INCIDENCE OF ADVERSE DRUG REACTIONS IN HOSPITALIZED PATIENTS AT A TERTIARY CARE HOSPITAL IN THAILAND USING ADMINISTRATION DATABASE, 2007 TO 2011

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ABSTRACT

Adverse drug reactions (ADRs) are a major public health problem that significantly leads to morbidity and mortality. This study aimed to examine incidences, characteristics and trends of ADR related hospitalizations at one tertiary care hospital in Thailand during a five-year period (2007-2011), using routine administrative database. This was a retrospective study using data obtained from the administrative database of all the patients hospitalized during the year 2007 to 2011. The 10th International Classification of Diseases (ICD-10) was used to identify patients with ADR. The number of admissions with the following diagnosis codes; “adverse drug reaction”, “drug-induced”, “due to drug”, “due to medicament”, “drug allergy” or “external causes code” (Y40-Y59) were obtained and analyzed.

From a total of 283,070 hospitalizations from the year 2007 to 2011, seven thousand seven hundred and fifty-six (7,756) ADRs were detected in the hospital database, representing 2.74% of the total hospitalizations. Over the period, incidences of ADR related to admissions increased from 1.29% (2007) to 3.75% (2010) and then slightly decreased to 3.47% in 2011. The most commonly drugs involved were hormones, their synthetic substitutes and antagonists (Y42; 23.8%), systemic antibiotics (Y40; 13.2%), agents primarily affecting blood constituents (Y44; 12.6%) and analgesics, antipyretics and anti-inflammatory drugs (Y45; 6.5%). Diagnoses that were most frequently associated with ADR were anaemia (46.83%), metabolic disorders (26.72%), and dermatitis (11.77%), respectively. The incidences of ADRs-related hospitalization during 2007 to 2011, estimated from spontaneous report and from both spontaneous report and hospital database using Capture-Recapture (CR) Methods were 0.71% and 6.45%, respectively.

This study indicated the potential use of routine administrative database for monitoring patient safety and pharmacovigilance purpose. Effort should be made to implement effective measures to reduce ADR and to make greater use of administrative database to monitor patient safety.

KEY WORDS: ADR / HOSPITALIZED PATIENT / INCIDENCE /
PHARMACOVIGILANCE / PHARMACOEPIDEMIOLOGY

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อุบัติการณ์ของอาการไม่พึงประสงค์จากการใช้ยาในผู้ป่วย ณ โรงพยาบาลตติยภูมิแห่งหนึ่ง จากฐานข้อมูลเพื่อการบริหารจัดการ พ.ศ. 2550 - 2554

INCIDENCE OF ADVERSE DRUG REACTIONS IN HOSPITALIZED PATIENTS AT ATERTIARY CARE HOSPITAL IN THAILAND USING ADMINISTRATION DATABASE, 2007 TO 2011

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บทคัดย่อ

อาการไม่พึงประสงค์จากการใช้ยาถือเป็นปัญหาสาธารณสุขที่สำคัญที่นำไปสู่อาการเจ็บป่วยและการเสียชีวิตอย่างมีนัยสำคัญ การศึกษานี้มีวัตถุประสงค์ในการที่จะศึกษาอุบัติการณ์ ลักษณะเฉพาะ และแนวโน้มของการเกิดอาการไม่พึงประสงค์จากการใช้ยาของผู้ป่วยในโรงพยาบาลตติยภูมิแห่งหนึ่งในประเทศไทย ในระยะเวลา 5 ปี คือ ตั้งแต่ปี พ.ศ. 2550 – 2554 จากฐานข้อมูลเพื่อการบริหารจัดการ โดยการศึกษานี้เป็นการศึกษาข้อมูลแบบย้อนหลัง ข้อมูลผู้ป่วยที่เข้ารับการรักษาตัวในโรงพยาบาลดังกล่าวในช่วงดังกล่าว จะถูกค้นจากฐานข้อมูลเพื่อการบริหารจัดการของโรงพยาบาล โดยใช้บัญชีจำแนกทางสถิติระหว่างประเทศของโรคและปัญหาสุขภาพที่เกี่ยวข้อง ฉบับทบทวนครั้งที่ 10 (ICD-10) ในการจำแนกผู้ป่วยที่เกิดอาการไม่พึงประสงค์จากการใช้ยา ซึ่งผู้ป่วยที่มีรหัสวินิจฉัยโรค ดังต่อไปนี้ “adverse drug reaction”, “drug-induced”, “due to drug”, “due to medicament”, “drug allergy” หรือ “external causes code” (Y40-Y59) จะถูกสืบค้นจากฐานข้อมูลและนำมาวิเคราะห์

ในระหว่างปี พ.ศ. 2550-2554 มีการเข้ารับการรักษาตัวในโรงพยาบาลจำนวนทั้งสิ้น 283,070 ครั้ง ผลการศึกษาพบว่ามีจำนวนอาการไม่พึงประสงค์จากการใช้ยาจำนวน 7,756 ครั้ง คิดเป็นร้อยละ 2.74 ของการเข้าพักรักษาตัวในโรงพยาบาลในระหว่างปีการที่ทำการวิจัย โดยพบว่าอุบัติการณ์การเกิดอาการไม่พึงประสงค์จากการใช้ยาในผู้ป่วยที่เข้ารับการรักษาตัวในโรงพยาบาลมีแนวโน้มเพิ่มขึ้นจากรร้อยละ 1.29 (พ.ศ. 2550) เป็นร้อยละ 3.75 (พ.ศ. 2553) และลดลงในปี พ.ศ. 2554 เป็นร้อยละ 3.47 กลุ่มยาที่ทำให้เกิดอาการไม่พึงประสงค์จากการใช้ยามากที่สุด 5 อันดับแรก ได้แก่ ฮอร์โมนและสารสังเคราะห์แทน รวมทั้งสารต้าน (Y42; 23.8%), ยาปฏิชีวนะที่ออกฤทธิ์ทั่วร่างกาย (Y40; 13.2%), สารที่มีผลเบื้องต้นต่อส่วนประกอบของเลือด (Y44; 12.6%), และยาระงับปวด ยาลดไข้ และยาต้านการอักเสบ (Y45; 6.5%) ในขณะที่อาการที่เกี่ยวข้องที่สำคัญ ได้แก่ ภาวะโลหิตจาง (ร้อยละ 46.83), ความผิดปกติด้านเมตาโบลิก (ร้อยละ 27.72), ผิวหนังอักเสบ (ร้อยละ 11.77) ตามลำดับ ทั้งนี้อุบัติการณ์ของอาการไม่พึงประสงค์ในช่วง พ.ศ. 2550-2554 ซึ่งประมาณจากรายงานอากรไม่พึงประสงค์ และประมาณโดยวิธี การจับ-ทำเครื่องหมาย-ปล่อย –จับใหม่ จากรายงานอาการไม่พึงประสงค์และฐานข้อมูลของโรงพยาบาล ได้แก่ ร้อยละ 0.71 และ ร้อยละ 6.45 ตามลำดับ ผลจากการศึกษาวิจัยในครั้งนี้แสดงให้เห็นว่าการใช้ฐานข้อมูลเพื่อการบริหารจัดการมีความสำคัญและมีประโยชน์อย่างยิ่งในการที่เฝ้าระวังอาการไม่พึงประสงค์จากการใช้ยา และการติดตามความปลอดภัยของยา จึงควรมีการสนับสนุน ส่งเสริมและสร้างมาตรการเพื่อลดการเกิดอาการไม่พึงประสงค์จากการใช้ยา และใช้ประโยชน์จากฐานข้อมูลเพื่อการบริหารจัดการเพื่อติดตามความปลอดภัยในการใช้ยาของผู้ป่วยให้มากขึ้น

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ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
ICD-9	The 9th International Classification of Diseases
ICD-10	The 10th International Classification of Diseases
IgE	Immunoglobobulin E
LOS	Length of Stay
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NTI	Narrow therapeutic index
WHO	World Health Organization

CHAPTER I
INTRODUCTION

1.1 Background and rationale

Nowadays, the pharmacotherapy has become increasingly complex. However, the benefits of medication use are always accompanied by potential harm. According to the World Health Organization (WHO), adverse drug reaction (ADR) is 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' (1). Adverse drug reactions (ADRs) are a known drawback of medication use and are recognized as a major public health problem leading to morbidity, mortality and economic burden. Specifically, ADRs induced hospitalization and hospital acquired ADR result in unnecessary loss of health, unnecessary loss of quality of life and waste of money.

