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The economic burden of preventable adverse drug reactions: a systematic review of observational studies

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Abstract

Introduction: Adverse drug reactions (ADRs) are an important cause of morbidity and mortality worldwide. They are associated with healthcare costs due to hospital admissions or prolonged length of stay (LOS), as well as additional interventions. The aim of this study was to conduct a systematic review of observational studies to evaluate the economic impact of preventable ADRs.

Areas covered: Published observational research investigating the cost of preventable ADRs in Western countries (limited to the US and European countries).

Expert opinion: Several reviews have been carried out in the field of the ADR epidemiology but fewer reviews have investigated the economic impact of ADRs, and at the time of writing, none has focused on preventable ADRs. The reason why future research should focus on the costs of preventable ADRs is that both the costs and the clinical outcomes are preventable, and as such, are a key point of public health policy action. Nevertheless, the present review highlights an important and sobering limitation of published research on the cost of preventable ADRs, of which the major limitation is the heterogeneity in methods and in reporting limit what can be known through a summarizing work of a systematic review.

Keywords:

adverse drug reaction, systematic review, cost, adverse drug events, health expenditure, preventability

Article highlights
Several observational studies suggest that adverse drug reactions (ADRs) have a significant economic impact in both in- and out-patient settings. However, to our knowledge no recent review has summarised and evaluated the economic impact of preventable ADRs.
The present study shows a significant heterogeneity among observational studies evaluating the economic impact of ADRs, whether in terms of ADR definition as well as in terms of ADR causality and preventability assessment, and also in terms of economic outcomes.
Among the studies included in the present review, there was a lack of information on preventable ADRs among elderly populations specifically, even though this population is arguably at a very high risk of ADRs and vulnerable to the ADR sequelae. Future studies should focus more on this population.
The costs due to preventable ADRs in an in-patient setting had a wider range than out-patient setting: a minimum of € 2,851 to a maximum of € 9,015 (in-patient setting) vs. a minimum of € 174 to a maximum of € 8,515 (out-patient setting). The impact of preventable ADRs in terms of length of stay was higher in the out-patient setting (9.2 ± 0.2 days) than in the in-patient setting (6.1 ± 2.3 days).
The differences among ADR definitions and detection as well as difference in economic outcomes made it difficult to compare study results and provide overall estimates. The diversity highlights the need to improve the harmonisation across drug event and economic outcomes, for example through the development of core outcome sets to define and standardise outcome definitions as well as conducting multi-centre studies using a common study protocol to provide large scale results.

1. Introduction

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality worldwide, with a significant and increasing health and economic burden. [1,2]. An ADR has been traditionally be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, usually predicting hazard from future administration and warranting prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [4]. More recently, the European Medicines Agency (EMA) has defined it as "A response to a medicinal product which is noxious and unintended" [4]. A related term, "adverse drug event (ADE)", is defined as "an injury resulting from medical intervention related to a drug" [5]. This definition includes harm caused by the drug (ADRs and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy) [6]. However, the terminology of ADRs and related concepts has proved to be very variable over time, as shown by the published terms in the patient safety literature [7]. A systematic review and meta-analysis of 39 prospective studies conducted in the USA found that the frequency of serious ADRs leading to hospitalization ranged from 1.0 % to 16.8% [1]. In this study, it was estimated that for hospitalized patients the overall incidence of serious ADRs was 6.7% and that of fatal ADRs was 0.32%. Furthermore, national USA Vital Statistics System data showed that from 1999 to 2006, the rate of ADR-related deaths increased from 0.08 to 0.12 per 100,000 persons [8]. A review of 22 observational studies in European countries found a similarly large variability in the frequency of ADRs leading to hospitalization, ranging from 0.5% to 12.8% [9]. Likely reasons for this variation in ADR occurrence rate among these studies include different ADR detection methods, length of study, setting (emergency departments, medical wards etc.) and sample size. Concerning preventable ADRs specifically, it was estimated that up to 70% of ADRs leading to emergency department visits are preventable [10]. Preventable ADRs may be due to medication errors, interactions with other drugs, underlying diseases or patient characteristics (idiosyncratic reactions and allergies, including unintended effects occurring at recommended doses), errors in prescribing or dispensing, poor adherence and poor monitoring of patient safety [11–13].

The occurrence of ADRs is influenced by several factors, for example the increased presence of polytherapy drug regimens [14] as well as the increasing longevity, leading to a large number of frail elderly

persons with multi-morbidity and exposed to polypharmacy[15]. ADRs have a significant impact not only from a clinical point of view but also from an economic one. A landmark study of almost 20,000 patients admitted to hospital in the UK found that ADRs lead to an average of eight additional days of hospital stay and are associated with approximately € 706 million per year, including ADRs which were judged potentially preventable [16]. A more recent systematic review of 29 observational studies found that the incremental total cost for each patient with an ADE ranged from roughly € 702 to € 7,318 [17]. However, this study did not investigate the economic impact of ADRs specifically, that is, reactions definitely associated with drug exposure. Given that ADRs are very common, and that many of these may be preventable, it is critical to understand and quantify the economic burden of such ADRs as both direct and indirect costs may be prevented while safeguarding patient health. The aim of the present study was therefore to conduct a systematic review of observational studies that evaluated the economic impact of preventable ADRs.

2. METHODS

2.1 Search strategy

Medline, Scopus and Web of Science were searched for a combination of the keywords and MeSH terms (see search query in **Additional file 1**) from database inception to 12th July 2017. If the full-text of the identified articles were not available online, the authors were contacted to request their article. The protocol of this systematic review was registered in Prospero: international prospective register of systematic reviews (CRD42017068428). The "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) checklist was used in the reporting of the present systematic review [18].

2.2 Eligibility criteria

Studies were eligible for inclusion in this systematic review if they were in English, were conducted in Western countries (limited to the US and European countries), were observational studies (e.g. retrospective or prospective repeated observational studies, cohort studies, case-control studies etc.), and studied preventable ADRs and their associated costs. Studies where drug safety data was obtained from spontaneous reports were not eligible for further screening.

