Preventable Patient Harm across Health Care Services:

A Systematic Review and Meta-analysis

(Understanding Harmful Care)

A report for the General Medical Council

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Glossary of technical terms

Heterogeneity: The variability in the reported effect sizes between studies which are greater than could be expected by chance alone. The indices for heterogeneity (I^2) quantify the degree of heterogeneity in percentages. When there is significant heterogeneity, subgroup analyses and sensitivity analyses are undertaken to explore the sources of heterogeneity (as done in this report). Very high levels of heterogeneity might caution against pooling the data.

Meta-analysis: The process of using statistical methods to combine the results of different studies. The aim is to integrate the findings, pool the data, and identify the overall trend of results.

Subgroup analysis: In the context of meta-analysis, refers to looking for patterns across subsets of the studies. For example, the main meta-analyses in this report examined the prevalence rates of all preventable harm across any healthcare setting whereas the subgroup analyses examined the distinct prevalence rates of preventable harm across each healthcare speciality.

Sensitivity analysis: A method to determine the robustness of an effect size by examining the extent to which this effect size is affected by changes in methods, models or assumptions. For example, in this report we have undertaken two sensitivity analyses to examine whether the results were affected by differences in research design and publication date of the studies.

Observational study designs in this review: i) *Prospective studies* are longitudinal cohort studies that follow over time a group of similar individuals with respect to a certain outcome (e.g. harm) . ii) *Retrospective studies* look backwards and examine exposures to suspected risk factors in relation to an outcome that is established at the start of the study; iii) *Cross-sectional studies* analyse data collected from a population at a single specific point in time (without following participants forward or backwards). Prospective studies usually have fewer potential sources of bias and confounding than cross-sectional and retrospective studies.

Summary

Background: Reducing the risk of patient harm during the process of healthcare delivery is at the forefront of policy and practice. A considerable number of empirical studies and systematic reviews have examined the prevalence, causes and consequences of patient safety incidents and harms. However, a key limitation in the current patient safety literature is that existing reviews examine patient harm in general but there is less emphasis on understanding the burden of preventable patient harm, which in the interest of improvement is of particular importance.

Aims: The primary aim was to identify the most common types of preventable patient harm and to examine the prevalence and severity of the identified harm. We also aimed to examine differences in the prevalence, types and severity of preventable harm across different healthcare settings and across studies published more recently, using more robust research designs and based in the UK.

Methods: The review was conducted and reported according to PRISMA guidelines. Five bibliographic databases (Medline, Embase, Cinahl, PsychInfo and Cochrane Library), were searched (from January 2000 to January 2017) and existing systematic reviews were screened to identify the relevant studies. Two reviewers were involved in the screening and data extraction of the identified studies. Meta-analysis was performed using random effects models to account for the between study heterogeneity.

Results: 149 studies were selected from 4,200 citations initially identified. The weighted pooled prevalence of preventable patient harm in patients was 6% (95% CI= 5 to 7, I^2=91%,

p<0.001). As a proportion, 13% of the identified preventable harm was reported as severe or lethal. The highest proportion of preventable patient harm was associated with medication incidents. The most extensive evidence was obtained from hospital settings. The evidence was less developed in medical specialties and in primary care. Differences in the research design (prospective studies), country setting (UK based studies) and publication date (2010 onwards) did not affect the findings of the main analyses.

Conclusion: Preventable patient harm affects nearly one out of 20 patients in health care services. There is an important need for standardising the research methods of evaluating and reporting preventable patient harm. Strategies for preventing and reducing medication and diagnostic incidents have the potential to improve patient safety standards in health care systems.

Chapter 1: Background and aims

Patient safety is defined as the ‘avoidance, prevention, and amelioration of adverse outcomes or injuries stemming from the processes of healthcare’ [1], while a patient incident is defined as ‘any unintended event or hazardous condition resulting from the process of care, rather than due to the patient's underlying disease, that led or could have led to unintended health consequences for the patient or health care processes linked to safety outcomes’ [2].

Preventing patient safety incidents occurring during the delivery of healthcare is paramount to prevent patient harm. Although much is likely to be preventable, some patient harm may be inevitable. There are several definitions of what constitutes preventable patient harm in the literature and consensus about the exact criteria of preventability has not been reached yet. The majority of studies typically classify patient harm as preventable if it occurs as a result of an identifiable modifiable cause, and its future recurrence can be avoided by reasonable adaptation to a process or adherence to guidelines [3]. Key sources of preventable patient harm may include the actions of healthcare professionals (errors of omission or commission), healthcare system failures or involve a combination of errors made by individuals, system failures and patient characteristics [4-9]. Therefore, although a goal of zero harm would be ideal, this may not be feasible because some types of harm cannot be prevented. For example, some adverse drug reactions which occur in the absence of any error in the medication process and without the possibility to be detected early in the process are less likely to be preventable.

An alternative, potentially more effective approach is to direct efforts in reducing the risk of preventable harm. Moreover, developing a better understanding of the prevalence and nature of preventable harm could help policy makers to devise more efficient and reliable plans to deal with preventable patient harm [3].

Several existing systematic reviews have examined patient safety and iatrogenic harm across different medical settings including hospitals and primary care. These systematic reviews either broadly examined patient safety (without focusing on preventable harm) or they explored a certain type of harm (e.g. adverse drug events) [8, 10-14]. Therefore, a key limitation of the current evidence is that it is not clear what are the prevalence, the core types of preventable iatrogenic harm and how often severe harm such as death and severe injuries are likely to occur.

The aim of this study was to produce an integrative systematic review with a focus on preventable iatrogenic harm (rather than any type of harm) across different medical settings including hospitals, primary care and various specialties. Specifically we aim to address the following research questions:

1) What are the prevalence rates and the most commonly occurring types of preventable harms?
2) What is the severity of preventable harms and what are the commonly occurring preventable harms that result in death or serious injury?
3) Do the findings for questions 1 and 2 differ across specialities or country (UK vs outside UK)?

Chapter 2: Research Methods

Our methodological approach fully adheres to the recommended standards for conducing and reporting systematic reviews including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15] and the Cochrane handbook recommendations [12].

2.1 Eligibility Criteria

We included:

Types of studies: Empirical quantitative studies and systematic reviews/meta-analyses which primarily report data on the frequency of preventable iatrogenic harm and secondarily on types and severity of harm in healthcare delivery.

Outcomes: Our main outcome was preventable harm resulting through patient interactions.

We were interested in studies that included data about one or more of the following:

- Prevalence of preventable patient harm
- Type of preventable patient harm
- Severity of preventable patient harm
- Geographical area: Any
- Date of publication: January 2000 onwards. This start date was selected because it coincides with when the published patient safety research began to increase in volume significantly [16, 17] following the publication of the landmark reports To Err is Human: Building a Safer Health System in 1999 in the US and An Organisation With a Memory in 2000 in the UK, including a number of reports addressing preventable iatrogenic harm [18].

We excluded:

- Case series and case reports
- Qualitative studies. As the main focus was on prevalence and severity of different types of preventable iatrogenic harm, it would be difficult to extract information on prevalence from qualitative evidence
- Studies that evaluated patient safety incidents without linking them to harm and studies reporting data on total harm but not preventable harm.
- Studies that evaluated harm on very specific populations (for example, patients with a particular disease).

2.2 Searches

The searches were devised by members of the research team with extensive relevant experience (MP) in collaboration with a librarian. Five electronic bibliographic databases were searched: Medline, Cochrane library, CINAHL, Embase and PsycINFO. These searches were supplemented by checking conference abstracts and screening grey literature sources including databases (WHOLIS, Google Scholar, SIGLE) and reports such as 'The Grey Literature Report' (http://www.greylit.org/) and the Agency for Healthcare Research and Quality (AHRQ) Patient Safety Network (http://www.psnet.arhq.gov). We also identified eligible studies by screening any existing systematic reviews in the area and through checking the reference lists of eligible studies identified by the searches.

Searches were deliberately designed to capture studies on preventable iatrogenic harm. An exemplar search strategy devised for this review (Medline) is listed in Appendix 1. Our search strategy included search combinations of two key blocks of terms limited by publication date (January 2000 to January 2017):

- Mesh terms and key words on preventable iatrogenic harm
- Mesh terms and key words on empirical quantitative study designs and systematic reviews

2.3 Study selection and data extraction

The results of the searches of each database were exported to a database and merged to identify and delete duplicates. Screening was completed in two stages. Initially, the titles and abstracts of the identified studies were screened for eligibility. The full-texts of studies initially assessed as "relevant" for the review were retrieved and checked against our inclusion/exclusion criteria. Title/abstract and full-text screening was completed by 2 researchers independently (Kanza Khan and Maria Panagioti/Aseel Abuzour/Richard Keers), with disagreements resolved by discussion involving the wider project team if required. The kappa statistic was calculated to quantify the inter-rater reliability between the reviewers. The kappa statistic suggested excellent inter-rater reliability (0.88 and 0.90 for the title/abstract and full-text screening, respectively).

An Excel data extraction sheet was devised, after being piloted, to extract the following information by the included studies:

- Study characteristics – year, objective, research design, setting, number of participants and methods of data collection (prospective or retrospective)
- Outcomes – primary endpoints were the prevalence of preventable iatrogenic harm, the type of harm (such as harm related medication error/adverse drug events, harm due to diagnostic errors, surgical/non-surgical procedures) and severity of resulted harm (mild, moderate, severe harm). The extraction of outcome characteristics was informed by reviewing existing taxonomies of patient harm.

Data extraction was completed by 1 researcher and a second researcher checking the extraction of the other (Kanza Khan, Maria Panagioti). Disagreements were resolved by discussion until consensus was reached and through the involvement of a third researcher if needed.

2.4 Taxonomy of preventable patient harm

An important goal of this report was the classification of the findings into a *taxonomy of preventable patient harm*. We searched the literature in the field of patient safety for existing taxonomies of patient safety incidents. Some of the most rigorously developed and well-recognised taxonomies of patient safety are the *World Health Organisation (WHO) Conceptual Framework for the international Classification of Patient Safety* and the *Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Patient Safety Event Taxonomy*. [4-9]. Following group discussions we decided to use the WHO taxonomy as a framework for organising and presenting the findings of the analyses. The identified types and severity of harm were inserted in the available figures of the WHO taxonomy. The main reason for this decision is that the WHO taxonomy provides explicit and widely acceptable definitions of key concepts such as *patient safety incident* and *harm/adverse events*. Consistent with our aims, the WHO taxonomy classifies safety incidents taking into account the *occurrence of harm* (no harm; near miss, adverse events), *the type of harm* (e.g. pathophysiology; injury; other), and *the severity levels of harm*. This comprehensive assessment is fully consistent with the main research questions of this review which focus on rates, types and severity of patient harm. Moreover, the use of the WHO taxonomy adds scientific rigour into our work because our data analysis process is based on an

internationally validated and recognised taxonomy instead of an unvalidated tool developed for this study.

2.5 Definitions of key concepts

Below, we outline the definitions of some key concepts to facilitate the understanding and interpretation of this systematic review. These definitions are mainly adapted from the WHO taxonomy which is used a framework in this review.

- A patient safety incident is "an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient".
- A harmful incident (adverse event) is 'an incident that results in harm to a patient' such as the wrong unit of blood was infused and the patient died from a haemolytic reaction). Harm implies impairment of structure or function of the body and/or any deleterious effect arising there from, including disease, injury, suffering, disability and death, and may be physical, social or psychological. All studies that used this or a similar definition for to evaluate the prevalence of harm were eligible for inclusion.
- A recent systematic review examined existing definitions of preventable harm with an aim to produce a standard and clear definition of preventable harm. Most of the studies included in this review suggested that harm is preventable (i) when occurring as a result of an identifiable and modifiable cause and (ii) when the prevention of future recurrence of harm is possible with reasonable adaptation to a process and adherence to guidelines [3]. In this review we will adopt these definitions of preventable harm.

- Classification of harm severity:
    - *Mild*: patient outcome is symptomatic, symptoms are mild, loss of function or harm is minimal or intermediate but short term, and no or minimal intervention (e.g., extra observation, investigation, review or minor treatment) is required. Mild harm is typically resolved within one month.
    - *Moderate*: patient outcome is symptomatic, requiring intervention (e.g., additional operative procedure; additional therapeutic treatment), an increased length of stay, or temporary disability or loss of function. Moderate harm is typically resolved within one year.
    - *Severe*: patient outcome is symptomatic, requiring life-saving intervention or major surgical/medical intervention, shortening life expectancy or causing major permanent or long term harm or loss of function. Severe harm results in permanent disability.
    - *Death*: on balance of probabilities, death was caused or brought forward in the short term by the incident.

2.6 Data synthesis

The results were structured according to two categories of studies:

- Studies investigating overall preventable harm (namely, preventable adverse events which resulted in harm) influenced by multiple contributory factors spanning two or more patient safety incidents such as medication, diagnostic, surgical incidents etc (Chapter 4). These studies reported prevalence rates of the overall preventable harm, proportions of the severity of overall preventable harm and proportions of harm caused by different types of incidents.

- Studies examining only medication-related preventable harm (mainly preventable adverse drug events or preventable adverse drug reactions which resulted in harm) (Chapter 5) which reported the prevalence rates of medication-related harm and proportions of the severity of medication-related incidents.

A series of meta-analyses were performed to estimate the weighted pooled prevalence rates, and the proportions of types and severity of preventable harm (generic harm; medication-related harm). The prevalence rates of preventable harm were calculated at the level of patients. When data on preventable harm was not available at patient level (studies reporting preventable harm as a proportion of the overall harm), authors were contacted to acquire this information. The severity proportion of preventable harm was classified in three categories as 'mild', 'moderate' and 'severe/death' and was analysed as proportion of the identified harm. Similarly, the common types/sources of preventable harm identified across the studies were also analysed as proportions of the identified harm. Weighted rates and associated confidence intervals (CI) for the prevalence rates, and weighted proportions of common types and the severity of preventable harm were calculated in Comprehensive Meta-Analysis (CMA) [19]. The pooled rates/proportions and the forest plots were computed using the metan command in Stata 14 [20].

One set of pre-specified subgroup analyses were carried out to examine whether the prevalence rates and the severity proportions of preventable harm differs across healthcare settings and specialties. Three sets of pre-specified sensitivity analyses were also performed. The first sensitivity analysis tested whether the rates and severity proportions of the reported preventable harm differed across studies with

more robust research designs (prospective study designs). The second sensitivity analyses investigated any differences in the effects of studies published from 2011 onwards. The third sensitivity analysis examined whether the findings of the main and subgroup analyses are similar in the UK context. The findings of the main, the subgroup and the sensitivity analyses were used to develop the taxonomy of preventable harm based on the WHO framework.

Heterogeneity was assessed using the I^2 statistic. Conventionally, I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity [21]. All analyses were conducted using a random effects model because we expected significant heterogeneity across the studies. Random-effects models are more conservative and have better properties in the presence of heterogeneity [22, 23].

Chapter 3: Flowchart of Study Selection

The initial search yielded 4,200 articles. After reviewing the titles and abstracts, 3920 articles were excluded. Of the remaining 280 studies, another 130 were excluded after reviewing the full article. Excluded articles were studies in specific populations/outcomes (for example people with chronic obstructive pulmonary disease or harm associated with the use of particular drug) (n=42), studies reporting only overall rates of harm without making reference/ providing sufficient detail to calculate preventability at patient level (n=27), studies which recorded patient safety incidents without linking them to patient harm (n=16), non-empirical studies such as narrative reviews and commentaries (n=16) and studies presenting data of patient populations already included in other publications (n=11). Twenty two articles were systematic reviews and meta-analyses which were not included in the review per se but were screened for relevant articles (n=6 studies were identified by screening the reviews). Overall, following full-text screening, 149 studies met the inclusion criteria of this study [24-167]. Seventy-one of these studies focused on generic preventable harm and 78 studies examined specifically preventable medication-related harm. The flowchart of the study selection process is presented in Figure 1.