According to the recent systematic review and meta-analysis of 22 prospective studies, prevalence of ADRs among hospitalized patients was estimated at 16.88% (2).With regard to the prevalence of ADR induced hospitalization, a recent systematic review of the 25 prospective studies using WHO's definition of ADR found that approximately 5.3% of hospital admissions were associated with ADR (3). However, the results from many reviews and meta-analyses indicated that there was a high variability in prevalence of ADR across studies (2-5). Methodology used for ADR identification, methodology quality, and ward studied contributed to the heterogeneity of the prevalence of ADR identified across studies (2-6). With respect to ADR identification methods, it was found that studies using more intensive methods for ADR detection such as medical chart screening consistently found higher prevalence rates than database monitoring or spontaneous reporting (3, 5). Other factors associated with the incidence of ADRs included sex (7), age (8), length of hospital stay (8-12), and number of drugs administered (7, 9).

Drug safety assessment and monitoring should be considered an integral part of everyday clinical practice (13). In fact, the latest Institute of Medication recommended hospitals to assess the safety of medication use through active monitoring and used this data to guide the development of prevention strategies (14). According to the recent review, the intensive ADR monitoring and medical record reviews were identified as the most reliable methods (3) to monitor patient safety as compared to the use of database and spontaneous ADR reporting. Nonetheless these 2 methods require highly resource and technical intensive. By contrast, the use of database has great potential for routine monitoring patient safety and pharmacovigilance purpose (15).

Although the use of routinely collected hospital administrative data was expected to underestimated the incidence of ADR due to under-recognition, under recording, and limitation of the coding systems the advantages of using such databases to routinely monitoring patient safety were that it was free of charge incurred for data acquisition and that can it evaluate safety of medication use over time, as supplement to established methods such as spontaneous reporting system. In addition, it covered information of all inpatients admitted to the hospital in relatively standardized format. In fact, in several countries, the use of hospital administrative data was proven to be a reliable and valid method for monitoring patient's safety and pharmacovigilance (16-19).

As compared to western countries, incidence rates of ADRs among hospitalized patients in Thailand were also high. According to the review, incidence of ADRs among hospitalized patients varied widely ranging between 0.07% to 38.64%, with the mean length of hospital stay ranging between 4.15 to 10 days (7-11). Nevertheless, most of the studies conducted in Thailand were short-term studies that were conducted by medical record review methods in a few wards (7-12).

To our knowledge, no study was conducted to examine the incidence of ADR related hospitalized patients in Thailand before.

1.2 Objectives

This study is considered the application of routinely collected administrative database to medication safety and pharmacovigilance in Thailand. The aims of this study are to

(1) examine incidence of ADRs-related hospitalization at one tertiary care hospital during the year 2007-2011, using routine administrative database

(2) examine characteristics of ADRs-related hospitalization at one tertiary care hospital during the year 2007-2011, using routine administrative database

(3) examine trend of ADRs-related hospitalization at one tertiary care hospital during the year 2007-2011

(4) examine incidence of hospital acquired ADRs at tertiary care hospital during the year 2011, using capture-recapture methods from routine administrative database and spontaneous database

1.3 Expected outcomes and benefits

In this study, the incidence of ADR related hospitalization as well as its trends and characteristics were studied. As the result, findings from this study can provide the important indicator for monitoring patient safety as well as information for increasing awareness of harms associated with ADR and for supporting policies to increase patient safety. In addition, the potential use of administrative database for monitoring patient safety and pharmacovigilance in Thailand can be assessed.

1.4 Definition of terms

Adverse drug reaction in hospitalized patients

Adverse drug reaction in hospitalized patients in this study was defined as hospitalization with the ICD-10th codes including the following keywords: “drug induced”, or “due to drug/medication or adverse drug reaction”, “drug allergy” in primary diagnosis or ICD-10th codes of Y40-Y59 in the secondary diagnosis.

CHAPTER II
LITERATURE REVIEW

2.1. Adverse drug reactions (ADRs) and Adverse Drug Events (ADEs)

2.1.1 Definition of Adverse Drug Reactions (ADRs)/ Adverse Drug Events (ADEs)

The World Health Organization defined an adverse drug reaction (ADR) as any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy (1).

Karch and Lasagna defined an adverse drug reaction (ADR) is any response to a drug that is noxious and unintended that occurs at doses used in man for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose (20).

Furthermore, Edwards and Aronson proposed the new definition of ADR as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the products (21).

In addition, Nebeker JR, et al defined Adverse Drug Events (ADE) as an injury related to the use of a drug although the causality of this relationship may not be proven (22). The term ADE therefore includes harms caused by both adverse drug reactions and overdoses.

2.1.2 Classification of ADRs

2.1.2.1 Classification based on predictabililty

ADRs can be classified into two types based on predictability;

2.1.2.1.1 Predictable ADR

Predictable ADR are predictable consequences of therapy though knowledge of the pharmacology of the drug in question. These ADRs can be further divided into 4 subtypes

a) Toxicity
b) Side effects
c) Interactions
d) Secondary effects

2.1.2.1.2 Non-predictable ADR

For Non-predictable ADR, knowledge of the pharmacology and activity of medication do not permit identification of individual patients who might be at risk for specific type of ADR. Non-predictable ADR results from number of mechanisms, some of which cannot correctly understood. These ADRs can be further divided into many subtypes such as intolerance, allergy, and idiosyncratic.

2.1.2.2 Classification based on severity.

As shown in table 2.1, ADRs can be classified based on their severities into 7 levels. Level 1, Level 2-4, Level 5-6, and Level 7 referred to mild, moderate, severe and lethal, respectively (23).

Table 2.1; Adverse Drug Reaction severity classification according to severity.

Level	Characteristics
Level 1	An ADR occurred but requires no change in treatment with the suspected drugs.
Level 2	The ADR requires that the suspected drugs be withheld, discontinued, or otherwise changed. No antidote or other treatment is required, and there

Table 2.1; Adverse Drug Reaction severity classification according to severity. (cont.)

Level	Characteristics
Level 2	is no increase in length of stay (LOS)
Level 3	The ADR requires that the suspected drugs be withheld, discontinued, or otherwise changed. No antidote or other treatment is required.
Level 4	Any level 3ADR that increase LOS by at least one day, or the ADR is the reason for admission.
Level 5	Any level 4 that intensive medical care.
Level 6	The adverse reaction causes permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly leads to the death of the patients.

2.1.2.3 Classification based on preventability

An ADR is considered as preventable if that ADR can answer "YES" to one or more of the following questions (24).

1. Was the drug involved in the ADR inappropriate for the patient's clinical condition?
2. Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?
3. Was required therapeutic drug monitoring or other necessary laboratory test not performed or not performed frequency enough?
4. Was there a history of allergy or previous reactions to the drug?
5. Was the drug interaction involved in the ADR?
6. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
7. Was poor compliance involved in the ADR?