2.3 Study selection

Two reviewers (DF and SL) independently screened the eligible studies for inclusion based on the relevance of the study title and abstract (first screening). Studies considered to meet the inclusion criteria were then selected for further review based on the full-text. Given the differences in nomenclature used by different researchers, when the reviewers were selecting studies investigating preventable ADRs, they also included studies that described a preventable drug-related event not termed an ADR, such as medication-

related adverse event. All discrepancies between the two reviewers were resolved by consensus and if necessary consultation with a third reviewer (JS).

2.4 Data analysis

The following general data were extracted from the articles included in the review: study design, population type and size as well as demographic characteristics, country within which the study was set, and duration of study, Where study follow-up was reported, the median duration in months with interquartile range was calculated, as the distribution of values was not normal. Data was also extracted regarding type of setting (in-patient, out-patient or both), type of drug-related event as termed by the authors, and whether and what type of causality and preventability assessment were carried out. Furthermore, we described whether suspected drugs causing preventable adverse events were reported, which the suspected drugs or drug classes were, and whether preventable event frequency was clearly reported.

Regarding the economic impact of ADRs, the type of costs (direct or indirect costs) and the expenditure in Euros associated with the preventable ADR was identified. Costs were converted into Euro from other currencies according to the closing exchange rate on the 1st March 2018 and were not adjusted for inflation or discounted. Direct monetary costs were categorized by a pharmacoeconomist (DF) as 1) hospitalization costs (all costs occurring after hospitalization, whether the study setting was in-patient or out-patient); 2) emergency department (ED) healthcare service costs; 3) ED and hospitalization costs combined; 4) out-patient healthcare service costs; 5) primary healthcare service costs, and 6) pharmacy service costs. The only indirect costs identified concerned loss of productivity.

Excess length of stay (LOS) was also identified because, although this is not a monetary cost, an increased LOS will lead to a greater cost. The added value of LOS to the analysis is that this measure is easily comparable across different studies. LOS in studies was most commonly described using the mean (n=7 out of 10 studies reporting the LOS) rather than the median (n=3 out of 10 studies). As a result, we used the grand mean of the reported means to describe the duration among those studies. The original descriptive measures were reported in all cases.

We stratified the costs as well as the excess LOS attributable to preventable ADRs for each study by in-patient, out-patient and both settings. Studies concerning patients who developed an ADR during their hospital stay were considered to reflect the “in-patient setting”, while studies with patients who experienced the ADR before hospital admission were considered to belong to the “out-patient setting”. These categories were not mutually exclusive, and it was possible for one study to have populations in both settings.

3. RESULTS

3.1 Studies identified

The initial search in the three online literature repositories identified 746 studies potentially relevant to the systematic review (**Figure 1**). In addition, 20 studies were identified outside the database search from the references cited in the publications retrieved from the systematic search. After excluding 313 duplicates, the title and abstract of 453 articles were screened based on the inclusion criteria, leading to the exclusion of 406 articles. Exclusion reasons included: no information on cost data or preventability of ADRs reported, study design was not observational (e.g.: probability pathway model, simulation-based cost-analysis, commentary articles or systematic reviews) and country where the study was carried out was not within Europe or the USA. The remaining 47 manuscripts records underwent full text examination and only 18 articles met the inclusion criteria and were accepted for final inclusion into the study analysis.

3.2 Characteristics of the selected studies

A summary of the study characteristics is available in **Table 1**. Ten studies (55.6%) were prospective [19–28] and seven (38.9%) were retrospective [29–35], while this was not clearly reported in one article (5.5%) [36]. The majority of the selected studies were cohort studies [20,22,23,26,27,30,32,33,35] (n= 9; 50.0%) and chart reviews [19,24,28,29,31,34,36] (n= 7; 38.9%) while only two [19,21] (11.1%) were case-control studies. The median (IQR) follow-up of the studies was 12.0 (6.0 to 19.5) months.

Regarding the characteristics of the patients, the overall age range was middle aged to elderly. The mean patient age among 12 studies (n= 12; 66.7%) reporting the mean ranged from 41.7 to 72.8 year . Two studies (11.2%) reporting the median age had a median population age of 57 and 65 [20,27] while no age information was 2; reported by four (22.1%) studies [22,29,30,35]. Furthermore, not all studies reported data on the patients'' sex (n=14; 77.8%). On average in the selected studies, the female: male ratio was 1.2.

Categories of analyzed adverse events in the included studies were heterogeneous, although most studies used the term ADE (n= 10; 55.6%). The causal relationship between drug exposure and an adverse clinical event was evaluated in 13 studies (72.2%). Among these studies, eight (61.5%) used a quantitative evaluation method such as operational causality algorithms [19,20,24–28,33], while the remaining five (38.5%) used a qualitative method such as adjudication by experts [22,30,31,35,36].

Most of the studies (n=8, 44.4%) were conducted in an out-patient setting [19,22,24–26,28,33,36]. None of the selected studies was performed in primary care without a hospitalisation or emergency visit. Overall, in the selected studies, the rate of preventable ADE/ADR in the populations studied was on average 37.9% (**Table 2**). This rate was slightly higher (39.6%) in studies conducted in an out-patient setting than those conducted in an in-patient setting (37.3%).

ADR preventability algorithms were used in over half of the studies (n= 10, 55.6%) [20,23–28,33–35], of which Schumock and Thornton's criteria were the most commonly used [37,38]. In seven studies (38.9%) the ADR preventability assessment was based on the judgment of physician reviewers [19,21,22,30–32,36]. Only one study [29] (5.5%) used a theoretical estimation of preventable of ADE using

published literature [21]. Seven studies [19,21,22,26,27,31,33] out of eighteen reported the suspected drugs causing ADRs. Eleven articles [20,23–25,28–30,32,34–36] did not evaluate any therapeutic group in particular **(Table 3).** However, among studies reporting the causative agent, cardiovascular agents, antiepileptic drugs, antibiotics and anticoagulant drugs were the most frequent drugs suspected to cause preventable ADRs.

3.3 Cost analysis

The overarching finding regarding the ADR cost analysis was the significant heterogeneity in the measures used to report the costs. Few studies (n= 7, 38.8%) analyzed a specific therapeutic group [19,21,22,26,27,31,33] associated with an ADR, but none of these reported information on the costs associated with that specific therapeutic group. Regarding the cost analysis, all studies evaluated the direct costs and only three studies (16.7%) evaluated both direct cost and indirect costs [25,35,36]; no study investigated the indirect costs only.