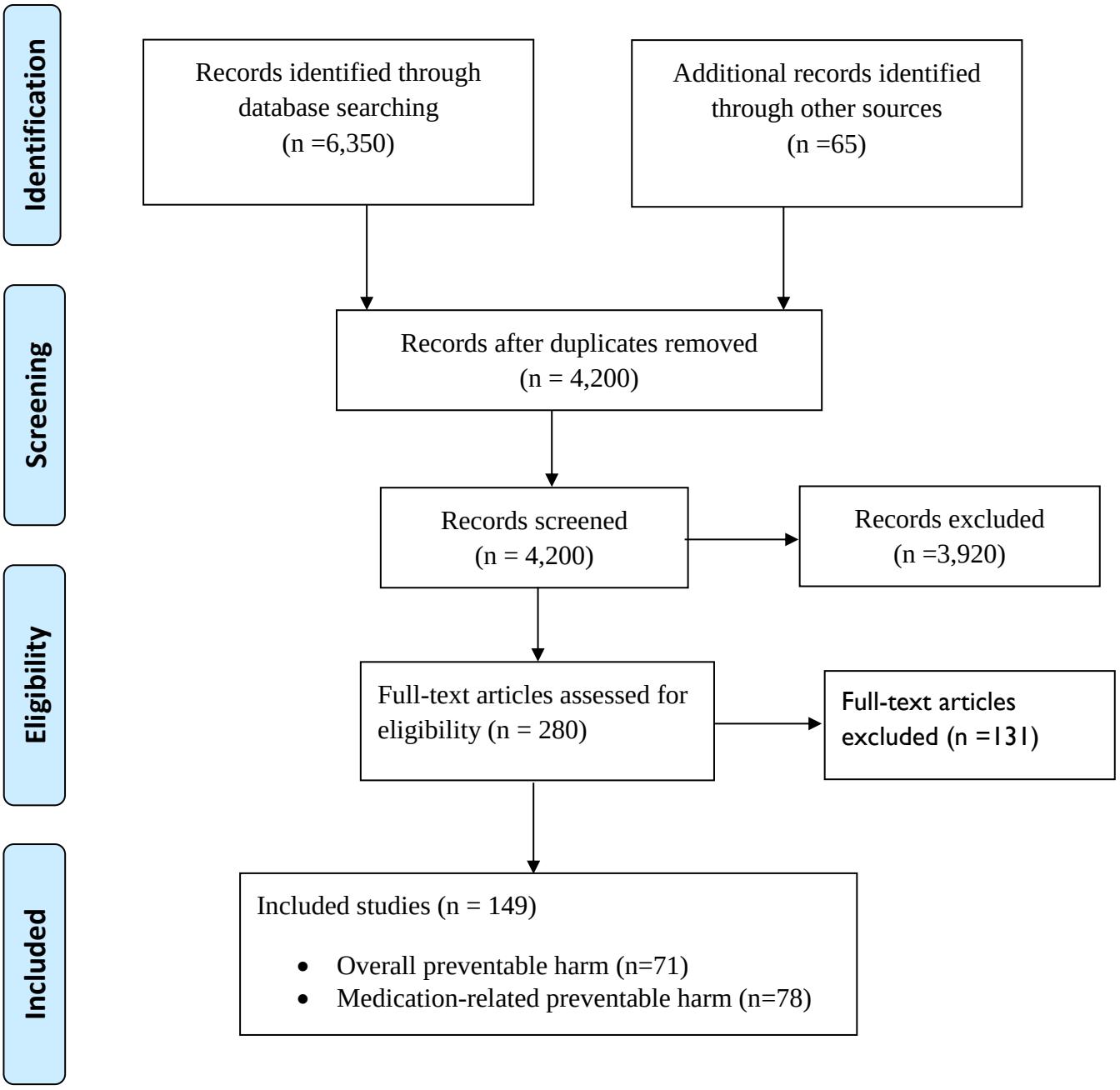

Figure 1 PRISMA Flowchart of the included studies

Chapter 4: Overall Preventable Harm

4.1 Characteristics of studies and populations

Preventable harm was operationalised as preventable adverse (harmful) events across the majority of the studies. The definition of adverse events across the studies was generally consistent with the WHO framework and synonymous with the definition of 'harm' in the majority of the studies. Thirty-one studies were conducted in North America (US and Canada), 19 studies were conducted in Europe and 21 elsewhere. The majority of the studies were retrospective studies which reviewed the medical records of patients (n=44 out of 71 studies). Across all 71 studies a total of 197,193 patients were included although the sample sizes ranged widely from n=93 to 17,179 patients (see details about the characteristics of included studies in Table 13 in appendices).

A significant number of studies (62 out of 71) focused on the prevalence of preventable overall harm, and subsequently described in more detail the nature/types of this generic harm. Seven major types of harm which contributed to the overall preventable harm were described across the included studies:

Medication-related harm (n=25 studies). This mainly involved adverse drug events and adverse drug reactions which occurred in prescribing/ordering of medication stage, administration stage, dispensing and monitoring stage. Specific examples of medication-related harm occurring were the prescription or administration of wrong medication, wrong dosage/route/frequency, wrong patient, failure or delay of drug treatment (e.g. failure to give prophylactic care) or failure to discontinue medication. Examples of side effects and adverse reactions included the following: nausea, vomiting, diarrhoea, pruritus, rash or

dermatological injuries reactive to drugs, drug-related neurological alterations, headache, pain or discomfort, anaemia acquiring transfusion secondary to inappropriate warfarin dosage, and anaphylaxis.

Diagnostic harm (n=20 studies). Harm resulted due to missed, wrong, delayed or inappropriate diagnostic processes resulting from failure to capture documented signs, symptoms, and laboratory tests, not ordering an indicated diagnostic test or not undertaking adequate patient assessment. Only one study provided details of the prevalence rates of different types of diagnostic harm, with the most frequent being failure or delay in the diagnosis (e.g. missed or delayed diagnosis of cancer, coronary syndromes or sepsis), followed by incomplete or wrong diagnosis [149]. Diagnostic harm was often reported to be preventable (in over 80% of the cases and were attributable to human errors) [167].

Clinical management harm (n=20 studies). Harm caused by suboptimal healthcare management such as inappropriate treatment and delegation, delay or failure in tracking and monitoring, wrong referral, or wrong use of healthcare resources. For example, clinical management harm included failure to act upon results of tests or clinical findings, set up monitoring systems and increase/adapt the intensity of care when required. Other examples of clinical management harm were when a patient was placed at an unnecessary risk of experiencing death or major disability by being sent home or when suboptimal follow-up arrangements were made that led to the development of new symptoms, unnecessary prolongation of symptoms, and unscheduled return visit to the ED or unscheduled hospitalisation.

Harm related to invasive medical procedures (n=20 studies). Harm due to errors, complications or injuries before, during or after invasive clinical procedures such as complications in central catheters, endoscopes, bronchoscopies, pacemakers, central line placement, intervention radiology, haematoma following venepuncture, bleeding or low saturation after tracheostomy. Please note that although surgical procedures and in hospital infections could be considered subcategories of invasive medical procedures, the vast majority of studies reported distinct and mutually exclusive proportions of harm related to hospital infections, to surgical procedures and other invasive medical procedures. We decided therefore to follow this format because is more informative for the reader.

Harm caused by in-hospital acquired infections (n=14 studies). These included infections related to healthcare and those occurring after medical procedures such as an infection in the surgical wound, nosocomial urinary tract infection, fungal sepsis, or central line associated blood stream infection. Staff training on hand washing and hygiene in patient rooms was proposed as one way in-hospital infections could be reduced [153].

Harm related to surgical procedures (n=18 studies). Harm related to errors or avoidable complications occurring during the operation or shortly after the operation (e.g. 30 days) such as infection, accidental tissue damage, bleeding, dysrhythmia, laceration of organ/blood vessel, urine retention, atelectasis, pericardial/pleural effusion, myocardial infraction.

System-related harm (n=6 studies): Harm from technical errors; equipment; electronic system and health records system failures. Examples include defective or non-available equipment or supplies, inadequate reporting or communication, inadequate training or supervision of doctors/other personnel, delay in provision or scheduling of services,

inadequate staffing, inadequate function of hospital services, no protocol/failure to implement protocol or plan (e.g. a patient with recent history of self-harm was admitted to hospital for pneumonia. A 24-hour watch was ordered but not implemented. On day 2 the patient walked out of the hospital and attempted suicide).

We have to note that each study provided data for at least two of these types of harm but did not provide data for all 7 categories and there were variations at the level of detail provided for each of these categories across the studies. Moreover, there were some incidents which were unique in each study and could not be meaningfully combined together.

4.2 Prevalence rate of overall preventable harm

Table 1 presents the results of the meta-analysis on the prevalence rates of preventable harm and total harm which included both preventable and non-preventable harm events. The prevalence rates have been calculated at the patient level and they refer to the percentage of patients who experienced preventable harm. The reported prevalence rates of harm were obtained after combining the prevalence rates reported by each individual study (all 71 studies) using a standardised combining and weighting system (which is done in meta-analysis). This system leads to a more accurate estimate of the pooled prevalence (as opposed to just averaging the prevalence rates of all 71 studies) because it takes into account differences across individual studies (e.g. different sample sizes) and adjusts the analyses accordingly.

Following this procedure, we found that the weighted pooled rate of preventable harm in patients across the healthcare was 6% (95% Confidence Interval= 5 to 7; see Figure 7). In comparison, the weighted pooled total harm (which includes preventable and non-preventable

harm events) across the included studies was 13% (95% CI= 10 to 15). In lay terms these results mean that 6% of patients experience preventable harm and 13% of patients experience total harm (any harm including preventable and non-preventable) in healthcare. However, the high heterogeneity (I^2=98%, p<0.001) suggests that there were large differences across the studies in the reported rates of preventable harm. Thus, some caution is recommended because the estimated pooled prevalence rate of preventable harm could have been affected by these large variations.

Table 1 Prevalence rates of preventable and total harm at patient level.

Outcome	**N**	**Preventable harm % (95% CI)**	**N**	**Total harm % (95% CI)**
Pooled prevalence rate (at patient level)	71	6 (5 to 7)	64	13 (11 to 14)

Notes: N= number of studies. Total harm (highlighted with grey) = the sum of preventable and non-preventable harm. Pooled rates of total harm were calculated in 64 of the 71 studies because 7 of the included studies only presented data on preventable harm.

4.3 Proportions of the most common types of overall preventable harm

Table 2 presents the types of harm which are expressed as weighted pooled proportions of the total number of harmful incidents identified across the studies. The key difference between the prevalence rates of harm and types of harm is that the former are percentages of harm at patient level (6% of patients experienced preventable harm) whereas the later are proportions of the identified harm (25% of the total number of harmful incidents identified in each study). The most common types of preventable patient harm were medication-related incidents and clinical management incidents (accounted for a weighted pooled proportion of 25% and 22% of the identified harm). To aid clarity we present another example: As shown in Table 1, 25

of the 71 studies reported that a 25% (95% CI=15 to 35) proportion of the preventable generic harm was due to medication incidents whereas 20 of the 71 studies reported that a 17% (95% CI=11 to 21) proportion of the preventable generic harm was due to diagnostic incidents. Similarly, 24 of the 64 studies reported that a 23% (95% CI=18 to 27) proportion of the total generic harm was due to medication incidents whereas 20 of the 64 studies reported that a 9% (95% CI=7 to 11) proportion of the total generic harm was due to diagnostic incidents.

Table 2 Types of harm expressed as proportions of preventable and total harm.

Outcome	**N**	**Preventable harm % (95% CI)**	**N**	**Total harm % (95% CI)**
Types of harm (proportions of the identified harm)				
Medication	25	25 (15 to 35)	24	23 (18 to 27)
Diagnostic harm	20	17 (11 to 21)	20	9 (7 to 11)
Procedure	20	21 (11 to 31)	19	21 (16 to 25)
Management	17	22 (20 to 31)	17	19 (13 to 24)
Surgical	18	16 (14 to 17)	16	26 (20 to 33)
Infections	14	17 (11 to 22)	14	18 (13 to 22)
System	6	20 (9 to 31)	6	28 (12 to 48)

Notes: N= number of studies. Total harm (highlighted with grey) = the sum of preventable and non-preventable harm. The proportions of types of harm do not add to 100% because each figure in the table is the pooled proportion which has been calculated by combining (after assigning appropriate weights) proportions extracted from several independent studies using meta-analysis. Moreover, not all studies reported all types of harm and therefore it is not appropriate to assume they add up to 100%.

The types and proportions of preventable harm were similar to the types and proportions of the total harm. The only significant difference between preventable harm and total harm was associated with the proportion of diagnostic harm and surgical harm. Specifically, a 17%

proportion of preventable harm was due to diagnostic incidents whereas only a 9% proportion of the total harm was due to diagnostic incidents; a 16% proportion of preventable harm was due to surgical incidents whereas 26% of the total harm was due to surgical incidents.

4.4 Severity proportions of overall preventable harm

Details about the severity of preventable and total harm are provided in Figure 8. As with types of harm, these are proportions of the total harm identified across the studies. The weighted pooled proportion of mild preventable harm was 42% (95% CI= 22 to 62), the weighted pooled proportion of moderate preventable harm was 39% (95% CI = 30 to 47) and the weighted pooled proportion of severe preventable harm such as permanent disability and deaths was 13% (95% CI= 10 to 16). These results mean that 42% of preventable harmful incidents (preventable adverse events) are associated with mild harm, 39% are associated with moderate harm and 13% are associated with severe harm and deaths. The heterogeneity levels were high in all analyses (I^2=96 to 99%, $p<0.001$). The severity of preventable harm was similar to the severity of the total harm.

We were not able to assess which specific types of preventable harms (such medication, diagnostic, and management incidents) were more likely to lead to severe harm and deaths. The reporting standards of all the studies on adverse events did not support this aim. All studies reported data on preventability and severity of the total identified harm but they did not report further details on which specific types of preventable adverse events led to severe injury and deaths.

Table 3 Severity proportions of preventable and total harm.

Outcome	N	Preventable harm % (95% CI)	N	Total harm % (95% CI)
Severity of harm (proportions of the identified harm)				
Mild	21	42 (22 to 62)	20	47 (38 to 55)
Moderate	18	39 (30 to 47)	17	35 (29 to 41)
Severe	22	13 (10 to 16)	20	13 (11 to 15)

Notes: N= number of studies. Total harm (highlighted with grey) = the sum of preventable and non-preventable harm. The proportions of the severity of harm do not add to 100% because each figure in the table is the pooled proportion which has been calculated by combining (after assigning appropriate weights) proportions extracted from several independent studies using meta-analysis.

4.5 Prevalence rate of overall preventable harm across healthcare specialities

The vast majority of the included studies were based in hospitals (n=62 of 71 studies; 87%), six studies were based in emergency departments and three studies in primary care. Although hospital studies typically recruited patients from several speciality units, they very rarely provided details about the prevalence rates of preventable harm in each recruited specialty unit. In total, 16 studies examined the prevalence of harm in specific specialty units. Eight of these studies were conducted in intensive care units, 6 studies in surgery units and 2 studies in obstetrics.

The highest weighted pooled prevalence rates of preventable patient harm were reported in intensive care (10%, 95% CI=7 to 14), followed by emergency department (9%, 95% CI= 7 to 12) and surgery units (9%, 95% CI= 8 to 10). The lowest weighted pooled prevalence rate of preventable harm was found in obstetrics but this analysis was only based on three studies (2%, 95% CI =1 to 2). The weighted pooled prevalence rate of preventable patent harm in

primary care was 5% (95% CI= 4 to 6) which is the same with the prevalence rate of preventable harm in hospitals. Heterogeneity was high throughout (I^2 ranged from 70-92%, p<0.001).

Table 4 Prevalence rates of preventable harm at patient level across specialities.

Outcome	Hospitals		ED		Intensive Care		Surgery		Obstetrics		Primary Care	
	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)
Prevalence rate (at patient level)	48	5 (4 to 6)	6	3 (1 to 4)	8	10 (7 to 14)	3	9 (8 to 10)	3	2 (1 to 2)	3	5 (4 to 6)

Notes: N= number of studies. Analyses based on up to 3 studies are highlighted with grey.

4.6 Proportions of types and severity of overall preventable harm across healthcare specialities

Although some variations were observed in the proportions of types and severity of preventable harm across settings (Table 5 and 6), statistical analyses to formally test these differences were not conducted due to the small number of studies included in these categories.

Table 5 Proportions of types of preventable harm across specialities.

Outcome	Hospitals		ED		Intensive Care		Surgery		Obstetrics		Primary Care	
	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)
Types of harm (proportions of the identified harm)												
Medication	19	23 (10 to 35)	1	7 (4 to 10)	3	15 (4 to 24)		n/r		n/t	3	33 (22 to 45)
Diagnostic	16	14 (8 to 20)	2	45 (33 to 57)	2	14 (5 to 24)		n/r		n/r		n/t
Procedure	14	17 (5 to 30)	1	10 (3 to 17)	2	29 (15 to 39)		n/r	1	56 (34 to 76)	2	8 (4 to 13)
Management	12	25 (18 to 31)	2	47 (34 to 59)	1	15 (8 to 27)		n/r	1	26 (9 to 44)	1	13 (11 to 15)

Notes: N= number of studies. n/r= not reported. Analyses based on up to 3 studies are highlighted with grey. The proportions of types of harm and the proportions of the severity of harm do not add to 100% because each figure in the table is the pooled proportion which has been calculated by combining (after assigning appropriate weights) proportions extracted from several independent studies using meta-analysis. Moreover, not all studies reported all types of harm and therefore it is not appropriate to assume they add up to 100%.

Table 6 Severity proportions of preventable harm across specialities.

Outcome	Hospitals		ED		Intensive Care		Surgery		Obstetrics		Primary Care	
	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)	N	Mean % (CI)
Severity of harm (proportions of the identified harm)												
Mild	12	43 (16 to 70)	1	30 (14 to 45)	3	61 (34 to 87)	3	23 (6 to 39)	1	53 (31 to 74)	1	35 (32 to 38)
Moderate	10	39 (25 to 53)	1	67 (50 to 83)	3	30 (11 to 50)	2	37 (15 to 60)	1	60 (39 to 81)	1	24 (21 to 27)
Severe	15	12 (9 to 15)	1	3 (1 to 3)	1	13 (4 to 22)	3	19 (3 to 35)	1	10 (5 to 15)	1	4 (3 to 5)

Notes: N= number of studies. Analyses based on up to 3 studies are highlighted with grey. The proportions of the severity of harm do not add to 100% because each figure in the table is the pooled proportion which has been calculated by combining (after assigning appropriate weights) proportions extracted from several independent studies using meta-analysis.

4.7 Sensitivity analyses testing the validity of the results

The results of the two sensitivity analyses which examined the validity of the results by retaining in the analyses only studies with more robust designs (prospective studies were retained; cross-sectional and retrospective studies were dropped), and more recent studies (studies published 2011 onwards were retained in the analyses; studies between 2000-2010 were dropped), showed the same pattern of findings for the prevalence rates of preventable harm, the proportions of types of preventable harm and severity proportions of preventable harm (these analyses are described in more details in Appendix 2).