2.1.2.4 Classification based on pharmacological properties

Rawlins and Thompson classified types of ADRs into 2 types according to pharmacological classification: Type A and Type B (25). Characteristics of both types are compared in the table 2.2.

2.1.2.4.1 Type A ADRs (A- augmented)

Type A ADRs are called predictable or anticipated events.

There are two subclasses:-

Exaggerated Desired Effect: The undesirable exaggeration of a desired pharmacologic effect after a normal dose in a susceptible subject or after a higher than normal dose.

Undesired Effect: The appearance of an undesired pharmacologic effect, known as lateral or parallel stimulation, can be seen after a normal dose or a higher than normal dose in a susceptible subject; it is due to the stimulation of untargeted receptors by the therapeutic agent.

2.1.2.4.2 Type B ADRs (B - bizarre)

Type B ADRs are called pharmacologically unexpected, unpredictable, or idiosyncratic adverse reactions.

There are two subclasses:-

Immunologic: An allergic or hypersensitivity reaction occurs as a result of an immunologic mechanism. A pseudoallergy or anaphylactoid reaction is the result of a mechanism involvingthe release of the same mediators released during an immunologic reactiondue to immunoglobobulin E (IgE).

Idiosyncratic: These reactions are qualitatively abnormal adverse reactions that occur in a given individual and whose mechanism is not yet understood. They are usually quite rare and in some cases may be due to a genetic or acquired enzyme abnormality with the formation of toxic metabolites. This is also known as primary toxicity.

Table 2.2: Comparison between type A and Type B Adverse Drug Reactions (ADRs) (25)

Characteristics	Type A	Type B
Predictable from pharmacology	Yes	No
Dose dependent	Yes	No
Incidence	High	Low
Morbidity	High	Low
Mortality	Low	High
Management	Dose adjustment	Stop treatment

2.1.3 Methods of Adverse Drug Reactions (ADRs) detection (2)

There are several methods of ADR detection. These include: Intensive monitoring, prospective monitoring, chart review, computerized system, analysis of database, and spontaneous reporting.

2.1.3.1 Intensive monitoring

Intensive monitoring applied to all patients. Monitoring was performed by specialized team member(s) with experience in ADR identification. Monitoring included a daily review of chart, visiting of the ward and interview of the patients. If necessary, the patient was examined. A daily chart review without patient interview nor examination was not considered intensive monitoring but chart review. Intensive monitoring has the largest detection rate and being considered as the gold standard. It is mostly used in short and/or specific drug studies.

2.1.3.2 Chart review

Chart review is also useful for ADR detection however it requires a lot of skilled human resources.

Retrospective chart review evaluates patient data that exists at the time the protocol is submitted to the IRB for initial approval. This type of chart review uses information that has usually been collected for reasons other than

research. On the other hand, prospective chart review evaluates patient data that does not yet exist at the time of protocol is submitted to the IRB for initial review.

2.1.3.3 Analysis of database (i.e. hospital episodes statistics and large insurance claims data)

Administrative database is useful and easily accessible method to determine incidence of adverse reactions in the hospitals. This method is not widely used but it have some advantages as follows; information already available in almost every hospitals and most countries; 2) few human resource and financial burden necessary to validate ADR, and 3) the possibility for national perspective (26). The limitations of this approach were probably incomplete and wrong information especially miscoding in some cases (26). In many countries including the United States, computerized methods and the search through large insurance databases are extensively used (26).

Based on our review, several studies were conducted to examine the incidence of ADR using administrative database search (8, 16-19, 27-31). The following codes were used to identified ADR ; ICD-9 diagnosis codes (a code between E930 and E949.9.) (32); 2) ICD-9-CM (Codes searched included E codes and the 40 diagnostic codes (from E930 to E949.9 and codes designed to mark ADRs, already excluding wrong doses, errors and intoxications) (26); 3) 10^{th} Revision, German Modification (ICD-10-GM), 505 codes indicating a possible ADE were identified (16), and 4) The 10th International Classification of Diseases (ICD-10), the primary diagnosis codes including ‘adverse drug reaction’, ‘drug-induced’, ‘due to drug’, ‘due to medicament’ or ‘drug allergy’ and the secondary diagnoses of ADR (Y40-59) (17).

2.1.3.4 Spontaneous reporting

Spontaneous adverse drug reaction (ADR) reporting is the main methodology used by WHO’s International Drug Monitory program and was used regularly in many countries. It is considered as one of the cheapest methods to detect ADR. However, its limitations were smallest detection rate mainly due to

under-reporting (33), absence of a control group and lack of denominator data so that incidence of ADRs cannot be accurately calculated.

2.1.3.5 Computerized system

Computerized system is a potentially useful method but attention is needed to build rules and algorithms with high specificity, otherwise it will be too resource consuming. Another problem is its high dependency of structured data i.e. the difficulty with using data from patient narrative notes.

2.1.4 Prevalence of Adverse Drug Reactions related hospitalizations

According to a systematic review of 25 prospective studies that used the WHO ADR definition found that prevalence of hospitalization associated with ADRs ranged from 0.16% to 15.7% with the overall median of 5.3% (3). The meta-analysis of 22 prospective studies found that ADR occur in 16.88% of patients during hospitalization. Subgroup analysis of studies conducted in Asia found that the incidence of ADR among hospitalized patients was about 10.04% (2). In addition, a review by Krähenbühl-Melcher A, et al. (6) found that prevalence of ADR among hospitalized patients was about 6.1%. A meta–analysis of 39 prospective studies from US hospitals found that incidence of serious ADR among hospitalization was 6.7% (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) making ADR between the fourth and sixth leading cause of death (34).

Regarding ADR among children, a meta-analysis of 17 prospective studies in pediatric indicated that the overall incidence of ADRs among hospitalized children was 9.53% while severe reactions were accounted for 12.2% of the total. The incidence of ADRs induced hospitalization among children was 2.09%. Of the ADRs causing hospital admission, 39.3% were life threatening reactions. On the other hand, incidence of ADRs in outpatient's clinic was estimated at 1.46% (35).

Another review found that incidence of ADR induced hospitalization ranged from 0.4% to 10.3% while incidence of ADR among hospitalized children ranged from 0.6% to 16.8% (36).

The result from all reviews and meta-analysis showed a high variability in term of ADR prevalence (2, 4, 18) which can be explained by the following factors;

methodology used for ADR identification (2, 3, 6), methodology quality, population (2-4, 6) and ward studied (2, 6).

With regard to method of ADR detection (2, 3, 6), Kongkaew, et al. found that studies that employed multiple ADR detection methods, such as medical record review and patient interview, reported higher ADR admission rates compared with studies that used medical record review alone. The comparison of database and spontaneous ADR reporting found that spontaneous reporting tended to underreport, however, with a fatal outcome this appear to be less (29).

2.1.4.1 Studies examining incidence of ADR-related hospitalization using administration database

Characteristics and results of studies examining incidence of ADR-related hospitalization using administration database were summarized in table 2.3

Table 2.3: Studies examining incidence of ADR-related hospitalization using administration database

Study	Setting/Year	Method used to identify ADR-related hospitalizations	Incidence of ADR-related hospitalizations
Carrasco-Garrido P, et al.(18)	Spain (2001-2003)	All hospitalization with drug-related (ICD-9-CM code E) code	1.69%

Table 2.3: Studies examining incidence of ADR-related hospitalization using administration database (cont.)

