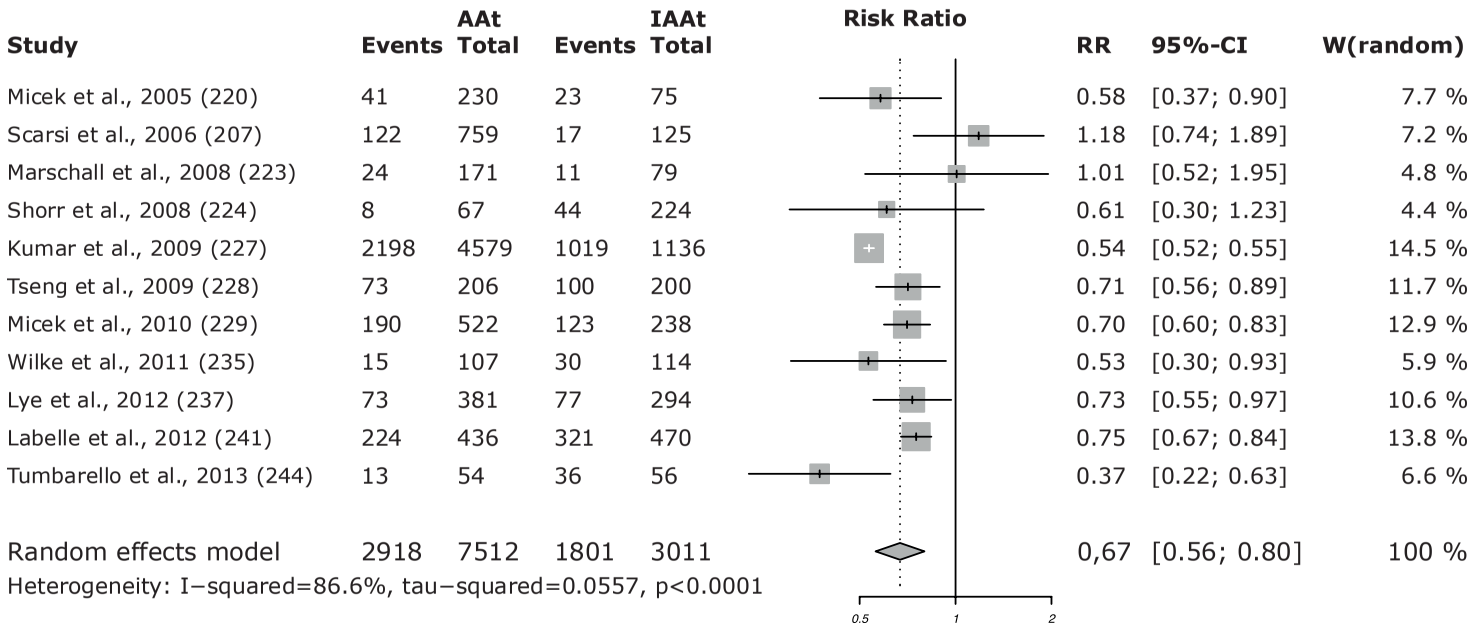

Figure 3 *Forest plot showing the effectiveness of appropriateness empirical antibiotics in severe infections on in-hospital mortality*

Table 4 Overview of studies evaluating the mortality rate on 28, 60 days, 12 weeks

Author(s), yr (reference)	Time of mortality assessment	AAT mortality rate	IAAT mortality rate	Significant differences
Luna et al., 2006 (221)	28 days	29.17	63.46	0.007
Chen et al., 2013 (242)	28 days	9.09	38.04	0.001
Tseng et al., 2012 (238)	60 days	28.17	55.43	0.023
Kim et al., 2006 (193)	12 weeks	28.10	38.46	NS

AAT: Appropriate Antibiotic Therapy
IAAT: Inappropriate Antibiotic Therapy
NS: Not Significant

The studies on 28-day (221,242) and 60-day (238) mortality reported significantly higher mortality ratios in patients receiving IAAT, respectively P=0.007 (221), P=0.001 (242) and P=0.023 (238). The study (193) that measures the mortality rate at 12 weeks did not reveal a significant difference (Table 4).

LOS and costs

Four studies reported the effect on LOS: total LOS (235,242) or LOS after the onset of infection (223,232). In one of the two studies (232) the mean LOS after infection onset was significantly (p=0.022) higher in the group sepsis patients with IAAT, indicating that IAAT independently increased the median attributable LOS by 2 days. However, the study by Marschall et al. (223) found no significant differences in LOS post-onset (p=0.09) in Gram-negative bacteraemia patients. Appropriate treated patients with ventilator-associated pneumonia had a significantly shorter total LOS (p=0.022) (235). Nevertheless, Chen et al. (242) found no differences in the total LOS of patients with community-onset bloodstream infections. The costs were only assessed in two studies (224,235). The total costs for patients with IAAT were significantly higher in both studies (p≤0.01).

DISCUSSION

The incidence of patients suffering from severe bacterial infections in substantial. Inappropriate therapy results in additional burden in terms of mortality, increased LOS and additional costs. Previous studies confirmed – as proved by the low number needed to treat - that correct antibiotic treatment is a crucial determinant of therapeutic success (252). Therefore, a systematic review with meta-analysis was conducted to investigate the incidence and consequences of IAAT on the outcome in hospitalized patients with severe infection.

Definitions and criteria items used to denote (I)AAT varied substantially between studies. Although, most definitions included the criterion 'matching with the in vitro susceptibility' or 'intermediate or full in vitro resistance'. The timing of administration of the antibiotics was taken into account in only 71% of the definitions. Timing of admission is however an important aspect of adequate antibiotic therapy. In patients with septic shock, each hour of delay in antimicrobial therapy is associated with an average decrease in survival of 7.6% (198). Rivers et al. (253) reported that early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. For SAB patients, the breakpoint between delayed and early treatment was 44.75 hours and delayed treatment was found to be an independent predictor of infection-related mortality (254). Based on this heterogeneity in the definitions, it was impossible to estimate the overall incidence of IAAT. However, IAAT ranged from 14.1% to 78.9%; with 46.4% of studies describing an incidence of IAAT of 50% or more. Considering this high incidence, healthcare professionals must become aware of this problem. Moreover, in an era of rising antimicrobial resistance rates, choosing empiric AAT is an increasing challenge. The meta-analysis, involving 13014 patients, suggest that the empiric AAT reduces 30-day mortality (RR 0.71, 95% CI 0.62-0.82) and in-hospital mortality (RR 0.67, 95% CI 0.56-0.80). In addition, empiric AAT also positively affects the LOS and the costs.

Strengths of this study include the comprehensive search strategy, the methodological quality assessment, and the random-effects model analysis combined with meta-regression. Besides the methodological strengths, the study also has limitations. Firstly, the present findings should be interpreted in the context of the included studies and their limitations: the heterogeneity in patients' characteristics, definitions of IAAT and the time span of outcome assessment. Secondly, the lack of randomized studies in this review could be seen as a major limitation. This lack regarding this topic stems from obvious ethical constrains. Given the methodological heterogeneity of the included studies, an overall meta-analysis was impossible. Meta-analysis was only performed for 30-day and in-hospital mortality. Thirdly, several potential biasing and confounding elements cause heterogeneity and might have hampered this meta-analysis. The reported diseases and the diagnosis process, the study quality-quantified by the Downs & Black instrument, the quality of the health care systems in the different countries and the definitions of adequate antibiotic therapy had a marked influence on the meta-analysis of in-hospital mortality. Nevertheless we aggregated all reported diseases to avoid a small numbers problem. Probably the cleanest data for assessing the impact of (I)AAT would be for bacteremia as this is the infection that can most accurately be defined. Finally, this analysis does not cover all areas, such as fungemia. However, this create opportunities for further research.

CONCLUSION

This systematic review demonstrates a very high incidence of IAAT in patients with severe bacterial infection, such as BSI, pneumonia, sepsis or septic shock. Accurate empirical treatment of these severe infections is not a simple process as seen in currently reported rates of IAAT. Meta-analysis provides evidence that empiric inappropriate use of empiric antibiotics increases 30-day and in-hospital mortality in these patients. Clinicians should be aware of this problem and further improvement actions should be taken. Inappropriate antibiotic treatment stems from several causes, mainly due to resistance, therefore it is not easy to find the most appropriate treatment option. As long as general recommendations about antibiotic stewardship are missing, problems will remain. Computerized decision support including complex and locally calibrated decision algorithms (208,255), early molecular identification or their combination might be helpful.

AUTHORS' CONTRIBUTIONS

KM conceived and designed the study; carried out the literature searches; selected the studies; assessed the included studies; analyzed, interpreted, synthesized the data; contributed to the statistical analysis and wrote the manuscript. AL carried out the literature searches; selected the studies; assessed the included studies. JB performed the statistical analysis, contributed to data interpretation, and revised the statistical portions of the report. NC and AV critically revised the manuscript for important intellectual content. All authors approved the final version to be published.

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Supplementary digital content

- Appendix 1 Literature search strategy
- Appendix 2 Description of exclusion criteria
- Appendix 3 Downs and Black checklist for methodological quality assessment of included studies
- Appendix 4 Data collection tool
- Appendix 5 Reference of studies only included in systematic review but not in the meta-analysis

Appendix 1. Literature search strategy

Used query
"antibiotic"[All Fields] AND "infection"[All Fields] AND ("appropriate"[All Fields] OR "inappropriate"[All Fields] OR "adequate"[All Fields] OR "inadequate"[All Fields]) AND ("outcome"[All Fields] OR "mortality"[All Fields] OR "survival rate"[All Fields] OR "cost"[All Fields] OR "length of stay"[All Fields]) AND "2004/08/20"[PDAT] : "2014/08/20"[PDAT] AND "humans"[MeSH Terms] AND ("loattrfull text"[sb] AND (English[lang] OR French[lang] OR Dutch[lang] OR German[lang]))
Result: 1097

Appendix 2. Description of exclusion criteria

Reason for exclusion	Description
Describe a type of diagnosis or treatment	Article describe a type of diagnosis or treatment not related to appropriate antibiotics
Describe a disease	Article describe epidemiology, current state of knowledge
Using inappropriate populations	Studies in pediatrics, burn or transplant patients, no hospital setting, veteran affairs center
Compare or describe antibiotics	Studies comparing the effectiveness of two or more antibiotics
Non clinical trials	Papers were guidelines, editorials, systematic reviews, case reports, letters, or comments
Study of prophylactic antibiotic treatment	
No comparison between inappropriate and appropriate antibiotic therapy	
Studies assessing specifically meningitis and endocarditis, where treatment effects are expected to largely deviate from any common effect	
No (quantitative) outcome	Studies report no (quantitative) data on mortality, length of stay of costs
Studies that recruited less than 75 patients	
Other infection than pneumonia, bloodstream infection (BSI) or bacteremia, sepsis, severe sepsis or septic shock	
Study compared survivors versus non-survivors	Studies compared survivors and non-survivors, without report not about inappropriate antibiotics
No full-text available	
The study give no definition for appropriate or inappropriate antibiotic therapy	

Appendix 3. Downs and Black checklist for methodological quality assessment of included studies

Appendix 3.1 Criteria per Downs and Black item

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described? (No patients lost to follow-up = 1 point)
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were the patients who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on 'data dredging', was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? (survival analysis should be answer by yes)
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/s reliable?
20. Were the main outcome measures used accurate (valid and reliable)? (always 1 point because definitions were reported: inclusion criteria)
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? (always 1 point because patients are recruited from the same study population)
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? (always 1 point because patients are recruited from the same study population during the same time)
23. Were study subjects randomized to intervention groups? (always 0 because all non-randomized studies should be answered no)
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (always 0 because all non-randomized studies should be answered no)
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (1 point if a difference in patient characteristics or severity index was corrected for)
26. Were losses of patients to follow-up taken into account?
27. Did the study have sufficient power to detect a clinically important effect?

Downs and Black score ranges were grouped into the following 4 quality levels:

- excellent (26 to 28),
- good (20 to 25),
- fair (15 to 19) and
- poor (less than 14)(216).

Appendix 3.2 Results of the Downs and Black checklist per study

First author/ year	Questions of the Downs and Black tool																												
	Reporting									External validity				Internal validity						Internal validity - confounding							Power	Total score	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		
Kim et al., 2004 (206)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	22	good
Kang et al., 2005 (256)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	0	1	1	1	22	good
Mueller et al., 2005 (219)	1	0	1	1	1	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0	19	fair
Micek et al., 2005 (220)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	21	good
Luna et al., 2006 (221)	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	1	0	22	good
Kim et al., 2006 (193)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	1	23	good
Scarsi et al., 2006 (207)	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	1	22	good
Fujita et al., 2008 (222)	1	0	1	1	0	0	1	0	0	1	0	0	0	1	0	1	1	1	1	1	1	1	0	0	0	1	0	14	poor
Marschall et al., 2008 (223)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	24	good
Shorr et al., 2008 (224)	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0	20	good

Rodriguez-Bano et al., 2009 (225)	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	22	good
Ammerlaan et al., 2009 (226)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	22	good
Erbay et al., 2009 (204)	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0	20	good
Kumar et al., 2009 (227)	1	0	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	20	good
Tseng et al., 2009 (228)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	21	good
Micek et al., 2010 (229)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	1	23	good
Paul et al., 2010 (230)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	21	good
Joung et al., 2010 (231)	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	21	good
Shorr et al., 2011 (232)	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	1	22	good
Suppli et al., 2011 (233)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	22	good
Reisfeld et al., 2011 (234)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	21	good
Wilke et al., 2011 (235)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	21	good
De Rosa et al., 2011 (236)	1	1	1	1	0	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	18	fair
Lye et al., 2012 (237)	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	1	21	good

Tseng et al., 2012 (238)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0	20	good
Chen et al., 2012 (239)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0	20	good
Kim et al., 2012 (240)	1	1	1	1	0	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0	19	fair
Labelle et al., 2012 (241)	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	21	good
Chen et al., 2013 (242)	1	1	1	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	1	1	22	good
Frakking et al., 2013 (243)	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	21	good
Tumbarello et al., 2013 (244)	1	0	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	21	good
Ortega et al., 2013 (245)	1	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	1	18	fair

Appendix 4. Data collection tool

Source - Study ID - Authors - Country - Publication date - Title Eligibility - Confirm eligibility - Reason for exclusion Method - Study design - Inclusion period Participants - Number of hospitals - Types of hospitals - Number of participants - Characteristics of the participants (disease, severity scale)	Conceptualization - Definition of (in)appropriate antibiotics - Elements of the definition of (in) appropriate antibiotics Outcomes - Primary outcome - Number of (in)appropriate antibiotics - Secondary outcome - Mortality rates - Time of mortality assessment - Total length of stay - Length of stay after onset - Direct medical costs Quality assessment - Downs and Black assessment tool

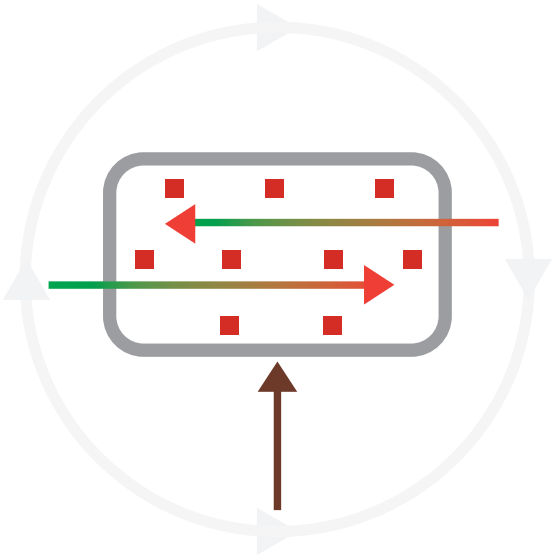
Appendix 5. Reference of studies only included in systematic review but not in the meta-analysis

These studies were not included for meta-analysis because either they did not report on mortality or they report on 28, 60 days or 12 weeks or they did not report raw data.

References	Reason for exclusion of the meta-analysis
Luna CM, Aruj P, Niederman MS, Garzon J, Violi D, Prignoni A, et al. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia´. Eur Respir. 2006;27(1):158–64.	Measuring mortality at 28 days
Kim S-H, Park W-B, Lee C-S, Kang C-I, Bang J-W, Kim H-B, et al. Outcome of inappropriate empirical antibiotic therapy in patients with Staphylococcus aureus bacteraemia: analytical strategy using propensity scores. *Clin Microbiol Infect*. 2006 Jan;12(1):13–21.	Measuring mortality at 12 weeks
Shorr AF, Micek ST, Welch EC, Doherty J a, Reichley RM, Kollef MH. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. *Crit Care Med*. 2011 Jan;39(1):46–51.	Did not report on mortality
Tseng C-C, Liu S-F, Wang C-C, Tu M-L, Chung Y-H, Lin M-C, et al. Impact of clinical severity index, infective pathogens, and initial empiric antibiotic use on hospital mortality in patients with ventilator-associated pneumonia. *Am J Infect Control*. Elsevier Inc; 2012 Sep;40(7):648–52.	Measuring mortality at 60 days
Chen R, Yan Z, Feng D, Luo Y, Wang L, Shen D. Nosocomial bloodstream infection in patients caused by factors for hospital mortality. *Chin Med J*. 2012;125(2):226–9.	Did not report raw data
Chen H-C, Lin W-L, Lin C-C, Hsieh W-H, Hsieh C-H, Wu M-H, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. *J Antimicrob Chemother*. 2013 Apr;68(4):947–53.	Measuring mortality at 28 days

CHAPTER 7

Drug related problems in residential care facilities for elderly: a systematic review



Drug related problems in residential care facilities for elderly: a systematic review

This study was submitted as

Storms H, **Marquet K**, Aertgeerts B, Claes N. Drug related problems in residential care facilities for eldery: a systematic review Submitted to Drugs & Ageing.

Chapter 7: Drug related problems in residential care facilities for elderly: a systematic review

ABSTRACT

The frailty of the elderly population including multi-morbidity and polypharmacy, enhances the probability of experiencing drug related problems (DRPs). Therefore, awareness and careful drug monitoring in residential care facilities for the elderly are necessary. The objective of this research is to review the literature in order to assess the incidence of DRPs in residential care facilities for the elderly.

Methods: Electronic databases were searched for literature from 2004 to 2014 (MEDLINE, EMBASE) to identify studies examining DRPs in residential care facilities for elderly. Studies were eligible for review when relying on Beers criteria, STOPP, START, RASP, PRISCUS list, ACOVE, BEDNURS or MAI. A DRP is defined as inappropriate medication use according to criteria used by these seven instruments. Consequently, a broad range of DRPs in residential care facilities for the elderly is explored, including drug-drug interactions, drug-disease interactions, over treatment, under treatment and prescribing omissions.

Results: Twenty-three studies met inclusion criteria. The majority of these studies (n= 20) assessed DRPs relying on a version of Beers criteria; they reported percentages of residents experiencing DRPs varying from 2.26% to 82.6%, with a median of 45.6%. The in 2003 updated Beers criteria are most frequently referred to. Studies relying on this update report a smaller range with a percentage of residents experiencing DRPs varying from 14.5% up to 63.0% and a median of 34.9%. The instrument second most referred to is "STOPP": the percentage of residents experiencing DRPs ranging from 23.7% up to 79.0% with a median of 59.4%.

Conclusion: Researchers mostly relied on a version of Beers criteria, in particular the update of 2003 and on the instrument "STOPP". Heterogeneity in data hampered meta-analysis, limiting definite statements on the incidence of DRPs: the number of residents experiencing DRPs strongly varies between studies, even in those with similar characteristics. However, the numerous studies that could be reviewed suggest that there's an awareness to monitor DRPs in residential care facilities in the elderly.

INTRODUCTION

Monitoring of drug related problems (DRPs) as experienced by the elderly is crucial because of the frailty of this population due to their multi-morbidity and associated polypharmacy (257,258). As medication is known to potentially cause adverse events, every drug therapy could be hazardous. Moreover, errors in medication management can affect patients' health outcomes. Therefore, attention should be given to adequate medication management to ensure high quality of care. This demands continuously monitoring of patients' drug therapy: the prescription, the transcription, the dispensing, the administration, as well as the intake of medication.

Residential care facilities are obviously an important setting for people of older age. Despite the frailty of this population, few research seems to have focused on DRPs in this setting. However, in hospital settings, extensive research has been carried out to investigate potential harm of drug therapies (27,137,138,162). Moreover, institutionalized care settings often do not have a physician or pharmacist on site, which may increase the chance for difficulties in medication follow-up. Other contributing factors can be the relatively high turnover of nurses which is common in this setting (259–261) and the often declining assertiveness of the elderly which may gradually limit their active role in the medication process.

It is of particular importance that appropriate drug choices are made when managing drug therapy for the elderly: research shows that inappropriate medication use is associated with higher hospitalization rates and mortality in elderly (262–265). This higher likelihood to be hospitalized is also seen in patients of older age attending the emergency department with drug-drug interactions (266–268). The existed instruments focuses on DRPs related to the prescription process. The aim of this systematic review is to determine the incidence of these DRPs due to inappropriate medication use in a broad range of residential care facilities for the elderly.

METHODS

Search strategy

Electronic databases (EMBASE, MEDLINE) were searched from January 2004 to July 2014 to identify studies in which DRPs are assessed in residential care facilities for the elderly. Studies had to rely on at least one of eight frequently used instruments [Beers criteria (269–272), STOPP (273), START (274), PRISCUS list (275), ACOVE (276), BEDNURS (277), MAI (278) or RASP (278)]. This list of instruments was combined with keywords "medication errors" and "adverse drug event" in the setting "nursing home". Articles written in English, Dutch, French and German were searched. Additional studies of interest were searched in reference lists of included articles (Figure 1).