Regarding direct healthcare costs, studies were stratified by setting: in-patient setting [21,27,29,31,32,34], out-patient setting [19,22,24–26,28,33,36] and both the in-patient and the out-patient setting [20,23,30,35]. In an in-patient setting, costs due to preventable ADRs (per hospitalization) ranged from a minimum of € 2,851 [31] to a maximum of € 9,015 [34] with an excess LOS, reported in five studies out of six, ranging from 4.2 [31] to 13.0 [27] days. On the other hand, in the studies carried out in the out-patient setting, costs due to preventable ADRs ranged from a minimum of € 174 [36] (mean cost of an ED visit) to a maximum of € 8,515 [22] (mean hospital cost per admission) with a LOS, reported in four studies out of eight, that ranged from 7.0 [22] to 9.3 [24] days. Finally, in the studies carried out in both the in-patient and out-patient setting, costs due to preventable ADRs ranged from a minimum of € 63.8 [30] (for prescribed medications) to a maximum of € 2,721 (per hospitalization). Among studies reporting the mean excess LOS (n=7), the overall mean was 8.5 ± 4.2 in all settings, but for ADRs detected in the in-patient setting, the mean excess LOS was 6.1 ± 2.3 days while for ADRs detected in the out-patient setting (n=2), the excess LOS was 9.2 ± 0.2 days (**Table 4**). Among the three studies that evaluated direct and indirect costs, Leendertse *et al.* [25] estimated a mean indirect healthcare cost of € 1,712 per admission for persons younger than 65 years old, taking into account productivity costs such as time off work and reduced productivity at work. Furthermore, the total production loss costs for one hospital admission varied between € 61 for a male aged 19 admitted for 1 day to € 13,234 for a male aged 37 admitted for 38 days[25]. Dennehy *et al* [36], calculated the mean indirect healthcare cost of services allocated to patient care centers by non-revenue centers (such as laundry or dietary department) for ED visits associated with a DRI occurring among non-hospitalized or hospitalized patients. This amounted to € 909 (± 248) and € 78 (± 62) respectively. Finally, in the study of Gyllensten et al [35], the societal mean indirect cost of illness for patients with at least one preventable ADE was equal to € 2,674 (95% CI: 2,066 to 3,282).

4. DISCUSSION

4.1 Main findings

This systematic review of observational studies confirms that preventable ADRs have an significant economic impact. The high heterogeneity found in the costs can be explained by the methodological differences between the included studies most of which evaluated direct costs compared to indirect costs. A total of 18 studies were included in this review, which reported on average a rate of preventable ADEs/ADRs corresponding to 37.9%. Most of the studies referred to out-patients who were admitted to Emergency Departments or hospitalized due to an ADR. Furthermore, no study in primary care was retrieved, showing a lack of information on ADR-related costs from general practitioners and pharmacies in community setting. The most studied cost categories concerned hospitalization costs and excess LOS after admission, both for out-patients and in-patients. The costs in the in-patient setting were higher than costs from the out-patient setting, but LOS was higher in the out-patient setting than the in-patient setting.

The present study highlights significant methodological differences in the preventable ADR cost calculations that makes it very difficult to pool the measures of cost across all studies, or even to compare them directly. Even under a broad umbrella term such as hospitalization costs, which is common to many studies, the components making up the costs varied significantly from study to study. This is an expected finding, since the data used to identify healthcare services and associated costs consist of secondary data, primarily routinely collected medical records and medical claims. As a result, the analysis that can be conducted in every data source are expected to vary significantly between one study and another, based on the data available.

Excess LOS was the only measure that was broadly comparable across in-patient's studies. However, even for this measure it was a challenge to provide a point estimate of the LOS, as the studies reported differing measures of location, and among those, reporting the same measure, such as the mean, the complementary measure of variance was often not reported. For example, of the 7 studies reporting the mean LOS, only four studies reported the standard deviation [19,20,24,32].

Another important finding from the present review concerns the populations studied in the published research articles. There was a notable lack of studies focusing specifically on elderly populations, even though this population is arguably at highest risk of ADRs and most vulnerable to the ADR sequelae [39,40]. This finding is particularly relevant considering that the increasing prevalence of polytherapy and comorbidity with aging may lead to an increased risk of drug–drug and drug–disease interactions, serious ADRs, inappropriate drug use, poor adherence and medication errors among elderly people. The implication is that elderly persons have a a potentially higher risk of preventable ADRs and related costs than in other populations. Indeed, a meta-analysis [41] on preventable ADEs including three studies [42–44] limited to elderly patients, found that 71% of ADRs were preventable. Hoonhout et al [31] also confirm

that the additional cost due to preventable ADEs increased by 8.6% among the subgroup of people over 65 years (€3097) compared to patients under 65 years (€2851).

ADR causality was only assessed in some of the studies included in the systematic review. The preventability of ADRs was evaluated in all the studies, but the definition and evaluation of preventability was often different. This is a significant methodological limitation of these studies. Since there are no standardized and universal methods to assess the causality and the preventability of ADRs, results contain a considerable variation due to the different methodological approaches used between the various studies. However, the criteria most commonly used to assess causality and preventability of ADEs were Naranjo's algorithm and Schumock and Thornton's criteria, respectively. The heterogeneity among studies concerning ADR preventability and causality assessment is very important both from a clinical and methodological point of view. Indeed, the heterogeneity in the types of adverse events included in the studies (i.e. ADEs, ADRs, DRIs, and MRAEs) could influence the results. For example, a more conservative definition (e.g. ADR) will produce a lower prevalence of preventable events with a resulting lower cost estimate [45,46]. Few studies included in this systematic review reported a detailed and clear description of the suspected drugs causing preventable events. Only seven studies out of 18 reported this information, but without a description of the specific drug-related costs. Over half of the studies included in this systematic review did not focus in any particular therapeutic group of drugs. The clinical implications of this are profound: research into drug safety should identify specific drugs that are potentially associated with increased preventable healthcare risks and preventable costs, otherwise the clinical and healthcare policy value of such research is dubious.