Study	Setting/Year	Method used to identify ADR-related hospitalizations	Incidence of ADR-related hospitalizations
Wu T, et al. (17)	England (1999-2009)	The number of admissions with primary (codes including "adverse drug reaction", "drug induced", "due to drug", "due to medicament" or "drug allergy") or secondary diagnosis of ADR (ICD-10 Y40-59)	0.9%
Stausberg J, et al. (16)	Germany (2003-2007)	the ICD-10-GM indicating an ADE were categorized in seven groups according to their certainty. Primary diagnoses were considered as a proxy for drug-related admissions, and secondary diagnoses as a proxy for hospital-acquired ADE.	5% (at least possibly drug-induced and 0.7% very likely drug-induced
Waller P, et al. (27)	England (1996-2000)	ICD-10 codes including the words "drug induced", "due to medicine or which are recognized to be invariably caused by a drug were extracted together with external cause codes (Y 40-59)	0.083% of admission were coded as "Drug induced" while 0.314% were associated with external cause code.

Table 2.3: Studies examining incidence of ADR-related hospitalization using administration database (cont.)

Study	Setting/Year	Method used to identify ADR-related hospitalizations	Incidence of ADR-related hospitalizations
Patel H, et al. (37)	England (1998-2005)	Using ICD -10 codes with a primary (codes including the words "drug induced or due to" or secondary diagnosis of ADR (Y40-59)	0.5%
Miguel A, et al. (38)	Portugal (2000-2009)	ICD 9th revision codes includes E 930 to E949.9 codes	1.26%

2.2. Factors associated with ADRs

2.2.1 Sex

Sex is associated with ADR occurrence (8, 10). Several studies confirmed the higher risk of women to be hospitalized due to an ADR, and suggested that differences in drug use play a role in this gender difference. The effect of a drug on the body depends on the combination of pharmacokinetic factors. Women have a different volume of distribution and clearance than men, which could result in differences ineffective drug concentrations. A sex difference in pharmacodynamics, the effect of the body on the drug, is, was also contributed to difference rate of ADRs between men and women.

2.2.2 Age

Age is also associated with ADR occurrence (9, 11, 35, 36). ADRs are acknowledged as a major health problem in older people (30). This can be possible due to multiple drugs that they receive to manage chronic diseases and also because of changes in pharmacokinetic and pharmacodynamics, and decline in renal or liver

function in the elderly. In addition, children are also at high risk of developing ADRs due to developmental stages, and the risk related to off-label drug uses.

2.2.3 Length of hospital stay

Many studies found that length of hospital stay is an important risk factor for ADRs in hospitalized patients (7, 9, 11). Long duration of admission was associated with higher use of medications that possibly induced adverse drug reactions in hospitalized patients.

2.2.4 Number of drugs administered or Polypharmacy (7, 9, 11)

Williamson reported increasing ADR rising from 11% with one medicine to 27% with six medicines in 1998 patients in a survey of 50 UK geriatric units conducted before 1980. (39)

2.2.5 Interaction between age and number of medicines (39)

Study found that ADR rates was associated with the number of medicines taken, and age. Possible reason that older people are more liable to adverse drug reactions includes drug interactions occur due to polypharmacy.

2.2.6 Types of drugs

The use of drugs with a narrow therapeutic range is a risk factor that induced adverse drug reaction in hospitalized patients. The therapeutic index (also known as therapeutic ratio) is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death (in animal studies) or toxicity (in human studies) (40).

Narrow therapeutic index (NTI) drugs are agents for which small changes in systemic concentration can lead to significant changes in pharmacodynamic response. This may result in potentially subtherapeutic or toxic effects, particularly in patients with advanced age, comorbid illness, or those receiving multiple medications (41).

Kongkeaw, et al found that anti-infective drugs were most often associated with adverse drug reaction (ADR) admissions in children while cardiovascular drugs

and central nervous system disorders, as well as non-steroidal anti-inflammatory drugs (NSAIDs) were most often associated with ADR admission in adults and elderly population (3). Other review indicated that the used of anticoagulants or diuretic were associated with ADRs among hospitalized patient (6).

Among children, anti-infective and anti-epileptics were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital and children in hospitals, while anti-infective and non-steroidal anti-inflammatory drugs (NSAIDs) were frequently reported as associated with ADRs in outpatient children (17).

2.2.7 Renal elimination of drugs (42)

Renal filtration accounts for most drug excretion. About one fifth of the plasma reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. With aging, renal drug excretion decreases at age 80, clearance is typically reduced to half of what it was at age 30 (12).

Because of this reason, some study found that renal elimination of drugs is a risk factor that induced adverse drug reaction in hospitalized patients (42).

2.3. Trend of prevalence of Adverse Drug Reactions (ADRs)

According to the review, trends of prevalence of adverse drug reaction (ADRs) were increase (in elderly, women>men and in general patients), as shown in table 2.4. Hartholt KA, et.al found that in the Netherlands, since 1981-2007, ADR related hospital admission is increasing by 143% (28). Stausberg J. and Hasford J. found that in Germany, during 2003-2007, there was a significant increase in the overall rate of drug-related admission over time (16). Wu TY, et al found that in UK, the annual number of ADRs increased by 76.8% between 1999-2008 (17). In addition, Patel H., et al found that between 1998 and 2005 there were 447,071 ADRs representing 0.50% of total hospital episodes and over this period the number of ADRs increased by 45% (43). In Australia; Zhang M., et al found that repeat ADR-related hospitalizations have

consistently increased in elderly Australians from 1980 to 2003 (30). On the other hand, a study by Garrido PC, et.al found that during the 2001-2006 periods incidence of ADR-induced hospitalization in Spain, decreased significantly (18).

Table 2.4; The studies examining trends of prevalence of ADRs

Study	Author	Setting	Year of study	Trend of prevalence
1	P. C. Garrido,et.al (18)	Spain	2001-2006	The estimated incidence of admissions due to ADR significantly decreased (145 cases per 100,000 people in 2001 to 136 cases per 100,000 people in 2006)
2	Hartholt KA, et al. (28)	Netherland	1981-2007	Between 1981 and 2007, ADR-related hospital admissions in persons >60 years increased by 143%. The overall standardized incidence rate increased from 23.3 to 38.3 per 10,000 older persons.
3	T. Y. Wu, et al. (17)	England	1999-2009	The number of ADR admissions has increased at a greater rate than the increase in total hospital admissions. Between 1999 and 2008, there were 557,978 ADR-associated admissions, representing 0.9% of total hospital admissions. Over this period the annual number

Table 2.4; The studies examining trends of prevalence of ADRs (cont.)

Study	Author	Setting	Year of study	Trend of prevalence
3	T. Y. Wu, et al. (17)	England	1999-2009	of ADRs increased by 76.8% (from 42,453 to 75,076).
4	H. Patel, et al. (37)	England	Between 1998 and 2005	Between 1998 and 2005 there were 447, 071 ADRs, representing 0.50% of total hospital episodes and over this period the number of ADRs increased by 45%.
5	S. Schneeweiss, et al.(44)	Germany	between October 1997 and March 2000.	The incidence of drug related hospitalization increased with age (4/10,000 to 20/10,000).
6	M. Zhang, C. D'A. J. Holman, D. B. Preen & K. Brameld (30)	Australia	1980–2003	The rate of repeat ADRs consistently increased from 1980 and had reached 30.3% of all ADRs by 2003.
7	J. Stausberg* and J. Hasford (16)	Germany	the period 2003 to 2007	There was a significant increase in the overall rate of drug-related admissions over time ($p < 0.038$).