Definitions

A drug related problem is an event or circumstance involving drug treatment that actually or potentially interferes with the patient's optimum outcome of medical care (279). In this review, DRPs are defined as inappropriate medication use according to criteria of the seven used instruments. These DRPs vary from inadequate medication use according to evidence-based practices, to drug-drug interactions, drug-disease interactions, over- and under treatment as well as prescribing omissions, as defined by the respective instruments; thereby excluding other problems related to the use of medication (wrong patient, wrong time) (32) (Table 1).

The generic terminology nursing homes was used to refer to residential care facilities that corresponded to a place of residence for elderly who require nursing and assistance with activities of daily living.

Instruments

Eight frequently used instruments were selected as a reference to identify studies assessing DRPs (280–283). The criteria created by Beers et al. (269–272) were the first to examine problems of medication use specifically in nursing homes. These criteria are considered as a standard to measure appropriateness of prescribed drugs (284). The explicit criteria as developed by Beers et al. (269–272) are an example of a guideline to help healthcare professionals in delivering evidence-based care by giving considerable attention to the risks of prescribing to elderly. In an attempt to improve measurement of medication errors, for instance by taking into account residents' diseases, the original list of criteria by Beers et al (271) has been revised (269,270,272) and several other assessment tools have been developed since (273–277,285). For instance, in 1994, the Medication Appropriateness Index (MAI), was created. MAI represents a weighing scheme intended to score every drug on appropriateness in a 'summated score' (285). To assess appropriateness, drugs are scored 'appropriate', 'marginally appropriate' or 'inappropriate' regarding ten criteria, each with a particular weighing [indication (3), effectiveness (3), dosage (2), direction (2), drug–drug interaction (2), drug–disease interaction (2), practicality (1), duplication (1), duration (1) and expense (1)]. The summated score is calculated by multiplying the weight of each criterion by '0' ('appropriate'), '0.5' ('marginally appropriate') or '1' ('inappropriate') and adding them all. Consequently, the maximum score per drug when inappropriate is '18'. In 1997, a study called 'Bergen District Nursing Home' (BEDNURS) was carried out, based on criteria of Beers 1997 (270), with adjustments to measure drug-drug interactions and overtreatment (277). In 2001, the tool 'Assessing Care Of Vulnerable Elders' (ACOVE) was created to assess the quality of care for vulnerable elderly (276). These criteria measure the appropriateness of medication management and have explicit criteria to measure underuse of medication (9 out of 68 specific medication-related criteria). In 2007, both 'Screening Tool of Older Persons' potentially inappropriate Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) were created (273,274). The STOPP is

a list of 65 indicators for potentially inappropriate prescriptions, including drug-drug interactions, drug-disease interactions, therapeutic duplication and drugs that increase the risk of cognitive decline and falls (281). The START is a list of 22 indicators for prescribing omissions (274). In 2010, the German 'PRISCUS' list was created. This list consists of 83 medications that are considered to be potentially inappropriate (275). The PRISCUS list has the same structure and should be used as the Beers criteria (269–272). Recently the RASP, Rationalization of home medication by an Adjusted STOPP list in older Patients, was developed and validated to reduce polypharmacy in the geriatric population (278) (Table 1).

Table 1 Characteristics of instruments

Instruments	Appropriateness of medication use	Drug-drug interactions	Drug-disease interactions	Overtreatment	Therapeutic duplications	Undertreatment Prescribing omissions
Beers criteria (269–272)	+		+			
STOPP (273)	+	+	+		+	
START (274)						+
PRISCUS (275)	+					
ACOVE (276)	+					+
BEDNURS (277)		+		+		
MAI (285)	+	+	+		+	
RASP (278)	+	+		+	+	

Selection of studies

Two independent researchers (HS, KM) screened titles, abstracts and full texts match with inclusion criteria as mentioned above. When abstracts were not available, the full text was consulted. Studies were found to be eligible for review when reporting on DRPs as defined by at least one of seven imposed instruments in a residential care facility for the elderly.

The following exclusion criteria were applied: irrelevant setting (community, hospital, veteran hospitals), less than 100 residents participating in the study, irrelevant study object [experimental research assessing pharmacokinetic/ pharmacodynamic properties (in patients with a particular pathology); research on discrepancies when transferred between settings; systematic reviews; describing methodology of a tool; describing a particular reimbursement status], research on medication administration errors only (Figure 1).

Data extraction and analysis

Data were independently extracted by the same researchers (HS, KM) using a pre-defined extraction form (Microsoft Excel). Discordances were solved by consensus. Studies were reviewed to determine the incidence of DRPs. The incidence of DRPs was considered as the single outcome. In case of studies in multiple settings, only data on the residential care facility for elderly was considered. With regard to intervention studies in one population, data of the initial review of medication (prior to intervention) were retained. In contrast, studies comparing intervention groups to control groups are regarded as generating two separate populations. Consequently, baseline data of both groups are analyzed. Although there is overlap between the seven used instruments, the incidence resulting out of the seven instruments cannot be compared. Therefore, incidence should be regarded per instrument. The incidence of DRPs is expressed as the percentage of residents

experiencing DRPs. However, for studies relying on MAI, DRPs are set out as a sum score with standard deviation. Additionally, descriptive data on number of drugs used by residents are reported. These data are expressed as total, mean with standard deviation or the range. Due to the heterogeneity in overall data, no meta-analysis could be realized.

RESULTS

Twenty-three out of the 480 studies identified met inclusion criteria. The main reasons for exclusion are described in the flow diagram of the study-selection process (Figure 1). Data of two studies are not analyzed (286,287) because of risk of bias on outcome level: part of Beers criteria were explicitly excluded.

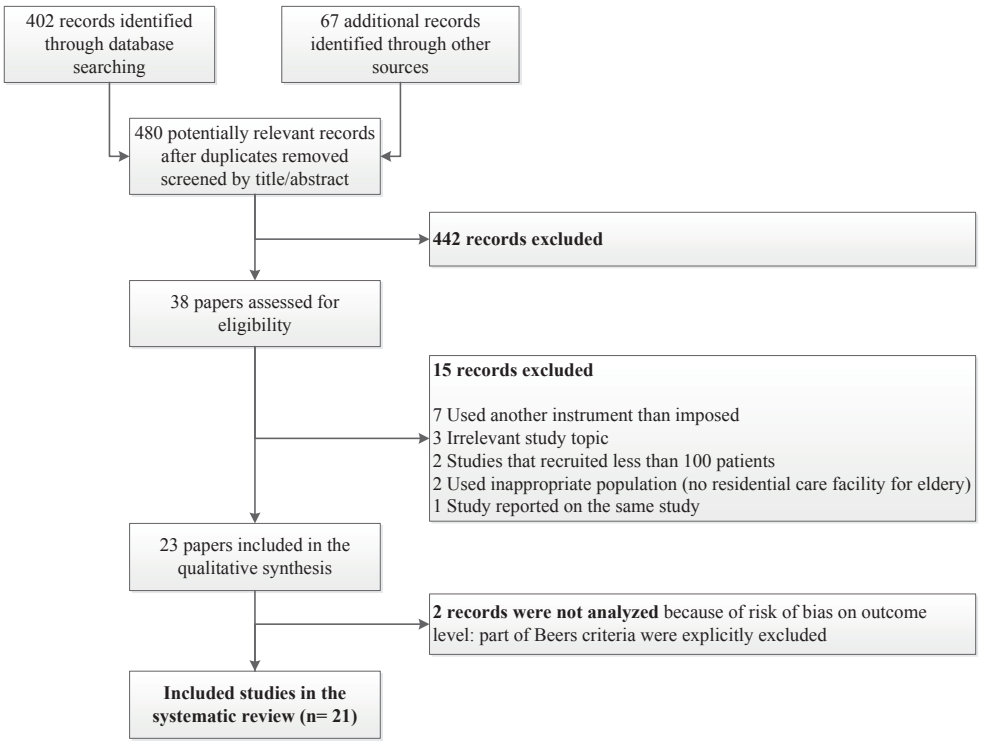


Figure 1 Flow diagram of study-selection process

Characteristics

Eleven studies were carried out in Europe (280,287–297), four in Asia (286,298–300), three in North-America (301–303), three in South-America (304–306) and two in Australia (307,308) (Table 2). In 87% (n=20) of the studies, researchers assessed inappropriateness of residents' medication by relying on criteria developed by Beers et al. (269–272). The majority (11 studies) (280,286,288–290,293,294,299,304,305,307) of these studies rely on the updated criteria from 2003 (272) (Table 2). Two studies report data on incidence of DRPs, based on the latest version (2012) of Beers criteria (304,306). Six studies (26%) (289,291,292,297–299) used the 'STOPP'-criteria (273). Some studies rely on additional (national) tools: these are often inspired by Beers criteria (280,287,288,293,301,307). Only one study (292) used the implicit tool 'MAI' (285). Six studies (280,289,291,292,297,299) relied on more than one instrument, with a maximum of five different instruments in the study carried out by Verrue et al. (292). We found no studies in the residential care facilities using the very recent RASP instrument.

The number of participants in the reviewed studies ranged from 100 to 58719 residents (Table 2). Eligibility for participation mostly depended on an age requirement, overall being aged 65 years or more. Furthermore, residents were excluded when requiring palliative care, when data were incomplete or if they were transferred or died during the study period. Data on DRPs were gathered through medical records (289,291,299,303–307), medication charts (280,288,290,292–294,298,300,308) and administrative databases with information on drug therapy (287,301,302) or assessment database for drawing care plans and monitoring quality (286).

Table 2 Characteristics of included studies (n= 23)

Author, year	Design	Country	Number residential care facilities	Number residents	Mean ±SD [range] of number of drugs used	Beers criteria (269–272)	STOPP (273)	START (274)	PRISCUS (275)	ACOVE (276)	BED NURS (277)	MAI (285)
Lane et al., 2004 (301)	Cohort	Canada	NM	58719	10.7 ± 6.79	1991 1997						
Blozik et al., 2010 (294)	Pre/post	Switzerland	1	173	7.8 ± 4	2003						
King et al., 2007 (308)	Cross-sectional	Australia	15	998		1991						
Varallo et al., 2012 (305)	Cross-sectional	Brazil	1	120		2003						
Hosia-Randell et al., 2008 (293)	Cross-sectional	Finland	20	1987	7.9	2003						
Stafford et al., 2011 (307)	Cross-sectional	Australia	41	2345		2003 (ID-CD)						
Barnett et al., 2011 (288)	Cohort	UK	NM	4557		2003						
Perri et al., 2005 (303)	Cohort	USA	15	1117	[0-30]	1997						
Ruggiero et al., 2010 (290)	Longitudinal	Italy	31	1716	[1-18]	2003 (ID-CD)						
Lau et al., 2004 (302)	Longitudinal	USA	NM	3372	[0-9]	1991 1997						
Raivio et al., 2006 (296)	Longitudinal	Finland	7	195		1997 (ID)						
Pinto et al., 2013 (304)	Cross-sectional	Brazil	5	151	3.31 ±1.8	2003 2012 (ID-CD)						

Mamun et al., 2004 (300)	Cross-sectional	Singapore	3	454		1997						
Bergman et al., 2007 (287)	Cross-sectional	Sweden	NM	7904	11.9	1997						
Vieira de Lima et al., 2013 (306)	Cross-sectional	Brazil	6	261	1452 D	2012 (ID-CD)						
Verrue et al., 2012 (292) control group	Non-randomised controlled intervention	Belgium	1	154	[0-19]	1997	+	+		+		+
Intervention group				230	[0-16]							
O'Sullivan et al., 2013 (289)	Cross-sectional	Ireland	14	732		2003 (ID-CD)	+					
Chen et al., 2012 (299)	Cross-sectional	Maleysia	4	211	4.7 ± 2.8	2003 (ID-CD)	+					
Elseviers et al., 2014 (280)	Cross-sectional	Belgium	76	1730		2003			+	+	+	
Ryan et al., 2013 (291)	Cross-sectional	Ireland	7	313			+	+				
Lao et al., 2013 (298)	Cross-sectional	China	1	156			+					
García-Gollarte et al., 2012	Cross-sectional	Spain	6	100	6.49		+	+				
Niwata et al., 2006 (286)	Cross-sectional	Japan	17	1669	-	B2003 (ID-CD)						

ID-CD = explicit distinction between independent from disease and considering disease
NM: Not Mentioned
SD= Standard Deviation
"+" = relying on

Incidence of DRPs

When relying on any version of Beers criteria the percentage of residents experiencing DRPs varies from 2.26% to 82.6% with a median of 45.6%. When only considering the most used version of 2003 it ranges from 14.5% up to 63.0% with a median of 34.9% (Table 3). In studies relying on the 2012 update of Beers criteria incidences of DRPs are 63.0% and 82.8% (302,304). Studies based on 'STOPP', report an incidence of 23.7% up to 79.0% with a median of 59.4%. When relying on 'START', 'ACOVE' and 'BEDNURS' the incidence of DRPs is: 19.0% to 74.0%; 21.5% to 58.0% and 56.0% respectively (Table 3).

Table 3 Percentage residents experiencing drug related problems (DRPs)

Author, year	Beers criteria (269–272)	STOPP (273)	START (274)	ACOVE (276)	BEDNURS (277)	MAI (285) (sum score)
Lane et al., 2004 (301)	2.26					
Blozik et al., 2010 (294)	14.5					
King et al., 2007 (308)	18.5					
Varallo et al., 2012 (305)	29.2					
Hosia-Randell et al., 2008 (293)	34.9					
Stafford et al., 2011 (307)	35.3					
Barnett et al., 2011 (288)	37.1					
Perri et al., 2005 (303)	46.5					
Ruggiero et al., 2010 (290)	48.0					
Lau et al., 2004 (302)	50.3					
Raivio et al., 2006 (296)	63.0					
Pinto et al., 2013 (304)	70.0					
Mamun et al., 2004 (300)	74.0					
Vieira de Lima et al., 2013 (306)	82.6					
Verrue et al., 2012 (292) control group	45.6	48.1	19.0	21.5		11.7 (SD 6.80)
Verrue et al., 2012 (292) intervention group	52.2	59.4	42.0	36.2		10.5 (SD 6.37)
O'Sullivan et al., 2013 (289)	53.6	70.8				
Chen et al., 2012 (299)	32.7	23.7				
Elseviers et al., 2014 (280)	27.0			58.0	56.0	
Ryan et al., 2013 (291)		59.8	42.2			
Lao et al., 2013 (298)		46.5				
García-Gollarte et al., 2012 (297)		79.0	74.0			

DISCUSSION

Twenty-three studies used at least one of the selected instruments to determine the incidence of DRPs. Five relied on more than one instrument, with a maximum of five instruments in one study (292). The instruments most frequently referred to are Beers criteria (269–272) and STOPP (273). Because of the limited data generated by instruments other than Beers criteria and STOPP any comparison was entangled. Moreover, divergence in scope as well as differently expressed results caused heterogeneity in the data. Consequently, a meta-analysis was hampered.

Although heterogeneity entangles statements on the incidence of DRPs in institutionalized care settings for the elderly, it is clear that the percentage of residents experiencing problems strongly varies. The lowest percentage is reported by Lane et al. (301), who conducted an assessment based on an extensive database, resulting in the largest sample size of the reviewed studies. Consequently, the percentage of residents with DRPs reported in this research actually represents a relatively high number residents. Additionally, the percentage of residents experiencing DRPs does not seem to correlate with the extent of the instrument; studies relying on more extensive Beers criteria (the most recent updates) do not report more residents experiencing DRPs in contrast to studies with an instrument assessing a limited number of problems. However, consistent with previous research indicating a higher detecting rate of unsuitable medication use when relying on STOPP-criteria (281) the incidence of DRPs detected by STOPP is, except for one study (299), higher than the incidence resulting out of an assessment with Beers criteria (289,292). To analyze the incidence of DRPs more thoroughly, studies with similar characteristics are compared.

In studies based on STOPP-criteria, DRPs are most frequently ascribed to duplicate drug prescriptions. Comparison of similar studies (292,298), same instrument,

similar sample size shows a similar proportions of residents with DRPs (48.1% and 46.5%). The limited availability of data on, for instance, medication use, hampers any further statement on contributing or causal factors. The same can be concluded when comparing studies based on Beers criteria updated in 2003: the similarities in characteristics – number of participating residents, similar average drug use, as well as (not) taking into account residents' diseases – are reflected in the number of residents experiencing DRPs. Remarkably, out of three studies based on the 2003 update, particularly making a distinction based on residents' diseases (289,290,307), the research with the smallest sample size (289) reports the highest percentage of residents experiencing DRPs (53.6%). This high number could be explained by the number of drugs used by the participating residents, which is higher than in the other two studies. An analogous trend is revealed when research based on the latest update of the Beers criteria of 2012 is compared (304,306): for these two studies as well, the population taking the highest number of drugs has the highest proportion of DRPs (306).

The hypothesis of an association between the number of drugs and the elevated risk on experiencing DRPs has been extensively documented and confirmed by numerous studies included in this review (286,289–291,293,300,302,306,307,309). Because polypharmacy can be expected in a population of higher age (257,258,286,290,303,310,311) and given the risk on DRPs due to this polypharmacy (290,293,303,310–313), it is of great importance to monitor DRPs in an elderly population. A significant association between polypharmacy and DRPs is valid for hospital settings (262,314), as well as in a home care setting (315). The data from the reviewed studies suggest that an analogous correlation between DRPs and polypharmacy exists in residential care facilities. Monitoring DRPs in the setting of residential care facilities is important because of the typically higher age and potential polypharmacy of residents in these facilities. Moreover, the intake of multiple drugs by residents, enhances the likelihood of masking new symptoms, as they may easily be interpreted as side-effects and may be overlooked (316).

To improve medication management in residential care facilities, systematically executed medication reviews should become standard practice. As shown by research, these kinds of pharmaceutical interventions improve detection of potentially problematic medication use (283,317,318). A multidisciplinary approach and in particular the involvement of a clinical pharmacist would be beneficial to enhance medication safety (318–320). This is not easy to realize in residential care facilities. Ideally, in the 'geriatric assessment teams' besides a general practitioner and a nurse both with geriatric education, a clinical pharmacist should be present. The residents' medication use should be continuously monitored and adjusted by specialized healthcare professionals (320,321).

In reviewing medication use healthcare professionals should rely on evidence-based guidelines. These guidelines can indicate the (in)appropriateness of the medication, taking into account individual characteristics of residents, such as their diseases, changed physiology and preferences (322). The eight instruments (269–278,285) that we used in this review as a reference to assess DRPs are exemplary as types of guidelines. Incorporating guidelines in clinical decision support systems (CDSS) can assist healthcare professionals to detect potential DRPs in their daily practice (282,323,324). When an electronic medical record is available, the CDSS can be organized to generate pop-up's during the prescribing process, alerting the prescriber of possible hazardous drug (-disease) combinations.

Additionally, to determine if medication is clinically indicated, it is important to have an accurate medication overview, particularly for elderly who are polymedicated (23,325–327). This medication overview is a prerequisite to inform healthcare professionals about all medication taken by the resident: a continuously updated overview is therefore crucial. Moreover, this updated medication overview should allow healthcare professionals to quickly detect DRPs like duplications or drug-drug interactions (23,325,326,328–331). The importance of adequate monitoring of DRPs in order to prevent serious adverse events is demonstrated in a recent

retrospective record review on adverse drug events in hospitals: older age, comorbidities and the number of medications taken before admission are shown to be risk factors for potential ADEs (138).

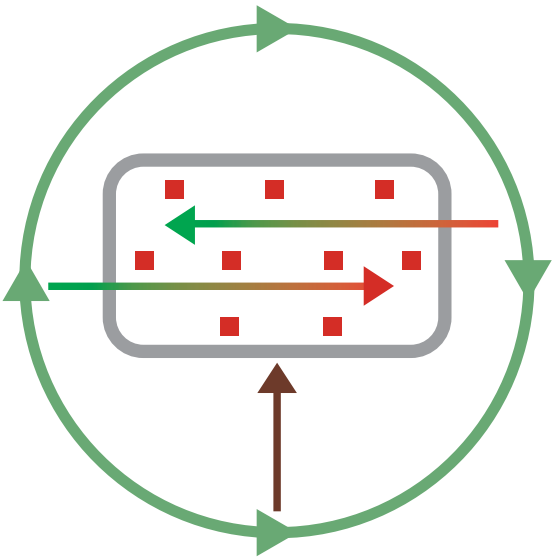
This review is based on a limited number of studies generating heterogeneous data, subsequently hampering meta-analysis. To assess the incidence of DRPs, overall medication use of residents was considered: research only evaluating specific drug classes or medication for certain diseases was excluded, therefore restricting the studies eligible for this review. Moreover, the assessment of DRPs was restricted to problems examined by the respective instruments because of the requirement to rely on at least one of seven imposed instruments. However, this requirement also broadens the range of criteria to evaluate medication use of residents. Consequently, this is the first review that gathers data on the incidence of DRPs taking into consideration various frequently used instruments. Despite the restrictions, this review indicates that researchers are aware of the importance to monitor DRPs in residential care facilities for the elderly. To assess DRPs the criteria of Beers' et al. (269–272) are most frequently used.

CONCLUSION

DRPs are defined as inappropriate medication use according to criteria used by the eight imposed instruments (Beers criteria, STOPP, START, PRISCUS list, ACOVE, BEDNURS, MAI, RASP). Most studies relied on some version of Beers criteria (269–272), in particular the update of 2003 (272) and on the tool 'STOPP' (273). Heterogeneity in data hampered meta-analysis, limiting statements on incidence of DRPs: the number of residents experiencing DRPs strongly varies between studies, even those with similar characteristics. However, the numerous studies that could be reviewed suggest that there's an awareness to monitor DRPs in residential care facilities in the elderly.