Chapter 5: Preventable Medication-related Harm

5.1 Characteristics of studies and populations

There is a fundamental difference between the medication-related harm described in this chapter and the medication-related harm described in the previous chapter. In this chapter we present prevalence rates of medication-related harm at patient level (the percentage of patients which experienced preventable harm) whereas in the previous chapter we reported proportions of overall preventable harm caused by medication-related harm. These two estimates (prevalence rates at patient level and proportions of overall preventable harm attributed to medication incidents) cannot be combined and presented together. Moreover, this chapter provides additional information about proportions of medication-harm occurring at different stages of the medication use as well as proportions of severity of medication-harm.

Seventy-eight studies investigated preventable patient harm caused by the use of medication and reported relevant data for the prevalence rates of harm, proportions of harm occurring at different stages of medication use and severity proportions of harm. Twenty-eight of the included studies were conducted in the US, 20 studies were conducted in Europe and 30 studies were based elsewhere. The majority of the studies were observational prospective studies (n=56 studies) and were based in hospitals (n=73 studies). Across all 78 studies a total sample of 184,279 patients were included although the sample sizes ranged widely from n=64 to 27,617 patients

In terms of types of medication-harms, the studies included in the review either focused on preventable adverse drug events (any type of preventable patient harm caused by medication

use; n=51 studies) or investigated preventable harm resulting from adverse drug reactions (n=25 studies). Preventability is determined as described in the methods: patient harm is considered preventable if it occurs as a result of identifiable and modifiable cause. There were two studies which focused on deaths caused by preventable medication-related harm:

- Adverse drug events (ADEs) are defined as 'injuries that result from medication use caused by preventable errors'.
- Adverse drug reactions (ADRs) are a subcategory of ADEs and are defined as 'undesirable responses associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both.' ADRs can be manifested as diarrhoea or constipation, rash, headache, or to more serious harm causing permanent disability or even death.

Studies reported that medication-related harm (ADEs and ADRs) occurred in five stages of the medication process:

- *Prescribing/ordering of medication* (n=14 studies). Examples such errors include prescribing or ordering the wrong drug, dose, or route.
- *Transcribing or dispensing of medication* (n=7 studies). Examples of errors that can be initiated at the transcribing, dispensing, and delivering stages include failure to transcribe the order, incorrectly filling the order, and failure to deliver the correct medication for the correct patient.
- *Administration of medication* (n= 13 studies). Such errors mainly take in the form of wrong time, wrong technique, wrong rate, or wrong dose of medication.
- *Monitoring of medication use* (n=10 studies) such as wrong duration of treatment
- *Noncompliance* (n=4) in medication use guidance and published recommendations.

5.2 Prevalence rate of preventable medication related harm

Table 7 presents the results of the meta-analysis on the prevalence rates of preventable medication-related harm and total medication-related harm which included both preventable and non-preventable. The prevalence rates have been calculated at the patient level and they refer to the percentage of patients who experienced preventable medication-related harm. The reported prevalence rates of medication-related harm were obtained by combining the prevalence rates reported by each individual study (all 78 studies) using a standardised combining and weighting system (which is done in meta-analysis).

The weighted pooled rate of preventable medication-related harm across the healthcare was 4% (95% CI= 4 to 5; I^2=98%, p<0.001) whereas the weighted pooled total medication-related harm (preventable and non-preventable) was 9% (95% CI=8 to 11; I^2=97%, p<0.001) (Figure 9 in appendices). In lay terms these results mean that on average 4% of patients experience preventable medication-related harm and 9% of patients experience any medication-related harm (including preventable and non-preventable) in the healthcare. However, the high heterogeneity suggests caution because there were large variations across the studies in the reported prevalence rates of preventable medication-related harm. The lowest rates of preventable medication-related harm were 0.3% (reported by studies focused on adverse reactions or deaths caused by adverse drug reactions or adverse drug events in hospitals). In contrast, the largest prevalence rate of preventable medication-related harm reported by individual studies was 20% (reported by two studies examining preventable adverse events leading to hospitalisations and emergency department visits).

Fifty-two of the 78 studies focused on ADEs whereas 26 of the 78 studies focused on ADRs (Table 7). The weighted pooled prevalence rate of preventable harm caused by ADEs (4%,

95% CI=4 to 5, I^2=85%, p<0.001) was slightly higher than the weighted pooled rate of preventable harm caused by ADRs (3%, 95% CI=2 to 3). This is not a surprising finding because adverse drug events capture both ADRs as well as other types of harm resulting from medication use.

Table 7 Prevalence rates of preventable and total medication-related harm at patient level.

Outcomes	**N**	**Preventable harm Mean % (95% CI)**	**N**	**Total harm Mean % (95% CI)**
Prevalence rate of harm (at patient level)				
Total prevalence rate	78	4 (4 to 5)	78	9 (8 to 10)
ADEs prevalence rate	52	5 (4 to 6)	52	10 (8 to 11)
ADRs prevalence rate	26	3 (2 to 3)	26	10 (8 to 11)

Notes: N= number of studies. Total harm (highlighted with grey) = the sum of preventable and non-preventable harm. ADEs= Adverse drug events. ADRs= Adverse drug reactions.

5.3 Proportions of preventable medication-related harm at stages of medication use

Table 8 presents the proportions of medication–related harm during the medication use stages. The highest proportion of medication-related harm was observed in the ordering/prescribing stage (40% of the harm was caused by errors in ordering or prescribing stage; 95% CI= 28 to 56) followed by the administration stage (30% of the harm was caused by errors in administration stage; 95% CI= 18 to 46) and the monitoring stage (20% of the harm; 95% CI=12 to 28). A lowest proportion of the medication related-harm occurred at transcription and dispensing stage (6% of harm caused by errors at transcription or dispensing stage, 95% CI=4 to 9) or due to non-adherence to guidelines (10% of harm was caused due low adherence to recommended medication use standards, 95% CI= 8 to 15). Heterogeneity

ranged from moderate to high (I^2=40-70%, p<0.01). The proportions of preventable harm at different stages of the medication process were similar to the proportions of total harm. For example, a 40% proportion of preventable medication-related harm occurred in ordering stage which is similar to the 41% of total medication harm occurring in this stage.

Table 8 Proportions of preventable and total medication-related harm at stages of medication use.

Outcomes	**N**	**Preventable harm Mean % (95% CI)**	**N**	**Total harm Mean % (95% CI)**
Harm at stage of medication use (proportions of identified harm)				
Ordering/prescribing	14	40 (28 to 56)	13	41 (28 to 55)
Transcribing/ dispensing	8	6 (4 to 9)	7	7 (4 to 10)
Administration	13	30 (18 to 46)	12	28 (18 to 42)
Monitoring	9	20 (12 to 28)	7	7 (4 to 10)
Noncompliance	4	10 (8 to 15)	4	11 (8 to 15)

Notes: N= number of studies. Total harm (highlighted with grey) = the sum of preventable and non-preventable harm. The proportions of harm occurring at different stages of medication use do not add to 100% because each figure in the table is the pooled proportion which has been calculated by combining (after assigning appropriate weights) proportions extracted from several independent studies using meta-analysis. Moreover, not all studies reported details of all stages of medication use and therefore it is not appropriate to assume they add up to 100%.

5.4 Severity proportions of preventable medication-related harm

Details about the severity of preventable and total medication-related harm are provided in Table 9. Our initial aim was to also analyse separately the rates of severe harm and deaths caused by preventable ADEs and ADRs. However, none of the studies focused on ADRs provided details about the severity proportions of resulted preventable harm. One reason for this lack of evidence regarding the severity of preventable harm caused by ADRs is that

ADRs were considered non-preventable in the past. Although this misconception is changing, the impact of preventable ADRs needs to be better reported by published studies. Thus, the severity proportions presented in this section are only based on data from ADEs. The weighted pooled prevalence rate of mild preventable harm was 47% (95% CI= 35 to 59), the weighted pooled prevalence rate of moderate preventable harm was 38% (95% CI = 29 to 47) and the weighted prevalence pooled rate of severe preventable harm such as permanent disability and deaths was 19% (95% CI= 15 to 24). Heterogeneity was high (I^2 ranged from75 to 83%, p<0.001). These results mean that 47% of adverse events are associated with mild preventable harm, 38% are associated with moderate preventable harm and 19% are associated with severe preventable harm and deaths. One interesting finding was that the proportion of severe harm caused by preventable medication incidents tended to be larger than the severe harm caused by all (preventable and non-preventable) medication incidents (19% compared to 10%, respectively).

Table 9 Severity proportions of preventable and total medication-related harm.

Outcomes	**N**	**Preventable harm Mean % (95% CI)**	**N**	**Total harm Mean % (95% CI)**
Severity of harm (proportions of identified harm)				
Mild	22	47 (35 to 59)	20	48 (40 to 55)
Moderate	24	38 (29 to 47)	22	40 (35 to 44)
Severe	21	19 (15 to 24)	19	10 (8 to 11)

Notes: N= number of studies. Total harm (highlighted with grey) = the sum of preventable and non-preventable harm. The proportions of the severity of harm do not add to 100% because each figure in the table is the pooled proportion which has been calculated by combining (after assigning appropriate weights) proportions extracted from several independent studies using meta-analysis.

5.5 Prevalence rate of medication-related harm across healthcare settings

Most of the included studies were based in hospitals (n=73 of 78 studies; 93%) and five studies were based in primary care. Only 29 of the 73 studies provided data on the prevalence of preventable harm in specific specialty units including internal medicine, intensive care, emergency department, surgery unit, obstetrics, geriatrics and psychiatry. The weighted pooled prevalence rates of preventable medication-related harm in studies which only reported data at hospital level without providing data on specialities separately (44 of 73 studies) was 5% (95% CI=4 to 6; see Table 10). Across the 34 studies which focused on specialities (5 in primary care and 29 studies in hospital specialities with some reporting data for more than one speciality) the highest pooled prevalence rates of preventable harm were observed in the and intensive care (7%, 95% CI=4 to 6) and the emergency department (5%, 95% CI=4 to 6). However, none of the differences across settings was statistically significant and heterogeneity was high (I^2 ranged from 60% to 92%, p<0.001).

Table 10 Prevalence rates of preventable medication harm at patient level across specialities.

Outcome	**Hospitals**		**Emergency department**		**Internal Medicine**		**Intensive Care**		**Surgery**	
	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)
Prevalence rate (at patient level)	44	5 (4 to 6)	6	5 (4 to 6)	9	4 (3 to 5)	4	7 (3 to 11)	1	4 (3 to 6)
Outcome	**Obstetrics**		**Geriatrics**		**Paediatrics**		**Primary care**		**Psychiatry**	
	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)
Prevalence rate (at patient level)	1	2 (1 to 2)	3	3 (1 to 5)	4	2 (1 to 3)	5	3 (2 to 4)	2	2 (1 to 3)

Notes: N= number of studies. Analyses based on up to 3 studies are highlighted with grey.

5.6 Severity proportions of medication-related harm across healthcare settings

As seen in Table 11, the proportion of preventable harm was more severe in emergency department, surgery and intensive care compared to geriatrics, primary care and psychiatry. However, no formal statistical tests were used to test the significance of these differences because some specialities only included 1 or 2 studies reporting data on the severity of preventable harm.

Table 11 Severity proportions of preventable medication-related harm across specialities.

Outcome	**Hospitals**		**Emergency department**		**Internal Medicine**		**Intensive Care**		**Surgery**	
	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)
Severe harm (proportion)	13	19 (13 to 28)	1	30 (18 to 46)		n/r	2	20 (11 to 30)	1	25 (8 to 42)
Outcome	**Obstetrics**		**Geriatrics**		**Paediatrics**		**Primary care**		**Psychiatry**	
	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)	N	Mean % (95% CI)
Severe harm (proportion)		n/r	2	13 (3 to 23)		n/r	2	10 (7 to 14)	2	8 (4 to 12)

Notes: N= number of studies. Analyses based on up to 3 studies are highlighted with grey.

5.7 Sensitivity analyses testing the validity of the results

Two sensitivity analyses were conducted which examined the validity of the results by retaining in the analyses only studies with more robust designs (prospective studies were retained; cross-sectional and retrospective studies were dropped), and more recent studies (studies published 2011 onwards were retained in the analyses).The main findings were not affected by the study design. However, studies published in 2011 onwards tended to report a higher rate of preventable harm (6% versus 4%) and more severe harm compared to the main analyses based on all studies from 2000 onwards. This finding might reflect improvements in

the assessment methods of preventable ADES and ADRs following the growing recognition that they are important sources of preventable harm (these analyses are described in more detail in Appendix 3).

Chapter 6: Findings in the United Kingdom

6.1 Characteristics of studies and populations

Details of data extracted from individual studies based in the UK are provided in Table 12. A total of 15 studies were based in the UK. Fourteen of the included studies were conducted in England and one study was conducted in Scotland which focused on adverse events. The majority of the studies were retrospective patient health record review studies (n=9) and the remainder were observational prospective studies (n=6). Across all 15 studies a total sample of 89,522 patients were included although the sample sizes ranged widely from n=207 to 18,820 patients. With the exemption of one study which was conducted in primary care, all the other studies were based in hospitals.

Consistent with the international literature, two categories of studies were distinguished:

- 7 studies which examined overall preventable harm (adverse events resulting from a range of safety incidents such as medication incidents, process failures and communication gaps).
- 8 studies specifically focused on preventable harm resulting from medication incidents (resulting from ADEs and ADRs)

6.2 Key findings for preventable patient harm in the UK

The weighted pooled prevalence rate of overall preventable patient harm was 5% (95% CI=4 to 7) across 7 studies which is similar to the 6% rate reported across all 71 studies. Approximately 13% of this harm led to permanent and severe disability. The main types of errors leading to preventable harm were also similar to the main types of harm described in

the total pool of studies. Medication-related errors and therapeutic/clinical management failures each accounted for 25% of the preventable harm, followed by diagnostic harm (18%). Procedural/administrative failures and surgical harm accounted for a smaller proportion of the identified preventable harm (8% and 6%, respectively).

Eight studies examined preventable harm resulting from medication incidents only. The weighted prevalence rate of preventable medication-related harm was 4% (95%CI=0.03 to 0.05; I^2=68%) in the UK which is similar to the preventable medication-related harm that we found across all 78 studies focused on medication-related harm. The rates of harm was relatively consistent across these eight studies (the lowest rate was 2% and the highest rate was 6%). However, the severity of resulted preventable harm was either not reported or not well reported in the UK based studies. Severe harm which included permanent disability and deaths typically ranged from 1 to 4% of the identified preventable medication related harm. Three studies reported that adverse drug events directly led to hospital admissions and/or an increased length of hospital stay suggesting that at least some mild to moderate harm occurred in these studies.

Table 12 Characteristics of included studies in the UK.

Study ID	Country	Research design	Population	Clinical setting/specialities	Sample size	Total Harm %	Preventable harm %	Severity proportion of preventable harm
Davies 2010	England	Prospective Cohort Study	Patients admitted to 12 wards	Hospitals	290	ADRS: 20.8%	Preventable: 14.3%; Possibly: 42.9%	Mild: n/r Moderate: n/r Severe: n/r Death: 10%
Davies 2009	England	Prospective Cohort Study	Patients admitted to 12 wards	Emergency department	3322	ADRS: 15.8%	Preventable:: 6.4%; Possibly: 46.9%	Mild: 77% Moderate: 20.7% Severe: 0.1% Death: 1%
de Wet 2009	Scotland	Retrospective patient health record review study	500 primary care patient records	General Practice Administration System for Scotland	500	AES: 9.4%	Preventable: 42%	Mild: 83% Moderate: 13% Severe: 4% Death: 0
Franklin 2010	England	Retrospective Case Record Review	Patient health records	Complex surgical ward	207		Preventable ADES= 2.4%	n/r
Gallagher 2012	England	Prospective Cohort Study	Patients admitted acutely to a paediatric hospital	A large tertiary children's hospital	6821	ADRS:2.9 %	Preventable: = 7.6% Possibly= 30.2%	Mild: 87% Moderate: 5.6% Severe: 1.2% Death: 0

Garry 2014	England	Retrospective Case Record Review	Patients admitted to intensive care units	Intensive care unit admission in five hospitals	280	AES: 27%	Preventable: 7.7%	Mild: 30% Moderate: 30% Severe: 21% Death: 11%
Hogan 2012	England	Retrospective Case Record Review	Case records of adults who died in 2009 in 10 acute hospitals in England	10 acute hospitals	1000	AES leading to deaths: 13.1%	Preventable:: 2.3% Possibly: 5.6%	Death: 13.1%
Howard 2003	England	Prospective Cohort Study	Patients seen by pharmacists on the medical admissions unit	1 Teaching hospital	4093	ADES: 6.5%	Preventable: 4.3%	Mild to severe:6.5%
Morris 2004	England	Retrospective Case Record Review	Medical records of general practice patients aged 18 and over	General Practice	49658	ADES: n/r	Preventable: 1%	n/r
Pirmohamed 2004	England	Prospective Cohort Study	Patients admitted to 2 hospitals over 6 months via A&E	Hospitals	18820	ADRS:6.5 %	Preventable:: 9% Possibly: 63%	Mild to severe:77.7% Death: 2.3%
Pucher 2013	England	Retrospective Case Record Review	Major Trauma patients admitted over 1 year	Hospitals	1752	AES: not reported	Preventable::3.6% Possibly: 6%	Mild: 56% Moderate: 21% Severe: 11% Death: 10%
Rogers 2009	England	Cross-Chapteral observation study	Patients ≥ 65 years admitted to acute medical admissions unit	Single north London hospital	409	ADES: 6.4%	Preventable: 3.9%	All harm should be mild to severe because they led to hospital admission

Sari 2007	England	Retrospective Case Record Review	Patient health records of all admissions lasting more than 24 hours in 8 specialties	Large NHS hospital	1006	AES: 8.7%	Preventable: 2.7%	Mild: 56% Moderate: 21% Severe: 11% Death: 10%
Symons 2013	England	Prospective observational study	Post-operative care - major elective general surgery	Large urban teaching hospital	350	AES: 8%	Preventable: 4%	Mild: 42% Moderate to severe: 9%
Vincent 2001	England	Retrospective Case Record Review	Patient health records from 4 specialties	Two acute hospitals in Greater London area	1014	Total:10.8 %	Preventable: 5.1%	Mild: 66% Moderate: 19% Severe: 6% Death: 8%

Note: n/r= not reported; ADES= adverse drug events; ADRS= Adverse drug reactions; A number of studies (listed in the table) provided data about possibly preventable prevalence rates of harm. These rates are provided for the reader's information but were not used in the analyses. All analyses were based on prevalence rates of harm which fully met the preventability criteria unless otherwise specified (analyses on prevalence rates of total harm).