2.4. The studies about ADRs in hospitalized patients in Thailand

In Thailand, several studies concerning ADRs among hospitalized patients were conducted, as shown in table 2.5. However, all studies (7, 9-12) were conducted

in short periods and were limited in a few wards. Most of all were prospective study and used patients charts review to detect Adverse Drug Reactions (ADRs). One study was a retrospective study using database and ADR reports to detect Adverse Drug Reactions (ADRs) (10).

Table 2.5; Summary of studies about ADRs prevalence in hospitalized patients in Thailand

No.	Author	Year of study	Duration of study	Patients	Prevalence/ Incidence*	Method of detection	Setting
1	Tragulpiankit P., et al. (7)	1994	3.5 months	Who performed in male and female medical ward 1	38.64%	Patients charts review	Ramathibodi hospital
2	Thiankhanithikun K., et al. (10)	2002	-1 month -1 fiscal year	- Hospitals throughout Thailand - ADR reports	-2.85%* -36.2%	- Database of first large-scale prospective intensive project of Thai FDA* - ADR reports	- The provincial Hospitals in Thailand - Phrae hospital
3	Chiewchantanakit D., et al. (9)	1999	7 months	All children patients who admitted in 5 wards	22.59%	Patients charts, interview	Samutsakhon hospital
4	Panrong A., et al. (11)	1998	4 months	All children patients who admitted in 3 wards	3.70%*	Patients charts review	Queen Sirikit National Institute of Child Health

Table 2.5; Summary of studies about ADRs prevalence in hospitalized patients in Thailand (cont.)

No.	Author	Year of study	Duration of study	Patients	Prevalence/ Incidence*	Method of detection	Setting
5	Choppradit C., et al. (12)	1999	11 months	Out/in-patients developing the ADRs in study period	0.07%	ADRs monitoring center at the hospital	Queen Sirikit National Institute of Child Health

*"the incidence of ADRs in hospitalized patients: a prospective observational study in 21 selected Thai hospital"

CHAPTER III
METHODOLOGY

3.1. Designs:

A retrospective study using hospital routinely administration database

3.2. Settings:

Buddhachinaraj hospital, Phitsanulok, Thailand

3.3. Outcome measure:

Primary outcome: Incidence of ADRs related hospitalization during the year 2007-2011

Secondary outcome: trend and characteristics of ADRs related hospitalization

3.4. Data sources:

This study was based on aggregated Buddhachinaraj hospital routinely administration databases containing records with admission dates from 1 January 2007 to 31 December 2011. The databases cover all patients admitted at Buddhachinaraj hospital during the study period. The data contains important demographic characteristics (i.e. age, gender, insurance type), administrative information (i.e. length of stay, Diagnosis Related Group), and clinical information (i.e. diagnoses, methods of discharge). In addition, information from spontaneous ADR reporting during the year 2007-2011 was also retrieved.

3.5. Participants:

All patients admitted at Buddhachinaraj hospital during 1 January 2007 to 31 December 2011, who were identified as having hospital-acquired ADR, or ADR induced hospitalization.

3.6. Data collection and data analysis

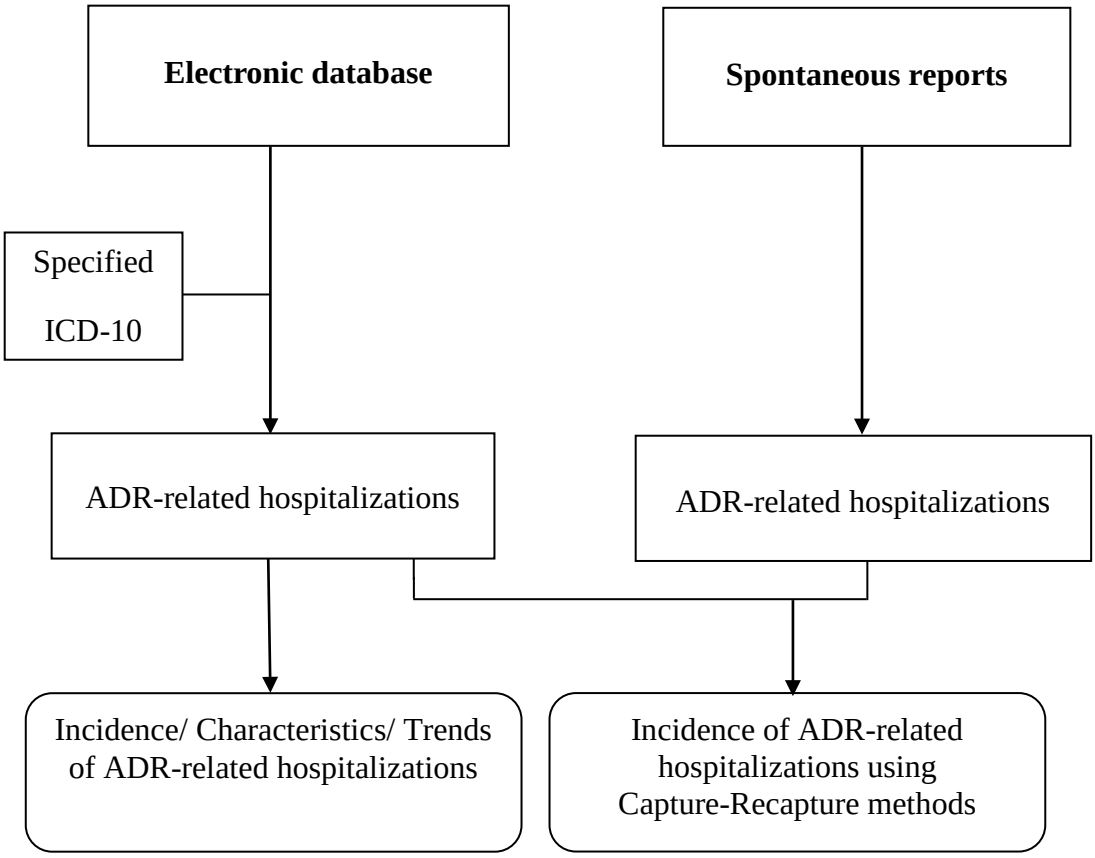

Figure 3.1; Framework for data collection and data analysis

Framework of data collection and data analysis were presented in figure 3.1. In this study, the routine administrative databases of the hospital during the year 2007-2011 were employed. Based on the specified ICD-10th Code, ADRs related hospitalizations were identified. It should be noted the data from spontaneous ADR reporting during the year 2011 were also be compared and integrated in examining the

incidence of ADRs induced hospitalization and hospital acquired ADRs using capture-recapture method. In doing so, duplicate records will be removed by matching hospital ID number, date of birth, sex, date of admission, and date of discharge. Characteristics of ADR related hospitalizations by ICD-10th and length of stays were also examined. Trend of ADRs incidence during 2007-2011 were reported.

3.7. Identification of ADR related hospitalization using ICD-10th codes

According to the literature review, the list of 225 codes indicating a possible ADR were classified into 6 categories as follows; “drug induced” (ICD-10 chapter D, E, G, H , J, K,L, M, R), “due to drug” (ICD-10 chapter D, K, L, M, N, O, P), “due to medication” (ICD-10 Chapter E), “adverse drug reaction”, “drug allergy” and “external causes code” (Y40-Y59). The list of ICD-10th codes is displayed in appendix A and summarized in table 3.1. (17)

Table 3.1; List of ICD-10th codes associated with ADR related hospitalization

Category	Definition	Number of codes
1	Drug induced	36
2	Due to drug	13
3	Due to medicament	1
4	Adverse drug reaction	-
5	Drug allergy	-
6	External cause code	175

In this study, ADR related hospitalization were identified using the ICD-10th with a primary (codes including the following keywords: “drug induced”, or “due to drug/medication or adverse drug reaction”, “drug allergy”) or secondary diagnosis of ADR (ICD-10th Y40-Y59).