CHAPTER 8

Discussion and recommendations



Chapter 8: Discussion & recommendations

Since the report "To err is Human" from the Institute of Medicine in 1999 (1), patient safety received ever more global public attention. The rate of adverse events is an important indicator of patient safety performance. An adverse event is defined by Wilson et al. (2) as *(1)* an unintended injury or complication, *(2)* which results in disability, death or prolongation of hospital stay, and *(3)* is caused by healthcare management (including omissions) rather than the patient's disease. An adverse event can be preventable. In order to learn from their experiences healthcare professionals must be aware of the occurrence of (preventable) adverse events and must have a reliably measurement system to identify adverse events and their associated factors. Methods can be divided into retrospective risk analysis which gives a clear view of the problem (detection of adverse events) and prospective risk analysis which provides insight into the safety practices that precipitate adverse events (estimation of risks). Both methods are complementary. The first research question focus on the retrospective risk analysis. A method of prospective risk assessment, the Healthcare Failure Mode & Effect Analysis was also used during the PhD to evaluate the process flow for ear, nose and throat one-day patients, and to redesign the process to enhance patient safety (332). However, this is not described in the dissertation. The second research question focuses on drug related events through literature research.

MAIN FINDINGS

The retrospective risk analysis, the first research question, was divided in four sub questions: '(1) How can retrospective record review be applied in acute hospitals for the detection of adverse events requiring a higher level of care the study?', '(2) What is the incidence and preventability of these type of adverse events?', '(3) What is the incidence and preventability of adverse drug events?' and '(4) What is the format, the availability and the completeness of the patient record?'. A multistage retrospective review study of patients requiring an unplanned transfer to a higher level of care is launched in six acute hospitals in the province of Limburg. Record selection is based on unplanned transfer to a higher level of care, which is defined as (1) (re)admission to the Intensive Care Unit from a general ward, (2) an intervention by a Medical Emergency Team (MET) due to an unanticipated change in the patient's clinical status. Adverse events were found in 465 (56%) of the 830 reviewed patient records. Of these, 215 (46%) were highly preventable. This means that 25.9% of all unplanned transfers to a higher level of care were associated with a highly preventable adverse event. The level of harm varied from temporary harm (55.7%) to permanent impairment (19.1%) and death (25.2%). Though the direct causality is often hard to prove, it is reasonable to consider these adverse events as a contributing factor. The adverse events were mainly associated with drug therapy (25.6%), surgery (23.7%), diagnosis (12.4%) and system issues (12.4%). Because of the high amount of adverse drug events, we further focus on these events. 83.8% of the ADE were preventable. Antibiotics and antithrombotic agents accounted both for one-fifth of all pADEs. Age, ASA score and the number of medications taken before admission are risk factors for pADEs. The records used during the record review, were a combination of manual and electronic documents and 26.4% of records were not completely available. Only 0.3% and 3.3% of the medical and nursing parts of the record were complete for all basic standards. Highly preventable adverse events are underestimated when the record is partly unavailable and the absence of a validated discharge letter is a predictor for these highly preventable adverse events.

The second research question focuses on medication therapy though literature research. Firstly, a systematic review with meta-analysis of the incidence of empiric inappropriate antibiotics and their impact on the outcome was conducted. The percentage of inappropriate empiric antibiotic use ranged from 14.1% to 78.9% (Q1-Q3: 28.1-57.8%); 13 of these 27 studies (48.1%) described an incidence of 50% or more. The meta-analysis provides evidence that inappropriate use of empiric antibiotics increases 30-day and in-hospital mortality in patients with a severe infection. Clinicians should be aware of this problem and further improvement actions should be taken. Secondly, a systematic review on the incidence of drug related problems in residential care facilities for elderly was conducted. Drug related problems are defined as inappropriate medication use according to criteria of the eight imposed measuring instruments (ACOVE, BEDNURS, Beers criteria, MAI, PRISCUS, START, STOPP, RASP). These drug related problems can vary from (1) inadequate medication use according to evidence-based practices, (2) to drug-drug interactions, (3) drug-disease interactions, (4) over- and (5) under- treatment as well as (6) prescribing omissions, as defined by the respective measuring instruments; thereby excluding other problems related to the use of medication (wrong patient, wrong time). The majority of these studies assessed DRPs relying on a version of Beers criteria (269–272) reporting percentages of residents experiencing DRPs varying from 2.26% to 82.6% with a median of 45.6%. The in 2003 updated Beers criteria are most frequently referred to. Studies relying on this update report a smaller range with a percentage of residents experiencing DRP’s varying from 14.5% up to 63.0% and a median of 34.9%. The instrument second most referred to is “STOPP”: the percentage of residents experiencing DRP’s ranging from 23.7% up to 79.0% with a median of 59.4%.

METHODOLOGICAL CONSIDERATIONS

The assessment of the incidence of adverse events

The selected records were reviewed in an implicit manner, meaning that no explicit screening criteria were applied. The whole patient record, the medical and nursing part with medication list, was taken into account during the record review. Clinical information on admission (such as allergies, patients history, medication list at home, reason for admission, report of physical examination) and the treatment and follow-up during hospitalization (such as progress notes, the medication list, vital signs, discharge letter and if applicable the surgical and anesthetic treatment) were investigated. By using the whole patient record, the clinical team tried to evaluate the causality by considering the impact of the healthcare management versus patient factors (a criteria of the definition of an adverse event).

The records were selecting using the trigger "unplanned transfer to a higher level of care". With this trigger, a high percentage of serious adverse events is detected, which makes this trigger with a positive predictive value of 56% a good criteria for patient selection. However, by using this specific focus a comparison with previous studies on in-hospital adverse events is difficult. In order to allow comparisons in the future, we apply a transparent study design.

The assessment of the preventability of adverse events

The preventability, the type and the level of harm were assessed. A preventable adverse event is an adverse event resulting from an error in management due to failure to follow accepted practice at an individual or system level. The accepted practice was taken to be the 'current' level of expected performance for the average practitioner or system that manages the condition in question (14). The

clinical team used international guidelines and databases (333–337), advice of the expert panel and guidelines from the participating hospital to evaluate the preventability. When there was no clear evidence of errors in the record, the team chose to underestimate the preventability. For example, a nosocomial infection with a notice of a symptom in record (e.g. patient with inflammation symptoms of rubor, calor, dolor, tumor at the catheter) without therapy was seen as highly preventable. A nosocomial infection without evidence of not-accepted practice was classified as low preventable, although based on a review of the literature 30% of the nosocomial infections may be preventable (338). However, sometimes the records exist of piecemeal data and probably the preventability of some cases will be underestimated.

The assessment of the level of harm

Most record reviews on adverse events differentiated between temporary, permanent harm and death (Table 1). Some reviews made a more detailed differentiation based on the timing of recovery (within 1, 6 or 12 months for temporary harm) and the percentage of permanent disability (≤ of > 50% for permanent harm), while other studies used the classification of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (29) to assess the harm. The NCC MERP classification provides a standard language and structure to analyze adverse drug events. Categories A to D describe situation without harm and categories E to I describe events that resulted in (temporary or permanent) patient harm or patient's death.

In this record review adverse (drug) events in patients with an unplanned need for a higher and more critical level of care were selected. In practice, record selection was based on (1) (re)admission to the Intensive Care Unit from other (general) wards in the hospital providing lower intensity care, (2) an intervention by a Medical Emergency Team due to an unanticipated change in the patient's

clinical status. Based on these inclusion criteria, these patients required a higher level of care to sustain life. Therefore only the categories H 'Required intervention to sustain life' and I 'Contributed to or resulted in the patient's death (mortality rate)' can be used. Furthermore, during the record review the researcher had no insights into the timing of recovery and the percentage of permanent disability after the hospitalization. Therefore, in this review the outcome was assessed as the level of harm at the moment of discharge from the hospital. It was divided into three categories: (1) temporary harm with a complete recovery expected within 12 months, (2) long term or permanent impairment or resulted in permanent institutional or nursing care and (3) all-cause mortality during hospitalization. This classification was also used by Wilson et al. (2).

Table 1 Overview of classification of harm in record reviews on adverse events

Categories of harm **Author(s), yr (reference)**	**No**	**Temporary**			**Permanent**		**Death**	**Unable to determine**
Brennan et al., 1991 (120)	No	Minimal impairment, recovery within 1 month	Moderate impairment, recovery within 1 to 6 months	Moderate impairment, recovery after 6 months	Permanent impairment, ≤ 50% disability	Permanent impairment, > 50% disability	Death	Yes
Wilson et al., 1995 (2)	No	Temporary harm from which complete recovery occurred within 12 months			AEs which caused permanent impairment or which resulted in permanent institutional or nursing care of death			No
Wolff et al., 1995 (339)	No	7-point scale used in Medical Management Analysis (368) Minor severity (score 0) Minor temporary (score 1) Minor permanent (score 2) Major temporary (score 3)			Major permanent (score 4) Potential major or major continuing (score 5)		Death (score 6)	No
Gawande et al., 1999 (130)	Disability ratings were first made by the physician record reviewers with use of the National Association of Insurance Commissioners severity-of-injury scale. (369) Next, 2 study researchers reviewed all available information about each adverse event and corrected disability scores in cases in which reviewers clearly misapplied criteria. These scores were then reviewed by 4 medical malpractice insurance claims adjusters from Utah and 6 from Colorado, and consensus was reached on a final disability score for each patient.							

Thomas et al., 2000 (129)	No	Emotional Insignificant Minor temporary Major temporary		Minor permanent Significant permanent Major permanent Grave		Death	No
Vincent et al., 2001 (128)	No	Minimal impairment, recovery within 1 month	Moderate impairment	Permanent impairment		Death	No
Schiøler et al., 2001 (122)		No full text in English available					
Davis et al., 2002 (124)	No	Minimal impairment, recovery within 1 month	Moderate impairment, recovery within 1 to 12 months	Permanent impairment, ≤ 50% disability	Permanent impairment, > 50% disability	Death	Yes
Baker et al., 2004 (121)	No	Temporary impairment of function lasting up to a year		Permanent impairment of function		Death	No
Sari et al., 2007 (123)	No	Impairment or disability which was resolved within a month	A more serious impairment or disability which was resolved within 6 months	Permanent disability		Contributed to patient death	Yes
			Impairment or disability which was resolved between 6 and 12 months				
Aranaz-Andrés et al., 2008 (52)	No	Slight impact	Moderate impact	Severe impact			No

Zegers et al., 2009 (50)	Yes	Minimal impairment, recovery within 1 month	Moderate impairment, recovery in 1 to 6 months	Moderate impairment, recovery within 6 to 12 months	Permanent impairment, ≤ 50% disability	Permanent impairment, > 50% disability	Death	Yes
Soop et al., 2009 (126)	No	Minimal impairment, recovery within 1 month	Moderate impairment, recovery within 1 to 6 months	Moderate impairment, recovery within 6 to 12 months	Permanent impairment, degree of disability ,50%	Permanent impairment, degree of disability .50%	Death	Yes
Letaief et al., 2010 (121)	No	Minimal impairment, recovery within 1 month	Moderate impairment, recovery within 1 to 6 months	Moderate impairment, recovery within 6 to 12 months	Permanent impairment, degree of disability ,50%	Permanent impairment, degree of disability .50%	Death	No
Landrigan et al., 2010 (131)	No	NCC MERP category E (temporary harms requiring intervention) NCC MERP category F (temporary harms requiring initial or prolonged hospitalization)			Category G (permanent harms) Category H (life-threatening harms)		NCC MERP category I (harms causing or contributing to death)	No
Classen et al., 2011 (84)	No	NCC MERP category E (temporary harms requiring intervention) NCC MERP category F (temporary harms requiring initial or prolonged hospitalization)			Category G (permanent harms) Category H (life-threatening harms)		NCC MERP category I (harms causing or contributing to death)	No

Sousa et al., 2014 (125)	No	Minimal impairment or disability, recovery within 1 month	Moderate impairment or disability, recovery within 1 to 12 Months	Permanent impairment or disability	Death	Yes
Garry et al., 2014 (68)	No	Contributed to or resulted in temporary harm to the patient	Contributed to or resulted in temporary harm to the patient and required prolonged ICU stay	Contributed to or resulted in permanent patient harm	Contributed to patient's death	No

The causality between the level of harm and the adverse event

In this retrospective record review study, the outcome was assessed as the level of harm at the moment of discharge from the hospital. Evidently, the outcome is also influenced by the underlying disease and comorbidities and other confounding factors such as the reason for hospital admission. Additional the causal relation between the adverse events and the outcome is often hard to prove with a record review, therefore during this retrospective cohort study the causality was not discussed. Although a few deaths were undoubtedly related to the adverse events, it was impossible to assess the causality for the majority of deaths. Previous Dutch research (50) made the differentiation between non-preventable and potentially preventable hospital deaths. They defined 'potentially preventable hospital deaths' as highly preventable adverse events which contributed to death during the hospital admission. They used the adjective ''potentially'' because of the multifactorial nature of hospital deaths and the retrospective assessment of causality.

In the group of 830 patients with an unplanned transfer to higher level of care 243 died. 98.4% of them had no pre-existing Do Not Resuscitate (DNR) order. Two assumptions can be made. Firstly, discussions about code status are generally stressful and difficult for both patients and clinicians involved (342). Maybe the prevalence of DNR orders was therefore low, or there was an under registration of the DNR order in patient records- despite the obligation by most hospital accreditation organizations. On the other hand, it is also possible that based on the patient condition a DNR order seemed not necessary and death was actually unexpected.

STRENGTHS AND LIMITATIONS

Overall strengths

One of strengths of this dissertation is that we used a combination of different study designs, including a systematic review (chapter 6, 7), a meta-analysis (chapter 6) and a large retrospective record review (chapter 2, 3, 4, and 5) for the detection of adverse events. A prospective risk analysis was also done during the PhD. The combination of both the detection and analysis of adverse events and failure modes (estimation of risks), provides more insight into the systematic barriers that should be implemented to reduce adverse events.

A second strength is the multicenter approach (chapter 3, 4, 5 and 6). The retrospective study was conducted in six acute hospitals.

A third strength is the use of a multidisciplinary approach in our record review study (chapter 2, 3, 4, and 5). The clinical team consisted of a research nurse, a physician, a clinical pharmacist and was supported by a multi-specialized panel of experts. The multidisciplinary approach enhances the acceptability of the research in the participating hospitals and increases the objectivity of the results. According to Lilford et al. (118), judgments regarding the causes of adverse events are influenced by the degree of heterogeneity in the reviewers' training and background. The assessment of the adverse events in a multidisciplinary approach differs from, and is superior to, the assessment by one or two disciplines. This is a strength of the methodology that we decided to use.

Strengths of the retrospective record review

The retrospective record review (chapter 2, 3, 4, and 5) shows several strengths. Firstly, we used a three-stage process of screening, record review and consensus judgment. The judgment of the occurrence of an adverse event is always sensitive to the subjectivity of the reviewers. By adding the three stage of consensus judgment, we (try to) minimalize the subjectivity. The hindsight bias is also minimized by using the same independent observers across all participating hospitals.

A second strength is that the patients for the record review were screened prospectively from the moment of the transfer to a higher level of care. This prospective approach leads to a more sensitive data collection. A disadvantage may be information bias which may influence the visibility of adverse events is a disadvantage. However, in our record review the selection of records was done by ICU head nurses or intensivists, who had no involvement with a possible adverse events on the general ward. The records were analyzed retrospectively since the review was performed once the record was closed and (completely) available to the reviewers. In this way the healthcare professionals experienced no disturbances of the research.

Thirdly, the protocol of the multicenter record study was tested in a pilot study. Based on this pilot study a sample size calculation was made and the protocol was optimized. The sample size of retrospective record review guarantees a sufficiently narrow confidence interval for the estimate (CI 95%). The study protocol was also published, which made the research transparent and repeatable.

Finally, we focused on patients with an unplanned transfer to a higher level of care. Therefore we could detect the most serious adverse events and focusing on one trigger has three positive consequences. Firstly, the selected records were reviewed in total (an implicit manner), meaning that no explicit criteria were

applied. This approach has the advantage of assessing every event on several criteria in detail, which leads to a global measurement of patient safety (343). Secondly, by selecting patients by one trigger, the positive predictive value of unplanned intensive care admission of our study is calculated on a larger sample size than reviews with the trigger tool. Thirdly, using this focus, adverse events with an impact could be detected. So 'an unplanned transfer to a higher level of care' is a good focus for risk management as it selects frequently severe adverse events (top priority for risk management due to their frequency and/or impact).

Limitations

Besides its methodological strengths, the record review also has limitations. Firstly, there is the lack of an actual gold standard for adverse events detection (136). Therefore the judgment of presence of adverse events is difficult and always susceptible to subjectivity. Record review is a standard method by which adverse events and their degree of preventability are measured (344) and it was proven valid to identify adverse events and estimate their incidence in hospitals (345). However, previous studies showed poor to moderate inter-rater agreement for the determination of adverse events and their preventability (2,119,121,123,124,173,345–348). Walshe (349) mentioned that the reliability for identifying adverse events depends on the quality of rater training and ongoing monitoring. By working with the same independent, experienced and multidisciplinary clinical team and an expert panel for the six hospitals, we tried to improve the reliability. Although we did not measured the inter-rater reliability during the record review.

A retrospective record review is currently considered to be the best method available to assess incidence of adverse events (29). However, an important second limitation is that the method of record review itself may lead to an underestimation of adverse events (136). A conservative approach was chosen to detect adverse events: in case of doubt, the event was not classified as an adverse event. Therefore

the results presented might be an underestimation of the true incidence.

Thirdly, the record review is hampered by the retrospective nature of the analysis, and by the dependence on the quality of note taking by healthcare professionals (350,351). The quality of the records was often suboptimal with piecemeal data, which again can lead to an underestimation. The structure and quality of the records also differed between the hospitals, which made the analysis additionally complicated. We tried to prevent or overcome these limitations by working with a multidisciplinary team consisting of a research nurse, a physician and a clinical pharmacist, each of them with experience in this area and focusing on their own expertise. At the end the assessment was always made collectively. Moreover this team was the same for all participating hospitals. An expert panel was available for additional advice when necessary. The principal researcher studied the different records and electronic programs for recording in advance to facilitate the work of the team.

Fourthly, the positive predictive value, which describe the performance of the trigger UIA, was 57.7%, reflecting a moderate reliability of this screening criterion. To predict the presence of an (preventable) adverse event among patients who had an UIA it would be interesting to create an additional step with a decision tree between the (1) screening with the trigger and (2) record review. To create a decision tree based on predictive variables, further research is necessary to define these predictive variables and to actually create and test. Such additional step would increase the positive predictive value of the record review.

Fifthly, we had to rely on a registration of the MET interventions that is not mandatory in Belgian hospitals. This can be another cause of under-registration.

Finally, retrospective record review is a time-consuming method and therefore costly (28,352–354). Taking into account the various strengths and limitations, as described above, we feel that this cost is acceptable.

IMPLICATIONS FOR CLINICAL PRACTICE

Important aims of this dissertation are *(1)* to raise a sense of urgency among healthcare professionals, hospital management, the government and the patients by measuring the situation and *(2)* to develop strategies to control adverse events and increase patient safety.

Measuring the situation

As healthcare professionals, management and policymakers attempt to operationalize the agenda for high-quality care, the current situation should be known. One of the challenges for safety improvement in healthcare is precisely the measurement of adverse events. Retrospective record review is one of the methods to measure the incidence of adverse events. Since this is a labor intensive and therefore costly method, its use is mostly restricted to research projects. The trigger 'unplanned intensive care admission' had a positive predictive value of 57.7% to detect adverse events. This means an adverse event was related to the unplanned transfer to intensive care in 57.7% of the cases. The number of unplanned transfers to intensive care itself is relatively easy to measure. It could therefore be proposed as a proxy indicator for the number of adverse events related to unplanned transfers, at least within similar settings as the hospitals involved in this study – which is, we feel, the case for most Belgian hospitals. Based on the finding of this study, we propose to introduce the rate of unplanned transfers to a higher level of care as a safety indicator for Belgian hospitals.

Retrospective risk analysis gives a clear view of the problem (detection of adverse events); prospective risk analysis provides insight into the safety practices that precipitate adverse events (estimation of risks). The patient safety management system of each healthcare organization must combine both approaches. Levtzion-Korach et al. (97) state that hospitals should use a broad portfolio of approaches

and then synthesize the messages from all individual approaches into a collated and cohesive whole. Promoting effective clinical risk management should empower clinical teams to change the way in which they deliver services. Process analysis, implementation of evidence-based practices, and a clear accountability system are effective tools not only for decreasing error rates, but also for improving effectiveness (70). Both government and hospital management should promote and continuously improve the context to realize effective clinical risk management as part of the everyday practice of all healthcare professionals. This requires good multidisciplinary interaction and a willingness to reflect on and to learn from errors (70).

Commonly used methods for analyses of unsafe hospital care and improvement of patient safety include accreditation, external peer reviews, internal audits, patient safety systems, and performance indicators (355,356). We feel that it must be possible that hospitals also investigate in prospective risk analysis and retrospective record review. Several studies (144,339,357–361) have shown strengths of record review as an auditing tool. Record review and process analysis can be useful strategies in quality improvement (144). After participation in the record review study, some hospitals already started to organize their own record review on unplanned intensive care admissions, unexpected hospital mortality or started with periodic morbidity, mortality, critical incident meetings and MET team evaluations.