Regarding the information on cost of ADRs, direct health costs were assessed in all studies while indirect costs were considered in only three studies [25,35,36]. This aspect is probably explained by the fact that information on indirect cost was difficult to obtain as it is associated with individual loss of productivity and because databases belonging to medical insurance companies and other medical databases contain information on direct cost, but no data on indirect cost [47]. It is difficult to compare costs from different countries because of differing definitions of costs, of sources of unit costs, of the reimbursement systems, delivery agreements and the price levels between countries. All this in addition to differences in exchange rates over time highlight the need to be cautious when interpreting the cost results

4.2 Strengths and limitations

The main strength of this study lies in the systematic approach undertaken, providing a robust identification of observational studies investigating the economic impact of preventable ADRs/ADEs in the last two decades. The focus on preventable ADRs specifically addresses a research gap which has not been addressed by other recent systematic reviews at the time of writing.

This study also has some limitations. The search includes only articles conducted in the US and Europe, therefore studies are not representative of global findings. The advantage of the geographic

restrictions applied is that, despite national differences, all the countries included (limited to the US and countries in Europe) can all be considered developed countries. We believe this introduces a broad but significant common element between all studies included in the present review. The description of costs must be interpreted in light of the fact that each country has its own complex and specific healthcare system. As a result, in addition to the fact that the economic data was collected in different years, the cost information may not be generalizable to other countries in the same or even different period. Indeed, it was not the aim of the study to make such generalizations. Similar limitations in generalizability arise from the different definitions of ADRs, study designs and study populations. Finally, it is important to bear in mind that some summary statistics stratified by setting are limited by the small number of studies therein. For example, the comparison of ADR impact on LOS in the in- and out-patient setting consisted of 2 studies in the out-patient setting and 4 in the in-patient setting.

5. EXPERT OPINION

Several reviews have been carried out in the field of the ADR epidemiology but fewer reviews have investigated the economic impact of ADRs, and at the time of writing, none have focused on preventable ADRs. The reason why future research should focus on the costs of preventable ADRs is that both the costs and the clinical outcomes are preventable, and as such, are a key point of public health policy action. Nevertheless, the present review highlights an important and sobering limitation of published research on the cost of preventable ADRs, of which the major limitation is the heterogeneity in outcome definitions, methods and in reporting limit what can be known through a summarizing work of a systematic review.

An important development that addresses this heterogeneity in outcomes is the COMET initiative, which aims to provide researchers with a framework to develop and implement outcome definitions known as “core outcome sets”, i.e., a minimum set of standardized library of outcomes which should be evaluated and reported [48]. Although the focus of the COMET initiative originally concerned core outcome sets in clinical trials, these initiatives can be and should be applied also to observational research or reviews of clinical research. One interesting example concerns a core outcome set that was developed to analyze polypharmacy among elderly people in a review of clinical trials [49]. The definition and use of appropriate outcomes is essential for healthcare research, as this increases the quality of an individual study and permits comparison to other studies if the outcome definition is harmonized. Such a definition should go beyond the clinical or economic aspect and try to address key questions of interest to healthcare service stakeholders, such as patients, healthcare professionals and healthcare service providers.

Based on findings from the present review, what can be known about the economic impact of preventable ADRs currently does not go beyond a single country, or perhaps even a single research centre. Nevertheless, the pyramid of scientific evidence places systematic reviews/meta-analyses of original research at the highest level of importance. Such secondary analysis is only possible if a minimum level of harmonization among studies exists. It is conceivable that future work in the area will continue be similarly

disparate unless action is taken to harmonize research through the publication of guidance on the best practice for carrying out research on the preventable ADR costs. To our knowledge, there is currently no guideline on the methods of carrying out pharmacoeconomic analyses on the cost of ADRs. The findings in the present review highlight the pressing need for such a guideline to promote the harmonized research in this field and increase the value of such research. Several such guides on the standard reporting of research have been published and are widely used, such as MOOSE (Meta-analyses of Observational Studies), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and STROBE (STrengthening the Reporting of OBservational studies in Epidemiology)[18,50,51]. These guidelines and checklists have arguably improved the reporting across the studies that implement them as well as introducing more transparency and harmonization in research reporting. The World Health Organization has published guidance on pharmacovigilance activities, including the reporting of ADRs and related costs. However, we suggest that more detailed guidance may improve research standards in this field [52].

Another approach to promote the generation of useful pharmacoeconomic data on a large scale could involve the creation of multi-center studies implementing a project-based common study protocol. This approach has been widely used with success in pharmacoepidemiology, where partnerships between international research centers has led to the creation of projects with patient data from different countries, healthcare system and data sources, to provide large-scale, harmonized and generalizable data. In these multi-database studies, there are common project-based outcome and covariate definitions are harmonized across all databases, since each database contains secondary data, i.e. data not collected specifically for the purposes of the studies. Such projects include: ARITMO, SAFEGUARD and SOS [53]. In the absence of uniform protocols in multi-database studies, a more concerted effort could be made on a wider scale to standardize the detection of ADRs/ADEs and medication errors in observational studies.

Among the study findings which could be deduced from the original study articles, it was seen that the costs associated with ADR related hospitalizations in an out-patient setting were generally higher than the costs related to excess LOS for ADRs detected in in-patient setting. This highlights that the ADRs occurring in the community are at least as, if not more, serious than those detected in an in-patient setting. Despite this fact, the present review did not identify even one study investigating the economic impact of preventable ADRs that was conducted in primary care. Research in a primary care setting could potentially provide further points for healthcare policy action in preventing ADRs and the associated costs. Further research gaps identified concerns the costs of preventable ADRs in the elderly. Finally, the practical value of the research on the costs of preventable ADRs, and indeed, of all biomedical research [54], should be critically analyzed and borne in mind. The value of ADR-centered research that does not provide an adequate level of detail on the suspected causative agent or even class of agents is dubious and cannot empower health stakeholders to act in favor of reducing the frequency of ADRs and of preventable costs.

6. CONCLUSION

Adverse drug reactions account for a large number of hospital admissions in out-patient settings as well as extended hospital stays, most of which are avoidable. Nevertheless, the methods used to quantify these preventable costs are so disparate that it is very difficult to understand the real economic impact of preventable ADRs. We recommend that future research should be more harmonized, either through the publication and implementation of detailed methodological and reporting guidelines and/or through multi-center studies implementing a shared study protocol.