3.8. Data analysis:

The data-set included the following variable: age, gender, admission method, primary, secondary and other diagnosis fields, length of stay, method of discharge (including in-hospital death), dates of admission and discharge, and DRGs. Duplicate records were removed by matching hospital ID number, date of birth, sex, date of admission, and date of discharge.

In this study, Incidences of ADR-related hospitalizations were calculated as the number of ADR related hospitalization divided by the total number of admissions during each year of study period.

In the year 2011, the incidences were calculated using information from 1) administrative database alone, and 2) administrative database + spontaneous ADR reporting system. The incidences were also classified by age (≤16 year and ≥60 year), gender, and ICD -10^{th} code. To better estimate the incidence of ADR using both hospital database and hospital spontaneously reported adverse drug reactions capture – recapture method were used.

Capture-recapture method was originally developed to estimate the size of a closed animal population. In this method, at one time (capture stage) animals in an area are captured, tagged and released. At the later time (recapture staged), the animals are captured again. The number of animals captured in each stage and the number common to both stages are used to estimate the number in the total population with the assumption that capture and recapture are independent. Capture-recapture method is increasingly be used in epidemiology studies to estimate incidence and prevalence of diseases in the population. (45),(46) , (47), (48), (49)

This method offers the potential to reduce bias in the estimation of incidence. In this method, at least two independent sources of cases need to be identified. The number of cases that are common to both sources (a), the total numbers of cases identified from each source (a+c) and a+b respectively) are required, as shown in table 3.2. A sample capture-recapture estimate of the total number of cases, N, is calculated using the following equation: (49)

$$N = \frac{(a+b+1)\,(a+c+1)}{(a+1)} - 1$$

Var (N) $= \frac{(a+b+1)(a+c+1)cb}{(a+1)^2(a+2)}$

95% CI $= N \pm 1.96 \sqrt{Var\ (N)}$

x $= N - (a+b+c)$

% Completeness of source 1 $= \frac{(a+c)}{N} * 100\%$

% Completeness of source 2 $= \frac{(a+b)}{N} * 100\%$

% Completeness of both sources $= \frac{(a+b+c)}{N} * 100\%$

Table 3.2; Capture-recapture method

Source 2	Source 1		Total
	Yes	No	
Yes	a	b	a+b
No	c	x	c+x
Total	a+c	b+x	N

In this study, the purpose of Capture-Recapture (CR) Methods is to solve a hidden in-patients problem and to estimate total in-patients with ADRs during the year 2007-2011 by using information from overlapping lists of cases from two data sources (hospital database and hospital spontaneously reported adverse drug reactions) to estimate the total number of ADR related hospitalization (N). Descriptive statistics were used to summarize the trend of patients with ADR induced hospitalization and hospital acquired ADRs (i.e. average LOS, age, sex, ICD-10th, and discharge status).

CHAPTER IV
RESULTS

In this chapter, incidence trend and characteristics of ADRs related hospitalization during 2007-2011were reported.

4.1. Incidences and 5-years trends of ADRs-related hospitalization

Table 4.1 summarizes the annual number of total hospitalization, the number of ADRs related to hospitalization, and incidences of ADRs-related hospitalization, identified from the specified ICD-10th codes, during the 5-year study period, there were 283,070 hospitalizations and 7,756 hospitalizations with diagnostic code indicative of ADRs (2.74%). Of these, 3,780 (1.34%) were “drug induced” codes and 3,976 (1.4%) were “external cause”.

As shown in figure 4.1 and table 4.1., during the 5-year study period, incidences of among hospitalized patients were increasing from 1.29% (2007) to 3.75% (2010) and then slightly decreasing to 3.47% in 2011. Between 2007 and 2011, the total number of hospitalization increased by 17.08% while the total number of hospitalization related to ADRs increased by 215.57% and incidence of ADRs-related hospitalization increased by about 169% (from 1.29% in 2007 to 3.74% in 2011).

Table 4.1; Total number and incidence of ADRs-related hospitalization during 2007-2011

Year	2007	2008	2009	2010	2011	total	% change 2007-2011
Total number of hospitalization	52,955	55,764	55,309	57,041	62,001	283,070	17.08

Table 4.1; Total number and incidence of ADRs-related hospitalization during 2007-2011 (cont.)

Year	2007	2008	2009	2010	2011	total	% change 2007-2011
Number with "Drug-induced" codes	479	507	882	1,003	909	3,780	89.77
Number with "external cause" codes	202	378	1,018	1,138	1,240	3,976	513.86
Total number of ADRs-related hospitalization	681	885	1,900	2,141	2,149	7,756	215.57
Incidence of ADRs-related hospitalization (%)	1.29	1.59	3.44	3.75	3.47	2.74	168.99

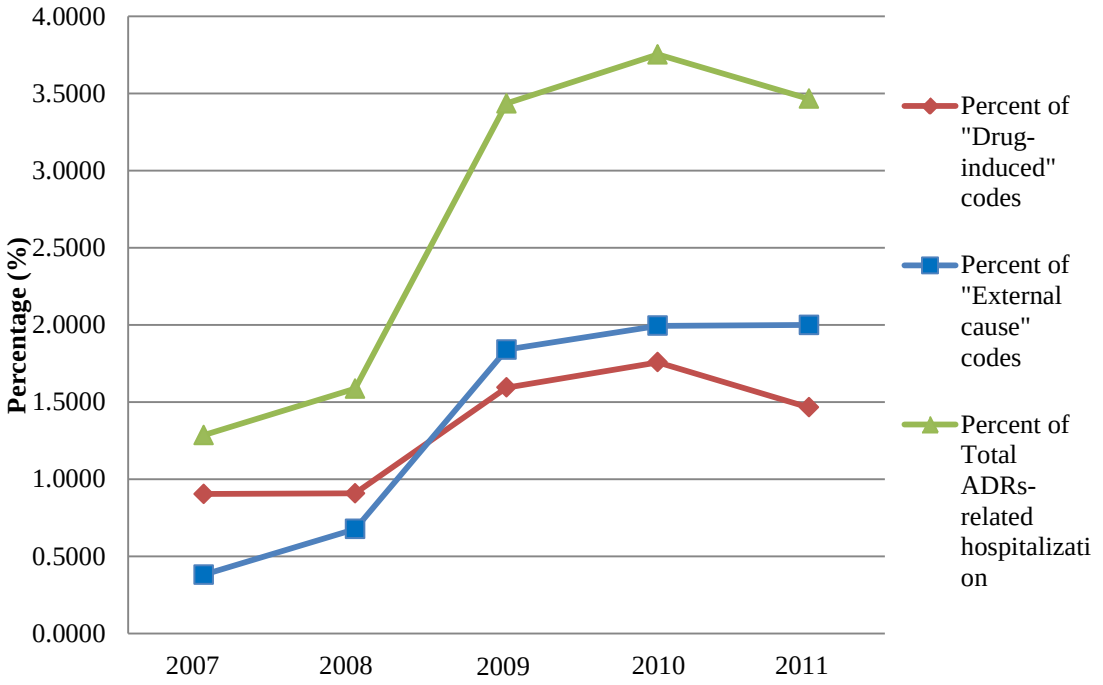

Figure 4.1: Incidences of ADRs-related hospitalization between 2007 to 2011

Table 4.2 describes the number of ADRs with an "external cause" code during 2007 to 2011. As shown in the table, the three commonest classes of ADR-related hospitalization, classified as an "external cause" code were hormones and their synthetic substitutes and antagonists (Y42; 24%), systematic antibiotic (Y40; 13%), and agents primarily affecting blood constitutes (Y44; 12.6%), respectively.