Development of strategies to control adverse events and increase patient safety

Aside from the monitoring of the present situation, strategies to control adverse events and to increase patient safety must be developed. This asks for the support from the management, the healthcare professionals, the government, the patients and their relatives. During our research it became clear that both the prospective and retrospective study were an eye-opener for the participating hospitals, and triggered the startup of several improvement projects. Our study suggests that improvement actions should focus on

- the medication process,
- the careful monitoring of patients and the early detection of clinical deterioration,
- the transfer of the patient between disciplines and wards,
- the improvement, standardization and implementation of an integrated (electronic) patient record,
- the standardization of the surgical process,
- the creation of a patient safety culture,
- the education of healthcare professionals,
- the detection of adverse events.

As an example, we explored a few of these:

The medication process

The multidisciplinary record review showed the incidence of adverse events that necessitate a higher level of care (137). These adverse events were mostly related to medication. Further improvement actions seems to be necessary for empiric and prophylactic antibiotics, anticoagulants and other high-risk medications as well as the medication reconciliation at hospital admission and discharge.

In one of the participating hospital, we worked together on the implementation of an inpatient Anticoagulation Management System (iAMS). Before the development of the iAMS, a medication safety self-assessment of the Institute for Safe Medication Practices (362) was performed and used to determine the needs for a safe hospital medication system. The most important concerns were the lack of standardized protocols and guidelines, education for patients and healthcare providers and the absence of a computer order entry system with clinical decision support and interface with the lab management system. All the

identified points from the self-assessment, critical and less critical, were used to determine the focus of the iAMS. The implementation of all these points was realized using seven different key areas of the iAMS: (1) protocols and guidelines, (2) implementation of a trigger tool method, (3) implementation of a new computer order entry system, (4) education of health care providers, (5) patient education, (6) care transitions and (7) outcomes and risk management. At the moment all improvement actions, except patient education, are realized. After implementation of the iAMS, the medication safety self-assessment will be used to evaluate the iAMS and to determine new needs for a safe hospital medication system. To make it a continuously process of improvement, two taskforces groups (medication management & high-risk medication) were formed.

The improvement, standardization and implementation of an integrated (electronic) patient record

The record review shows the importance of having a complete view of the demographic and clinical data of the patient. The different parts - medical, a nursing part and a medication list – are inter-related; however, not systematically integrated. The existence of different parts leads to missing or duplication of information. The preference should be an integrated patient record with a standardized layout for all healthcare workers. All records relating to the same patient should be kept in a single patient record rather than be distributed over several hospital departments or sites which we observed in our study (184). Physicians, paramedical and nursing staff should be trained in proper maintenance of patient records because it is an integral part of good medical practice. However, our findings on the format, availability and completeness of patient records should create greater awareness. We suggest that improved quality of patient records may be stimulated through the use of a standardized format for records in all wards of the same hospital and adoption of guidelines for patient record keeping.

Regularly audits of the patient records on elementary elements, e.g. registration of allergy, progress notes, etc., by the CMO and the quality and patient safety department can be a motivation for improvement.

The careful monitoring of patients and the early detection of clinical deterioration

The record review also shows the importance of (1) the implementation of a (Modified) Early Warning System ((M)EWS), which is a simple physiological scoring system suitable for bedside application (363) to indicate early signs of a patient's detoriation in combination with (2) the implementation of the Situation Background Assessment Recommendation (SBAR) – a communication method for a correct transfer and follow-up of the patient between different professionals. An integrated (digital) patient record will certainly support the working with EWS and SBAR. Another important issue is the existence of a pre-existing Do Not Resuscitate (DNR) order. 98.4% of deceased patients with an unplanned transfer to higher level of care had no pre-existing DNR order. Two assumptions can be made. Firstly, discussions about code status are generally stressful and difficult for both patients and clinicians involved (342). On the other hand, it is also possible that based on the patient condition a DNR order seemed not necessary and death was actually unexpected. The EWS system will maybe support the clinical team in the discussions about the DNR order.

Next to using the SBAR to support the transfer, one hospital is thinking to install a 'liaison nurse intensive care' to prepare and to follow-up the discharge of intensive care patients with a high care-dependency (e.g. patient with a tracheostomy) to prevent readmissions.

Measuring the situation and development of strategies to control adverse events and increase patient safety is a continuous process

Quality and safety measurement, monitoring and improvement are not endless. It is always a continuous process. Vincent et al. described that we have to focus on 5 fundamental questions:

- *Past harm: Has patient care been safe in the past?*
  There exist a broad range of retrospective methods and data source to assess harm. However, we need to devise the measure of harms that are relevant for the clinical setting.

- *Reliability: Are our clinical systems and processes reliable (failure-free)?*
  Reliability can be assessed by prospectively clinical audits about standardized aspects of care (364), e.g. compliance with hand hygiene procedure, the timely administration of antibiotics pre-per-postoperative, or by looking at essential clinical systems for delivery of care.

- *Sensitivity to operations: Is care safe today?*
  Working at quality and patient safety is a continuous process. Things that are fine yesterday can be dangerous today. Therefore continuous awareness is necessary. Specific mechanisms to support sensitivity include safety walk-rounds, patient interviews and conservations (93).

- *Anticipation and preparedness: Will care be safe in the future?*
  All organizations in healthcare work in complex, fluctuating conditions. Anticipation, preparedness and the ability to intervene is necessary.

- *Integration and learning: Are we responding and improving?*
  Different data sources can be used to collect safety information: incidents

reported, patient safety indicators, complaints, claims, clinical audits, observations, informal conservations with patients, family and staff, record review, etc. (93). Instead of relying on recommendations from single incidents, hospitals should integrate and analyze safety information from across the unit or organization and use it to support longer term organizational learning and sustainable improvements (365).

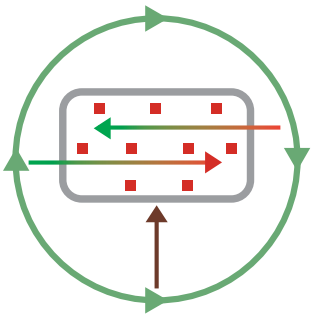


Figure 1: Continuous improvement process

AVENUES FOR FUTURE RESEARCH

Based on the work presented in this doctoral work several studies in different fields can be launched. We think about

- A longitudinal study to measure the effect of detection of adverse events and implementation of quality improvement projects
- A study to assess risk factors (conditions, barriers, patient involvement, patients typology, demographic characteristics, etc.) of adverse events
- Research on the methodology for detection of adverse events
- Research to examine a possible correlation between the incidence rate of unplanned transfer to a higher level of care and patient safety culture measurement
- Research to assess their financial implications
- Similar research as ours on the incidence, the nature, the consequences and preventability of adverse events in hospitals can be done in other healthcare sectors

A longitudinal study to measure the effect of detection and implementation

Zegers and Wollersheim (366) discuss some reasons for the very slow progress in improving patient safety, such as the almost complete lack of proof of effectiveness of improvement interventions and the methodological complexity in evaluating the effectiveness of safety interventions. This evaluation is difficult due to the contextual complexity, the requirement for a large number of patients, the lack of reliable instruments for measuring and the lack of systematical registration of the experienced problems when implementing safety interventions. Leistikow et al. (367) mentioned visibility, ambiguity, complexity, and autonomy as important factors of success of patient safety actions. Therefore it will be useful to evaluate

in a longitudinal study the incidence of these severe and highly preventable adverse events in relation to the implementation of safety interventions, such as early warning score with SBAR communication, the use of the surgical safety checklist, safety walk rounds, etc. The most effective safety interventions could then be identified and healthcare providers could exchange their experiences in successful implementation.

A study to assess risk factors of adverse events

Referring to Reasons Swiss cheese model (368) we can identify several latent conditions as well as defensive barriers that intervene before an adverse event occurs. The system approach concentrates on the conditions under which individuals work and tries to build defenses to avert errors or to mitigate their effects (368). Further research on the occurrence of adverse events, promoting conditions and defensive barriers is needed. The conditions are related to the working context such as the role of healthcare management, staffing, educational qualifications and safety culture. Previous research (146,369–374) emphasized that inadequate nursing staffing might adversely affect patient outcomes. Data on the educational qualifications of nurses and patient – to-nurse staffing ratios could be linked with data on the occurrence of (preventable) adverse events that induce the need for a higher level of care. Further research can be done on the link between these conditions, the safety culture of the organization and the incidence of these adverse events. Next to the latent conditions, barriers are also an important factor in Reasons model (368). Further investigations on the effects and weaknesses of the barriers in relation to the occurrence of adverse events can be useful.

Original research could be started on the conditions, barriers, patient involvement, patients typology (surgical versus medical, different disciplines), and demographic characteristics as related to and the incidence, the nature, the consequences and preventability of adverse events.

Research on the methodology for detection of adverse events

Detection method

It is necessary to continue researching on the efficacy and effectiveness of the measurement of preventable adverse events. To detect other and so far unidentified adverse events, similar record review using different selection triggers should be done. Suggested triggers could be e.g. hospital readmissions, readmissions to the ICU and redo operations. On the other hand, the method of record review is very costly. To investigate whether the same data can be collected by other detection methods, data from record review studies could be compared to data harvested from administrative databases, such as B-HDDS and other.

Optimization of the record review

Since record review is a labor intensive and therefore costly method, its use is mostly restricted to research projects. To make the approach more useful in research and clinical practice, it would be interesting to create an additional step in the three-stage record review of (1) screening, (2) record review and (3) consensus. An additional step between the patient screening and the record review can enable an earlier selection of the records. This selection of the records could be made with the aid of a decision tree based on predictive variables. Further research would be useful to define these predictive variables and to actually create and test. Such additional step would increase the positive predictive value of the record review.

Safety indicator

Our retrospective record review from six hospitals from in one Belgian province, revealed that adverse events were related to the unplanned transfer to a higher level of care in 56% of the cases. We described that one fourth of all unplanned transfers to a higher level of care were associated with a highly preventable adverse event. The number of unplanned transfers to a higher level of care itself

is relatively easy to measure and could be proposed as a proxy indicator for the number of AEs related to unplanned transfers, at least within similar settings as the hospitals involved in this study. Based on the finding of this study, we propose to introduce the rate of unplanned transfers to a higher level of care as a safety indicator or a (proxy) trigger for unplanned transfers to a higher level involving adverse events for Belgian hospitals. These data give new opportunities for research such as a Belgian benchmark and are much more feasible method to do for routine measurement.

Research to examine a possible correlation between the incidence of unplanned transfer to a higher level of care and patient safety culture measurement

A national patient safety culture measurement was done in which the majority of Belgian hospitals participated (375). Though this study provided a good insight into the patient safety culture in Belgian hospitals, so far limited knowledge exists about the relationship between safety culture and patient outcomes. Therefore, it can be useful to examine if a correlation exists between the incidence of unplanned transfer to a higher level of care and the dimensional scores from the hospital patient safety culture measurement.

Financial impact of adverse events

Based on and inspired by our findings a cost study can be undertaken from two perspectives to assess the impact of adverse events:

- The costs of care for the healthcare provider and society of the severe (preventable) adverse events we described in our study
- The social-economic costs in the terms of outcome such as the level of patient harm, disability, mortality versus quality of life for the patients with (preventable) adverse events

In the current economic situation, escalating hospital costs and individual and societal costs afterwards due to harm and disability are important to patients, healthcare providers and the society. Insights from this study can provide information to the hospital management, healthcare professionals, policy makers and insurance companies on how improvement actions can substantially reduce healthcare cost.

Research on the incidence, the nature, the consequences and preventability of adverse events in other healthcare sectors

Some elements of these study can be translated to other healthcare settings such as nursing homes, psychiatric hospitals and primary care. However, more specific studies on the incidence, the type, the level of harm and the preventability of adverse (drug) events are need in these different healthcare sectors.

CONCLUSION

Working on quality and patient safety is an endless but satisfying work. By doing prospective or retrospective risk analysis, failure modes and adverse events are detected and the necessary improvement actions become clear. By implementing improvement interventions, the processes, the organizational structure and even the culture can change, which hopefully positively effects the quality, safety and outcome. However, at the same time new failure modes and (possible) adverse events will be detected and the need for further improvement actions will emerge. By continuing research, new solutions and new problems will be detected. Working continuously on quality and patient safety in the healthcare field and in the related research results.

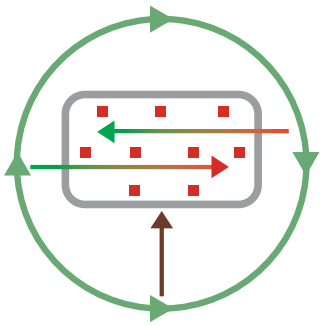
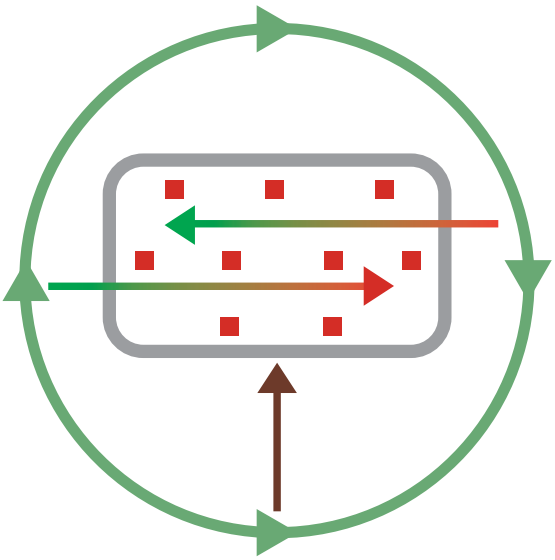


Figure 1 *Improvement projects following the prospective and retrospective analysis*

General summary



GENERAL SUMMARY

Reason (18) described that humans are fallible and errors are to be expected, even in the best organizations. Defenses, barriers and safeguards occupy a key position in the system approach. Therefore it is important to analyze processes, to detect failure modes and adverse events through prospective and retrospective risk management. The following questions guide the research carried out for this dissertation:

- What are the incidence rate, preventability, harm and type of adverse events requiring a higher level of care (multidisciplinary record review)?
- What does the literature learn us of adverse drug events?

What are the incidence rate, preventability and harm of adverse events requiring a higher level of care as measured by a multidisciplinary record review?

The objectives of this study were to determine the incidence and preventability of adverse events requiring an unplanned higher level of care - defined as an unplanned transfer to the intensive care unit or an in-hospital medical emergency team intervention - and to assess the type and the level of harm of each adverse event. A three-stage retrospective review process of screening, record review and consensus judgment was performed in six Belgian acute hospitals.

Adverse events were found in 56% of the 830 reviewed patient records, of which almost half were considered highly preventable. This means that one fourth of all unplanned transfers to a higher level of care were due to a highly preventable adverse event. The overall incidence rate of patients being transferred to a higher level of care involving an adverse event was 117.6 (95% CI 106.9–128.3) per 100,000 patient days at risk, of which 54.4 (95% CI 47.15–61.65) per 100,000 patient days at risk involving a highly preventable adverse event.

Because of the high number of adverse drug events, we further focused on adverse drug events. 83.8% of the ADE were preventable. The overall incidence of patients transferred to a higher level of care because of a pADE was 33.9 per 100,000 patient days at risk. Antibiotics and antithrombotic agents accounted both for one-fifth of all pADEs. Age, ASA score and the number of medications taken before admission are risk factors for pADEs.

By doing the record review, we could also (1) assess the format, the availability, the completeness of the record and (2) analyze their relation with the occurrence of adverse events in patients with an unplanned transfers to a higher level of care. Although standard note keeping is an important aspect of patient management, physicians and nurses fail to register continuously and accurately the delivered care. Highly preventable adverse events are underestimated when the record is partially unavailable and the absence of a validated discharge letter is a predictor for these highly preventable adverse events.

What does literature learn us of adverse drug events?

A systematic review with meta-analysis was performed to explore the incidence of in-hospital inappropriate empiric antibiotic use in patients with severe infection and to identify its relationship with patient outcomes. The percentage of inappropriate empiric antibiotic use ranged from 14.1% to 78.9% (Q1-Q3: 28.1-57.8%); 48.1% of the studies described an incidence of 50% or more. The meta-analysis provides evidence that inappropriate use of empiric antibiotics increases 30-day and in-hospital mortality in patients with a severe infection. Clinicians should be aware of this problem and further improvement actions should be taken.

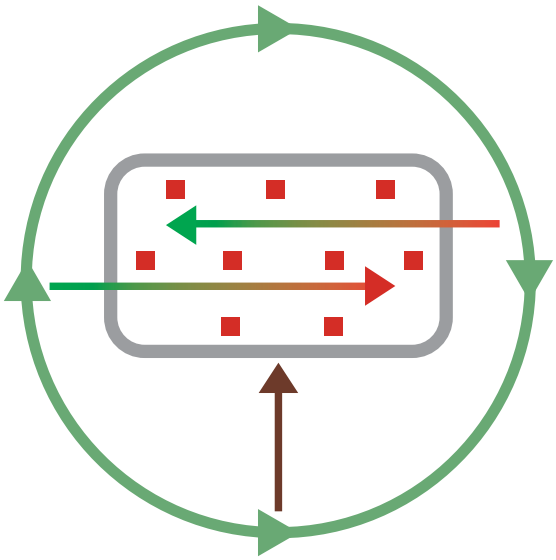
To investigate the safety issue in residential care for elderly a systematic review to assess the incidence of drug related problems in these facilities was performed.

In the majority of studies, researchers relied on the criteria of Beers et al. (in particular the update of 2003) and on the measuring instrument 'STOPP'. Relying on a version of Beers criteria (269–272) reporting percentages of residents experiencing DRP's varying from 2.26% to 82.6% with a median of 45.6%. Studies relying on the in 2003 updated Beers criteria update report a smaller range with a percentage of residents experiencing DRP's varying from 14.5% up to 63.0% and a median of 34.9%. The instrument second most referred to is 'STOPP': the percentage of residents experiencing DRP's ranging from 23.7% up to 79.0% with a median of 59.4%. Heterogeneity in data hampered meta-analysis. Further research about quality and patient safety in other healthcare setting is necessary.

Future perspectives

Based on this dissertation, several quality improving interventions have already been implemented in the participating hospitals. However, the need for new and additional improvement actions and research remains open.

Samenvating



SAMENVATTING

Reason (18) stelt dat mensen feilbaar zijn en er waar mensen werken dus fouten te verwachten zijn, zelfs in de beste organisaties. Risicomanagement met het analyseren van processen om faalwijzen en adverse events te detecteren als startpunt voor systeemverbeteringen zijn daarom belangrijk in een systeembenadering. De volgende onderzoeksvragen werden gesteld in het proefschrift:

- Wat is de incidentie, vermijdbaarheid, schade en type van in-hospitaal adverse events gerelateerd aan een ongeplande transfer naar een hoger niveau van zorg (multidisciplinair dossieronderzoek)?
- Wat leert de literatuur ons over verwante thema's?

Wat is de incidentie, vermijdbaarheid, schade en type van in-hospitaal adverse events die gepaard gaan met een ongeplande transfer naar een hoger niveau van zorg gemeten (multidisciplinair dossieronderzoek)?

Een retrospectief dossieronderzoek naar in-hospitaal adverse events die gepaard gaan met een ongeplande transfer naar een hoger niveau van zorg werd uitgevoerd in zes Belgische acute ziekenhuizen. Een adverse event werd gedefinieerd als *(1)* onbedoelde schade of complicatie *(2)* die resulteert in een verlenging van hospitalisatie, een (blijvende) handicap of zelfs overlijden en *(3)* is veroorzaakt door het gezondheidszorgsysteem eerder dan door de ziektetoestand van de patiënt. Een ongeplande hoger niveau van zorg werd gedefinieerd als *(1)* een ongeplande transfer naar de intensive care unit of *(2)* een interventie van een interne Mobiele Urgentie Groep (MUG).

Adverse events werden gedetecteerd in 56% van de 830 beoordeeld patiëntendossiers; bijna de helft was hoog vermijdbaar. Dit betekent dat een

kwart van alle ongeplande transfers naar een hoger niveau van zorg gerelateerd is aan een hoog vermijdbaar adverse event. De totale incidentie van patiënten met adverse event en een ongeplande transfer naar een hoger niveau van zorg bedroeg 117.6 per 100,000 verpleegdagen

Adverse drug events (ADEs) zijn een belangrijk type adverse events. 83,8% van de ADEs waren vermijdbaar (pADEs). De totale incidentie van patiënten met pADEs en een ongeplande transfer naar een hoger niveau van zorg was 33,9 per 100,000 verpleegdagen. Eén vijfde van de pADEs zijn gerelateerd aan antibiotica en antitrombotische middelen. Leeftijd, ASA score en het aantal thuismedicatie zijn risicofactoren voor pADEs.

Door het uitvoeren van een dossieronderzoek, kunnen de onderzoekers ook (1) het format, de beschikbaarheid en de volledigheid van het dossier beoordelen en (2) analyseren of deze factoren in verband staan met adverse events. Het bijhouden van een patiëntendossier is een belangrijk aspect van alle klinische zorg, toch was het dossier niet steeds beschikbaar en volledig. De incidentie van hoog vermijdbare adverse events worden onderschat bij een onvolledig dossier en bij de afwezigheid van een gevalideerde ontslagbrief.

Wat leert de literatuur ons over adverse drug events?