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Table 1: Summary of included studies. All numbers in brackets refer to percentages unless indicated otherwise.

	All studies included in review **N=18**
Recency of publication	
2006-2016	10 (55.6)
1996-2005	8 (44.4)
Geographic setting	
Europe	12 (66.7)
USA	6 (33.3)
Temporal aspect of study design	
Prospective	10 (55.6)
Retrospective	7 (38.9)
Ambiguous	1 (5.5)
Observational aspect of study design	
Cohort studies	9 (50.0)
Chart reviews	7 (38.9)
Case-control studies	2 (11.1)
Clinical setting	
Out-patient	8 (44.4)
In-patient	6 (33.3)
In-patient and out-patient	4 (22.3)
Adverse event definition employed	
Adverse drug event	10 (55.6)
Adverse drug reaction	6 (33.3)
Drug-related illnesses	1 (5.6)
Medication-related adverse events	1 (5.6)
Evaluation of drug-event causality	
Yes, using quantitative method	8 (61.5)
Yes, using qualitative method	5 (38.5)
No	5 (27.9)
Event preventability assessment	
Yes, using algorithms	10 (55.6)
Yes, using expert reviewers	7 (38.9)
Yes, using estimates from scientific literature	1 (5.6)
Specified suspected causative agents	
Yes	7 (38.9)
No	11 (61.1)

Table 2: **Characteristics of the selected studies.**

Author, Year of Publication	Study design	Eligible study population	Population with drug-related events	Characteristics of Patients		Country	Duration of study
				Age (years)	F/M ratio		
Hoonhout et al (2010) [31]	Retrospective chart review	7,889 patients from 7,926 of 21 of the 101 Dutch acute care hospitals with 744 AEs	140 patients with 148 (19.8% of 744) Medication-related AEs of which 60 were preventable (41.0%)	Mean age ± SD: 68.0 ± 15.0	1.2	Netherlands	12 months
Leendertse et al (2011) [25]	Prospective, case-control study	12,793 unplanned acute admissions from 4 universities and 17 general hospitals of which 714 (5.6%) were classified as HARM	332 hospital admissions (46.0% of 714 HARM) were considered to be due to potentially preventable ADR corresponding to 331 patients	Mean age ± SD: 70.0 ± 17.0	1.0*	Netherlands	12 months
Wasserfallen et al (2001) [19]	Prospective chart review	4,840 Patients admitted to the medical ED of a Swiss University Hospital	229 patients (7.1% of 3,195) with ADRs of which 73 (32.0% of 229) with a preventable ADR	Mean age (min-max range): 61.4 (16 to 93)	1.1	Switzerland	6 months
Dormann et al (2004) [20]	Prospective cohort study	630 Patients of 1st IMD at the University Hospital of Erlangen-Nuremberg	145 (23.0% of 305) ADRs were observed of which 135 (44.3% of 305) ADRs were considered preventable; corresponding to 99 patients	Median age ± SD: 57.0 ±16.6	-	Germany	18 months
Perrone et al (2014) [33]	Retrospective cohort study	2,561,400 ED admissions of 16 general hospitals only	8,862 ED admissions were ADR related, of which 3,725 (42.0% of 8,862) were considered preventable ADR; corresponding number of patients not reported	Mean age ± SD: 55.9 ± 24.3	1.3	Italy	24 months
Hug et al (2012) [32]	Retrospective cohort study	109,641 patients hospitalized in six community hospitals	230 patients had one or more ADEs, of whom 190 (82.6% of 230) patients with preventable ADE that had 217 ADEs	Mean age (min-max range): 63.2 (18 to 107)	1.4	USA	20 months
Bates et al (1997) [21]	Nested case-control study within a prospective cohort study	4,108 admissions in 2 large tertiary hospitals and a general hospital, of which 247 ADEs were identified in 207	70 (28.0% of 247) ADEs were preventable corresponding number of patients not reported	Mean age ± SD: 56.9 ± 18.8	0.9	USA	6 months

		admissions of 204 patients					
Einbinder et al (2001) [29]	Retrospective chart review	11,181 patients with ADE (data from clinical and administrative computer system of University of Virginia, Department of Health Evaluation Sciences)	3,533 (31.5% of 11,181) patients had experienced one or more preventable ADEs	-	-	USA	48 months
Meier et al (2014) [26]	Prospective cohort study	2,262 Patients admitted to ED	366 patients (16.2%) had one or more caADEs, of whom 227 (62.0% of 366) had caADEs were classified as preventable	Mean age ± SD: 72.8 ± 15.7	1.4	Germany	3 months
Lagnaoui et al (2000) [23]	Prospective cohort study	444 patients admitted to IMD	116 (26.1% of 444) patients had one or more ADR and 31 patients had 32 ADRs leading to hospitalization; 8 (25.0% of 32) ADRs were considered preventable; corresponding number of patients not reported	Mean age (min-max range): 59.0 (15 to 94)	1.1	France	4 months
Rottenkolber et al (2011) [24]	Prospective chart review	1,834 patients admitted to IMD	368 (20.1% of 1,834) patients had an ADR classified as preventable	Mean age ± SD: 71.0 ± 14.7	1.4	Germany	24 months
Jolivot et al (2016) [27]	Prospective cohort study	743 admissions for 701 patients	173 (23.3% of 743) admissions were due to an ADE; 102 (13.7% of 743) admissions were related to preventable ADE	Median age (IQR): 65.0 (51.0; 78.0)	0.7	France	12 months
Magdelijns et al (2014) [34]	Retrospective chart review	284 patients with 324 admissions due to a health care-related AE from IMD after ED admission	90 (27.0% of 324) admissions due to a drug related AE were judged preventable; corresponding number of patients not reported	Mean age ± SD: 66.0 ± 16.0	1.0	Netherlands	5 months
Rottenkolber et al (2012) [28]	Prospective chart review	6,099 patients admitted to IMD of 4 regional pharmacovigilance centers in German hospitals due to an outpatient ADR	1,170 (19.2% of 6,099) patients with one or more preventable ADR	Mean age ± SD: 70.2 ± 15.7	1.5	Germany	84 months
Dennehy et al (1996) [36]	Chart review**	1,260 admissions to ED	49 (3.9%) ED admissions were DRI; 33 (67.3% of 49) DRI were	Mean age ± SD: 41.7 ± 22.5	-	USA	12 months