Chapter 7: Taxonomy of Preventable Harm

In this chapter we present the taxonomy of preventable harm. We used the WHO taxonomy instead of developing a new taxonomy because it was fully consistent with results of the systematic review described in the previous chapters. The WHO taxonomy has three levels of classification:

1. Major types of preventable harm;
2. Process and problem underlying each type of preventable harm;
3. Degree of harm associated with preventable harm.

The results of our systematic review and meta-analysis about types of preventable harm were inserted in the existing WHO taxonomy. This process was agreed following discussions within our research team. As shown in Figures 2 to 6, most types of harm described in this review relate to clinical process/procedure safety incidents and medication-related incidents. In all figures data available from our systematic review are highlighted with green whereas data not available from our systematic review are highlighted with yellow. Non-available data mainly reflect lack of evidence (rather than low preventability) because studies on total harm do not provide detailed descriptions of preventable types of harm in the published reports. Only for medication-related harm, data were provided about the process in which the harm occurred and also about the actual problem/nature of the harm (e.g. adverse drug reactions). For all other types of harm only the process proportions were reported across included studies but the proportion of the problems were not reported. Some studies provided narrative descriptions of the problems as part of definitions of types of harm they were examining but did not provide any data to understand which problems led more often to harm. To aid interpretation of the figure, we provide an example: Medication-related harm could have occurred in the prescription process because the potential for a preventable ADR

(problem) was not detected (e.g. by reviewing the history of the patient or the drug combinations). We believe that this taxonomy is a useful resource for researchers, practitioners and policy makers because it clearly illustrates the gaps in reporting standards of the preventable patient harm and where improvements are mostly needed.

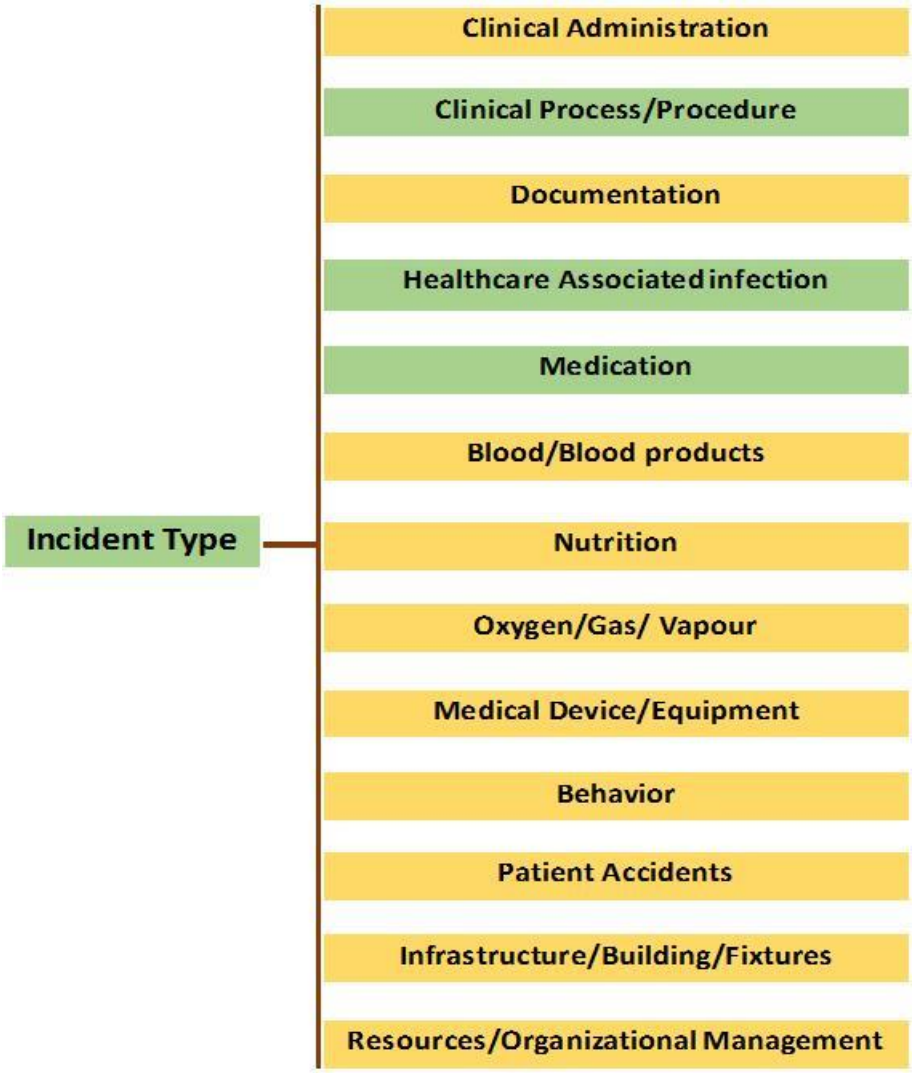

Figure 2 Major types of harm based on the WHO framework.

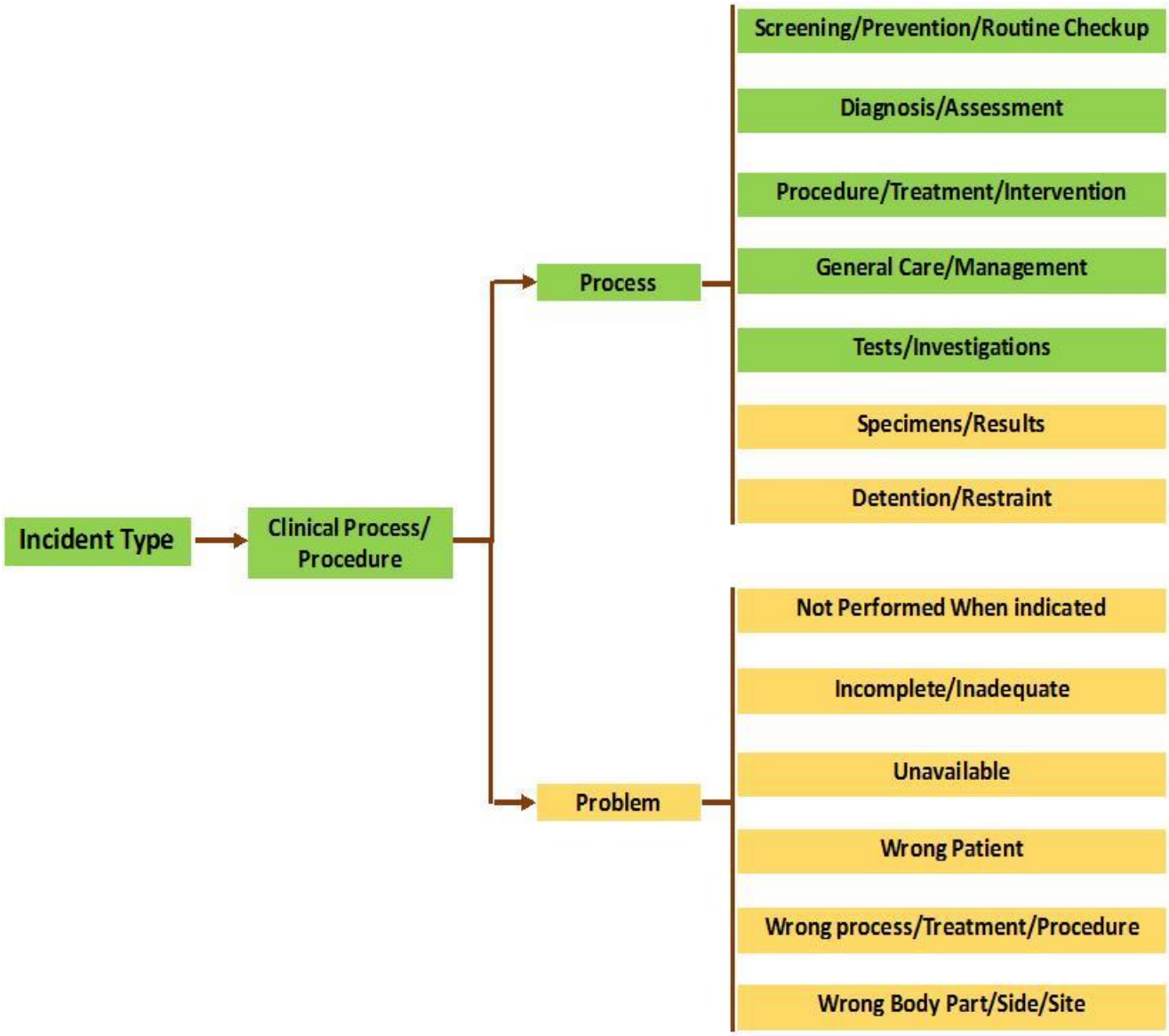

Figure 3 The processes and the problems underlying clinical procedure harms.

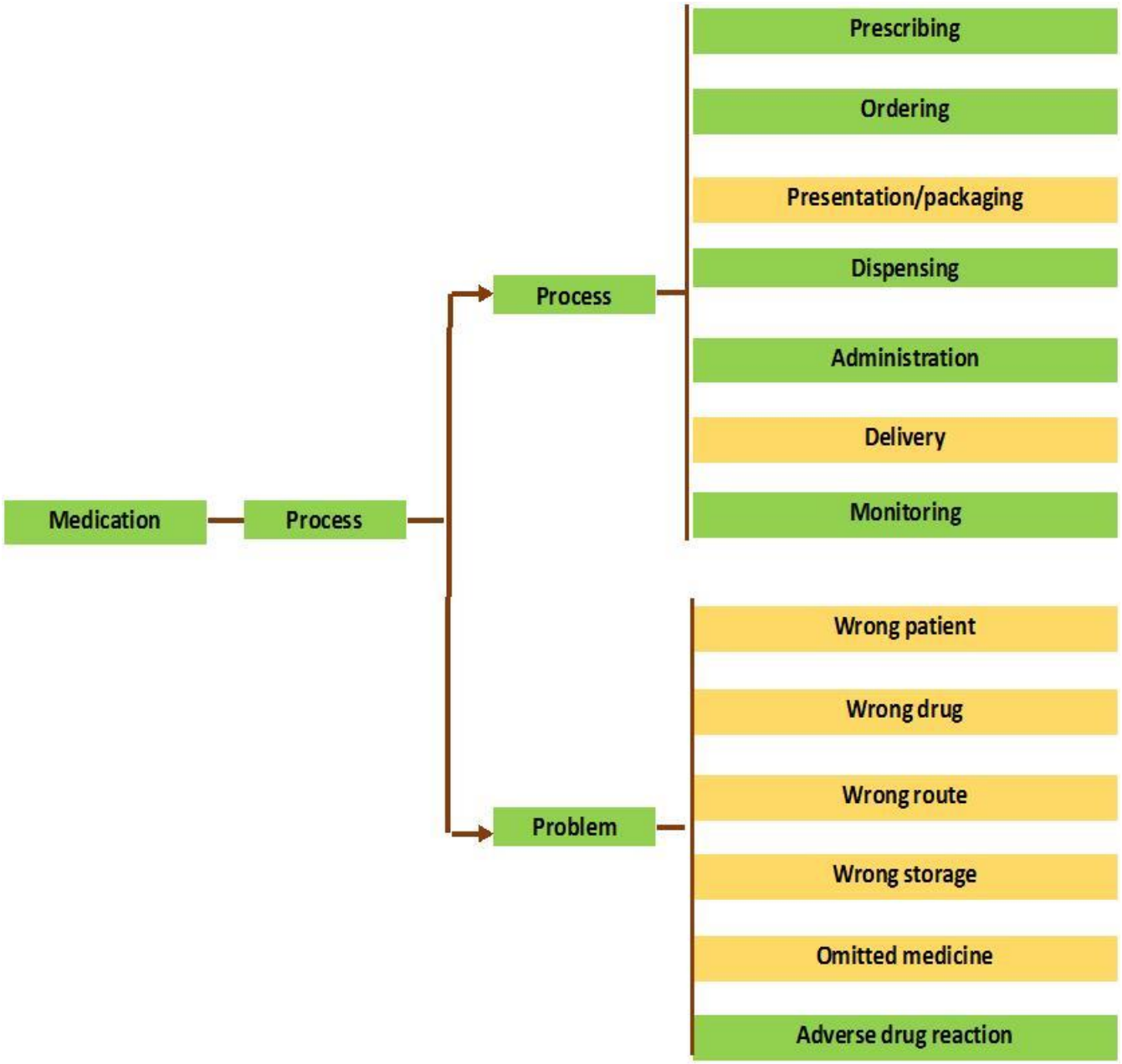

Figure 4 The processes and the problems underlying medication-related harms

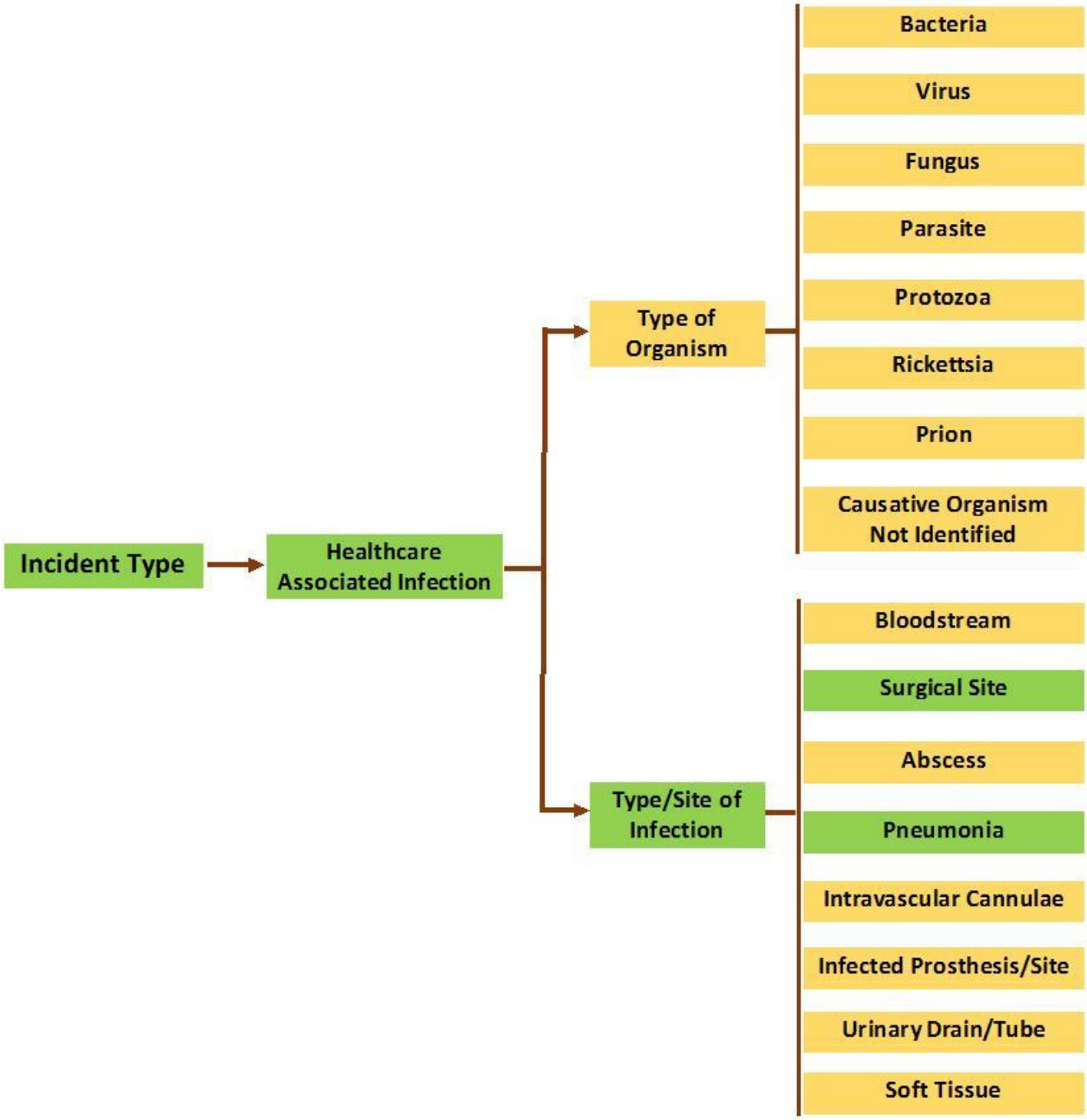

Figure 5 Type/site and organisms underlying harm associated with healthcare infections.