Een systematische review met meta-analyse werd uitgevoerd om de incidentie van (in)adequaat gebruik van empirische antibiotica bij patiënten met een ernstige infectie te meten en de relatie ervan met het resultaat van zorg te identificeren. Het percentage inadequaat empirisch antibiotica gebruik varieerde van 14.1% tot 78.9% (Q1-Q3: 28.1-57.8%); 48.1% van de studies beschreven een incidentie van 50% of meer. De meta-analyse beschreef een verhoging van de 30-dagen mortaliteit en in-hospitaal mortaliteit bij inadequaat empirisch antibiotica gebruik. Artsen moeten zich bewust zijn van dit probleem en verdere verbeteringsacties zijn noodzakelijk.

Om een idee te krijgen van de veiligheidssituatie in de residentiële zorg voor ouderen, werd een systematische review naar de incidentie van 'drug related problems' uitgevoerd. In het merendeel van de studies, hanteerden de onderzoekers de criteria van Beers et al. en het meetinstrument 'STOPP'. Baserend op de Beers criteria varieerden de percentages bewoners met een DRP tussen 2.26-82.6% met een mediaan van 45.6%. De range van de percentages was kleiner bij de in 2003 geüpdatet versie van Beers (range: 14.5-63.0%, mediaan: 34.9%). De percentages bewoners met een DRP gemeten met de STOPP varieerde tussen 23.7-79.0% met een mediaan van 59.4%. De heterogeniteit in data maakte een meta-analyse onmogelijk. Verder onderzoek over de kwaliteit en patiëntveiligheid in andere types gezondheidszorginstellingen is noodzakelijk.

Toekomst perspectieven

Op basis van dit proefschrift, zijn reeds diverse kwaliteit verbeterende interventies geïmplementeerd in de deelnemende ziekenhuizen. Verdere verbeteracties en voortgezet onderzoek blijven noodzakelijk.

REFERENCES

1. Kohn LT, Corrigan JM, Donaldson MS et al. To Err is Human: Building a Safer Health System. Washington DC: National Academy Press; 2000.

2. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. Med J Aust. 1995;163:458–71.

3. Institute of Medicine (US). Patient Safety: Achieving a new standard for care: The National Academies. Washington (DC); 2004.

4. Hofer TP, Kerr E, Hayward R. What is an error? Eff Clin Pract. 2000;3(6):261–9.

5. Hofer TP, Hayward RA. Are Bad Outcomes from Questionable Clinical Decisions Preventable Medical Errors ? A Case of Cascade Iatrogenesis. Ann Intern Med. 2014;137(5):327–33.

6. Wu AW, Cavanaugh TA, McPhee SJ, Lo B, Micco GP. To tell the truth: ethical and practical issues in disclosing medical mistakes to patients. J Gen Intern Med. 1997 Dec;12:770–5.

7. Battles JB, Lilford RJ. Organizing patient safety research to identify risks and hazards. Qual Saf Heal Care. 2003;12 Suppl 2:ii2–7.

8. Leape LL, Brennan T, Laird N, Lawthers A, Localio A, Barnes B, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991 Feb 7;324(6):377–84.

9. Andrews LB, Stocking C, Krizek T, Gottlieb L, Krizek C, Vargish T, et al. An alternative strategy for studying adverse events in medical care. Lancet. 1997 Feb 1;349(9048):309–13.

10. Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. BMJ Qual Saf. 2013 Oct;22(10):809–15.

11. Wachter RM. Understanding patient safety. Second Edi. The McGraw-Hill Companies; 2012.

12. Levinson D. Adverse events in hospitals: National incidence among medicare beneficiaries. 2010.

13. Heylen R. The Relevant Cause in Anesthetic Death. Critique on concrete, singular causal opinions in research on avoidable anesthetic mortality and morbidity highlighted by legal and philosophical causation theories. Catholic University Leuven; 1995.

14. Zegers M, de Bruijne MC, Wagner C, Groenewegen PP, Waaijman R, van der Wal G. Design of a retrospective patient record study on the occurrence of adverse events among patients in Dutch hospitals. BMC Health Serv Res. 2007 Jan;7:27–37.

15. De Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care. 2008 Jun;17(3):216–23.

16. Geraci J, Ashton C, Kuykendall D, Johnson M, Wu L. International classification of diseases, 9th revision, clinical modification codes in discharges abstracts are poor measures of complication occurrence in medical inpatients. Med Care. 1997;35(6):589–602.

17. Institute Of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. 2001.

18. Reason J. Human error: models and management. BMJ. 2000 Jun;320:768–70.

19. Reason J. Human error. New York: Cambridge University Press; 1990.

20. Vincent C, Taylor-Adams S, Stanhope N. Framework for analysing risk and safety in clinical medicine. Bmj. 1998 Apr 11;316(7138):1154–7.

21. Reason J. Beyond the organisational accident: the need for "error wisdom" on the frontline. Qual Saf Heal Care. 2004 Dec 1;13(suppl_2):ii28–33.

22. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, et al. Systems Analysis of Adverse Drug Events. JAMA. 1995;274(1):35–43.

23. Jha A, Kuperman G, Teich J, Leape L, Shea B, Rittenberg E, et al. Identifying Adverse Drug Events: Development of a Computer-based Monitor and Comparison with Chart Review and Stimulated Voluntary Report. J Am Med Inf Assoc. 1998;5(3):305–14.

24. Otero M-J, Schmitt E. Clarifying terminology for adverse drug events. Ann Intern Med. 2005 Jan 4;142(1):77–8. A

25. Von Laue NC, Schwappach DLB, Koeck CM. The epidemiology of preventable adverse drug events : A review of the literature. Wien Klin Wochenschr. 2003;115(12):407–15.

26. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. Arch Intern Med. 2003 Sep 22;163(17):2014–8.

27. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence

of Adverse Drug Events and Potential Adverse Drug Events. Implications for Prevention. JAMA. 1995;274(1):29–34.

28. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. Int J Qual Health Care. 2000 Feb;12(1):69–76.

29. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). Available from: www.nccmerp.org Accessed March 8, 2015.

30. Bates D, Boyle D, Vander Vliet M, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995;10(4):199–205.

31. Nebeker JR, Barach P, Samore MH. Clarifying Adverse Drug Events : A Clinician ' s Guide to Terminology , Documentation, and Reporting. Ann Intern Med. 2004;140:795–801.

32. Hepler C, Strand L. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533–43.

33. Hallas J, Harvald B, Gram L, Grodum E, Brøsen K, Haghfelt T, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med. 1990;228(2):83–90.

34. Beijer H, de Blaey C. Hospitalisations caused by adverse drug reactions (ADR): a meta- analysis of observational studies. Pharm World Sci. 2002;24(2):46–54.

35. Cunningham G, Dodd TRP, Grant DJ, McMurdo MET, Michael R, Richards

E. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. Age Ageing. 1997;26(5):375–82.

36. Mannesse C, Derkx F, De Ridder M, Man in ’t Veld A, Van der Cammen T. Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing. 2000;29:35–9.

37. Nelson K, Talbert R. Drug-related hospital admissions. Pharmacotherapy. 1996;16(4):701–7.

38. Onder G, Pedone C, Landi F, Cesari M, Della Vedova C, Bernabei R, et al. Adverse Drug Reactions as Cause of Hospital Admissions: Results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc. 2002 Dec;50(12):1962–8.

39. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ. 2004;329(July):15–9.

40. Hallas J, Worm J, Beck-Nielsen J, Gram L, Grodum E, Damsbo N, et al. Drug related events and drug utilization in patients admitted to a geriatric hospital department. Dan Med Bull. 1991;38(5):417–20.

41. Kaiser R, Schmader K, Pieper C, Lindblad C, Ruby C, Hanlon J. Therapeutic failure-related hospitalisations in the frail elderly. Drug Ageing. 2006;23(7):579–86.

42. Somers A. Detection and prevention of drug related problems in older hospitalized patients - the role of the clinical pharmacist. Ghent University; 2011.

43. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther. 2007;32:113–21.

44. Lindley C, Tully M, Paramsothy V, Tallis R. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age ageing. 1992;21(4):294–300.

45. Passarelli M, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population : inappropriate prescription is a leading cause. Drugs Ageing. 2005;22(9):767–77.

46. Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BHC. Attitudinal survey of voluntary reporting of adverse drug reactions. Br J Clin Pharmacol. 1999 Dec 24;48(4):623–7.

47. Hellings J. Medicatiefouten in ziekenhuizen. Een literatuuroverzicht van inzichten en uitdagingen. Acta Hosp. 2005;1:5–24.

48. Wagner LM, Castle NG, Handler SM. Use of HIT for adverse event reporting in nursing homes: barriers and facilitators. Geriatr Nurs. Elsevier Ltd; 2013;34(2):112–5.

49. Smits M, Zegers M, Groenewegen PP, Timmermans DRM, Zwaan L, van der Wal G, et al. Exploring the causes of adverse events in hospitals and potential prevention strategies. Qual Saf Health Care. 2010 Oct;19(5):e5.

50. Zegers M, de Bruijne MC, Wagner C, Hoonhout LHF, Waaijman R, Smits M, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. Qual Saf Health Care. 2009 Aug;18(4):297–302.

51. Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Burillo J, Requena-Puche J, Terol-García E, Kelley E, et al. Impact and preventability of adverse events in Spanish public hospitals: results of the Spanish National Study of Adverse Events (ENEAS). Int J Qual Health Care. 2009 Dec;21(6):408–14.

52. Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Murillo J, Ruiz-López P, Limón-Ramírez R, Terol-García E. Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events. J Epidemiol Community Health. 2008 Dec;62(12):1022–9.

53. Aranaz-Andrés JM, Limón R, Mira JJ, Aibar C, Gea MT, Agra Y. What makes hospitalized patients more vulnerable and increases their risk of experiencing an adverse event? Int J Qual Health Care. 2011 Dec;23(6):705–12.

54. Hoonhout LHF, de Bruijne MC, Wagner C, Zegers M, Waaijman R, Spreeuwenberg P, et al. Direct medical costs of adverse events in Dutch hospitals. BMC Health Serv Res. 2009 Jan;9:27–36.

55. Lin F, Chaboyer W, Wallis M. A literature review of organisational, individual and teamwork factors contributing to the ICU discharge process. Aust Crit Care. 2009 Feb;22(1):29–43.

56. Cooper A, Leigh J, Tring I. Admissions to the intensive care unit after complications of anaesthetic techniques over 10 years. 1. The first 5 years. Anaesthesia. 1989 Dec;44(12):953–8.

57. Darchy B, Le Mière E, Figueredo B, Bavoux E, Cadoux G, Domart Y. Patients admis en réanimation pour pathologie iatrogène: facteurs de risque et conséquences. Rev Méd Interne. 1998;19:470–8.

58. Darchy B, Le Mière E, Figuérédo B, Bavoux E, Domart Y. Iatrogenic Diseases

as a Reason for Admission to the Intensive Care Unit. Arch Intern Med. 1999;159:71–8.

59. Leigh J, Tytler J. Admissions to the intensive care unit after complications of anaesthetic techniques. Anaesthesia. 1990;45(10):814–20.

60. Swann D, Houston P, Goldberg J. Audit of intensive care unit admissions from the operating room. Can J Anaesth. 1993 Feb;40(2):137–41.

61. Australian Council on Healthcare Standards. Available from: http://www.achs.org.au/ Accessed March 8, 2015.

62. Baker DR, Pronovost PJ, Morlock LL, Geocadin RG, Holzmueller CG. Patient flow variability and unplanned readmissions to an intensive care unit. Crit Care Med. 2009 Nov;37(11):2882–7.

63. Haller G, Myles PS, Langley M, Stoelwinder J, McNeil J. Assessment of an unplanned admission to the intensive care unit as a global safety indicator in surgical patients. Anaesth Intensive Care. 2008 Mar;36(2):190–200.

64. Mercier E, Giraudeau B, Giniès G, Perrotin D, Dequin P-F. Iatrogenic events contributing to ICU admission: a prospective study. Intensive Care Med. 2010 Jun;36(6):1033–7.

65. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med. 2010 Jan;38(1):65–71.

66. Tan S, Bakker J, Hoogendoorn M, Kapila A, Martin J, Pezzi A, et al. Direct cost analysis of intensive care unit stay in four European countries : applying a standardized costing methodology. Value Heal. 2012;15(1):81–6.

67. Vlayen A, Verelst S, Bekkering GE, Schrooten W, Hellings J, Claes N. Incidence and preventability of adverse events requiring intensive care admission: a systematic review. J Eval Clin Pract. 2012 Apr;18(2):485–97.

68. Garry DA, McKechnie SR, Culliford DJ, Ezra M, Garry PS, Loveland RC, et al. A prospective multicentre observational study of adverse iatrogenic events and substandard care preceding intensive care unit admission (PREVENT). Anaesthesia. 2014 Feb;69(2):137–42.

69. Lehmann LS, Puopolo AL, Shaykevich S, Brennan TA. Iatrogenic events resulting in intensive care admission: frequency, cause, and disclosure to patients and institutions. Am J Med. 2005 Apr;118(4):409–13.

70. Chiozza ML, Plebani M. Clinical Governance: from clinical risk management to continuous quality improvement. Clin Chem Lab Med. 2006 Jan;44(6):694–8.

71. Brickell TA, McLean C. Emerging issues and challenges for improving patient safety in mental health: a qualitative analysis of expert perspectives. J Patient Saf. 2011;7(1):39–44.

72. Jayaram G. Measuring Adverse Events in Psychiatry. Psychiatry. 2008;5(11):17–9.

73. Zorg en Gezondheid Referentiekader WZC. Available from: www.zorg-en-gezondheid.be/referentiekaderwzc/ Accessed March 8, 2015.

74. Agentschap Zorg en Gezondheid [Agency for Care and Health]. Available from: www.zorg-en-gezondheid.be/zorgaanbod Accessed March 8, 2015.

75. Van Gaal BGI, Schoonhoven L, Mintjes-de Groot JA, Defloor T, Habets H, Voss

A, et al. Concurrent incidence of adverse events in hospitals and nursing homes. J Nurs Scholarsh. 2014 May;46(3):187–98.

76. Davis P, Lay-Yee R, Briant R, Scott A. Preventable in-hospital medical injury under the "no fault" system in New Zealand. Qual Saf Health Care. 2003 Aug;12(4):251–6.

77. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. BMJ. 2000 Mar 18;320(7237):741–4.

78. Phillips R, Baryholomew L, Dovey S, Fryer G, Miyoshi T, Green L. Learning from malpractice claims about negligent, adverse events in primary care in the United States. Qual Saf Heal Care. 2004 Apr 1;13(2):121–6.

79. Rubin G. Medical errors. Terminology of error is important. BMJ. 2001;322(7299):1422.

80. Dovey SM, Meyers DS, Phillips RL, Green LA, Fryer GE, Galliher JM, et al. A preliminary taxonomy of medical errors in family practice. Qual Saf Health Care. 2002 Sep;11(3):233–8.

81. Sears N, Baker GR, Barnsley J, Shortt S. The incidence of adverse events among home care patients. Int J Qual Heal care. 2013;25(1):16–28.

82. Canadian Home Care Association. Available from: htt://www.cdnhomecare.ca/ Accessed March 8, 2015.

83. Sari AB, Cracknell A, Sheldon TA. Incidence, preventability and consequences of adverse events in older people: results of a retrospective case-note review. Age Ageing. 2008 May;37(3):265–9.

84. Classen DC, Resar R, Griffin F, Federico F, Frankel T, Kimmel N, et al. "Global trigger tool" shows that adverse events in hospitals may be ten times greater than previously measured. Health Aff (Millwood). 2011 Apr;30(4):581–9.

85. Barker KN, Flynn EA, Pepper GA, Bates DW, Mikeal RL. Medication Errors Observed in 36 Health Care Facilities. Arch Intern Med. 2002 Sep 9;162(16):1897–903.

86. World Alliance for Patient Safety. WHO Draft Guidelines for Adverse Event Reporting and Learning Systems: From information to action. 2005.

87. Campbell EG, Susan R, Gruen RL, Ferris TG, Rao SR, Cleary PD, et al. Professionalism in Medicine: Results of a National Survey of Physicians. Ann Intern Med. 2007;147:795–802.

88. Thomas EJ, Sexton JB, Neilands TB, Frankel A, Helmreich RL. The effect of executive walk rounds on nurse safety climate attitudes: a randomized trial of clinical units[ISRCTN85147255] [corrected]. BMC Health Serv Res. 2005 Apr 11;5(1):28.

89. Frankel A, Neppl C, Simmonds T, Gustafson M, Tk G. Patient Safety Leadership WalkRounds . Jt Comm J Qual Improv. 2003;29(1):16–26.

90. Hughes D, DuMont K. Using focus groups to facilitate culturally anchored research. Am J Community Psychol. 1993;21(4):775–806.

91. Weissman JS, Schneider EC, Weingart SN, Epstein AM, David-Kasdan J, Feibelmann S, et al. Comparing patient-reported hospital adverse events with medical record review: Do patients know something that hospitals do not? Ann Intern Med. 2008;149(July):100–8.

92. Davis RE, Sevdalis N, Neale G, Massey R, Vincent CA. Hospital patients' reports of medical errors and undesirable events in their health care. J Eval Clin Pract. 2013;19:875–81.

93. Vincent C, Burnett S, Carthey J. Safety measurement and monitoring in healthcare: a framework to guide clinical teams and healthcare organisations in maintaining safety. BMJ Qual Saf. 2014;23:670–7.

94. O'Neil A, Petersen L, Cook E, Bates D, Lee T, Brennan T. Physician reporting compared with medical-record review to identify adverse medical events. Ann Intern Med. 1993 Sep 1;119(5):370–6.

95. Cullen D, Bates D, Small S, Cooper J, Nemeskal A, Leape L. The incident reporting system does not detect adverse drug events: a problem for quality improvement. J Qual Improv. 1995 Oct;21(10):541–8.

96. Murff HJ, Patel VL, Hripcsak G, Bates DW. Detecting adverse events for patient safety research: a review of current methodologies. J Biomed Inform. 2003 Feb;36:131–43.

97. Levtzion-Korach O, Frankel A, Alcalai H, Keohane C, Orav J, Graydon-Baker E, et al. Integrating incident data from five reporting systems to assess patient safety: making sense of the elephant. Jt Comm J Qual Patient Saf. 2010 Sep;36(9):402–10.

98. Leape LL. Reporting of adverse events. N Engl J Med. 2002 Nov 14;347(20):1633–8.

99. Weingart SN, Pagovich O, Sands DZ, Li JM, Aronson MD, Davis RB, et al. Patient-reported service quality on a medicine unit. Int J Qual Health Care. 2006 Apr;18(2):95–101.

100. Donaldson L. An organisation with a memory. Clin Med. 2002;2(5):452–7.

101. Reader TW, Gillespie A, Roberts J. Patient complaints in healthcare systems: a systematic review and coding taxonomy. BMJ Qual Saf. 2014 Aug;23(8):678–89.

102. Hickson GB, Federspiel CF, Pichert JW, Miller CS, Gauld-Jaeger J, Bost P. Patient complaints and malpractice risk. JAMA. 2002 Jun 12;287(22):2951–7.

103. Bismark MM, Brennan TA, Paterson RJ, Davis PB, Studdert DM. Relationship between complaints and quality of care in New Zealand: a descriptive analysis of complainants and non-complainants following adverse events. Qual Saf Health Care. 2006 Feb;15(1):17–22.

104. Oyebode F. Clinical errors and medical negligence. Med Princ Pract. 2013 Jan;22(4):323–33.

105. Localio A, Lawthers A, Brennan T, Laird N, Hebert L, Peterson L, et al. Relation between malpractice claims and adverse events due to negligence. N Engl J Med. 1991;325(4):245–51.

106. Somville FJMP, van Sprundel M, Somville J. Analysis of surgical errors in malpractice claims in Belgium. Acta Chir Belg. 2010;110(1):11–8.

107. Iezzoni LI. Assessing quality using administrative data. Ann Intern Med. 1997;127:666–74.

108. Van den Heede K, Sermeus W, Diya L, Lesaffre E, Vleugels A. Adverse outcomes in Belgian acute hospitals: retrospective analysis of the national hospital discharge dataset. Int J Qual Health Care. 2006 Jun;18:211–9.

109. France RF, Mertens I. Case Mix In Belgium: A rapid Coverage and a Progressive AP-DRG use. In: Press I, editor. Case Mix: Global Views, Local Actions: Evolution in Twenty Countries. Amsterdam; 2001. p. 60750.

110. Romano PS, Chan BK, Schembri ME, Rainwater JA. Can administrative data be used to compare postoperative complication rates across hospitals? Med Care. 2002 Oct;40(10):856–67.

111. McCarthy E, Iezzoni L, Davis R, Palmer R, Cahalane M, Hamel M, et al. Does Clinical evidence support ICD-CM diagnosis coding of complications? Med Care. 2000;38(8):868–76.

112. Moro ML, Morsillo F. Can hospital discharge diagnoses be used for surveillance of surgical-site infections? J Hosp Infect. 2004 Mar;56(3):239–41.

113. Quan H, Parsons GA, Ghali WA. Assessing accuracy of diagnosis-type indicators for flagging complications in administrative data. J Clin Epidemiol. 2004 Apr;57(4):366–72.

114. Thomas EJ, Petersen LA. Measuring errors and adverse events in health care. J Gen Intern Med. 2003 Jan;18(1):61–7.

115. Zhan C, Miller M. Administrative data based patient safety research: a critical review. Qual Saf Heal Care. 2003;12:ii58–63.

116. Woloshynowych M, Neale G, Vincent C. Case record review of adverse events: a new approach. Qual Saf Health Care. 2003 Dec;12:411–5.