			considered preventable; corresponding to 33 patients				
Jha et al (2001) [22]	Prospective cohort study	76 (2.3% of 3,238) admissions to 9 secondary care units (2 MICU, 1 SICU, 4 MGCU and 2 SGCU) were caused by an ADE	21.2 (28.0 % of 76) admissions caused by an ADE were preventable; corresponding number of patients not reported	-	-	USA	8 months
Field et al(2005) [30]	Retrospective cohort study	1,225 ADE in 1,210 patients enrolled in a Medicare + Choice Plan***	323 (26.3% of 1,225) ADE were preventable; corresponding number of patients not reported	-	1.5	USA	12 months
Gyllensten et al (2014) [35]	Retrospective cohort study	4,970 adults in a Swedish county council (data from medical records)	596 (12.0% of 4,970) patients with at least one ADE. In 278 patients (46.6% of 596) ADE were considered preventable	-	1.5	Sweden	3 months

Abbreviations

AE: Adverse Event; **ADE:** Adverse Drug Event; caADEs: Community-Acquired Adverse Drug Events; ADR: Adverse Drug Reaction; ED: Emergency Department; F/M ratio: female to male ratio; DRI: Drug-Related Illnesses; IMD: Internal Medicine Departments, **MICU:** Medical Intensive Care Unit; MGCU: Medical General Care Unit; SGCU: Surgical General Care Unit; SICU: Surgical Intensive Care Unit; SD: Standard Deviation; USA: United States of America.

Legend

* Data derived from previous publications [47] of the author.
** Unclear whether retrospective or prospective.
*** Medicare Choice Plan health insurance.

Table 3: Overview of adverse drug reactions investigated in the included studies.

	Author, Year of Publication	Suspected Drug(s)	Type of Event	Causality Assessment	Preventability Assessment
In-patient setting	Hoonhout et al (2010) [31]	Over 50% of all MRAE related to NSAID, antiplatelet drug associated with NSAIDs, and anticoagulants were preventable	MRAE	Consensual Expert judgment based on supportive questions*	Consensual Expert judgement based on supportive questions**
	Hug et al (2012) [32]	-	ADE	Not performed/reported	Clinical judgement of physician reviewers
	Bates et al (1997) [21]	The largest proportion of preventable ADEs was caused by: · Analgesic drugs (29.0%) · Sedative drugs (10.0%) · Antibiotic drugs (9.0%) · Antipsychotic drugs (7.0%)	ADE	Not performed/reported	Clinical judgement of physician reviewers
	Einbinder et al (2001) [29]	-	ADE	Not performed/reported	Not performed***
	Jolivot et al (2016) [27]	Preventable ADEs were most commonly due to: · Antineoplastic/immunomodulating agents (n=3; 3%) · Cardiovascular system agents (n= 36; 30%) · Blood and blood- forming organ agents (n= 20; 17%) · Nervous system agents (n= 30; 25%) · Systemic hormonal preparations (n= 9; 8%) · Anti-infectives for systemic use (n= 7; 6%) · Alimentary tract/ metabolism agents (n=4; 3%) · Musculoskeletal system agents (n= 6; 5%) · Other agents (n= 4; 3%)	ADE	· French official method by Begaud et al (1985) [6] · Naranjo algorithm [7] · Karch and Lasagna methods [8]	Schumock and Thornton's criteria [9]
	Magdelijns et al (2014) [34]	-	ADE	Not performed/reported	Schumock and Thornton's criteria [9]
	Leendertse et al (2011) [25]	-	ADE	Kramer et al algorithm (adjusted version) [12]	Schumock and Thornton's criteria [9]

Out-patient setting	Wasserfallen et al (2001) [19]	Preventable ADR were related to: ・Psycholeptic drugs (60% of 18); ・Antidiabetic drugs (56% of 17); ・Psychoanalytic drugs (47% of 13); ・Analgesic drugs (44% of 30); ・Cardiotonic drugs (44% of 21); ・Diuretic drugs (43% of 23); ・NSAID (42% of 30); ・Hypotensive drugs (35% of 27); ・Anticoagulant drugs (31% of 31); ・Corticosteroid drugs (27% of 14); ・Beta-blocker drugs (20% of 5); ・Sexual steroid drugs (19% of 9); ・Antibiotic drugs (19% of 16); ・Cytostatic drugs (4% of 84)	ADR	WHO Probability Scale [14]	Specific ten-item questionnaire developed by the study authors [15]
	Perrone et al (2014) [33]	Probably/definitely preventable ADR were related to: ・Warfarin (n= 355; 48.6%); ・Acetylsalicylic acid (n= 323; 34.5%); ・Amoxicillin-clavulanate (n= 282; 32.1%); ・Insulins and analogues (n= 250; 66.3%); ・Ketoprofen (n= 153; 43.3%); ・Ibuprofen (n=95; 38.8%); ・Diclofenac (n= 96; 49.7%); ・Amoxicillin (n= 186; 38.8%); ・Acetaminophen (n= 54; 29.7%); ・Levofloxacin (n= 55; 32.0%)	ADR	Naranjo algorithm [7]	Schumock and Thornton's criteria [9]