Table 4.2; Annual numbers of hospitalizations with an "external cause" code

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y40	Systemic antibiotics	32 (15.842)	61 (16.138)	156 (15.324)	147 (12.917)	130 (10.484)	526 (13.23)
Y41	Other systemic anti-infectives and antiparasitics	8 (3.960)	11 (2.910)	57 (5.599)	66 (5.800)	75 (6.048)	217 (5.46)

Table 4.2; Annual numbers of hospitalizations with an "external cause" code (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y42	Hormones and their synthetic substitutes and antagonists	12 (5.941)	11 (2.910)	226 (22.200)	324 (28.471)	381 (30.726)	954 (23.99)
Y43	Primarily systemic agents	8 (3.960)	11 (2.910)	82 (8.055)	125 (10.984)	142 (11.452)	368 (9.26)
Y44	Agents primarily affecting blood constituents	51 (25.248)	100 (26.455)	112 (11.002)	112 (9.842)	126 (10.161)	501 (12.60)
Y45	Analgesics, antipyretics and anti-inflammatory drugs	11 (5.446)	18 (4.762)	76 (7.466)	82 (7.206)	70 (5.645)	257 (6.46)
Y46	Antiepileptics and anti-Parkinsonism drugs	11 (5.446)	19 (5.026)	37 (3.635)	26 (2.285)	39 (3.145)	132 (3.32)
Y47	Sedatives, hypnotics and anti-anxiety drugs	7 (3.465)	4 (1.058)	14 (1.375)	8 (0.703)	12 (0.968)	45 (1.13)
Y48	Anaesthetics and thera-peutic gases	0 (0.000)	0 (0.000)	2 (0.196)	0 (0.000)	2 (0.161)	4 (0.10)
Y49	Psychotropic drugs, not elsewhere	2 (0.990)	4 (1.058)	15 (1.473)	13 (1.142)	15 (1.210)	49 (1.23)

Table 4.2; Annual numbers of hospitalizations with an "external cause" code (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y49	classified						
Y50	Central nervous system stimulants, not elsewhere classified	0 (0.000)	1 (0.265)	1 (0.098)	0 (0.000)	0 (0.000)	2 (0.05)
Y51	Drugs primarily affecting the autonomic nervous system	2 (0.990)	8 (2.116)	36 (3.536)	33 (2.900)	36 (2.903)	115 (2.89)
Y52	Agents primarily affecting the Cardiovascular system	18 (8.911)	25 (6.614)	72 (7.073)	63 (5.536)	60 (4.839)	238 (5.99)
Y53	Agents primarily affecting the gastrointestinal system	1 (0.495)	1 (0.265)	5 (0.491)	4 (0.351)	3 (0.242)	14 (0.35)
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	4 (1.980)	13 (3.439)	58 (5.697)	66 (5.800)	76 (6.129)	217 (5.46)

Table 4.2; Annual numbers of hospitalizations with an "external cause" code (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	1 (0.495)	1 (0.265)	6 (0.589)	3 (0.264)	4 (0.323)	15 (0.38)
Y56	Topical agent primarily affecting skin/mucous membranes and opth/ otrhlary/dental drugs	1 (0.495)	2 (0.529)	5 (0.491)	3 (0.264)	1 (0.081)	12 (0.30)
Y57	Other and unspecified drugs and medicaments	32 (15.842)	84 (22.222)	51 (5.010)	51 (4.482)	63 (5.081)	281 (7.07)
Y58	Other and unspecified drugs and medicaments	0 (0.000)	2 (0.529)	4 (0.393)	4 (0.351)	2 (0.161)	12 (0.30)
Y59	Other and unspecified vaccines and biological substance	1 (0.495)	2 (0.529)	3 (0.295)	8 (0.703)	3 (0.242)	17 (0.43)
Total		202	378	1018	1138	1240	3,976

Table 4.3 shows the characteristics of hospitalizations with an "external cause" code for ADR. During the year of study period, we found that hospitalizations with an "external cause" code for ADR occurred more in female (55.6%) and in patients aged higher than 60 years old (50.5%) with the average length of stay, estimated at 8.56 days.

Table 4.3: Characteristics of hospitalizations, with an "external cause" code for ADR: gender, age, and length of stay

Characteristics	2007	2008	2009	2010	2011	Total
Gender (percentage)						
Male	99	157	472	504	533	1,765
	(49.01)	(41.53)	(46.37)	(44.29)	(42.98)	(44.4%)
Female	103	221	546	634	707	2,211
	(50.99)	(58.47)	(53.63)	(55.71)	(57.02)	(55.6%)
Age (percentage)						
≤16	18	32	64	59	59	232
	(8.91)	(8.47)	(6.29)	(5.18)	(4.76)	(5.84%)
17-59	77	159	468	495	537	1,736
	(38.12)	(42.06)	(45.97)	(43.50)	(43.31)	(43.66%)
≥60	107	187	486	584	644	2,008
	(52.97)	(49.47)	(47.74)	(51.32)	(51.93)	(50.50%)
Length of stay						
Mean (days)	8.72	6.94	9.64	9.08	8.42	8.56

During the 5-year study period, incidences of ADR-associated hospitalizations were increasing (1.29% to 3.47%). As shown in table 4.4, diagnoses most frequently associated with ADR were anaemia (46.83%), metabolic disorders (27.72%), and dermatitis (11.77%), toxic liver (5.61%), and cardiovascular consequence (4.21%), respectively. As shown in appendix, most of anemia cases were

related to drug-induced neutropenia while most of metabolic disorders were related to drug-induced hypoglycaemia.

Table 4.5 shows the characteristics of hospitalizations with “drug induced” code for ADR. During the years of study period, we found that hospitalizations with an “drug induced” code for ADR occurred more in female (53.54%) and on patients aged between 17 to 59 years old (50.5%) with the average length of stay estimated at 12.01 days. On the other hand, table 4.6 describes characteristics of ADR related hospitalization (both “drug induced” code and “external cause” code). We found that ADR related hospitalization occurred more frequent in female (54.6%), aged between 17-59 years old (45.9%), with the average length of stay of 10.29 days.

Table 4.4: Annual number of hospitalization with “drug induced” codes

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
D	Drug-induced anaemia	303 (63.26)	324 (63.91)	405 (45.92)	392 (39.08)	346 (38.06)	1,770 (46.83)
E	Drug-induced metabolic disorders	48 (10.02)	58 (11.44)	209 (23.70)	387 (38.58)	346 (38.06)	1,048 (27.72)
G	Drug-induced neuromuscular disorders	10 (2.09)	24 (4.73)	39 (4.42)	28 (2.79)	30 (3.30)	131 (3.47)
H	Drug-induced cataract and hearing loss	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
I	Cardiovascular consequences due to drugs	19 (3.97)	18 (3.55)	52 (5.90)	38 (3.79)	32 (3.52)	159 (4.21)
J	Drug-induced lung disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
K	Toxic liver disease	25 (5.22)	39 (7.69)	59 (6.69)	42 (4.19)	47 (5.17)	212 (5.61)

Table 4.4: Annual number of hospitalization with "drug induced" codes (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
L	Dermatitis due to drugs	72 (15.03)	44 (8.68)	117 (13.27)	107 (10.67)	105 (11.55)	445 (11.77)
M	Drug-induced immune disorders	2 (0.418)	0 (0)	0 (0)	1 (0.100)	1 (0.110)	4 (0.11)
O	Pregnancy, childbirth and the puerperium due to drugs	0 (0)	0 (0)	1 (0.11)	0 (0)	0 (0)	1 (0.03)
P	Certain conditions originating in the perinatal period due to drugs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
R	Drug-induced symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0 (0)	0 (0)	0 (0)	8 (0.80)	2 (0.22)	10 (0.26)
Total		479	507	882	1003	909	3,780