117. Christiaans-Dingelhoff I, Smits M, Zwaan L, Lubberding S, van der Wal G, Wagner C. To what extent are adverse events found in patient records reported by patients and healthcare professionals via complaints, claims

and incident reports? BMC Health Serv Res. BioMed Central Ltd; 2011 Jan;11(1):49–58.

118. Lilford R, Mohammed M, Braunholtz D, Hofer T. The measurement of active errors: methodological issues. Qual Saf Health Care. 2003 Dec;12 Suppl 2:ii8–12.

119. Thomas EJ, Lipsitz SR, Studdert DM, Brennan TA. The Reliability of Medical Record Review for Estimating Adverse Event Rates. Ann Intern Med. 2002 Jun 4;136(11):812–6.

120. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of Adverse Events and Negligence in Hospitalized patients: Results of the Harvard Medical Practice Study I. N Engl J Med. 1991;324(6):370–6.

121. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ. 2004 May 25;170(11):1678–86.

122. Schiøler T, Lipczak H, Pedersen BL, Mogensen TS, Bech KB, Stockmarr A, et al. [Incidence of adverse events in hospitals. A retrospective study of medical records]. Ugeskr Laeger. 2001 Sep 24;163(39):5370–8.

123. Sari AB, Sheldon TA, Cracknell A, Turnbull A, Dobson Y, Grant C, et al. Extent, nature and consequences of adverse events: results of a retrospective casenote review in a large NHS hospital. Qual Saf Health Care. 2007 Dec;16(6):434–9.

124. Davis P, Lay-Yee R, Briant R, Ali W, Scott A, Schug S. Adverse events in New Zealand public hospitals I: occurrence and impact. N Z Med J. 2002 Dec 13;115(1167):U271–81.

125. Sousa P, Uva AS, Serranheira F, Nunes C, Leite ES. Estimating the incidence of adverse events in Portuguese hospitals: a contribution to improving quality and patient safety. BMC Health Serv Res. 2014 Jan;14(1):311–6.

126. Soop M, Fryksmark U, Köster M, Haglund B. The incidence of adverse events in Swedish hospitals: a retrospective medical record review study. Int J Qual Health Care. 2009 Aug;21(4):285–91.

127. Letaief M, El Mhamdi S, El-Asady R, Siddiqi S, Abdullatif A. Adverse events in a Tunisian hospital: results of a retrospective cohort study. Int J Qual Heal care. 2010 Oct;22(5):380–5.

128. Vincent C, Neale G, Woloshynowych M. Adverse events in British hospitals: preliminary retrospective record review. BMJ. 2001 Mar 3;322(7285):517–9.

129. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care. 2000 Mar;38(3):261–71.

130. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA. The incidence and nature of surgical adverse events in Colorado and Utah in 1992. Surgery. 1999;126:66–75.

131. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Phil M, Goldmann DA, et al. Temporal Trends in Rates of Patient Harm Resulting from Medical Care. N Engl J Med. 2010;363(22):2124–34.

132. Verelst S, Jacques J, Van den Heede K, Gillet P, Kolh P, Vleugels A, et al. Validation of Hospital Administrative Dataset for adverse event screening. Qual Saf Health Care. 2010 Oct;19(5):e25.

133. Hellings J. Patiëntveiligheid in het ziekenhuis: een evaluatieonderzoek over medicatieveiligheid. Katholieke Universiteit Leuven; 2009.

134. Griffin F, Resar R. IHI Global Trigger Tool for Measuring Adverse Events (Second edition). Cambridge, Massachusetts; 2009. Available from: www.IHI.org Accessed March 8, 2015.

135. Layde PM, Cortes LM, Teret SP, Brasel KJ, Kuhn EM, Mercy JA, et al. Patient safety efforts should focus on medical injuries. JAMA. 2002 Apr 17;287(15):1993–7.

136. Vlayen A, Marquet K, Schrooten W, Vleugels A, Hellings J, De Troy E, et al. Design of a medical record review study on the incidence and preventability of adverse events requiring a higher level of care in Belgian hospitals. BMC Res Notes. 2012;5:468–76.

137. Marquet K, Claes N, De Troy E, Kox G, Droogmans M, Schrooten W, et al. One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals. Accepted for Publication Crit Care Med, 2015.

138. Marquet K, Claes N, De Troy E, Kox G, Droogmans M, Vleugels A. Multicentre medical record review on Adverse Drugs Events requiring a higher level of care. Submitted.

139. Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: A systematic review with meta-analysis. Accepted for publication to Critical Care, 2015.

140. Leape LL, Brennan TA, Laird N, Lawthers A, Localio AR, Barnes BA, et al.

The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991;324(6):377–84.

141. Zegers M, De Bruijne M, Spreeuwenberg P, Wagner C, Groenewegen PP, Van Der Wal G. Quality of patient record keeping: an indicator of the quality of care? BMJ Qual Saf. 2011;20(4):314–8.

142. Woods D, Thomas E, Holl J, Altman S, Brennan T. Adverse events and preventable adverse events in children. Pediatrics. 2005 Jan;115(1):155–60.

143. Institute for Healthcare Improvement. Available from: www.ihi.org Accessed March 8, 2015.

144. Dunn KL, Reddy P, Moulden A, Bowes G. Medical record review of deaths, unexpected intensive care unit admissions, and clinician referrals: detection of adverse events and insight into the system. Arch Dis Child. 2006 Feb;91(2):169–72.

145. Hayward RA, Hofer TP. Estimating Hospital Deaths Due to Medical Errors Preventability Is in the Eye of the Reviewer. JAMA. 2001;286(4):415–20.

146. Jarman B, Gault S, Alves B, Hider A, Dolan S, Cook A, et al. Explaining differences in English hospital death rates using routinely collected data. BMJ. 1999 Jun 5;318(7197):1515–20.

147. Michel P, Quenon JL, de Sarasqueta AM, Scemama O. Comparison of three methods for estimating rates of adverse events and rates of preventable adverse events in acute care hospitals. BMJ. 2004 Jan 24;328(7433):199–204.

148. Park RE, Brook RH, Kosecoff J, Keesey J, Keeler E, Kahn KL, et al. Explaining Variations in Hospital Death Rates Randomness, Severity of Illness, Quality of Care. JAMA. 1990;264(4):484–90.

149. Classen DC, Resar R, Griffin F, Federico F, Frankel T, Kimmel N, et al. "Global Trigger Tool" shows that adverse events in hospitals may be ten times greater than previously measured. Health Aff. 2011;30(4):581–9.

150. Collopy BT, Ansari MZ, Booth JL BrJ. The Australian Council on Healthcare Standards care Evaluation. Med J Aust. 1995;163(9):477–80.

151. Posa PJ, Yonkee DE, Fields WL. Development and implications of an interdisciplinary quality assurance monitor on unplanned transfers into the intensive care units. J Nurs Care Qual. 1992 Jan;6(2):51–5.

152. IHI Global Trigger Tool for Measuring Adverse Events. Second edition. Available from: www.ihi.org Accessed March 8, 2015.

153. Knaus W, Draper E, Wagner D, Zimmerman J. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.

154. OpenClinica. Available from: https://community.openclinica.com/ Accessed March 8, 2015.

155. Saklad M. Grading of patients for Surgical procedures. Anesthesiology. 1941;2:281–4.

156. Anesthesiologists ASo. New classification of physical status. Anesthesiology. 1963;24:111.

157. Daabiss M. American Society of Anaesthesiologists physical status

classification. Indian J Anaesth. 2011 Mar [;55(2):111–5.

158. Kruispuntbank van de Sociale Zekerheid en eHealth-platform [Privacy Commission]. Available from: https://www.ksz-bcss.fgov.be/ Accessed March 8, 2015.

159. Aljadhey H, Mahmoud MA, Mayet A, Alshaikh M, Ahmed Y, Murray MD, et al. Incidence of adverse drug events in an academic hospital: a prospective cohort study. Int J Qual Heal care. 2013 Dec;25(6):648–55.

160. Hug BL, Witkowski DJ, Sox CM, Keohane CA, Seger DL, Yoon C, et al. Adverse drug event rates in six community hospitals and the potential impact of computerized physician order entry for prevention. J Gen Intern Med. 2010 Jan;25(1):31–8.

161. Morimoto T, Sakuma M, Matsui K, Kuramoto N, Toshiro J, Murakami J, et al. Incidence of adverse drug events and medication errors in Japan: the JADE study. J Gen Intern Med. 2011 Feb;26(2):148–53.

162. Benkirane R, R-Abouqal R, Haimeur C, S. Ech. Cherif El Kettani S, Azzouzi A, M'daghri Alaoui A, et al. Incidence of Adverse Drug Events and Medication Errors in Intensive Care Units: A Prospective Multicenter Study. J Patient Saf. 2009;5(1):16–22.

163. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse Drug Events in Hospitalized Patients Excess Length of Stay, Extra Costs, and Attributable Mortality. JAMA. 1997;277(4):301–6.

164. Kunac D, Kennedy J, Austin N, Reith D. Incidence, preventability, and impact of Adverse Drug Events (ADEs) and potential ADEs in hospitalized children in New Zealand: a prospective observational cohort study. Paediatr drugs.

2009;11(2):153–60.

165. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. Int J Qual Health Care. 2003 Dec;15 Suppl 1:i49–59.

166. Hoonhout LHF, de Bruijne MC, Wagner C, Asscheman H, van der Wal G, van Tulder MW. Nature, Occurrence and Consequences of Medication - Related Adverse Events During Hospitalization. Drug Saf. 2010;33(10):853–64.

167. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255–9.

168. WHO Collaborating Centre for Drug Statistics Methodoly. Available from: http://www.whocc.no/atc_ddd_index/ Accessed March 8, 2015.

169. Franklin BD. Medication errors: do they occur in isolation? BMJ Qual Saf. 2014 Feb 27;1–3.

170. Galappathie N, Jethwa K, Andonovska B. An audit of basic record keeping standards: lessons learnt from the Royal College of Physicians. Med Sci Law. 2008 Apr 1;48(2):155–8.

171. Mann R, Williams J. Standards in medical record keeping. Clin Med. 2003;3(4):329–32.

172. De Vries E, Ramrattan M, Smorenburg S, Gouma D, Boermeester M. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Heal Care. 2008;17:216–23.

173. Brennan T, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et

al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. Qual Saf Heal Care. 2004;324(13):145–53.

174. Landry E, Pett C, Fiorentino R, Ruminjo J, Mattison C. Assessing the quality of record keeping for cesarean deliveries: results from a multicenter retrospective record review in five low-income countries. BMC Pregnancy Childbirth. BMC Pregnancy and Childbirth; 2014 Jan;14(1):139–49. A

175. Gabbay J, McNicol MC, Spiby J, Davies SC, Layton AJ. What did audit achieve ? Lessons from preliminary evaluation of a year 's medical audit. BMJ. 1990;301:526–9.

176. Heath DA. Random review of hospital patient records. BMJ. 1990;300:651–2.

177. Mashru M, Lant A. Interpractice audit of diagnosis and management of and review of medical records. BMJ. 1997;314:942–6.

178. Hansebo G, Kihlgren M, Ljunggren G. Review of nursing documentation in nursing home wards - changes after intervention for individualized care. J Adv Nurs. 1999 Jun;29(6):1462–73.

179. Webb C, Pontin D. Evaluating the introduction of primary nursing: the use of a care plan audit. J Clin Nurs. 1997 Sep;6(5):395–401.

180. Royal College of Physicians (RCP): A Clinician's Guide to Record Standards. Available from: https://www.rcplondon.ac.uk/resources/standards-clinical-structure-and-content-patient-records Accessed March 8, 2015.

181. Koninklijk besluit van 3 mei 1999 houdende bepaling van de algemene minimumvoorwaarden waarvan het medisch dossier, bedoeld in artikel 15

van de wet op de ziekenhuizen, gecoördineerd op 7 augustus 1987, moet voldoen. [Belgian law of 1999].

182. Arotiba J, Akinmoladun V, Okoje V. An audit of medical record-keeping in maxillofacial surgery at the University College Hospital, Ibadan using the CRABEL Scoring system. Afr J Med Sci. 2006;35(1):93–5.

183. Crawford J, Beresford T, Lafferty K. The CRABEL score - a method for auditing medical records. Ann R Coll Surg Engl. 2001;83:65–8.

184. Wilson RM. Reviewing case record review. Qual Saf Health Care. 2003 Dec;12(6):402–3.

185. Pullen I, Loudon J. Improving standards in clinical record-keeping. Advances in psychiatric treatment. Adv Psychiatr Treat. 2006;12:280–6.

186. WHO (2012) World health statistics 2012. Available from: http://www.who.int/gho/publications/world_health_statistics/EN_WHS2012_Full.pdf. Accessed March 8, 2015.

187. Heron M, Hoyert S, Murphy J, Kochanek K, Tejada-Vera B. Deaths: final data for 2006. Division of Vital Statistics, Centers for Disease Control and Prevention. Natl Vital Stat Rep. 2009;57:1–136.

188. Wenzel RP, Edmond MB. The Impact of Hospital-Acquired Bloodstream Infections. Emerg Infect Dis. 2001;7(2):174–7.

189. Dellinger RP. Cardiovascular management of septic shock. Crit Care Med. 2003 Mar;31(3):946–55.

190. Eagye KJ, Kim A, Laohavaleeson S, Kuti JL, Nicolau DP. Surgical site

infections: does inadequate antibiotic therapy affect patient outcomes? Surg Infect (Larchmt). 2009 Aug;10(4):323–31.

191. Fraser A, Paul M, Almanasreh N, Tacconelli E, Frank U, Leibovici L. Benefit of Appropriate Empirical Antibiotic Treatment : Thirty-day Mortality and Duration of Hospital Stay. Am J Med. 2006;119:970–6.

192. Fowler RA, Flavin KE, Barr J, Weinacker A, Parsonnet J, Gould M. Variability in Antibiotic Prescribing Patterns and Outcomes in Patients With Clinically Suspected Ventilator- Associated Pneumonia *. Chest. 2003;123(3):835–44.

193. Kim S-H, Park W-B, Lee C-S, Kang C-I, Bang J-W, Kim H-B, et al. Outcome of inappropriate empirical antibiotic therapy in patients with Staphylococcus aureus bacteraemia: analytical strategy using propensity scores. Clin Microbiol Infect. 2006 Jan;12(1):13–21.

194. Schweizer ML, Furuno JP, Harris AD, Johnson JK, Shardell MD, McGregor JC, et al. Empiric antibiotic therapy for Staphylococcus aureus bacteremia may not reduce in-hospital mortality: a retrospective cohort study. PLoS One. 2010 Jan;5(7):e11432–8.

195. Thom KA, Schweizer ML, Osih RB, McGregor JC, Furuno JP, Perencevich EN, et al. Impact of empiric antimicrobial therapy on outcomes in patients with Escherichia coli and Klebsiella pneumoniae bacteremia: a cohort study. BMC Infect Dis. 2008 Jan;8:116–24.

196. Osih RB, McGregor JC, Rich SE, Moore AC, Furuno JP, Perencevich EN, et al. Impact of empiric antibiotic therapy on outcomes in patients with Pseudomonas aeruginosa bacteremia. Antimicrob Agents Chemother. 2007 Mar;51(3):839–44.

197. Kang C, Kim S, Park WB, Lee K, Kim H, Kim E, et al. Bloodstream Infections Caused by Antibiotic-Resistant Gram-Negative Bacilli : Risk Factors for Mortality and Impact of Inappropriate Initial Antimicrobial Therapy on Outcome. Antimicrob Agents Chemother. 2005;49(2):760–6.

198. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589–96.

199. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The Influence of Inadequate Antimicrobial Treatment of Bloodstream Infections on Patient Outcomes in the ICU Setting *. Chest. 2000;118:146–55.

200. Labelle A, Micek S, Roubinian N, Kollef M. Treatment-related risk factors for hospital mortality in Candida bloodstream infections. Crit Care Med. 2008;36(11):2967–72.

201. Schramm G, Johnson J, Doherty J, Micek S, Kollef M. Methicillin-resistant Staphylococcus aureus sterile-site infection : The importance of appropriate initial antimicrobial treatment. Crit Care Med. 2006;34(8):2069–74.

202. Romero-Vivas J, Rubio M, Fernandez C, Picazo J. Mortality associated with nosocomial bacteremia due to methicillin- resistant Staphylococcus aureus. Clin Infect Dis. 1995;21(6):1417–23.

203. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998 Nov;244(5):379–86.

204. Erbay A, Idil A, Gözel MG, Mumcuoğlu I, Balaban N. Impact of early

appropriate antimicrobial therapy on survival in Acinetobacter baumannii bloodstream infections. Int J Antimicrob Agents. 2009 Dec;34(6):575–9.

205. Lin MY, Weinstein RA, Hota B. Delay of Active Antimicrobial Therapy and Mortality among Patients with Bacteremia: Impact of Severe Neutropenia. Antimicrob Agents Chemother. 2008;52(9):3188–94.

206. Kim S, Park W, Lee K, Kang C, Bang J, Kim H, et al. Outcome of inappropriate initial antimicrobial treatment in patients with methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicriobial Chemother. 2004;54(2):489–97.

207. Scarsi KK, Feinglass JM, Scheetz MH, Postelnick MJ, Bolon MK, Noskin GA. Impact of inactive empiric antimicrobial therapy on inpatient mortality and length of stay. Antimicrob Agents Chemother. 2006 Oct;50(10):3355–60.

208. Paul M, Andreassen S, Tacconelli E, Nielsen AD, Almanasreh N, Frank U, et al. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. J Antimicrob Chemother. 2006 Dec;58(6):1238–45.

209. Khatib R, Saeed S, Sharma M, Riederer K, Fakih MG, Johnson LB. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. 2006 Mar;25(3):181–5.

210. Mcgregor JC, Rich SE, Harris AD, Perencevich EN, Osih R, Lodise TP, et al. A Systematic Review of the Methods Used to Assess the Association between Appropriate Antibiotic Therapy and Mortality in Bacteremic Patients. Clin Infect Dis. 2007;45(2007):329–37.

211. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998 Jun;52(6):377–84.

212. Deeks J, Dinnes J, D'Amico R, Sowden A, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003 Jan;7(27):iii – x, 1–173.

213. Saunders LD, Soomro GM, Buckingham J, Jamtvedt G, Raina P. Assessing the methodological quality of nonrandomized intervention studies. West J Nurs Res. 2003 Mar;25(2):223–37.

214. Chudyk AM, Jutai JW, Petrella RJ, Speechley M. Systematic review of hip fracture rehabilitation practices in the elderly. Arch Phys Med Rehabil. the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation; 2009 Feb;90(2):246–62.

215. Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. Can J Ophthalmol. 2008 Apr;43(2):180–7.

216. Samoocha D, Bruinvels DJ, Elbers NA, Anema JR, van der Beek AJ. Effectiveness of web-based interventions on patient empowerment: a systematic review and meta-analysis. J Med Internet Res. 2010 Jan;12(2):e23.

217. Team RDC. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. 2012th ed. Vienna; 2012.

218. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.

219. Mueller EW, Hanes SD, Croce MA, Wood GC, Boucher BA, Fabian TC. Effect From Multiple Episodes of Inadequate Empiric Antibiotic Therapy for Ventilator-Associated Pneumonia on Morbidity and Mortality Among Critically Ill Trauma Patients. J Trauma Inj Infect Crit Care. 2005 Jan;58(1):94–101.

220. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. Pseudomonas aeruginosa Bloodstream Infection : Importance of Appropriate Initial Antimicrobial Treatment. Antimicrob Agents Chemother. 2005;49(4):1306–11.

221. Luna CM, Aruj P, Niederman MS, Garzon J, Violi D, Prignoni A, et al. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. Eur Respir. 2006;27(1):158–64.

222. Fujita T, Ishida Y, Yanaga K. Impact of appropriateness of initial antibiotic therapy on outcome of postoperative pneumonia. Langenbecks Arch Surg. 2008 Jul;393(4):487–91.

223. Marschall J, Agniel D, Fraser VJ, Doherty J, Warren DK. Gram-negative bacteraemia in non-ICU patients : factors associated with inadequate antibiotic therapy and impact on outcomes. J Antimicriobial Chemother. 2008;61:1376–83.

224. Shorr AF, Micek ST, Pharm D, Kollef MH. Inappropriate therapy for methicillin-resistant Staphylococcus aureus: Resource utilization and cost impliczations. Crit Care Med. 2008;36(8):2335–40.

225. Rodríguez-Baño J, Millán AB, Domínguez MA, Borraz C, González MP, Almirante B, et al. Impact of inappropriate empirical therapy for sepsis due to health care-associated methicillin-resistant Staphylococcus aureus. J Infect. 2009 Feb;58(2):131–7.

226. Ammerlaan H, Seifert H, Harbarth S, Brun-Buisson C, Torres A, Antonelli M, et al. Adequacy of antimicrobial treatment and outcome of Staphylococcus aureus bacteremia in 9 Western European countries. Clin Infect Dis. 2009 Oct 1;49(7):997–1005.

227. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parillo J, et al. Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock. Chest. 2009;136(5):1237–48.

228. Tseng C-C, Fang W-F, Huang K-T, Chang P-W, Tu M-L, Shiang Y-P, et al. Risk factors for mortality in patients with nosocomial Stenotrophomonas maltophilia pneumonia. Infect Control Hosp Epidemiol. 2009 Dec;30(12):1193–202.

229. Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, et al. Empiric Combination Antibiotic Therapy Is Associated with Improved Outcome against Sepsis Due to Gram-Negative Bacteria : a Retrospective Analysis. Antimicrob Agents Chemother. 2010;54(5):1742–8.

230. Paul M, Kariv G, Goldberg E, Raskin M, Shaked H, Hazzan R, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2010 Dec;65(12):2658–65.