	Meier et al (2014) [26]	Preventable ADEs were most commonly due to: · Antithrombotic agents (60.9% of 69); · Beta blocking agents (76.9% of 65); · Antipsychotics (77.1% of 48); · High ceiling diuretics (75.0% of 44); · Antidepressant drugs (86.0% of 43); · ACE inhibitors (87.2% of 39); · Anti-inflammatory and non-steroidal anti-rheumatics (69.7% of 33); · Dopaminergic agents (94.4% of 18); · Selective calcium channel blockers (100% of 18); · Insulins and analogues (47.1% of 17); · Others (56.7% of 190)	ADE	WHO Probability Scale [14]	Schumock and Thornton's criteria [9]
	Rottenkolber et al (2011) [24]	-	ADR	French official method by Begaud et al (1985) [6]	· Schumock and Thornton's criteria [9] · Hartwig and Siegel Scale [19]
	Rottenkolber et al (2012) [28]	-	ADR	French official method by Begaud et al (1985) [6]	· Schumock and Thornton's criteria [9] · Hartwig and Siegel Scale [19]
	Dennehy et al (1996) [36]	-	DRI	Expert judgement of reviewers	Expert judgement (DRI were considered preventable if they could have been avoided through appropriate prescribing, outpatient monitoring or patient compliance)
	Jha et al (2001) [22]	Of the 21 preventable ADE admissions, seven involved cardiovascular agents, four involved antiepileptic medications, two involved antibiotics and two involved anticoagulants. Digoxin was the single most commonly involved agent, contributing to four preventable admissions	ADE	Expert judgement of reviewers	Expert judgement of physician reviewers. (ADE were considered preventable if they were due to an error or were preventable by any means available)
	Field et al (2005) [30]	-	ADE	Expert judgement of reviewers	Expert judgement of physician reviewers. (ADE were considered preventable if they were due to an error or were preventable by any means available)
In-patient and out-patient setting	Dormann et al (2004)**** [20]	-	ADR	Naranjo algorithm [7]	Schumock and Thornton's criteria [9]
	Lagnaoui et al (2000) [23]	-	ADR	Not performed/reported	Fatality preventability evaluation algorithm [26]

	Gyllensten et al (2014) [35]	-	ADE	Expert judgement of reviewers	Hallas criteria [28]

Abbreviations
MRAEs: Medication Related Adverse Events; **ADE:** Adverse Drug Event; **ADR:** Adverse Drug Reaction; **DRI:** Drug-Related Illnesses.

Notes
*Reviewers used their clinical experience and knowledge of professional standards as references to answer their questions.
**Inter-rater agreement between two physician reviewers (+ third physician in case of disagreement) based on supportive questions.
***Estimate on preventability was obtained by applying the rate of preventable ADR from Bates's study.
****The authors use describe "community acquired" term to refer to outpatient setting and "in-house" to inpatient setting.

Table 4: Overview of costs for preventable ADRs.

	Author, Year of Publication	Direct / Indirect Costs	Type of Cost	*Value description (€)	LOS (days)
In-patient setting	Hoonhout et al (2010) [31]	Direct	· Excess hospital LOS · Hospitalization costs	The excess costs per preventable MRAE was € 2,851 in patients under 65 years and € 3,097 in patients over 65.	· Mean (95% CI): 4.2 in patients under 65 years (0; 7.7) · Mean (95% CI): 7.2 in patients over 65 years (5.5; 17.7)
	Hug et al (2012) [32]	Direct	· Excess hospital LOS · Hospitalization costs	Preventable ADEs were associated with a mean cost of € 8,552 (± 422).	Mean ± SD: 9.45 ± 0.39
	Bates et al (1997) [21]	Direct	· Excess hospital LOS · Hospitalization costs	Preventable ADEs were associated with a mean cost of € 3,846.	Mean: 4.6 with variability measures (e.g. SD or IQR) were not reported
	Einbinder et al (2001) [29]	Direct	· Excess hospital LOS · Hospitalization costs	Preventable ADEs were associated with a mean cost of € 3,993.	Mean: 4.6 with variability measures (e.g. SD or IQR) were not reported
	Jolivot et al (2016) [27]	Direct	· Excess hospital LOS · Hospitalization costs	Median costs of hospital admissions due to preventable ADEs was € 9,015 (IQR: 5,823; 18,043).	Median (IQR): 13 (5; 28)
	Magdelijns et al (2014) [34]	Direct	· Hospitalization costs	Preventable health care-related AEs accounted for € 277,665 with a mean cost of € 3,085 (SD ± 2,383) per patient.	-

Out-patient setting	Leendertse et al (2011) [25]	Direct and Indirect	・Hospitalization costs ・Excess hospital LOS ・Cost of lost productivity	On average, combining direct costs and indirect costs resulted in an average cost of € 6,009 per potentially preventable ADE. ・The mean health care direct cost for one preventable medication-related hospital admission was € 5,461. ・The mean production loss indirect cost for one admission was € 1,712 (for a person younger than 65 years of age).	Median: 8.0 with variability measures (e.g. SD or IQR) were not reported
	Wasserfallen et al (2001) [19]	Direct	・Hospitalization costs ・Excess hospital LOS ・	Mean cost of € 3,119 per ADR and € 999 per preventable ADR.	Mean ± SD: 9.0 ± 0.6
	Perrone et al (2014) [33]	Direct	・Hospitalization costs	The total cost of preventable ADRs was € 3,009,800 of which the mean cost per preventable ADR was equal to € 808 ± 2,584).	-
	Meier et al (2014) [26]	Direct	・Hospitalization costs	Total hospitalization cost amounted to € 535,371, with a mean cost per preventable ADE equal to € 2,637 (± 1,638).	-
	Rottenkolber et al (2011) [24]	Direct	・Excess hospital LOS ・ADR treatment costs	The average treatment cost of a single ADR was € 2,250. The total cost was € 434 million per year, considering the proportion of preventable cases (20.1%).	Mean ± SD: 9.3 ± 7.1
	Rottenkolber et al (2012) [28]	Direct	・Hospitalization costs	Preventable ADR accounted for € 2,430,720 (19.2% of € 12.6 million) per year in all 4 regional pharmacovigilance centers in German hospitals.	-
	Dennehy et al (1996) [36]	Direct and Indirect	・ED and hospitalization costs Out-patient healthcare services	Preventable DRI accounted for € 321,368. Mean direct cost due to hospitalization was € 1,350 (± 1,089). Indirect cost due to hospitalization was € 909 (± 248). For patients not hospitalized, direct cost (weighted mean) due to out-patient care was € 174 (± 134). Indirect cost due to patient hospitalized amounted to € 78 (± 62).	-