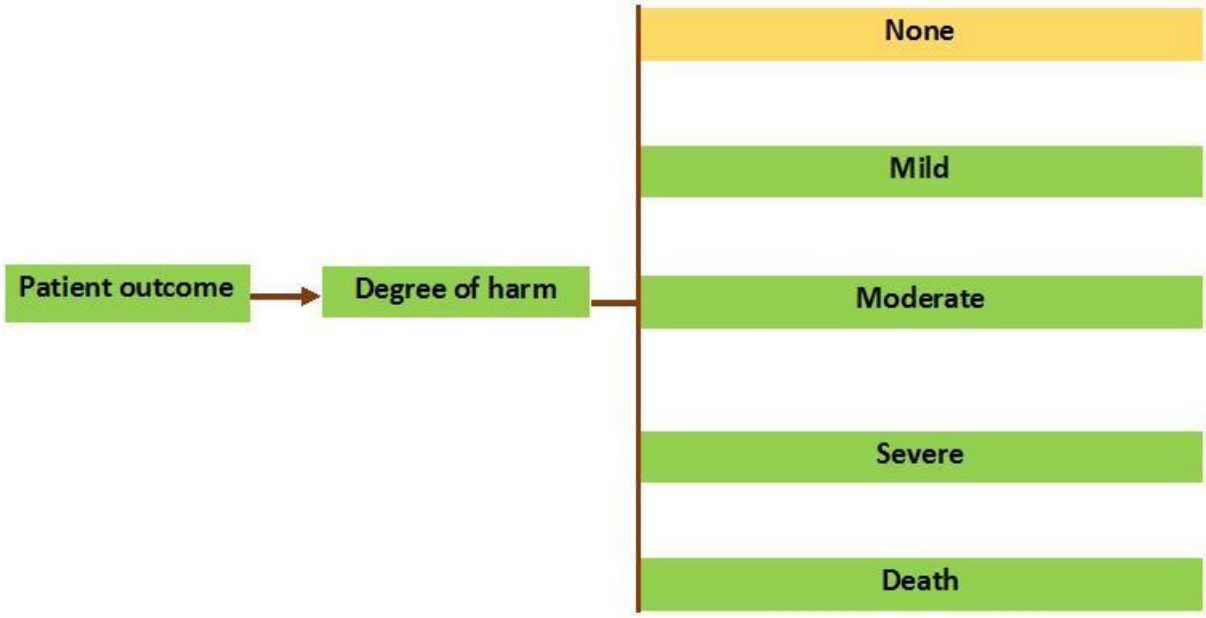

Figure 6 Classification of the severity levels (degree) of the identified harm.

'None' was not relevant because only harmful incidents (which caused at least mild harm) were included in the review.

Chapter 8: Discussion

8.1 Summary of main findings

In this large systematic review of 149 distinct studies we were able to respond to the following core questions:

How common is preventable patient harm across the healthcare? At least 6 percent of patients experience preventable iatrogenic harm across the healthcare service.

How severe is preventable patient harm? Thirteen percent of the identified preventable harm causes prolong or permanent disability or leads to death.

Which are the main sources of preventable patient harm? The main types of patient safety incidents which contribute to preventable harm are medication incidents (25% of preventable harm incurs from medication incidents), diagnostic incidents and incidents occurring following the receipt of suboptimal clinical management/therapies. Particularly medication and diagnostic incidents were more likely to be associated with preventable harm than non-preventable harm. Moreover, a large proportion of studies in this review (78 out of 149) solely focused on preventable harm caused by medication incidents; these studies showed that preventable medication harm alone affects 4 percent of patients and is most likely to occur at the stage of prescription/ordering of medication and administration of medication.

In which medical setting or speciality is preventable patient harm more likely to occur? The most extensive evidence on preventable harm (in terms of number of studies) was produced in general hospitals whereas less evidence was available for medical specialties and the primary care. Some evidence suggests that preventable harm is higher in certain medical specialities such as intensive care and surgery but these findings should be treated with caution due to the small numbers of studies which provided data for each specialty.

What is the current stage of knowledge and the next steps for future research, policy and practice? Almost half of the evidence summarised in this report has been published the past five years which is indicative of the research and policy focus on understanding and preventing harmful patient incidents in healthcare delivery. Future research and policy should focus on improving the assessment methods of preventable patient harm and apply strategies to eliminate major sources of preventable harm such as medication incidents and diagnostic incidents.

8.2 Key strengths and limitations

The major strength of this review is the focus on preventable iatrogenic harm and the consideration of all healthcare settings in the synthesis. A number of systematic reviews have been published in the past but these reviews focused on total harm (combined total of preventable and non-preventable) rather than preventable harm and were restricted on specific settings such as in-hospital patient harm [16, 168-170]. This is the largest and most comprehensive systematic review which examined the prevalence, the severity and key types of preventable patient harm. Therefore this report uniquely advances the current evidence base on preventable patient harm. We employed rigorous search methods to identify the relevant studies, and the review was prepared and reported according to published guidelines.

Two independent researchers were involved in data screening and extraction; reliability tests were performed which indicated high levels of inter-rater agreement. We are aware that as with all systematic reviews, publication bias may be present, whereby certain types of studies may be more likely to be published. We minimised the risk for this important caveat by searching for unpublished literature and sense-checking findings with international experts in patient safety within the NIHR Greater Manchester Patient Safety Translational Research Centre where we are based. Moreover, we have also conducted and we report formal tests of publication bias.

However, there are also limitations. The searches of this review were restricted to studies which stated in abstract/titles that they assessed preventable iatrogenic harm. Studies which did not explicitly state that they assessed preventability of harm might not have been captured by the searches. However, structuring the searches around the main inclusion criteria of the review is a standard practice when dealing with a large volume of research evidence as done here; capture the evidence on preventable harm out of the much larger volume of evidence around patient safety/harm. We also undertook additional measures to account for this limitation. We screened through the available published systematic reviews to identify any studies missed from the searches and we checked the reference lists of the citations of the included studies for more eligible studies. Only a handful of studies were identified through these additional methods suggests that our approach was credible.

In this report we used meta-analysis because it allows a better understanding of the results when many studies are included in the synthesis [171]. However, large heterogeneity was observed in all the analyses. The large heterogeneity is most likely due to inconsistencies in the terminology of key outcomes (e.g., the definition of preventability and severity of harm

was not always consistent across the study), and the different healthcare contexts of these studies. We dealt with the heterogeneity according to published guidelines (by applying random effects models) and we carried out further analyses (subgroup and sensitivity analyses) to explore differences across healthcare specialties, research designs and publication dates of the studies. However, there are other factors for which we did not control in the analyses because conducting too many analyses can lead to inaccurate results. The use of advanced statistical techniques such as meta-regression is a recommended option to advance further these findings because it allows to account simultaneously for several factors in a single statistical model including factors tested in this report (research design, setting, publication date) and factors not tested in this report such as the sample size, patient population (children; adults; older adults) and method for collecting harm data (e.g. medical record review, observational and ethnographic methods, patient-experience surveys).

8.3 Implications for research, policy and practice

The headline finding of this review is that more than one in twenty patients in the healthcare delivery is exposed to preventable harm. There is an urgent need for improving the patient safety standards to minimise preventable patient harm which is devastating and costly for both patients and the healthcare system.

Improving the reporting standards of future research studies on patient harm can have a major contribution in ensuring safe care for patients. Despite the large number of studies included in this review, the quality and depth of data presented on preventable patient harm is very low. Preventability was reported as a secondary outcome across the vast majority of the studies. This flawed reporting practice needs to be revised because some types of harms are more amenable (preventable) than others. Research on patient safety should better reflect and

meet the needs of clinical practice. Increasing the emphasis on preventable patient harm is a critical step towards this direction. Research to identify the major preventable sources of severe patient harm as well as the stages, the systems and the practitioners involved in the occurrence of preventable harmful incidents is warranted. This detailed analysis is fundamental for designing more efficient strategies to prevent patient harm in the healthcare process.

We found that medication-related incidents represent a leading cause of preventable patient harm in the hospitals, the primary care and in many specialities. Interventions to reduce medication-related harm are encouraged by these findings, particularly at the stages of prescribing and administration of medication where most preventable harms occur. Although it is challenging to recommend any specific type of intervention due to lack of consensus in the literature and differences across setting, these could target practitioners and systems responsible for prescribing medication (mainly physicians and pharmacists) and administering medication (mainly nurses). The content of these interventions could involve educational interventions for practitioners or organisational interventions such as revision of professional roles, involvement of clinical multidisciplinary teams and introducing quality monitoring services [172, 173].

The findings of this review confirmed that diagnostic errors are also an important source of preventable harm which remains an underemphasised and understudied area of patient safety research. Future studies should focus on obtaining more precise estimates on types and sources of preventable diagnostic harm in different settings of care. This would lay the foundation for designing and evaluating interventions targeting the identified causes of diagnostic harm. While the literature has suggested many potentially fruitful interventions for

reducing diagnostic errors, most have not been systematically evaluated and/or widely implemented in practice [174]. Research is needed to study promising intervention areas such as enhanced patient involvement in diagnosis, improving diagnosis through the use of electronic tools [175] and emotion-cognitive interventions for boosting practitioners' confidence in making diagnoses and reducing diagnostic uncertainty.

Finally, our review findings suggest that preventable harm might be a serious concern in certain specialities such as intensive care whereas there is lack of evidence in other specialties such as primary care and psychiatry. Studies investigating preventable patient harm in primary care and other medical specialities are strongly recommended.

8.4 Conclusion

This is the largest review which examined the prevalence, the severity and the most common types of preventable patient harm in healthcare. Our findings affirm that preventable patient harm is a serious problem across all healthcare settings. Important questions remain about the quality of methods of collecting and reporting data on preventable patient harm. Further research should concentrate on introducing strategies to mitigate major sources of preventable patient harm such as medication-related harm and in advancing the evidence base for specific sources of preventable harm such as diagnostic errors and in specific medical specialities.

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Appendix 1: Search strategy in Medline

	Searches	Results
1	((preventable or avoidable or unnecessary or untoward or ameliorable) adj2 (harm or complication* or omission)).mp.	1668
2	exp Medical Errors/cl, mt, pc, st, sn [Classification, Methods, Prevention & Control, Standards, Statistics & Numerical Data]	23681
3	exp medical error/pc or medical error.mp.	19329
4	"Drug-Related Side Effects and Adverse Reactions"/	28899
5	((Adverse drug or adverse medication) adj1 (event* or incident or reaction* or effect* or outcome*)).mp.	18911
6	Human error*.mp.	1603
7	((service* or system* or communication* or organization* or organisation* or treatment or therap* or diagnos*) adj1 (weak* or fail* or error* or mistake* or delay*)).mp.	129170
8	(adverse* adj1 (event* or outcome* or complication* or effect* or reaction*)).mp.	285222
9	((psychological or emotional or physical) adj1 (harm or complication*)).mp.	1129
10	patient safety.mp. or Patient Safety/	26908
11	(death* or accident or serious incident* or injur* or adverse event*).mp.	1770259
12	10 and 11	4389
13	(never event* or near miss*).mp.	1797
14	(iatrogenic adj (harm or injur* or complication*)).mp.	2862
15	Patient Harm/ or patient harm.mp.	914
16	Diagnostic Errors/	38362
17	(preventable or avoidable or unnecessary or untoward or ameliorable).mp.	76388
18	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 12 or 13 or 14 or 15 or 16	441852
19	17 and 18	7129
20	1 or 19	8482

21	Prevalence/ or prevalence.mp.	547386
22	incidence.mp. or Incidence/	698801
23	Epidemiologic Studies/	8042
24	exp Case-Control Studies/	897333
25	(epidemiologic* adj (study or studies)).mp.	78191
26	case control.mp.	282010
27	exp Cohort Studies/	1765445
28	Cross-Sectional Studies/	259191
29	(cohort adj (study or studies)).mp.	302778
30	Cohort analy*.mp.	5992
31	(follow up adj (study or studies)).mp.	634329
32	longitudinal.mp.	237282
33	Retrospective.mp.	730249
34	Prospective.mp.	648409
35	(observ* adj1 (study or studies)).mp.	88143
36	(analytical adj (study or studies)).mp.	3110
37	(comparative adj (study or studies)).mp.	1977764
38	(evaluation adj (study or studies)).mp.	379513
39	Meta-analysis/	82995
40	((Systematic or narrative) adj review).mp.	75440
41	Clinical Trial/ or Randomized Controlled Trial/	798769
42	or/23-41	4859990
43	20 and 42	3466
44	21 or 22	1176178

45	20 and 44	1662
46	43 or 45	4150
47	limit 46 to (english language and yr="2000 -Current")	3090

Table 13 Characteristics of studies on overall preventable harm

Study ID	Country	Design	Clinical setting	Assessment method	N	Population	Type	Details of overall preventable harm
Agarwal 2010	USA	Retrospective	15 hospital PICUs	Patient record review	734 patients	Pediatric patients discharged from 15 PICUs	AEs	AEs relevant to PICU's. preventability: 6-point scoring scale used.
Aibar 2015	Spain	Retrospective	41 hospitals	Patient record review	836 patients	Women admitted to the obstetrics departments for more than 24 hours	AEs	AEs defined as any unforeseen and unexpected accident recorded in the medical record that cause injury and/or disability and/or prolonged the hospital stay and/or led to death which was the result of health care and not the patient's underlying condition. Severity: Permanent injury or death =severe, a new consultation, surgical treatment, medication or admission to a hospital=moderate.
Amaral 2015	Canada	Prospective	Pediatrics	Patient record review	247 patients	Pediatric inpatients	AEs	AEs defined as any event causing harm to the patient that was perceived to be more related to the healthcare management rather than to the patient's underlying condition. Preventability: perceived adequacy of the care provided, given the existing standards of care and the resources available. Severity: causing death of the patient or permanent disability= severe; lengthened hospital stay = moderate mild=others were considered slight.
Aranas-andres 2008/2009	Spain	Retrospective	24 hospitals	Patient record review	5,624 patients	Patients of any age with a clinical record indicating an inpatient stay of >24 h and discharge.	AEs	AEs defined as any health care-associated incident which caused harm, with a causation score of at least 4. Preventability: A score of 4 using a 6-point scale, with 1 being no or minimal evidence and 6 practically certainly evidence of health care-related contributory factors to harm. Severity: causing death of the patient or permanent disability= severe; lengthened hospital stay = moderate mild=others were considered slight.
Aranaz-andres 2011	Argentina, colombia, Mexico, Peru	Cross-sectional	458 secondary and tertiary acute care hospitals	Patient record review	11,379 patients	2000 patients per country, any patients admitted to the included secondary and tertiary acute care hospitals during study period.	AEs	AEs defined as any event causing harm to the patient that was perceived to be more related to the healthcare management rather than to the patient's underlying condition. Preventability: perceived adequacy of the care provided, given the existing standards of care and the resources available. Severity: causing death of the patient or permanent disability= severe; lengthened hospital stay = moderate mild=others were considered slight.
Aranaz-andres 2012	Spain	Cross-sectional	48 primary care centres	Reporting form by clinicians	9,6047 consultations	Primary care consultations	AEs	AEs defined as any incident causing harm to the patient and related to the healthcare provided. Preventability: 6-point scoring scale used (score of at least 4). Severity: Permanent injury or death =severe, a new consultation, surgical treatment, medication or admission to a hospital=moderate.
Baines 2013a	Netherlands	Retrospective	20 hospitals	Patient record review	4,023 admissions	Admissions from 2008. 50% patients discharged from hospital after 24 hours, 50% patients deceased in hospital.	AEs	AEs defined as unintended injury that results in temporary or permanent disability, death or prolonged hospital stay, and is caused by healthcare management rather than by the patient's underlying disease process. Severity: causing death of the patient or permanent disability= severe; lengthened hospital stay = moderate mild=others were considered slight.
Baker 2004	Canada	Retrospective	20 hospitals	Patient record review	4,64 patients	All admissions for patients over 18 years old who had a minimum stay in acute care hospitals of 24 hours	AEs	AEs defined as an unintended injury or complication that results in disability at the time of discharge, death or prolonged hospital stay and that is caused by health care management rather than by the patient's underlying disease

								process. Severity: Moderate=temporary impairment of function lasting up to a year; severe= permanent impairment of function or death.
Bartlett 2008	Canada	Retrospective	20 hospitals	Patient record review	2,355 patients	Patients aged 18 or over	AEs	AEs defined as unintended injury or complication caused by the delivery of clinical care rather than by the patient's underlying condition.
Blais 2013	Canada	Retrospective	Healthcare services	Patient record review	1261 patients	Patients discharged from publically funded healthcare services	AEs	AEs defined as an unintended injury or complication that results in disability at the time of discharge, death or prolonged hospital stay and that is caused by health care management rather than by the patient's underlying disease process. Severity: Moderate=temporary impairment of function lasting up to a year; severe= permanent impairment of function or death.
Calder 2015	Canada	Prospective	Tertiary care emergency department	Patient record review	13,495 patients	All patients having an ED encounter	AEs	AEs defined as an adverse outcome related to the care received during the index visit.
Calder 2010	Canada	Prospective	2 emergency departments	Patient interviews	503 patients	Patient over the age of 18 who received treatment in the resuscitation or observation areas of ED.	AEs	AEs as unintended injuries that result from health care management. Preventability: caused by a health care management problem such as a diagnostic issue, management issue, unsafe disposition decision, suboptimal follow-up, medication adverse effect or procedural complication. Severity: Moderate=temporary impairment of function lasting up to a year; severe= permanent impairment of function or death.
Calland 2001	USA	Retrospective	Operating suite of University health sciences centre	Patient record review	6,380 patients	Patients undergoing an operation during the study period. Cross references with patients dying within 30 days of their procedure during the study period	AEs	AEs defined as unintended injury (death in this case) caused by medical treatment, and thus not primarily attributable to the patient's primary disease process.
Davis 2013	New Zealand	Retrospective	General hospital	Patient record review	6,579 patients	Patients admitted in the calendar year 1998	AEs	AEs defined as an unintended injury resulting in disability and caused by healthcare management rather than the underlying disease process. Severity: Serious=permanent disability (lasting more than 1 year) or death.
De Wet 2009	UK	Retrospective	Primary care	Patient record review	500 patients	Patients in general practice	AEs	Es defined as an injury resulting from medical management rather than the underlying disease. Preventability: AEs severity could have been substantially reduced if different actions or procedures had been performed or followed. Severity: mild=laboratory abnormality only, one day of symptoms; moderate= several days of symptoms, non-permanent disability, Serious=permanent disability, or death.
Florea 2010	Canada	Retrospective	Hospital obstetric unit	Patient record review	6,752 patients	Adult female, hospital, obstetric unit	AEs	AEs associated with communication errors e.g. caused to the mother or baby with communication, record keeping and wrong results.
Fordyce 2003	USA	Prospective	Academic emergency department	Interviewing ED staff	1,935 patients	Emergency department patients	AEs	AEs defined as injuries resulting from a medical intervention. Any incident causing pain, distress, or harm to a patient was regarded as involving an adverse event.
Forster 2003	Canada	Prospective	Tertiary care academic hospital	Patient record review	400 patients	Patients discharged from general medical service	AEs	AEs defined as an injury resulting from medical management rather than the underlying disease. Preventability: AEs severity could have been substantially reduced if different actions or procedures had been performed or followed. Severity: mild=laboratory abnormality only, one day of symptoms; moderate= several days of symptoms, non-permanent disability, Serious=permanent disability, or death.
Forster 2004	Canada	Prospective	General internal medicine	Patient record review and interviews	328 patients	Older adults discharged home or senior residence	AEs	AEs defined as adverse drug event, procedure related injury, nosocomial infection, fall, therapeutic error, diagnostic error or other. Preventability: 2 reviewers agreed, using implicit judgement, on whether AE could have been