231. Joung M, Kwon K, Kang C, Cheong H, Rhee J, Jung D, et al. Impact of inappropriate antimicrobial therapy on outcome in patients with hospital-acquired pneumonia caused by Acinetobacter baumannii. J Infect. Elsevier Ltd; 2010;61(3):212–8.

232. Shorr AF, Micek ST, Welch EC, Doherty JA, Reichley RM, Kollef MH. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. Crit Care Med. 2011 Jan;39(1):46–51.

233. Suppli M, Aabenhus R, Harboe ZB, Andersen LP, Tvede M, Jensen J-US. Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy. Clin Microbiol Infect. 2011 Jul;17(7):1078–83.

234. Reisfeld S, Paul M, Gottesman BS, Shitrit P, Leibovici L, Chowers M. The effect of empiric antibiotic therapy on mortality in debilitated patients with dementia. Eur J Clin Microbiol Infect Dis. 2011 Jun;30(6):813–8.

235. Wilke MH, Grube R, Bodmann KF. Guideline - Adherent Initial Intravenous Antibiotic Therapy for Hospital-Acquired, Ventilator-Associated Pneumonia is Clinically Superior, Saves Lives and is Cheaper Than Non Guideline Adherent Therapy. Eur J Med Res. 2011;16:315–23.

236. De Rosa FG, Pagani N, Fossati L, Raviolo S, Cometto C, Cavallerio P, et al. The effect of inappropriate therapy on bacteremia by ESBL-producing bacteria. Infection. 2011 Dec;39(6):555–61.

237. Lye DC, Earnest A, Ling ML, Lee T, Yong H, Fisher DA, et al. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay : cohort study. Clin Microbiol Infect. 2012;18:502–8.

238. Tseng C-C, Liu S-F, Wang C-C, Tu M-L, Chung Y-H, Lin M-C, et al. Impact of clinical severity index, infective pathogens, and initial empiric antibiotic use on hospital mortality in patients with ventilator-associated pneumonia. Am J Infect Control. Elsevier Inc; 2012 Sep;40(7):648–52.

239. Chen R, Yan Z, Feng D, Luo Y, Wang L, Shen D. Nosocomial bloodstream infection in patients caused by factors for hospital mortality. Chin Med J. 2012;125(2):226–9.

240. Kim YJ, Kim S Il, Hong K, Kim YR, Park YJ, Kang M. Risk Factors for Mortality in Patients with Carbapenem-Resistant Acinetobacter baumannii Bacteremia: Impact of Appropriate Antimicrobial Therapy. J Korean Med Sci. 2012;27:471–5.

241. Labelle A, Juang P, Reichley R, Micek S, Hoffmann J, Hoban A, et al. The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment*. Crit Care Med. 2012 Jul;40(7):2016–21.

242. Chen H-C, Lin W-L, Lin C-C, Hsieh W-H, Hsieh C-H, Wu M-H, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. J Antimicrob Chemother. 2013 Apr;68(4):947–53.

243. Frakking FNJ, Rottier WC, Dorigo-Zetsma JW, van Hattem JM, van Hees BC, Kluytmans JAJW, et al. Appropriateness of empirical treatment and outcome in bacteremia caused by extended-spectrum-β-lactamase-producing bacteria. Antimicrob Agents Chemother. 2013 Jul;57(7):3092–9.

244. Tumbarello M, De Pascale G, Trecarichi EM, Spanu T, Antonicelli F, Maviglia R, et al. Clinical outcomes of Pseudomonas aeruginosa pneumonia in intensive care unit patients. Intensive Care Med. 2013 Apr;39(4):682–92.

245. Ortega M, Marco F, Soriano A, Almela M, Martínez JA, Pitart C, et al. Epidemiology and prognostic determinants of bacteraemic catheter-acquired urinary tract infection in a single institution from 1991 to 2010. J Infect. 2013 Oct;67(4):282–7.

246. Charlson M, Pompei P, Ales KL, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987 Jan;40(5):373–83.

247. Vincent J-L, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–10.

248. Le Gall J-R, Lemeshow S, Saulnier F. New Simplified Acute Physiology Score (SAPS II) Based on a European/North American Multicenter Study. JAMA. 1993;270:2957–63.

249. Marshall JC, Cook DJ, Christou N V, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995 Oct;23(10):1638–52.

250. Paterson DL, Wen-Chien K, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. International Prospective Study of Klebsiella pneumoniae Bacteremia: Implications of Extended-Spectrum β-Lactamase Production in Nosocomial Infections. Ann Intern Med. 2004 Jan 6;140(1):26–32.

251. McCabe WR, Jackson GG. Gram-Negative Bacteremia I. Etiologie and Ecology. JAMA. 1962;110(6):847–55.

252. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L, et al. Systematic Review and Meta-Analysis of the Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis. Antimicrob Agents Chemother. 2010;54(11):4851–63.

253. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.

254. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes Analysis of Delayed Antibiotic Treatment for Hospital-Acquired Staphylococcus aureus Bacteremia. Clin Infect Dis. 2003;36:1418–23.

255. Paul M, Nielsen AD, Goldberg E, Andreassen S, Tacconelli E, Almanasreh N, et al. Prediction of specific pathogens in patients with sepsis: evaluation of TREAT, a computerized decision support system. J Antimicrob Chemother. 2007 Jun;59(6):1204–7.

256. Kang C, Kim S, Park WB, Kim H, Kim E, Oh M, et al. Bloodstream Infections Caused by Antibiotic-Resistant Gram-Negative Bacilli : Risk Factors for Mortality and Impact of Inappropriate Initial Antimicrobial Therapy on Outcome. Antimicrob Agents Chemother. 2005;49(2):760–6.

257. Page RL, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient : Defining the problem , evaluation tools , and possible solutions. Clin Interv Aging. 2010;5:75–87.

258. Hanlon JT, Schmader KE, Ruby CM, Morris W. Suboptimal prescribing in older inpatients and outpatients. J Am Geriatr Soc. 2001;49:200–9.

259. Pierson S, Hansen R, Greene S, Williams C, Akers R, Jonsson M, et al. Preventing medication errors in long-term care: results and evaluation of a large scale web-based error reporting system. Qual Saf Health Care. 2007 Aug;16(4):297–302.

260. Barber ND, Alldred DP, Raynor DK, Dickinson R, Garfield S, Jesson B, et al. Care homes' use of medicines study: prevalence, causes and potential harm of medication errors in care homes for older people. Qual Saf Health Care. 2009 Oct;18(5):341–6.

261. American Health Care Association Washington DC. Results of the 2002 AHCA Survey of Nursing Staff Vacancy and Turnover in Nursing Homes Health Services Research and Evaluation. 2002 p. 40.

262. Gallagher P, Lang PO, Cherubini A, Topinková E, Cruz-Jentoft A, Montero Errasquín B, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol. 2011 Nov;67(11):1175–88.

263. Garfield S, Barber N, Walley P, Willson A, Eliasson L. Quality of medication use in primary care--mapping the problem, working to a solution: a systematic review of the literature. BMC Med. 2009 Jan;7:50.

264. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. Drugs Aging. 2005;22(1):69–82.

265. Lau DT, Kasper JD, Potter DEB, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. Arch Intern Med. 2005 May;165:68–74.

266. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med. 1996 Sep;14(5):447–50.

267. Hohl CM, Dankoff J, Colacone a, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001 Dec;38(6):666–71.

268. McDonnell P, Jacobs M. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002;36:1331–6.

269. American Geriatrics Society. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 Apr;60(4):616–31.

270. Beers MH. Explicit Criteria for Determining Potentially Inappropriate Medication Use by the Elderly An Update. Arch Intern Med. 1997;157(14):1531–6.

271. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit Criteria for Determining Inappropriate Medication Use in Nursing Home Residents. Arch Intern Med. 1991;151(9):1825–32.

272. Fick D, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults. Arch Intern Med. 2003;163(27):2716–24.

273. O'Mahony D, Gallagher P, Ryan C, Byrne S, Hamilton H, Barry P, et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. Eur Geriatr Med. Elsevier Masson SAS; 2010 Feb;1(1):45–51.

274. Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing. 2007;36(6):632–8.

275. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010 Aug;107(31-32):543–51.

276. Wenger N, Shekelle P. Assessing care of vulnerable elders: ACOVE project overview. Ann Intern Med. 2001;135(8 (Part2)):642–6.

277. Nygaard HA, Naik M, Ruths S, Straand J. Nursing-home residents and their drug use: a comparison between mentally intact and mentally impaired residents. The Bergen district nursing home (BEDNURS) study. Eur J Clin Pharmacol. 2003 Sep;59(5-6):463–9.

278. Van der Linden L. INT-013 Reduction of inappropriate prescribing in older persons using the RASP list: a cluster-randomised controlled trial. Eur J Hosp Pharm Sci Pract. 2014;21:A212.

279. Strand LM, Morley PC, Cipolle RJ, Ramsay R, Lamsam GD. Drug-related problems: their structure and function. Drug Interact Clin pharmacy, Ann Pharmacother. 1990;24(11):1093–7.

280. Elseviers MM, Vander Stichele RR, Van Bortel L. Quality of prescribing in Belgian nursing homes: an electronic assessment of the medication chart. Int J Qual Health Care. 2014 Feb;26(1):93–9.

281. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing. 2008 Nov;37(6):673–9.

282. Koper D, Kamenski G, Flamm M, Böhmdorfer B, Sönnichsen A. Frequency of medication errors in primary care patients with polypharmacy. Fam Pract. 2013 Jun;30(3):313–9.

283. Farmaka vzw. Kwaliteit van voorschrijven in het WZC verbeteren. Geneesmiddelenbrief. 2011;18(4):33–40.

284. Lund BC, Steinman MA, Chrischilles EA, Kaboli PJ. Beers criteria as a proxy for inappropriate prescribing of other medications among older adults. Ann Pharmacother. 2011 Nov;45(11):1363–70.

285. Samsa G, Hanlon J. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol. 1994 Aug;47(8):891–6.

286. Niwata S, Yamada Y, Ikegami N. Prevalence of inappropriate medication using Beers criteria in Japanese long-term care facilities. BMC Geriatr. 2006 Jan;6:1.

287. Bergman A, Olsson J, Carlsten A, Waern M, Fastbom J. Evaluation of the quality of drug therapy among elderly patients in nursing homes. Scand J Prim Health Care. 2007 Mar;25(1):9–14.

288. Barnett K, McCowan C, Evans JMM, Gillespie ND, Davey PG, Fahey T. Prevalence and outcomes of use of potentially inappropriate medicines in older people: cohort study stratified by residence in nursing home or in the community. BMJ Qual Saf. 2011 Mar;20(3):275–81.

289. O'Sullivan DP, O'Mahony D, Parsons C, Hughes C, Murphy K, Patterson S, et al. A prevalence study of potentially inappropriate prescribing in Irish long-term care residents. Drugs Aging. 2013 Jan;30(1):39–49.

290. Ruggiero C, Dell'Aquila G, Gasperini B, Onder G, Lattanzio F, Volpato S, et al. Potentially inappropriate drug prescriptions and risk of hospitalization among older, Italian, nursing home residents: the ULISSE project. Drugs Aging. 2010 Sep;27(9):747–58.

291. Ryan C, O'Mahony D, Kennedy J, Weedle P, Cottrell E, Heffernan M, et al. Potentially inappropriate prescribing in older residents in Irish nursing homes. Age Ageing. 2013 Jan;42(1):116–20.

292. Verrue C, Mehuys E, Boussery K. A pharmacist-conducted medication review in nursing home residents: impact on the appropriateness of prescribing. Acta Clin Belgica 2012;423–29.

293. Hosia-Randell H, Muurinen S, Pitkälä K. Exposure to potentially inappropriate

drugs and drug-drug interactions in elderly nursing home residents in Helsinki, Finland. Drugs Aging. 2008;25(8):683–92.

294. Blozik E, Born A, Stuck A, Benninger U. Reduction of Inappropriate Medications among Older Nursing-Home Residents. Drugs Aging. 2010;27(12):1009–17.

295. Nascimento MMG, Pereira ML, Souza ACS, Ribeiro AQ, Dias Jr. CAC. Potential drug therapy problems on an elderly nursing home population. Lat Am J Pharm. 2011;30(10):1985–90.

296. Raivio MM, Laurila J V., Strandberg TE, Tilvis RS, Pitkälä KH. Use of inappropriate medications and their prognostic significance among in-hospital and nursing home patients with and without dementia in Finland. Drugs and Aging. 2006;23(4):333–43.

297. García-Gollarte F, Baleriola-Júlvez J, Ferrero-López I, Cruz-Jentoft AJ. Inappropriate drug prescription at nursing home admission. J Am Med Dir Assoc. 2012;13(1):83.e9–15.

298. Lao CK, Ho SC, Chan KK, Tou CF, Tong HHY, Chan A. Potentially inappropriate prescribing and drug-drug interactions among elderly Chinese nursing home residents in Macao. Int J Clin Pharm. 2013 Oct;35(5):805–12.

299. Chen LL, Tangiisuran B, Shafie AA, Hassali MAA. Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. Int J Clin Pharm. 2012 Aug;34(4):596–603.

300. Mamun K, Lien CTC, Goh-Tan CYE, Ang WST. Polypharmacy and inappropriate medication use in Singapore nursing homes. Ann Acad Med Singapore. 2004 Jan;33(1):49–52.

301. Lane CJ, Bronskill SE, Sykora K, Dhalla I a, Anderson GM, Mamdani MM, et al. Potentially inappropriate prescribing in Ontario community-dwelling older adults and nursing home residents. J Am Geriatr Soc. 2004 Jun;52(6):861–6.

302. Lau DT, Kasper JD, Potter DE, Lyles A. Potentially inappropriate medication prescriptions among elderly nursing home residents: their scope and associated resident and facility characteristics. Health Serv Res. 2004;39(5):1257–76.

303. Perri M, Menon AM, Deshpande AD, Shinde SB, Jiang R, Cooper JW, et al. Adverse outcomes associated with inappropriate drug use in nursing homes. Ann Pharmacother. 2005 Mar;39(3):405–11.

304. Pinto MCX, Malaquias DP, Ferré F, Pinheiro MLP. Potentially inappropriate medication use among institutionalized elderly individuals in southeastern Brazil. Brazilian J Pharm Sci. 2013;49(4):709–17.

305. Varallo FR, Ambiel ISS, Nanci LO, Galduróz JCF, De Carvalho Mastroianni P. Assessment of pharmacotherapeutic safety of medical prescriptions for elderly residents in a long-term care facility. Brazilian J Pharm Sci. 2012;48(3):477–85.

306. Vieira de Lima TJ, Garbin CAS, Garbin AJI, Sumida DH, Saliba O. Potentially inappropriate medications used by the elderly: prevalence and risk factors in Brazilian care homes. BMC Geriatr. 2013 Jan;13:52–8.

307. Stafford AC, Alswayan MS, Tenni PC. Inappropriate prescribing in older residents of Australian care homes. J Clin Pharm Ther. 2011 Feb;36(1):33–44.

308. King MA, Roberts MS. The influence of the Pharmaceutical Benefits Scheme (PBS) on inappropriate prescribing in Australian nursing homes. Pharm World Sci. 2007 Feb;29(1):39–42.

309. Levinson DR. Adverse events in hospitals: National incidence among medicare beneficiaries (OEI-06-09-00090). 2010.

310. Hayes BD, Klein-Schwartz W, Barrueto F. Polypharmacy and the geriatric patient. Clin Geriatr Med. 2007 May;23(2):371–90, vii.

311. Kaur S, Roberts JA, Roberts MS. Evaluation of medication-related problems in medication reviews: a comparative perspective. Ann Pharmacother. 2014;46(7-8):972–82.

312. Shah S, Carey I, Harris T. Quality of prescribing in care homes and the community in England and Wales. Br J Gen Pract. 2012;62(598):e329–36.

313. Laroche M-L, Charmes J-P, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? Br J Clin Pharmacol. 2007 Feb;63(2):177–86.

314. Frazier S. Health outcomes and polypharmacy in elderly individuals: an integrated literature review. J Gerontol Nurs. 2005;31:4–11.

315. Fialová D, Topinková E. Potentially inappropriate medication use among elderly home care patients in Europe. Jama. 2005;293(11):1348–58.

316. Rochon PA, Gurwitz JH. Optimizing drug treatment for elderly people: the prescribing cascade. BMJ Br Med J. 1997;315:1096–9.

317. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J,

et al. Clinical medication review by a pharmacist of elderly people living in care homes-randomised controlled trial. Age Ageing. 2006 Nov;35(6):586–91.

318. Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatr. BioMed Central Ltd; 2011 Jan;11(1):16–31.

319. Ostyn G. Geneesmiddelengebruik in RVT's: een mooie taak is weggelegd voor de apotheker. Het apothekersmagazine. 2009;11:24–5.

320. Schmader K, Hanlon J, Pieper C, Sloane R, Ruby C, Twersky J, et al. Effectiveness of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med. 2004;116:394–401.

321. Ellis G, Langhorne P. Comprehensive geriatric assessment for older hospital patients. Br Med Bull. 2004 Jan;71:45–59.

322. Chang C, Liu P, Yang Y, Yang Y, Wu C, Lu F. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. Pharmacotherapy. 2005;25:831–8.

323. Gurwitz JH, Field TS, Rochon P, Judge J, Harrold LR, Bell CM, et al. Effect of computerized provider order entry with clinical decision support on adverse drug events in the long-term care setting. J Am Geriatr Soc. 2008 Dec;56(12):2225–33.

324. Lapane KL, Hughes CM, Daiello L a, Cameron K a, Feinberg J. Effect of a pharmacist-led multicomponent intervention focusing on the medication

monitoring phase to prevent potential adverse drug events in nursing homes. J Am Geriatr Soc. 2011 Jul;59(7):1238–45.

325. Storms H, Marquet K, Nelissen K, Hulshagen L, Lenie J, Remmen R, et al. Implementing an electronic medication overview in Belgium. BMC Res Notes. 2014;7:915–20.

326. Storms H, Claes N, Hulshagen L, Conings S, Nelissen K. Bevindingen van zorgverleners bij de implementatie van een papieren medicatieschema. APB. 2014;94(3):24–9.

327. Viktil KK, Blix HS, Moger T a, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol. 2007 Feb;63(2):187–95.

328. Steinman M a, Lund BC, Miao Y, Boscardin WJ, Kaboli PJ. Geriatric conditions, medication use, and risk of adverse drug events in a predominantly male, older veteran population. J Am Geriatr Soc. 2011 Apr;59(4):615–21.

329. Steinman MA, Rosenthal GE, Landefeld CS. Conflicts and Concordance Between Measures of Medication Prescribing Quality. 2007;45(1):95–9.

330. Steinman M, Rosenthal G, Landefeld C, Bertenthal D, Kaboli P. Agreement between drugs-to-avoid criteria and expert assessments of problematic prescribing. Arch Intern Med. 2009;169:1326–32.

331. Budnitz D, Shehab N, Kegler S, Richards C. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007;147:755–65.

332. Marquet K, Claes N, Postelmans T, Lemkens P, Rosseel M, Torfs A, et al.

ENT One Day Surgery : critical analysis with the HFMEA method. B-ENT. 2013;9:193–200.

333. Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten [Federal Agency for Medicines and Health products]. Available from: www.fagg.be Accessed March 8, 2015.

334. Belgisch Centrum voor Farmacotherapeutische Informatie [Centre Belge d'Information Pharmacothérapeutique]. Available from: www.bcfi.be Accessed March 8, 2015.

335. UpToDate. Available from: www.uptodate.com Accessed March 8, 2015.

336. American Society for Clinical Oncology. Available from: www.asco.org Accessed March 8, 2015.

337. Clinical pharmacology. Available from: https://www.clinicalpharmacology.com Accessed March 8, 2015.

338. Gastmeier P. Nosocomial infection surveillance and control policies. Curr Opin Infect Dis. 2004 Aug;17(4):295–301.

339. Wolff A. Limited adverse occurrence screening: an effective and efficient method of medical quality control. J Qual Clin Pract. 1995 Dec;15(4):221–33.

340. Craddick JW. The medical management analysis system: a professional liability warning mechanism. QRB Qual Rev Bull. 1979 Apr;5(4):2–8.

341. National Association of Insurance commissioners. National Association of Insurance Commissioners, malpractice claims: final compilation. Swoka M, editor. Washington; 1980.

342. Holley A, Kravet SJ, Cordts G. Documentation of code status and discussion of goals of care in gravely ill hospitalized patients. J Crit Care. Elsevier Inc.; 2009 Jun;24(2):288–92.

343. Brown C, Hofer T, Johal A, Thomson R, Nicholl J, Franklin B, et al. An epistemology of patient safety research: a framework for study design and interpretation. Part 4. One size does not fit all. Qual Saf Health Care. 2008 Jul;17(3):178–81.

344. Baker G. Commentary. Harvard Medical Practice Study. Qual Saf Heal Care. 2004;13:151–2.

345. Brennan TA, Localio RJ, Laird NL. Reliability and validity of judgments concerning adverse events suffered by hospitalized patients. Med Care. 1989 Dec;27(12):1148–58.

346. Thomas EJ, Studdert D, Burstin, Helen R, Orav EJ, Zeena T, Williams EJ, et al. Incidence and Types of Adverse Events and Negligent Care in Utah and Colorado. Med Care. 2000;38(March):261–71.

347. Localio AR, Weaver SL, Landis JR, Lawthers AG, Brennan TA, Hebert L, et al. Identifying Adverse Events Caused by Medical Care: Degree of Physician Agreement in a Retrospective Chart Review. Ann Intern Med. 1996;125(September):457–64.