	Jha et al (2001) [22]	Direct	· Excess hospital LOS · Hospitalization costs	Average hospital cost per preventable ADE was € 8,515. Yearly costs to the hospital were of € 5.1 million per year for all ADEs and € 0.98 million for preventable ADEs	Median: 7.0 with variability measures (e.g. SD or IQR) were not reported
In-Patient and Out-patient Setting	Lagnaoui et al (2000) [23]	Direct	· Hospitalization costs	The mean cost per patient with an ADR leading to hospitalization was € 2,721. The total cost over the 4 months was € 87,073 over the study period, extrapolated to € 261,220 annually for the 23-bed medical unit. The yearly cost per hospital bed was € 11,357.	-
	Dormann et al (2004) [20]	Direct	· Excess hospital LOS · Hospitalization costs	The cost of preventable ADRs was € 350,280 during the study period of 12 months (on average € 360 per day)	Mean ± SD: 16.7 ± 13.4
	Field et al (2005) [30]	Direct	· Hospitalization costs · ED healthcare service costs · Out-patient healthcare service costs · Pharmacy services costs ·	** Increase in costs after a preventable ADE (95% CI) was €1,603 (€ 156 - € 305; *P= 0.03*) of which: · Costs for hospitalization was € 98.8 · Costs for ED visits: € 89.8 · Costs for out-patient care and doctor's fees: € 462.3 · Costs for prescribed medications: € 63.9	-
	Gyllensten et al (2014) [35]	Direct and Indirect	· Primary healthcare service costs · Hospitalization costs · Out-patient healthcare service costs · Pharmacy services costs · Productivity loss	· Mean Direct Costs per patient was € 2,450 (95% CI: 1,839 to 3,062) · Mean Indirect Costs per patient was € 2,674 (95% CI: 2,066 to 3,282)	-

Abbreviations

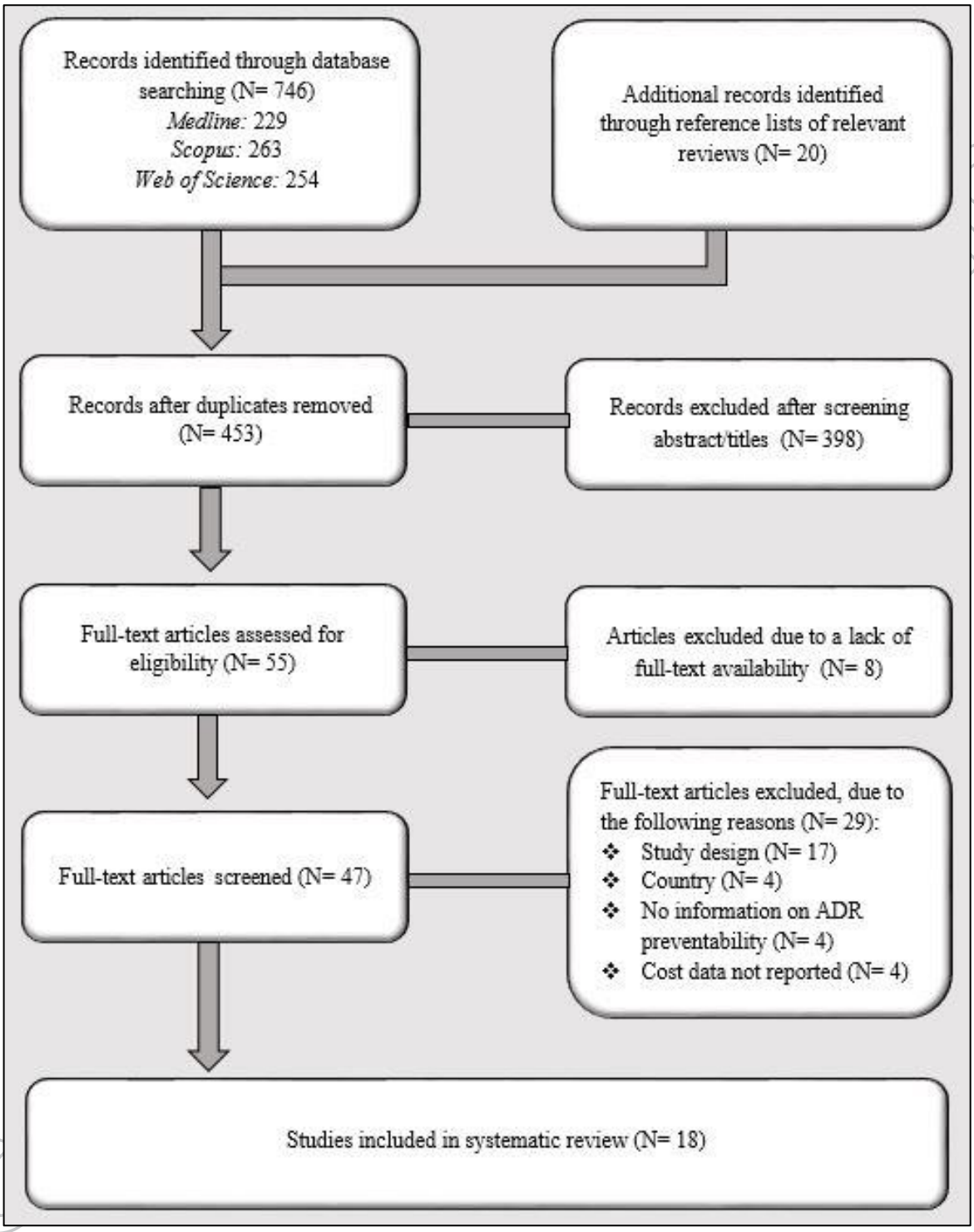
ADR: Adverse drug reactions; **ADE:** Adverse Drug Event; **CI:** confidence intervals; **DRI:** Drug-Related Illnesses; **ED:** Emergency Department; **IQR:** Interquartile range; **LOS:** Length of Stay; **MRAE:** Medication Related Adverse Events; **SD:** Standard Deviation;

Legend

* Costs were not adjusted for inflation or discounted. Currencies were converted into Euros according to the closing exchange rate on 1st March 2018.

** Additional costs for cases above those of comparison group, calculated as costs during the 6-week beginning the day of the preventable adverse drug event minus costs during the 6 weeks before that adverse drug event.

Figure 1. Flowchart of the process of study selection.



Additional File 1: Search query used for the systematic review.

Search Queries
#1 Drug AND #2 (adverse AND (event OR events)) OR (adverse AND (reaction OR reactions)) AND #3 (economic AND burden) OR ((cost OR costs) AND (analysis OR analyses)) OR (health AND care AND (cost OR costs)) OR (hospital AND (costs OR cost)) AND #4 preventable OR preventability OR avoidable OR avoidability