			tertiary care hospital					prevented. Severity: mild=laboratory abnormality only, one day of symptoms; moderate= several days of symptoms, non-permanent disability, Serious=permanent disability, or death.
Forster 2006	Canada	Prospective	Obstetrics unit in teaching hospital	Patient record review	425 patients	Obstetrics consecutive patients admitted to the labour and delivery unit of the ottawa hospital	AEs	AEs defined as as an adverse outcome due to health care management as opposed to progression of natural disease. Preventability: AE judged to be avoidable by means available in routine practice.
Forster 2008	Canada	Prospective	Academic tertiary care intensive care unit (ICU)	Observation	207 patients	Critically ill ICU patients for 3 months in 2006, prospective followed patients admitted until discharge or death.	AEs	AEs defined as patient injuries caused by medical care. For each adverse clinical occurrence, the review panel determined whether the occurrence was truly an event in which the patient's status changed. Preventability: All AEs were reviewed by the panel to determine if they were avoidable with the available resources and currently accepted practices. Severity: 'significant', 'severe', 'life-threatening', or 'fatal.
Forster 2011	Canada	Prospective	hospital.	Clinical surveillance	1,406 patients	Patients admitted to cardiac surgery intensive care, intensive care, general internal medicine and obstetrics.	AEs	AEs defined as treatment-related harm (harms caused by medical care). Preventability: AEs caused by errors. Severity: mild=laboratory abnormality only, one day of symptoms; moderate= several days of symptoms, non-permanent disability, Serious=permanent disability, or death.
Fowler 2008	USA	Prospective	17 hospitals	Patient survey and interview	2,582 patients	Hospital patients	ADEs	Severe AEs defined as events leading to intensive care treatment or death. Severity: serious=intensive care treatment or death.
Friedman 2008	Toronto	Prospective	Emergency department of teaching hospital	Patient interviews	292 patients	Patients admitted to emergency department	AEs	AEs defined as unintended injury or complication caused by health care management rather than the patient's underlying disease. Severity: Serious=permanent injury or death, moderate=a new consultation, surgical treatment, medication or admission.
Garry 2014	UK	Retrospective	Intensive care unit in 5 hospitals	Patient record review	280 patients	Patients admitted to intensive care units	AEs	AEs defined as unintended injury or complication caused by health care management rather than the patient's underlying disease. Severity: mild=temporary harm; moderate=temporary harm and prolonged ICU stay; serious=permanent harm, death.
Healey 2002	USA	Prospective	Teaching hospital	Patient record review	3,395 patients	Surgical patients	AEs	AEs defined as an unintended injury or complication resulting in disability, death, prolong hospital stay and caused by health care management rather than patient disease. Preventability: Injuries or problem normally survivable. Evaluation and management are suspect. Errors directly or indirectly cause patient's death.
Hendrie 2007	Australia	Retrospective	Hospital emergency department	Patient record review	3,332 patients	Emergency department patients' hospital	AEs	AEs defined as is an unintended injury or complication resulting in disability, death, prolong hospital stay and caused by health care management rather than patient disease. Severity: Serious=permanent injury or death; Moderate: new consultation, surgical treatment, medication or admission.
Herrera 2005	Mexico	Retrospective	Hospital	Patient record review	4,555 patients	Inpatients in Mexico	AEs	AEs defined as an unintended injury or complication resulting in disability, death, prolong hospital stay and caused by health care management rather than patient disease. Preventability: Injuries or problem normally survivable. Evaluation and management are suspect. Errors directly or indirectly cause patient's death.
Hogan 2012	UK	Retrospective	10 acute hospitals	Patient record review	1,000 patients	Case records of adults who died in 2009 in 10 acute hospitals in England	Deaths	Preventability: First, problems in care were defined as patient harm resulting from acts of omission or commission. Therefore, each case where a problem in care that had contributed to death had been identified, reviewers judged the preventability of death

Hoorgervorst-schiilp 2015	Holland	Retrospective	Hospital	Patient record review	2,975 patients	Hospital	ADEs	AEs defined as those resulting in prolong hospital stay and increase the cost of management
Hwang 2014	South Korea	Retrospective	Tertiary teaching hospital	Patient record review	629 patients	Patients discharged between January and June 2011	AEs	AEs defined as unintended harm to the patient, which occurred because of medical care or services rather than as a cause of underlying diseases or medical conditions. AEs related to the active delivery of care (acts of commission), but excluded those by acts of omission related to substandard care. Severity: mild, moderate, severe and death.
Kable 2002	Australia	Retrospective	Acute care hospitals	Patient record review	17,179 patients	Surgical and medical admissions 1992	AEs	AEs defined as an 'unintended injury or complication which results in disability, death or prolongation of hospital stay, and is caused but health care management rather than the patient's disease'. Severity: Severe=permanent injury or death, moderate=a new consultation, surgical treatment, medication or admission.
Kennerly 2014	USA	Prospective	8 acute care hospitals	Patient record review using the global trigger tool	9,017 patients	Adults admitted to eight acute care hospitals from 2007 to 2011 with lengths of stay ≥3 days were reviewed	AEs	AEs defined as an 'unintended injury or complication which results in disability, death or prolongation of hospital stay, and is caused but health care management rather than the patient's disease'. Severity: Severe=permanent injury or death, moderate=a new consultation, surgical treatment, medication or admission.
Khan 2016	USA	Prospective	Hospital	Written survey	383 patients	Children	AEs	AEs defined as harm prolonging admission.
Larsen 2007	USA	Retrospective	Hospital paediatric	Patient record review	259 patients	Paediatrics intensive care	AEs	AEs defined as an 'unintended injury or complication which results in disability, death or prolongation of hospital stay, and is caused but health care management rather than the patient's disease'. Severity: Severe=permanent injury or death, moderate=a new consultation, surgical treatment, medication or admission.
Letaief 2010	Tunisia	Retrospective	University hospital	Patient record review	620 patients	Patients admitted to university hospital	AEs	AEs defined as injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Preventability: AEs occurred because recommendations for care were not followed. Severity: Mild=recovery within 1 month, Moderate= resolved within 12 months, Serious=permanent impairment, degree of disability ,50%, death.
Lehmann 2005								
Lopez 2009	USA	Retrospective	Medical and surgical acute care hospitals	Patient interviews	603 patients	Patients admitted between April 1 and October 2003	AEs	No definition provided.
Lu 2006	USA	Retrospective	University affiliated Emergency department	Patient record review	124 patients	Adverse events resulting to preventable mortality (defined as mortality occurred within 24 hours after admission from the ED) over a 3 year period	Deaths	Preventable death. Preventability: actions or missed actions were identified that would have prevented death, types of preventability were categorised as – misdiagnosis, delayed diagnosis, and inappropriate medical management
Magdalijns 2015	Netherlands	Retrospective	Hospitals	Patient record review	3095	Patients admitted to hospitals	AEs	AEs defined as an unintended injury or harm resulting in death, temporary or permanent. Preventability: according to a six-point scale, with an adverse event classified as preventable when rated as 4 or more. disability or dysfunction, or prolonged hospital stay that arises from health care.
Maflow 2012	Canada	Cross-sectional	Hospitals	Patient record review	3669	Patients in pediatrics	AEs	AEs defined as an unintended injury or harm resulting in death, temporary or permanent. Preventability: according to a six-point scale, with an adverse event classified as preventable when rated as 4 or more. disability or dysfunction, or prolonged hospital stay that arises from health care.

Mendes 2009	Brazil	Retrospective	Hospitals	Patient record review	1,103 patients	Patients admitted in 2003 with a stay over 24 hours, over the age of 18, not psychiatric patients.	AEs	AEs defined as an unintended injury or harm resulting in death, temporary or permanent. Preventability: according to a six-point scale, with an adverse event classified as preventable when rated as 4 or more. disability or dysfunction, or prolonged hospital stay that arises from health care.
Merino 2012	Spain	Retrospective	Hospital intensive care	Observational	1,017 patients	Intensive care patients	AEs	AEs defined as an incident that results in harm to the patient. Harm implied impairment of structure or function of the body. Severity: Mild=recovery within 1 month, Moderate= resolved within 12 months, Serious=permanent impairment, degree of disability ,50%, death.
Merten 2013 (a,b)	Netherlands	Retrospective	University, tertiary and general hospitals	Patient record review	7,926 patients	Admitted in 2004 - deceased and discharged patients with a stay over 24 hrs and above the age of 18	AEs	AEs defined as (i) an unintended physical or mental injury, which (ii) resulted in the prolongation of hospital stay, temporary or permanent disability or death, and was (iii) caused by healthcare management rather than the underlying disease. Preventability: resulting from an error in management due to failure to follow accepted practice at an individual or system level and was measured on a six-point scale.
Michel 2004 (a,b,c)	France	Cross-sectional; Prospective; Retrospective.	Hospitals	Patient record review	778 patients	Medical, surgical and obstetric patients.	AEs	AEs defined as an unintended injury caused by medical management rather than by a disease process and which resulted in death, life threatening illness, disability at time of discharge, admission to hospital, or prolongation of hospital stay. Preventability: AEs would not have occurred if the patient had received ordinary standards of care appropriate for the time of the study.
Montserrat-capella 2015	Mexico. Peru, brazil, Colombia	Prospective	Outpatient clinics	Interviews	2,080 patients	Patients included were over 18 years of age visiting outpatient departments	AEs	AEs defined as an unintended harm to the patient resulting from the direct provision of health care or because of it. Preventability: 6-point scale of confidence that the AE could have been prevented using a cut-off point of ≥4 for the AE to be deemed preventable. Severity: Mild=recovery within 1 month, Moderate= resolved within 12 months, Serious=permanent impairment, degree of disability ,50%, death.
Najjar 2013	Israel	Retrospective	Hospital	Patient record review	640 patients	Hospital	AEs	AEs defined as harm causing increase hospital stay and death
Nilsson 2012	Sweden	Retrospective	Hospital	Patient record review	128 patients	Hospital in intensive care	Severe AEs	AEs defined as events that will prolong hospital stay or caused death
Nilsson 2016	Sweden	Retrospective	Hospital	Patient record review	3,301 patients	Hospitals surgical patients	AEs	AEs defined as events that will prolong hospital stay or caused death. Preventability: six-grade scale. Grades 4–6 are considered avoidable harm. Severity: Level of harm according to National Coordination Council for Medication Error Reporting and Prevention (NCC MERP) index*. Only Categories E–I is included in Global Trigger Tool.
Nuckols 2007	USA	Retrospective	Hospital	Patient record review	2244 patients	Hospital and an affiliated community centre	AEs	AEs defined as an unintended event the event resulted in patient harm (prolongation of hospital stays, disability at discharge and/or extra cost of treatment) caused by healthcare rather than by disease process alone.
Pucher 2013	UK	Retrospective	Hospital	Patient record review	1,752	Hospitals (Trauma care)	AEs	AEs defined as an unintended injury or harm resulting in death, temporary or permanent. Preventability: according to a six-point scale, with an adverse event classified as preventable when rated as 4 or more. disability or dysfunction, or prolonged hospital stay that arises from health care.
Rajasekaran 2016	India	Prospective	Orthopedics	Patient record review	4,906	Patients admitted to Orthopedics	AEs	AEs defined as an unintended injury or harm resulting in death, temporary or permanent. Preventability: according to a six-point scale, with an adverse event classified as preventable when rated as 4 or more. disability or dysfunction, or prolonged hospital stay that arises from health care.
Rothschild	USA	Retrospective	Hospital	Patient record	391 patients	Hospital critical care & coronary care	AEs	AEs defined as events prolonging duration of admission & causing serious

2005			critical care	review		patients		harm & death. Preventability: defined as failure a planned action to be completed as intended or the use of a wrong plan to achieve the aim
Sari 2007/2008	UK	Retrospective	Large NHS hospital	Patient record review	1,006 admissions	All admissions lasting more than 24 hours in 8 specialties	AEs	AEs defined as an unintended event the event resulted in patient harm (prolongation of hospital stays, disability at discharge and/or extra cost of treatment) caused by healthcare rather than by disease process alone. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Sari 2015	Iran	Retrospective	Hospitals	Patient record review	1,162 patients	Adult hospital patients	AEs	AEs defined as events requiring prolonged admission. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Soop 2009	Sweden	Retrospective	Hospitals	Patient record review	1,967 patients	All medical records acute care hospitals from October 2003 - 2004.	AEs	AEs defined as unintended injuries or complications (fulfilling 4 criteria using a scale from 1 to 6). Preventability: using a scale from 1 to 6. At ratings of at least 4, adverse events were classified as preventable. Severity: Serious=permanent disability or death
Sousa 2014	Portugal	Retrospective	Acute hospitals	Patient record review	1,669 patients	All patients above 18 in 3 acute hospital beds in emergency departments, intensive care units and high-volume surgery.	AEs	AEs defined as an unintended event the event resulted in patient harm (prolongation of hospital stays, disability at discharge and/or extra cost of treatment) caused by healthcare rather than by disease process alone. Preventability: using a scale from 1 to 6. At ratings of at least 4, adverse events were classified as preventable. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Stockwell 2015	USA	Retrospective	6 academic children's hospitals	Patient record review	600 patients	Pediatrics inpatients discharged in February 2012 from 6 selected children's acute hospitals	AEs	AEs defined as an unintended event the event resulted in patient harm (prolongation of hospital stays, disability at discharge and/or extra cost of treatment) caused by healthcare rather than by disease process alone. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Suarez 2014	Spain	Retrospective	Acute geriatric hospital	Patient record review	1,440 patients	All geriatric patients between January 2007 - December 2012	AEs	AEs defined as "unintended physical injuries resulting from medical care that require additional monitoring, treatment, or hospitalization, or that result in death." Preventability: using a scale from 1 to 6. At ratings of at least 4, adverse events were classified as preventable. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Thomas 2000(a,b)	USA	Retrospective	State psychiatric hospital	Patient record review	93 patients	Psychiatric inpatients	AEs	AEs defined as an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalization, produced a disability at the time of discharge, or both. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Vincent 2001	UK	Retrospective	Two acute hospitals	Patient record review	1,014 patients	Patient health records from 4 specialties (general medicine, including geriatrics; general surgery; orthopaedic surgery and obstetrics)	AEs	AEs defined as an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalization, produced a disability at the time of discharge, or both. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Weingart 2005	USA	Prospective	Medical unit	Patient record	228 patients	Patients admitted to study unit during study	AEs	AEs defined as injuries because of medical care rather than the natural history

			of teaching hospital	review and patient interviews		period		of the illness. Preventability: AEs caused by errors. Involving parties, and process of care deficiencies. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Wilson 2012	8 African countries	Retrospective	Hospitals		15,548 patients	Inpatients	AEs	AEs defined as an unintended injury or harm resulting in death, temporary or permanent. Preventability: according to a six-point scale, with an adverse event classified as preventable when rated as 4 or more. disability or dysfunction, or prolonged hospital stay that arises from health care.
Woods 2006	USA	Retrospective	5 hospitals	Patient record review	879 patients	Adolescent (13-20 years old) in comparison to other age groups	AEs	AEs defined as an injury caused by medical intervention or management, rather than the disease process, which either prolonged the hospital stay or caused disability at discharge. Preventability: an AE where there was enough information currently available to have prevented the event using currently accepted practices. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Zegers 2009	Netherlands	Retrospective	21 hospitals	Patient record review	7,926 patients	Randomly selected admissions of discharged and deceased patients	AEs	AEs defined as an unintended injury that results in temporary or permanent disability, death or prolonged hospital stay, and is caused by healthcare management rather than by the patient's underlying disease process. Severity: Mild=Impairment or disability resolved within a month; Moderate= impairment or disability resolved within 12 months; serious= permanent disability or patient death.
Zwaan 2010	Netherlands	Cross-sectional	21 acute care hospitals	Patient record review	7,926 patients	Hospital inpatients	AEs	AEs defined as an unintended injury that results in temporary or permanent disability, death or prolonged hospital stay, and is caused by healthcare management rather than by the patient's underlying disease process.