348. Zegers M, de Bruijne MC, Wagner C, Groenewegen PP, van der Wal G, de Vet HCW. The inter-rater agreement of retrospective assessments of adverse events does not improve with two reviewers per patient record. J Clin Epidemiol. Elsevier Inc; 2010 Jan;63(1):94–102.

349. Walshe K. Adverse events in health care: issues in measurement. Qual Health Care. 2000;9:47–52.

350. Downey G, O'Connell A. Audit of unbooked paediatric post-anaesthesia admissions to intensive care. Anaesth Intensive Care. 1996 Aug;24(4):464–71.

351. El Shobary H, Backman S, Christou N, Schricker T. Use of critical care resources after laparoscopic gastric bypass: effect on respiratory complications. Surg Obes Relat Dis. 2008;4:698–702.

352. Habraken MMP, Van der Schaaf TW, Leistikow IP, Reijnders-Thijssen PMJ. Prospective risk analysis of health care processes: a systematic evaluation of the use of HFMEA in Dutch health care. Ergonomics. 2009 Jul;52(7):809–19.

353. Shebl NA, Franklin BD, Barber N. Failure mode and effects analysis outputs: are they valid? BMC Health Serv Res. 2012 Jan;12:150–9.

354. Dean Franklin B, Shebl NA, Barber N. Failure mode and effects analysis: too little for too much? BMJ Qual Saf. 2012 Jul;21(7):607–11.

355. Shaw CD. External quality mechanisms for health care: Summary of the ExPeRT project on visitatie, accreditation, EFQM and ISO assessment in European Union countries. Int J Qual Heal Care. 2000;12(3):169–75.

356. Groene O, Klazinga N, Walshe K, Cucic C, Shaw CD, Suñol R. Learning from MARQuIS: future direction of quality and safety in hospital care in the European Union. Qual Saf Health Care. 2009;18 Suppl 1(Suppl I):i69–74.

357. Kafy S, Huang JYJ, Al-Sunaidi M, Wiener D, Tulandi T. Audit of morbidity and mortality rates of 1792 hysterectomies. J Minim Invasive Gynecol. 2006;13(1):55–9.

358. Kurowski I, Sims C. Unplanned anesthesia-related admissions to pediatric intensive care - a 6-year audit. Paediatr Anaesth. 2007 Jun;17(6):575–80.

359. Yehia M, McDonald M, Walker R. The management and outcome of oocluded haemodialysis access: a retrospective audit. N Z Med J. 2002;115(1166):1–5.

360. McGloin H, Adam SK, Singer M. Unexpected deaths and referrals to intensive care of patients on general wards. Are some cases potentially avoidable? J R Coll Physicians Lond. 1999;33(3):255–9.

361. Wolff A. Limited adverse occurrence screening: using medical record review to reduce hospital adverse patient events. Med J Aust. 1996 Apr 15;164(8):458–61.

362. Institute for Safe Medication Practices. ISMP - Medication Safety Self Assessment. 2006.

363. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. Q J Med. 2001;94:521–6.

364. Vincent C. Patient safety. 2nd edn. Oxford: Wiley Blackwell; 2010.

365. Greene SM, Reid RJ, Larson EB. Implementing the learning health system: From concept to action. Ann Intern Med. 2012;157(August):207–10.

366. Zegers M, Wollersheim H. [Dutch national safety programme will not lead to a fifty per cent reduction in avoidable mortality in hospitals]. Ned Tijdschr Geneeskd. 2012 Jan;156(33):A4768.

367. Leistikow IP, Kalkman CJ, de Bruijn H. Why patient safety is such a tough nut to crack. BMJ. 2011;342:d3447–50.

368. Reason J. Human error : models and management. BMJ. 2000;320:768–70.

369. Thomas S, Keegan C, Barry S, Layte R. The Irish health system and the economic crisis. Lancet. Elsevier Ltd; 2012 Sep 22;380:1056–7.

370. Legido-Quigley H, Otero L, la Parra D, Alvarez-Dardet C, Martin-Moreno J, McKee M. Will austerity cuts dismantle the Spanish healthcare system ? BMJ. 2013;346:f2363–7.

371. Aiken LH, Sloane DM, Bruyneel L, Van den Heede K, Griffiths P, Busse R, et al. Nurse staffing and education and hospital mortality in nine European countries: a retrospective observational study. Lancet. 2014 Feb 25;6736(13):1–7.

372. Rafferty AM, Clarke SP, Coles J, Ball J, James P, Mckee M, et al. Outcomes of variation in hospital nurse staffing in English hospitals: cross-sectional analysis of survey data and discharge records. Int J Nurs Stud. 2007;44(2):175–82.

373. Van den Heede K, Sermeus W, Diya L, Clarke SP, Lesaffre E, Vleugels A, et al. Nurse staffing and patient outcomes in Belgian acute hospitals: cross-sectional analysis of administrative data. Int J Nurs Stud. 2009 Jul;46(7):928–39.

374. Diya L, Van den Heede K, Sermeus W, Lesaffre E. The relationship between in-hospital mortality, readmission into the intensive care nursing unit and/or operating theatre and nurse staffing levels. J Adv Nurs. 2012 May;68(5):1073–81.

375. Vlayen A, Hellings J, Claes N, Peleman H, Schrooten W. A nationwide Hospital Survey on Patient Safety Culture in Belgian hospitals: setting priorities at the launch of a 5-year patient safety plan. BMJ Qual Saf. 2012;21(9):760–7.

CURRICULUM VITAE

Kristel Marquet (°1979) behaalde in 2000 het diploma van gegradueerd (bachelor) verpleegkundige, met optie ziekenhuis en in 2003 het diploma van licentiaat (master) in de medisch-sociale wetenschappen aan de Katholieke Universiteit Leuven. Ze startte haar professionele loopbaan in 2003 als wetenschappelijke medewerker aan de Katholieke Universiteit Leuven op het Centrum voor Biomedische Ethiek en Recht (CBMER). Gelijktijdig behaalde ze tevens haar diploma van geaggregeerde in het secundair onderwijs aan de Katholieke Universiteit Leuven in 2004. Ze startte vervolgens als lector aan de Provinciale Hogeschool Limburg. Ze combineerde deze tewerkstelling met het behalen van de bijzondere beroepstitel in de intensieve zorgen en spoedgevallenzorg in 2007. Sinds 2006 combineerde ze lector zijn met het werken als verpleegkundige op de cardiac care unit (CCU) van het Ziekenhuis Oost Limburg (ZOL). In 2008 werd zij stafmedewerker in Ziekenhuis Maas & Kempen (ZMK), waar ze functioneerde als kwaliteit & patiëntveiligheidscoördinator en zorgcoördinator voor de afdelingen revalidatie, geriatrie, het geriatrisch dagziekenhuis, het liaison team geriatrie en de dienst patiëntenvervoer. Eind 2010 begon ze aan een nieuwe uitdaging en startte ze een doctoraat aan de Universiteit Hasselt, Faculteit Geneeskunde bij de onderzoeksgroep “Patient safety”. Begin 2015 startte ze als coördinator voor de dienst kwaliteit en patiëntveiligheid in het Jessa ziekenhuis.

PUBLICATION LIST

Scientific publications in peer-reviewed journals during the PhD

Marquet K*,* Claes N, De Troy E, Kox G, Droogmans M, Schrooten W, Weekers F, et al. One fourth of unplanned transfers to a higher level of care is associated with a highly preventable adverse event: a patient record review in six Belgian hospitals. Accepted for publication in Critical Care Medicine (IF 6.147; ranking critical care medicine 3/27)

Marquet K*,* Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Accepted for publication in Critical Care (IF 5.04)

Storms H, **Marquet K***,* Nelissen K, Hulshagen L, Lenie J, Remmen R, Claes N. Implementing an electronic medication overview in Belgium. BMC Research Notes, 2014, Dec 16;7(1):915-20. (IF 2.11)

Marquet K*,* Claes N, Postelmans T, Lemkens P, Rosseel M, Torfs A, Vleugels A. Critical analysis of the ENT one day surgery using the HFMEA method. B-ENT, 2013, 9: 193-200. (IF 0.504)

Vlayen A, **Marquet K**, Schrooten W, Vleugels A, Weekers F, Helling J, Claes N. Design of a retrospective record study on the occurrence of adverse events among patients admitted to ICU units in Flemish hospitals. BMC Research Notes, 2012, 5 (1): 468-76. (IF 2.11)

In preparation

Marquet K, Claes N, De Troy E, Kox G, Droogmans M, Vleugels A. Multicenter medical record review of Adverse Drugs Events requiring a higher level of care.

Marquet K, Claes N, Weekers F, Vleugels A. The quality of patient records and its relationship to the quality of care.

Scientific publications in peer-reviewed journals before the PhD

Moons P, Van Deyk K, **Marquet** K, De Bleser L, De Geest S, Budts W. Profile of adults with congenital heart disease having a good, moderate, or poor quality of life: a cluster analytic study. Eur J Cardiovasc Nurs. 2009 Jun; 8(2):151-7. Epub 2008 Dec 18.

Moons P, Van Deyk K, **Marquet K**, De Bleser L, Budts W, De Geest S. Sexual functioning and congenital heart disease: Something to worry about? International Journal of Cardiology 2007, 121 (1): 30-5. E-pub ahead of print, Dec 18. (IF 7.08)

Moons P, Van Deyk K, De Bleser L, **Marquet K,** Raes E, Budts W, De Geest S. Quality of Life and Health Status in Adults with Congenital Heart Disease: A direct comparison with healthy counterparts. European Journal of Cardiovascular Prevention and Rehabilitation 2006; 13: 407-413. (IF 2.63)

Moons P, Van Deyk K, **Marquet K,** Raes E, De Bleser L, Budts W, De Geest S. Individual quality of life of adults with congenital heart disease: a paradigm shift. European Heart Journal 2005; 26: 298-307. (IF 10.48)

Moons P, **Marquet K**, Budts W, De Geest S. Validity, Reliability and Responsiveness of "the Schedule for the Evaluation on Individual Quality of Life Direct Weighting"

(SEIQoL-DW) in congenital heart disease. Health and Quality of Life Outcomes, 2004, 2: 27-34. (IF 2.11)

Scientific publications in not peer-reviewed journals before the PhD

Moons P, Van Deyk K, **Marquet K**, De Bleser L, Raes E, Budts W. De Geest S, Kwaliteit van leven bij volwassenen met een aangeboren hartaandoening: Beter dan verwacht?! [Quality of life in adults with congenital heart disease: Better than expected?!] Psychologie en Gezondheid 2012; 34 (4): 144-152. (IF 0.17)

Moons P, Van Deyk K, De Bleser L, **Marquet K**, Raes E, De Geest S, Budts W. Kwaliteit van leven bij volwassenen met een aangeboren hartaandoening: Beter dan verwacht?! [Quality of life in adults with congenital heart disease: Better than expected?!] Gedrag en Gezondheid 2006; 3: 209-222.

Moons P, Van Deyk K, De Bleser L, **Marquet K**, Raes E, Budts W, De Geest S. Qualité de la vie chez les adultes atteints d'une affection du coeur congénitale: meilleure qu'attendue?! [Quality of life in adults with congenital heart disease: Better than expected?!] Education du patient et enjeux de santé 2006; 24: 131-137.

Moons P, Van Deyk K, **Marquet K**, De Bleser L, Raes E, Budts W, De Geest S. Kwaliteit van leven bij congenitale hartaandoeningen. [Quality of life in congenital heart disease]. Nieuwsbrief WVVV 2005; 16: 8-9.

Moons P, Cnuts R, Decat W, Goeminne D, Halans N, Verbeke J, Verdoodt R, **Marquet K**, Pasquasy N, Gosset C. Performantiemaatstaven voor ontslagmanagement: een aanzet tot kwaliteitsmeting. [Performance measures for discharge management: Initiating quality assessment]. Acta Hospitalia, 2005, Vol 45, 51-64.

Published abstracts during the PhD

Liesenborgs A, **Marquet K**, Weekers F, Vandijck D, Claes N. PiCCO guided fluid management in early phase in patients with severe sepsis and septic shock at the ED. Fluids 2013;2(2):174.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Multidisciplinaire dossierstudie naar de incidentie en vermijdbaarheid van adverse events die leiden tot een ongeplande transfer naar een hoger niveau van zorg: een pilootstudie. Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen. Jaarboek van de Intensieve zorgen verpleegkundige. Acco: Leuven. 2011: 153.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vleugels A. Dossieronderzoek naar de klinische indicator "ongeplande opnames op intensieve zorgen komende vanuit een hospitalisatieafdeling. Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen. Jaarboek van de Intensieve zorgen verpleegkundige. Acco: Leuven. 2011:154.

Marquet K, Claes N, De Troy E, Weekers F, Vleugels A. Frequentie van opvolging van de parameters voorafgaande aan een ongeplande transfer naar intensieve zorgen. Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen. Jaarboek van de Intensieve zorgen verpleegkundige. Acco: Leuven. 2011:155.

Published abstracts before the PhD

Marquet K, Moons P, Van Deyk K, De Bleser L, Budts W. Does quality of life in adults with a congenital heart disease evolve over time? European Journal of Cardiovascular Nursing 2004; 3: 105-106.

Claessens P, **Marquet K**, Menten J, Schotsmans P, Broeckaert B. Validation of the Dutch Translation of the Edmonton Symptom Assessment Scale. Palliative Medicine 2004; 18: 318.

Claessens P, **Marquet K**, Menten J, Schotsmans P, Broeckaert B. The difficulty of gathering accurate data regarding palliative sedation: a methodological challenge. Palliative Medicine 2004; 18: 340.

Moons P, Van Deyk K, **Marquet K**, Raes E, De Bleser L, De Geest S, Budts W. Individual quality of life in adults with congenital heart disease is equivalent to that of healthy counterparts. European Journal of Cardiovascular Nursing 2004; 3: 86-87.

Moons P, Van Deyk K, **Marquet K**, Raes E, De Bleser L, De Geest S, Budts W. Quality of life in adults with congenital heart disease is better than that of healthy counterparts. European Heart Journal 2004; 25 (abstract suppl.): 617.

Moons P, Van Deyk K, **Marquet K**, Raes E, De Bleser L, De Geest S, Budts W. Adults with congenital heart disease have a better quality of life than healthy counterparts. Circulation 2004; 110 (suppl. III): 392.

Van Deyk K, Moons P, **Marquet K**, Raes E, De Bleser L, De Geest S, Budts W. Is quality of life and perceived health of adults with congenital heart disease determined by age or gender? Acta Cardiologica, 2004; 59: 109-110.

Van Deyk K, Moons P, **Marquet K**, Raes E, De Bleser L, De Geest S, Budts W. Age and gender differences in quality of life and perceived health of adults with congenital heart disease. European Journal of Cardiovascular Nursing, 2004; 3: 113.

Moons P, Van Deyk K, **Marquet K**, De Bleser L, Budts W, De Geest S. Sexual

functioning in adults with congenital heart disease. European Journal of Cardiovascular Nursing 2005; 4: 55.

Moons P, Van Deyk K, **Marquet K**, De Bleser L, Budts W, De Geest S. Symptom experience in adults with congenital heart disease. European Heart Journal 2006, 27 (abstract suppl.): 791.

International conferences

Oral presentation on international conferences

Marquet K. Claes N, De Troy E, Kox G, Droogmans M, Vleugels A. A multicenter record review study concerning in-hopsital adverse drug events requiring a higher level of care. European Society Clinical Pharmacology Annual Symposia: Patient Safety: Research, Bridging the gaps. Copenhagen, Denmark, 22nd-24th October 2014.

Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and Outcome Of Inappropriate In Hospital Empiric Antibiotic Therapy For Severe Infection: A Systematic Review and a meta-analysis. ISQua's 31th International Conference, Rio de Janeiro, Brazil, 5th-8th October 2014.

Marquet K, Claes N, Postelmans T, Lemkens P, Torfs A, Rosseel M, Vleugels A. Critical analysis of current system and processes in ENT one day surgery. ISQua's 29Th International Conference, Geneve, Swiss, 21st-24th October 2012.

Poster presentation on international conferences

Theuwissen J, De Troy E, Claes N, Droogmans M, Vleugels A, **Marquet K**. Implementation of an inpatient anticoagulation management system. European Society Clinical Pharmacology Annual Symposia: Patient Safety: Research, Bridging the gaps. Copenhagen, Denmark, 22nd-24th October 2014.

Storms H, **Marquet K**, Claes N. Implementing an electronic medication overview in Belgium. ISQua's 31th International Conference, Rio de Janeiro, Brazil, 5th-8th October 2014.

Liesenborgs A, **Marquet K**, Weekers F, Vandijck D, Claes N. PiCCO guided fluid management in early phase in patients with severe sepsis and septic shock at the ED. International Fluid Academy Day (IFad), Antwerp, 29th November 2013.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Medical record review on adverse events requiring a higher level of care. International Student Congress of (Bio) Medical Sciences (ISCOMS), Groningen, 5th-8th June 2012.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Medical record review on adverse events requiring a higher level of care. International Forum on Quality and Safety in Healthcare, BMJ, Paris, 17th-20th April 2012.

Marquet K, Claes N, Postelmans T, Lemkens P, Torfs A, Rosseel M, Vleugels A. Critical analysis of current system and processes in ENT one day surgery. International Forum on Quality and Safety in Healthcare, BMJ, Paris, 17th-20th April 2012.

National conferences

Oral presentation on national conferences

Marquet K. Ongeplande verhoging van zorg. Gastspreker op symposium Kwaliteit en patiëntveiligheid: Voorkomen is veel beter dan genezen. Georganiseerd door Sint-Franciscus Ziekenhuis- Heusden-Zolder, 25 november 2014.

Marquet K. Multidisciplinair dossieronderzoek naar adverse events met een ongeplande transfer naar een hoger niveau van zorg. Uhasselt research conference, georganiseerd door Uhasselt en Federale Overheid Dienst Volksgezondheid, Veiligheid van de voedselketen en Leefmilieu, Brussel, 17 oktober 2014.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Multidisciplinaire dossierstudie naar de incidentie en vermijdbaarheid van adverse events die leiden tot een ongeplande transfer naar een hoger niveau van zorg: een pilootstudie. [Multidisciplinary medical record review on incidence and preventability of adverse events requiring a higher level of care: a pilot study in a Belgian hospital]. 29ste jaarcongres, georganiseerd door Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen, Gent, 25 november 2011.

Poster presentation on national conferences

Marquet K, Claes N, Postelmans T, Lemkens P, Torfs A, Rosseel M, Vleugels A. Prospectieve risicoanalyse met behulp van de SAFER binnen het dagchirurgisch proces van NKO patiënt. [A prospective risk analyses of current system and processes in ENT one day surgery]. 5de week voor kwaliteit en patiëntveiligheid, georganiseerd door Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu, Brussel, 28 november 2011.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Multidisciplinaire dossierstudie naar de incidentie en vermijdbaarheid van adverse events die leiden tot een ongeplande transfer naar een hoger niveau van zorg: een pilootstudie. [Multidisciplinary medical record review on incidence and preventability of adverse events requiring a higher level of care: a pilot study in a Belgian hospital]. 5de week voor kwaliteit en patiëntveiligheid, georganiseerd door Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu, Brussel, 28 november 2011.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Multidisciplinaire dossierstudie naar de incidentie en vermijdbaarheid van adverse events die leiden tot een ongeplande transfer naar een hoger niveau van zorg: een pilootstudie. [Multidisciplinary medical record review on incidence and preventability of adverse events requiring a higher level of care: a pilot study in a Belgian hospital]. 29ste jaarcongres, georganiseerd door Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen, Gent, 25 november 2011.

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vleugels A. Dossieronderzoek naar de klinische indicator "ongeplande opnames op intensieve zorgen komende vanuit een hospitalisatieafdeling. [Record review on the clinical indicator unplanned intensive care unit admissions]. 29ste jaarcongres, georganiseerd door Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen, Gent, 25 november 2011.

Marquet K, Claes N, De Troy E, Weekers F, Vleugels A. Frequentie van opvolging van de parameters voorafgaande aan een ongeplande transfer naar intensieve zorgen. [Frequency of follow-up of parameters before an unplanned intensive care unit admission]. 29ste jaarcongres, georganiseerd door Vlaamse Vereniging Intensieve Zorgen Verpleegkundigen, Gent, 25 november 2011.

Marquet K. Implementatie en een eerste evaluatie van een patiëntveiligheidssysteem, namelijk identificatiearmbandjes, in ziekenhuis Maas

& Kempen. [Implementation and the first evaluation of a patient safety system, namely identification bracelets, in ziekenhuis Maas & Kempen]. 4de week voor kwaliteit en patiëntveiligheid, georganiseerd door Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu, Brussel, 24-25 november 2010.

Marquet K, Moons P, Van Deyk K, De Bleser L, Budts W. Does quality of life in adults with a congenital heart disease evolve over time? European Journal of Cardiovascular Nursing 2004; 3: 105-106. 4th Annual Spring Meeting Cardiovascular Nursing: From Science to Practice from the Working Group on Cardiovascular Nursing & European Society of Cardiology, Amsterdam, the Netherlands, 2-3 April 2004.

Overige posterpresentaties

Marquet K, Claes N, De Troy E, Kox G, Weekers F, Vlayen A, Vleugels A. Multidisciplinaire dossierstudie naar de incidentie en vermijdbaarheid van adverse events die leiden tot een ongeplande transfer naar een hoger niveau van zorg: een pilootstudie. Posterpresentatie kwaliteitshappening Jessa ziekenhuis, Hasselt, 8 november 2011.

Prijs: Eervolle vermelding vanwege directie Jessa

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