AEs=Adverse events. n/r=not reported

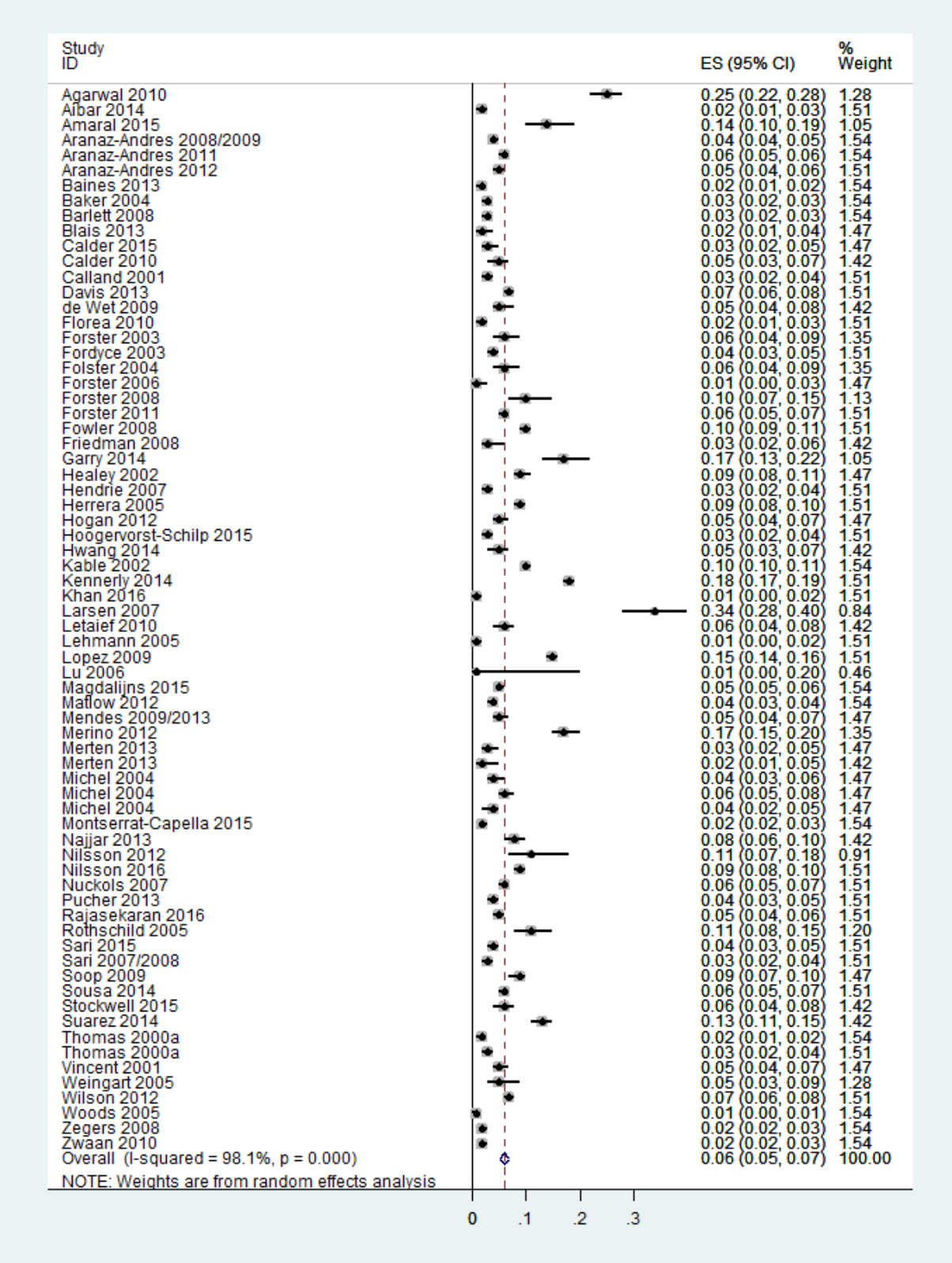

Figure 7 Forest plot of the pooled prevalence rates of overall preventable harm

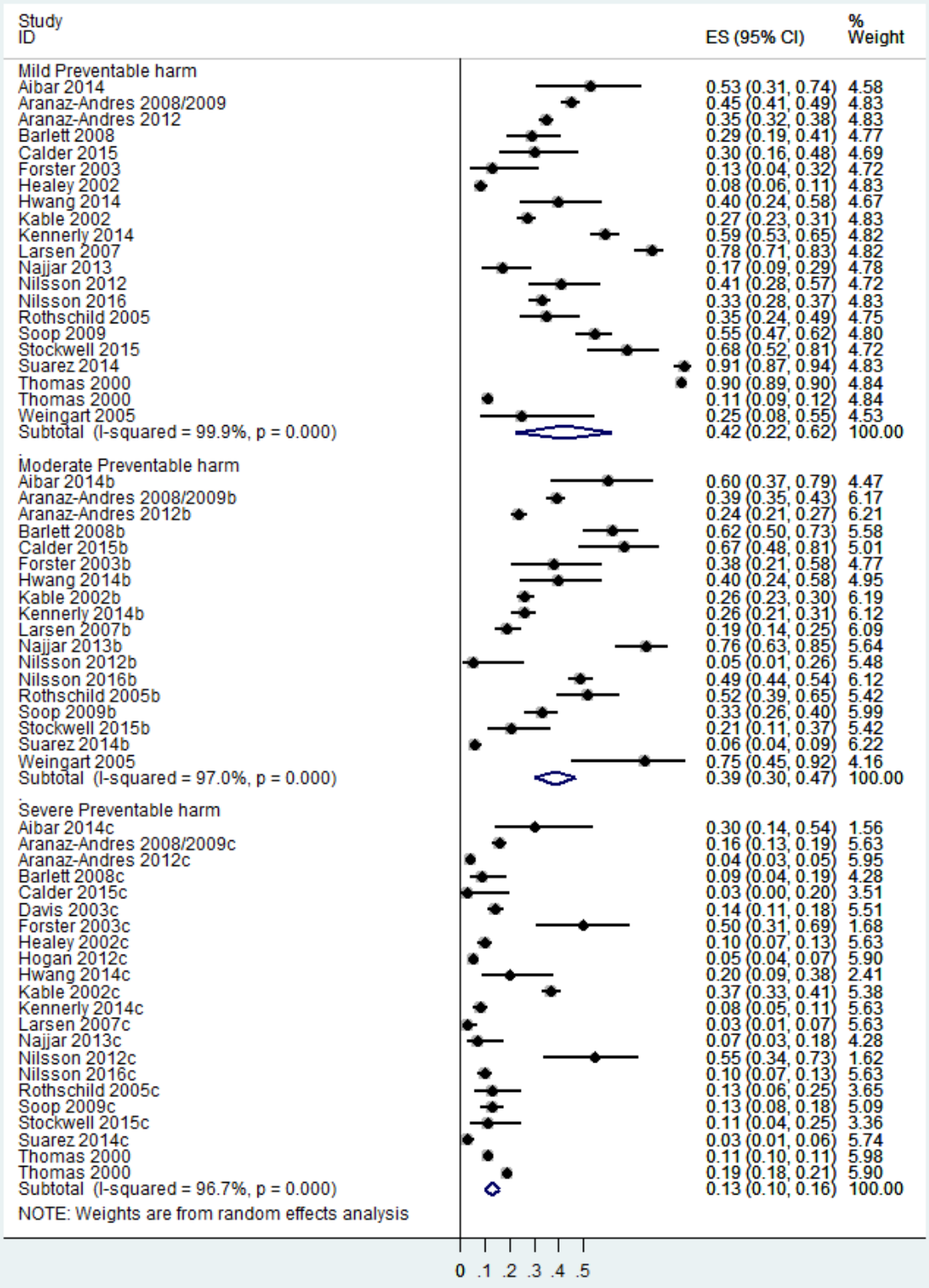

Figure 8 Forest plot of the pooled severity proportions of the overall preventable harm

Appendix 2: The validity of the results on overall preventable harm

A considerable number of studies (29 out of 71 studies; 40%) were published between January 2011 and December 2016. We carried out a sensitivity analysis, in which we retained in the analyses only studies published between 2011 and 2017. The results across the studies published 2011 onwards did not differ significantly in any of our core outcomes including the prevalence rates, the severity proportions and types of preventable harm compared to the main analyses based on all studies from 2000 onwards. There were only some methodological improvements in recent studies such as that they tended to provide more clear/comprehensive definitions of harm and preventability and severity of harm. Although this is an encouraging observation because it suggests that the reporting standards have been improved over time, key reporting limitations still exist. In particular, only 1/3 of the studies reported consistent and usable data for meta-analysis on the severity of harm and described types/sources of preventable harm irrespective of publication date (all studies 22/71; 11/29 studies published from 2011 onwards).

The majority of the included studies were retrospective reviews of the medical records of patients (n=41 of 71 studies) followed by prospective studies (n=20 of 71 studies) studies and cross-sectional studies (10 of 71 studies). We conducted a sensitivity analysis which examined the prevalence rates, proportions of common types and the severity proportions of harm based on prospective studies only. As shown in Table 14, the prevalence rate of preventable harm in prospective studies was similar to the prevalence rate of preventable harm found across all 71 studies. In terms of proportions of common types of harm, the medication-related and clinical management and diagnostic incidents accounted for the largest proportion of the preventable harm as in the main analyses of all 71 studies.

Table 14 Sensitivity analyses on overall preventable harm

Outcome	N	All studies Mean % (95% CI)	N	Studies 2011-2017 Mean % (95% CI)	N	Prospective studies Mean % (95% CI)
Prevalence rates (at patient level)	71	6 (5 to 7)	32	6 (5 to 8)	20	6 (4 to 8)
Types of harm (proportions of the identified harm)						
Medication	25	25 (15 to 35)	12	21 (13 to 28)	5	30 (10 to 50)
Diagnostic harm	20	17 (11 to 21)	9	17 (11 to 22)	2	23 (10 to 32)
Procedure	20	21 (11 to 31)	8	21 (14 to 26)	3	13 (4 to 23)
Management	17	25 (20 to 31)	8	32 (15 to 49)	2	33 (20 to 47)
Surgical	18	16 (14 to 17)	9	27 (1 to 53)	2	17 (4 to 11)
Infections	14	17 (11 to 22)	7	17 (9 to 24)	2	14 (8 to 20)
Severity of harm (proportions of the identified harm)						
Mild	21	42 (22 to 62)	10	47 (28 to 65)	5	37 (10 to 45)
Moderate	18	39 (30 to 47)	10	37 (24 to 49)	4	50 (25 to 75)
Severe	22	13 (10 to 16)	11	8 (5 to 10)	4	12 (5 to 19)

Notes: N= number of studies; n/r= not reported; The proportions of types of harm and the proportions of the severity of harm do not add to 100% because each figure in the table is the pooled proportion which has been calculated by pooling (combining using appropriate weights) proportions extracted from several independent studies using meta-analysis.

Table 15 Characteristics of studies on preventable medication-related harm

Study ID	Country	Research design	Setting	Assessment method	N	Population	Type	Details
Ahern 2014	Ireland	Prospective	Emergency department in University Hospital	Observational study	856	Patients admitted to ED	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Hallas criteria. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Alam 2014	Nepal	Cross-sectional	General medical ward in a tertiary care teaching hospital	Patient record review	1,105	Patients who stayed at least 24 hours and used at least one medicine	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Aljadhey 2013	Saudi Arabia	Prospective	Tertiary academic hospital	Patient record review	977	Patients admitted to two medical, one surgical and two intensive care units	ADEs	ADEs defined as an injury caused by a medication, which include both ADRs as well as harmful effects arising from errors at any medication use stage including ordering, transcribing, dispensing, administering or monitoring of a drug. Severity: Moderate= requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Alsbou 2010	Jordan	Cross-sectional	Internal medicine and Intensive Care Unit (ICU) of a hospital	Patient record review	200	Patients admitted to internal medicine/ICU over a 4-week period	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Hartwig scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Alsbou 2015	Jordan	Cross-sectional	Teaching hospital	Patient record review and patient interviews	64	Patients that developed/suffered an ADR	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Hartwig scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Al tajir 2005	Arab Emirates	Prospective	Urban tertiary care hospital	Observational study	828	Patients in urban tertiary care hospital	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.
Baena 2014	Spain	Cross sectional	Emergency departments of 9 hospitals	Patient record review and patient interviews	4,611	Patients attending ED of 9 Spanish hospitals	ADEs	ADEs defined as outcomes that are not consistent with the objectives of pharmacotherapy and are associated with the use or errors in the use of medicines. Severity: Measured according to the classification criteria of the Spanish pharmacovigilance system for adverse drug reactions
Benkirane 2009a,b,c,d	Morocco	Prospective	7 ICU wards in academic and military hospital of Rabat.	Observational study with incident reports	696	Adult and paediatric patients in medical/surgical intensive care units for 3 months	ADEs	ADEs defined as any injury resulting from medical interventions related to a drug and includes both ADRs in which no error occurred and complications resulting from ADEs. Severity: according to WHO; Moderate=requires treatment/prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.

Benard-laribiere 2015	France	Prospective	Public, teaching and general hospitals of metropolitan France.	Patient record review	2,692	All patients admitted during a 2-week period in public hospitals	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.
Buckley 2007	USA	Prospective	Intensive care	Incident report and Patient record review and patient interviews	4,321	Patients with medication error reports	ADEs	ADEs defined as an injury from a medication (or lack of intended medication). Severity: The institution categorizes medication error severity using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index.
Calderon-Ospina 2010	Columbia	Cross-sectional	Clinical universitaria teletón, a level three complexity care institution	Patient record review	104	All adult patients admitted	ADEs	ADE defined as any injury resulting from medical interventions related to a drug and includes both ADRs in which no error occurred and complications resulting from ADEs. Severity: according to WHO; Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Carayon 2014	USA	Cross-sectional	A 24-bed adult medical/surgical ICU and an 18-bed cardiac ICU in a tertiary care hospital	Patient care documents and incident reports	630	All adult inpatients Consecutive ICU patient admissions	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Schumock and Thornton criteria.. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Castro 2013	Spain	Cross-sectional	Emergency department of a 650-bed university tertiary hospital.	Questionnaire and emergency department Patient record review	588	Emergency department patients' Consecutive ICU patient admissions	ADEs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: ADEs due to medical erros. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Chan 2001	Australia	Prospective	Acute medical units of the Royal Hobart Hospital	Patient record review and patient interview	240	Acute, unplanned, emergency admissions to medical wards of patients who were 75 years or older	ADEs	ADEs defined as patient health outcomes that are not consistent with the objectives of pharmacotherapy and are associated with the use or errors in the use of medicines. Preventability: assessed using the guidelines published by the Pharmaceutical Care Research Group at the University of Granada, Spain. Severity: According to Spanish Surveillance system Fatal=death as a result of the event; Severe= a directly-related life-threatening event; Moderate= a non-life-threatening event, requiring hospitalization or care in the emergency department, or sick leave Mild=all others
Chane Esthetie 2015	US	Prospective	Emergency department of a 650-bed university tertiary hospital.	Questionnaire and emergency department Patient record review	588	Emergency department patients' Consecutive ICU patient admissions	ADEs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: ADEs due to medical erros. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Chen 2012	Taiwan	Prospective	Urban, tertiary medical centre	Patient interview	452	Patients 18 years and older presenting to the ED	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: ADRs related to wrong dosage, poor monitoring, poor drug selection or incorrect administration. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Damen 2017	US	Prospective	Urban, tertiary medical centre	Patient interview	452	Patients 18 years and older presenting	ADEs	ADE cases were defined as the following mechanisms of injury: allergic reactions (immunologically mediated effects), adverse effects (undesirable pharmacologic effects at recommended doses) and

						to the ED		unintentional overdoses (toxic effects linked to excess dose or impaired excretion). Preventability: ADRs related to wrong dosage, poor monitoring, poor drug selection or incorrect administration. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Davies 2009	UK	Prospective	Emergency department	Observational study	3,322	Patients admitted to 12 wards	ADEs	ADE cases were defined as the following mechanisms of injury: allergic reactions (immunologically mediated effects), adverse effects (undesirable pharmacologic effects at recommended doses) and unintentional overdoses (toxic effects linked to excess dose or impaired excretion). Preventability: ADRs related to wrong dosage, poor monitoring, poor drug selection or incorrect administration. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Davies 2010	UK	Prospective	Hospitals	Observational study	1,000	Patients admitted to 12 wards	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.ADRs that occurred during admission as a result of drugs initiated or continued in hospital were included, while community acquired
De Boer 2013	Holland	Prospective	Hospital, multicentre using eight surgical wards	Observational Patient record review screening using surgical trigger tool	567	Surgical patients from 3 hospitals with a hospital stay longer than 48 h	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. ADRs that occurred during admission as a result of drugs initiated or continued in hospital were included, while community acquired
Dequito 2011	Netherlan ds	Prospective	Hospital	Patient record review	603	Patients admitted to two Dutch hospitals	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: ADRs caused by a medication error.
Easton 2003	France	Prospective	60-bed geriatric unit of a French university hospital	Information obtained from patient, patient's GP and patient's family if cognitively impaired.	2,814	Inpatients over 70 years of age who were consecutively admitted	ADRs	ADRs defined any response to a drug that is undesirable, unexpected, and occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease'. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requir
Farcas 2010	USA	Retrospective	Internal medicine	Patient record review	n/r	n/r	ADRs	ADRs defined any response to a drug that is undesirable, unexpected, and occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease'. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requir
Farcas 2014	USA	Retrospective	Internal medicine	Patient record review and reports froms	1,523	All persons aged 65 or older receiving health care services	ADRs	ADRs defined any response to a drug that is undesirable, unexpected, and occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease'. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Forster 2004	Canada	Prospective	Teaching hospital	Pharmaceutical surveillance	543	All patients admitted to the general medicine service	ADEs	ADEs defined as an injury resulting from the use of a drug. Preventability: ADEs due to an error and were preventable by any means available.
Forster 2005	USA	Prospective	Urban academic health sciences centre.	Patient record review and telephone	400	Consecutive patients discharged home from the general	ADEs	ADEs defined as any adverse outcome or patient injury that was caused by medication use. ADEs due to an error and were preventable by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-

				interview.		medical service		threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Francesc hi 2008	Italy	Prospective	Geriatric hospital unit	Structured interview and clinical visits including standard laboratory and instrumental tests.	1,756	All the patients aged ≥65 years admitted to the Geriatric unit	ADEs	ADEs defined as any adverse outcome or patient injury that was caused by medication use. ADEs due to an error and were preventable by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Gallagher 2012	UK	Prospective	A large tertiary children's hospital	Observational study	6,821	Patients admitted acutely to a paediatric hospital	ADRs	ADRs defined as appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product. Preventability: whether hazard can be predicted from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.
Gandhi 2003	USA	Prospective	Four adult primary care practices in Boston	Survey of patients and Patient record review	661	Outpatients older than 18 years	ADRs	ADEs defined as any adverse outcome or patient injury that was caused by medication use. ADEs due to an error and were preventable by any means available. Severity: According to Hartwig Mild=does require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Geer 2016	Kashmir, India	Prospective	In- and Out-patient departments of Internal Medicine and Accident & Emergency department of a tertiary care hospital	Medical/nursing record review.	5,482	Adult patients admitted in Internal Medicine in-patient department	ADEs	ADEs defined as any harm in the medication process (ordering, transcribing, dispensing, administering, and monitoring). Preventability: caused by preventable errors. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Grenouill et-delacre 2007	France	Prospective	A teaching hospital medical intensive care unit	Computerised medical information according to the international classification of diseases	405	All patients aged over 15 years and who had received documented drug treatment	ADRs	ADRs defined as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of.disease or for the restoration, correction or modification of physiological function. Severity: According to Hartwig Mild=does require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Gurwitz 2000	USA	Retrospective	Multi-speciality group practice	Reports from health care providers and Patient record review	27,617	Medicare enrolees receiving medical care	ADRs	Life-threatening ADRs, defined as serious ADRs that resulted in acute organ failure leading to ICU admission, in artificial life support or in death. Preventability: when all conditions for avoidance of the ADR occurrence were fulfilled. Severity: Mild=does require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Gurwitz 2003	USA	Retrospective	18 community-based nursing homes	Self-report by nursing home staff and Patient record review	2,916	All long-term care residents of 18 community-based nursing homes	ADEs	ADEs defined as an injury resulting from the use of a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Gurwitz 2005	Canada	Retrospective	2 academic long-term care facilities	Patient record review	1,247	All long-stay residents of two academic long-term care facilities	ADEs	ADEs efined as an injury resulting from the use of a drug. Adverse drug events may have resulted from medication errors (ie, errors in prescribing, dispensing, administration, and monitoring) or from adverse drug reactions in which no error was involved. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does require

								treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Haile 2013	India	Prospective	Tertiary care hospital	Patient record review	1,033	Subjects admitted to hospital	ADEs	ADEs defined as an injury resulting from the use of a drug. Adverse drug events may have resulted from medication errors (ie, errors in prescribing, dispensing, administration, and monitoring) or from adverse drug reactions in which no error was involved. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Hamilton 2011	Ireland	Prospective	University teaching hospital	Patient record review and patient/caregiver interviews.	600	Consecutive patients 65 years or older who were admitted with acute illness	ADEs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Hallas criteria. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Hardmeier 2004	Switzerland	Prospective	Two hospitals	Patient record review	6,383	Patients with ADE or ADE related hospital admissions	ADRs	ADRs defined as the noxious and unintended drug responses which occur at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function". Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Harkanen 2015	Finland	Retrospective	800-bed university hospital	Patient record review using Global Trigger Tool	463	Randomly selected adult hospital inpatients records using the Global Trigger Tool	ADEs	ADEs defined as drug related events resulting in considerable discomfort, drug withdrawal or dose reduction and/or initiation of therapeutic measures. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Harugeri 2011	India	Prospective	Medicine wards of two tertiary care teaching hospitals	Patient record review	920	Hospitalised medical Indian elderly inpatients of 60 years	ADEs	ADEs defined as unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalisation, or that results in death'. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Hayward 2001	USA	Retrospective	Hospital	Patient record review	889	Patient records deceased patients	ADEs	ADEs defined as unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalisation, or that results in death'. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: death of patient
Hoonhout 2011	Netherlands	Retrospective	Hospital	Patient record review	7,889	Patients admitted to 21 hospitals in 2004	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Howard 2003	USA	Retrospective	Hospital	Patient record review	1,889	Patient records	ADEs	ADEs defined as unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalisation, or that results in death'. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means

								available.
Hug 2010	USA	Retrospective	6 community hospitals with 100 to 300 beds.	Patient record review	1,200	Adult patients hospitalized	ADEs	ADEs defined on three criteria: (i) an unintended physical or mental injury, which (ii) resulted in prolongation of the hospital stay, temporary or permanent disability or death, and was (iii) caused by healthcare management rather than the underlying disease. Preventability: Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Jha 2001	USA	Prospective	Tertiary care hospital	Patient record review	3,238	Patients admitted to medical and surgical unites	ADEs	ADEs was defined as an injury resulting from medical intervention related to a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Jonsson 2010	Sweden	Retrospective	Unclear	Patient record review	1,574	Deceased patients from Fatal adverse drug reaction	ADEs	ADEs was defined as an injury resulting from medical intervention related to a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Kalish 2012	USA	Retrospective	Hospital	Patient record review	14,041	Medication administrations	ADEs	ADEs was defined as an injury resulting from medical intervention related to a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Kaushal 2001	USA	Prospective	2 urban teaching hospitals.	Patient record review and observational	1,120	Paediatric, 6 weeks	ADEs	ADEs were defined as injuries that result from medication use. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Kaushal 2007	USA	Prospective	Office practices	Patient record review and patient surveys	1,788	Ambulatory Paediatric patients under the age of 21	ADES	ADEs were defined as injuries that result from medication use. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Klopotowska 2013	Netherlands	Retrospective	Hospital	Patient record review using the global trigger tool	250	Older hospitalised patients	ADEs	ADEs were defined as injuries that result from medication use. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Kopp 2006	USA	Prospective	Tertiary care academic medical study	Direct observation	185	Patients in a medical/ surgical intensive care unit.	ADEs	ADEs defined as any harmful event occurring during drug therapy. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Kunac 2009	New Zealand	Prospective	Hospitalised children	Patient record review, interviews and reports from staff	495	Paediatric, neonatal intensive care unit	ADEs	ADEs defined as an injury or patient harm occurring as the result of a medication intervention. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death

								of patient, is permanently disabling, requires intensive medical care.
Lopez 2009	USA	Prospective	Medical and surgical acute care department of hospital	Telephone interviews	4,163	Adults above 18 , who were medical or surgical patients	ADEs	ADEs defined as injuries to patients' due to a medication. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Lovborg 2012	Sweden	Retrospective	ADR records sent to the Medical products Agency	Patient record review	702	All patient records indicating ADR	ADEs	ADEs defined as injuries to patients' due to a medication. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Meier 2015	Germany	Prospective	Tertiary care hospital	Patient record review	2,262	All adult non-trauma ED admissions	ADEs	ADRs defined as all noxious and unintended responses to a medicinal product related to any dose.
Miller 2006	Australia	Prospective	GP surgeries	Observational study	8,215	Patients visiting General Practice appointments	ADEs	ADEs as wrong and inadequate use of medication comprising, for example, ignored contra-indications, missing indications, and wrong dosage.
Morimoto 2011	Japan	Prospective	Medical and surgical wards, intensive care units in 2 tertiary hospitals	Daily reviews of charts, laboratories, incident reports,	3,459	Adults admitted to medical, surgical, or intensive care units in tertiary hospitals	ADEs	ADEs defined as injuries to patients' due to a medication. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Morris 2004	UK	Prospective	Primary Care	Observation and Patient record review	370	Patients to hospital via emergency department	ADEs	ADEs in exaggeration of drugs normal pharmacologic action when given in the usual therapeutic dose, or B those representing a novel response not expected from known pharmacologic action. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Olivier 2002	France	Prospective	Hospital	Patient record review	671	Patients over 15 admitted to an emergency department.	ADEs	ADE defined as an injury due to a medication. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Park 2013	South Korea	Retrospective	Tertiary care teaching hospital, intensive care unit	Patient record review	346	Patients admitted to ICU over 4 months	ADRs	ADRs defined as harmful and undesirable manifestations attributed to a drug, whose occurrence is apparently related to a known pharmacological property of this drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available.
Patel 2007	India	Prospective	Hospital - medical division of Emergency department	Observation	6,899	Patients above the age of 18	ADRs	ADRs defined as a response to a medicine that is noxious and unintended, and that occurs at doses normally used in humans. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Peyriere 2003	France	Prospective	Hospital internal medicine department	Patient record review	156	All patients admitted to the internal medicine	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.

Phillips 2014	Australia	Prospective	Metropolitan teaching hospital	Observation and Patient record review	370	Patients to hospital via emergency department	ADEs	ADEs in exaggeration of drugs normal pharmacologic action when given in the usual therapeutic dose, or B those representing a novel response not expected from known pharmacologic action. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Pirmohamed 2004	UK	Prospective	Hospitals	Patient record review, staff / patient interview	18,820	Patients admitted to 2 hospitals	ADEs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Pourseyed 2009	Iran	Prospective	Internal medicine ward of a general university hospital	Questionnaires	400	Patients admitted to the internal medicine ward.	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Remesh 2014	India	Prospective	Tertiary care hospital	Observation	91	Patients who had experienced at least one suspected ADR after hospitalisation	ADRs	ADRs defined as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function'. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Rothschild 2007	USA	Prospective	Academic psychiatric hospital	Patient record review	1,559	Patients admitted to psychiatric hospital	ADRs	ADRs defined as a response to a medicine that is noxious and unintended, and that occurs at doses normally used in humans. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Sakuma 2014	Japan	Prospective	2 tertiary care teaching hospitals in japan	Patient record review	1,189	Paediatric inpatients	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Samoy 2006	USA	Retrospective	Hospital surveillance programme	Patient record review	565	n/r	ADEs	ADEs defined as injuries due to medication use. medication errors, which were defined as any deviation from appropriate use of medication in any step of the medication use process including ordering, transcribing, dispensing, administering or monitoring. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Sriram 2011	India	Prospective	General medicine department of a tertiary hospital	ADR notification form, telephone reporting, direct access, referral of patients	3,117	All patients of either sex and of any age who developed an ADR	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.

Takata 2008	USA	Retrospective	Children's hospitals	Patient record review using trigger tool	960	Paediatrics	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Preventability: Based on Modified Hartwig and Siegel scale. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Tangiisuran 2012	United Kingdom	Cross-sectional	Elderly wards in two hospitals	Observation	560	Patients over 80 years of age admitted to elderly wards in hospitals	ADEs	ADEs defined as "an injury, large or small, caused by the use (including non-use) of a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available.
Van der Hooft 2008	Netherlands	Prospective	General practice research database	Patient record review	3,515	Patients who had been registered with the GP	ADRs	ADRs defined as an unexpected, unintended, undesired, or excessive response to a drug. This includes allergic reactions and idiosyncratic reactions that are an abnormal susceptibility to a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available.
Van doormaal 2009	Netherlands	Prospective	Five internal medicine wards in 2 hospitals	Patient record review	592	Patients admitted to internal medicine wards of hospital	ADRs	ADRs defined as unwanted, negative consequence associated with the use of pharmacological agents at a therapeutic dose leading to hospital admission. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available.
Zandieh 2008	USA	Prospective	Boston office paediatric practices & teaching hospitals	Patient surveys and Patient record review	1,689	Paediatrics patients under the age of 21	ADRs	ADRs defined according to WHO any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Severity: Mild=does not require treatment or prolongation of hospital stay. Moderate=requires treatment or prolongs hospitalisation. Severe: life-threatening or contributes to death of patient, is permanently disabling, requires intensive medical care.
Zed 2008	USA	Retrospective	Teaching hospital	Patient record review	2,571	ADR reports	ADEs	ADEs defined as "an injury, large or small, caused by the use (including non-use) of a drug. Preventability: ADEs were considered preventable if they were due to an error and could be prevented by any means available.

ADES= Adverse drug events; ADRs=Adverse drug reactions; n/r=not reported.

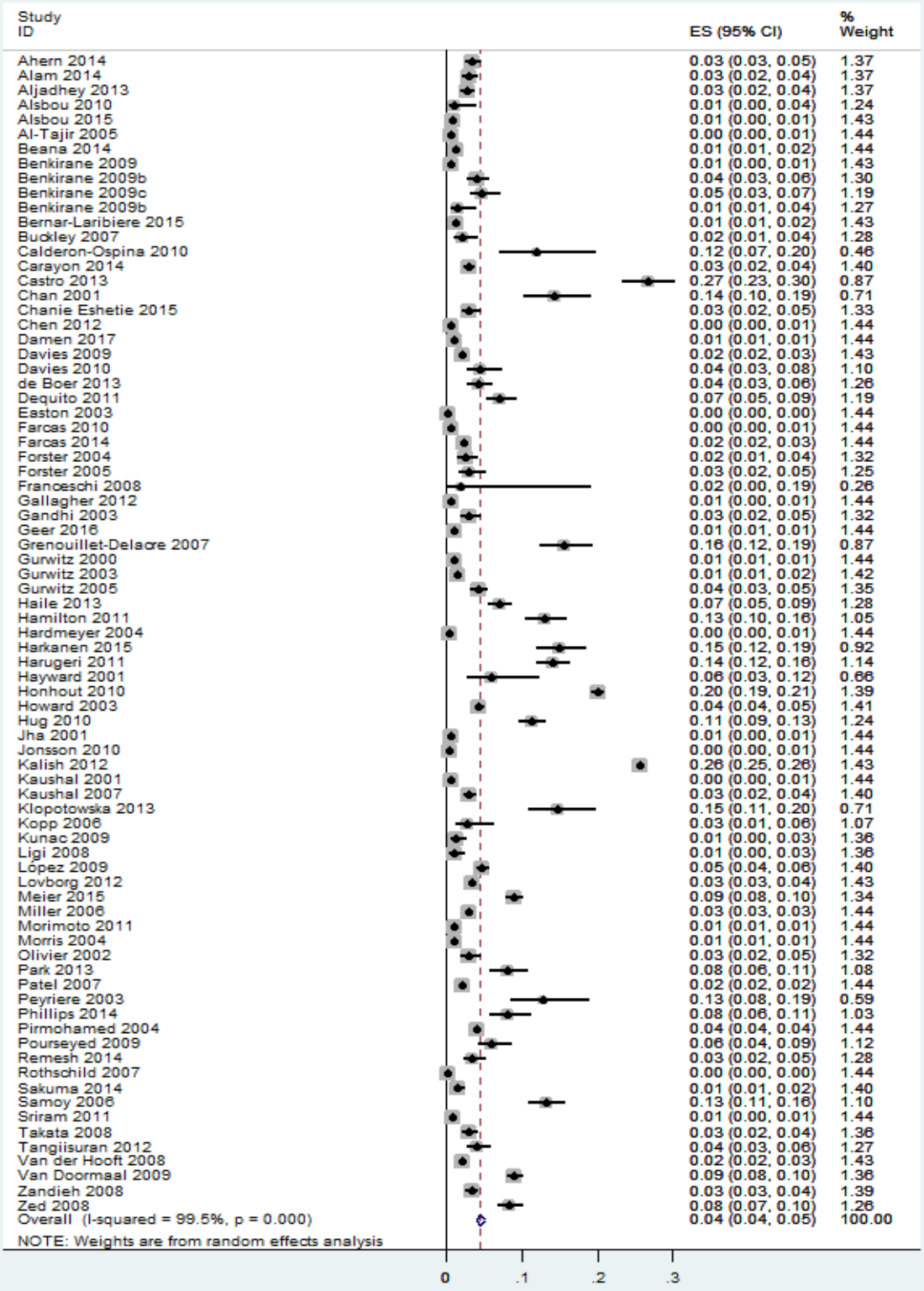

Figure 9 Forest plot of the pooled prevalence rates of overall medication preventable harm

Appendix 3: The validity of the results on preventable medication-related harm

Thirty-one out of 78 (40%) were published between January 2011 and January 2017. As shown in Table 6, studies published in 2011 onwards tended to report a higher rate of preventable harm (6% versus 4%) and more severe harm compared to the main analyses based on all studies from 2000 onwards. This finding might reflect improvements in the assessment methods of preventable ADES and ADRs following the growing recognition that they are important sources of preventable harm.

The second sensitivity analysis examined the prevalence rates and the severity of medication-related harm based on prospective studies only (n=56 out of 78 studies; 72%). The prevalence rate and severity proportions of preventable medication-related harm in prospective studies was similar to the prevalence rate and severity of preventable medication-related harm proportions found across all 78 studies (see Table 16).

Table 16 Sensitivity analyses on preventable medication-related harm.

Outcome	**N**	**All studies** **Mean % (95% CI)**	**N**	**Studies 2011-2017** **Mean % (95% CI)**	**N**	**Prospective studies** **Mean % (95% CI)**
Prevalence rate of harm (at patient level)	78	4 (4 to 5)	31	6 (4 to 7)	20	3 (3 to 4)
What proportion of this harm is severe?	21	19 (15 to 24)	11	28 (18 to 44)	14	18 (12 to 24)

Notes: N= number of studies; n/r= not reported.