Table 4.5: Characteristics of hospitalizations with "drug induced" code for ADRs: gender, age, and length of stay

Characteristics	2007	2008	2009	2010	2011	Total
Gender						
(percentage)						
Male	232	233	408	452	431	1,756
	(48.43)	(45.96)	(46.26)	(45.06)	(47.41)	(46.4)
Female	247	274	474	551	478	2,024
	(51.57)	(54.04)	(53.74)	(54.94)	(52.59)	(53.54)
Age (percentage)						
≤16	78	83	104	149	119	533
	(16.28)	(16.37)	(11.79)	(14.86)	(13.09)	(14.1)
17-59	263	257	432	437	432	1,821
	(54.91)	(50.69)	(48.98)	(43.57)	(47.53)	(48.17)
≥60	138	167	346	417	358	142
	(28.81)	(32.94)	(39.23)	(41.57)	(39.38)	(37.72)
Length of stay						
Mean (days)	12.92	10.60	13.05	11.31	12.19	12.01

Table 4.6: Characteristics of ADR related hospitalizations: gender, age, and length of stay

Characteristics	N (%) or Mean (SD)
Gender (N= 7,756)	
Male	3,521 (45.4%)
Female	4,235 (54.6%)
Age (N= 7,756)	
≤16	765 (9.9%)
17-59	3,557 (45.9%)
≥60	3,434 (44.2%)
Length of stay (N=7,756)	10.29 (2.1)

Table 4.7 describes the number of death with ADRs-related hospitalization during the 5-year study period, there were 7,756 ADR-related hospitalizations and 847 deaths resulting, a case-fatality rate of 10.92%.

Table 4.7; Total number of death with ADRs-related hospitalization during 2007-2011

Year	2007	2008	2009	2010	2011	total
Total number of hospitalization	52,955	55,764	55,309	57,041	62,001	283,070
Total number of ADRs-related hospitalization	681	885	1,900	2,141	2,149	7,756
Total number of death with ADRs-related hospitalization	68	66	226	273	214	847
Case fatality (%)	9.99	7.46	11.89	12.75	9.96	10.92

Table 4.8 describes the number of death with an “external cause” code during 2007 to 2011. As shown in the table, the three commonest classes of ADR-related hospitalization, classified as an “external cause” code were Insulin and oral hypoglycaemic [antidiabetic] drugs (Y423; 32.86%), Anticoagulants (Y442; 18.98%), and other antineoplastic drugs (Y433; 7.08%), respectively.

Table 4.8: Annual number of death during admission with an “external cause” code

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y40	Y400	1 (6.67)	1 (5.88)	2 (1.96)	3 (2.40)	1 (1.06)	8 (2.27)

Table 4.8: Annual number of death during admission with an "external cause" code (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
	Y401	2 (13.33)	0 (0.00)	5 (4.90)	5 (4.00)	4 (4.25)	16 (4.53)
	Y404	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.80)	1 (1.06)	2 (0.57)
	Y405	0 (0.00)	0 (0.00)	2 (1.96)	1 (0.80)	1 (1.06)	4 (1.13)
	Y407	0 (0.00)	0 (0.00)	1 (0.98)	0 (0.00)	1 (1.06)	2 (0.57)
	Y408	2 (13.33)	0 (0.00)	4 (3.92)	3 (2.40)	2 (2.13)	11 (3.12)
	Y409	0 (0.00)	0 (0.00)	1 (0.98)	1 (0.80)	0 (0.00)	2 (0.57)
Y41	Y411	0 (0.00)	0 (0.00)	7 (6.86)	9 (7.20)	8 (8.51)	24 (6.80)
	Y414	0 (0.00)	0 (0.00)	1 (0.98)	0 (0.00)	0 (0.00)	1 (0.28)
	Y415	0 (0.00)	0 (0.00)	1 (0.98)	2 (1.60)	0 (0.00)	3 (0.85)
	Y418	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.13)	2 (0.57)
Y42	Y420	0 (0.00)	0 (0.00)	2 (1.96)	2 (1.60)	1 (1.06)	5 (1.42)
	Y422	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.13)	2 (0.57)
	Y423	0 (0.00)	0 (0.00)	41 (40.20)	44 (35.20)	31 (32.98)	116 (32.86)
	Y427	0 (0.00)	0 (0.00)	3 (2.94)	1 (0.80)	0 (0.00)	4 (1.13)
	Y428	0	0	0	0	1	1

Table 4.8: Annual number of death during admission with an "external cause" code (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y42	Y428	(0.00)	(0.00)	(0.00)	(0.00)	(1.06)	(0.28)
Y43	Y431	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.60)	1 (1.06)	3 (0.85)
	Y433	0 (0.00)	0 (0.00)	4 (3.92)	12 (9.60)	9 (9.58)	25 (7.08)
Y44	Y442	1 (6.67)	6 (35.29)	17 (16.67)	25 (20.00)	18 (19.15)	67 (18.98)
	Y445	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.06)	1 (0.28)
	Y449	0 (0.00)	0 (0.00)	1 (0.98)	0 (0.00)	0 (0.00)	1 (0.28)
Y45	Y451	1 (6.67)	0 (0.00)	0 (0.00)	1 (0.80)	1 (1.06)	3 (0.85)
	Y452	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.80)	0 (0.00)	1 (0.28)
	Y453	0 (0.00)	1 (5.88)	1 (0.98)	4 (3.20)	2 (2.13)	8 (2.27)
	Y455	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.80)	0 (0.00)	1 (0.28)
	Y459	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.06)	1 (0.28)
Y46	Y466	0 (0.00)	1 (5.88)	4 (3.92)	2 (1.60)	2 (2.13)	9 (2.55)
Y48	Y482	0 (0.00)	0 (0.00)	1 (0.98)	0 (0.00)	0 (0.00)	1 (0.28)
Y49	Y493	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.06)	1 (0.28)
Y51	Y517	0 (0.00)	0 (0.00)	1 (0.98)	0 (0.00)	0 (0.00)	1 (0.28)

Table 4.8: Annual number of death during admission with an "external cause" code (cont.)

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
Y52	Y520	1 (6.67)	1 (5.88)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.57)
	Y521	0 (0.00)	0 (0.00)	1 (0.98)	0 (0.00)	0 (0.00)	1 (0.28)
Y54	Y548	1 (6.67)	1 (5.88)	1 (0.98)	1 (0.80)	1 (1.06)	5 (1.42)
Y57	Y576	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.80)	0 (0.00)	1 (0.28)
	Y578	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.80)	0 (0.00)	1 (0.28)
Y57	Y579	6 (40.00)	6 (35.29)	1 (0.98)	2 (1.60)	2 (2.13)	17 (4.82)
Total		15	17	102	125	94	353

As shown in table 4.9, an in-hospital mortality rate most frequently associated with ADR were agranulocytosis (45.86%), hypoglycaemia (29.09%), and toxic liver disease (7.67%), nondiabetic hypoglycaemic (7.47%), and dermatitis (6.46%), respectively.

Table 4.9: Annual number of death during admission with "drug induced" codes

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
D	D611	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.83)	1 (0.20)
	D70	43 (79.63)	40 (81.63)	52 (41.93)	54 (36.49)	38 (31.67)	227 (45.86)
E	E150	0	1	0	22	14	37

Table 4.9: Annual number of death during admission with "drug induced" codes

ICD-10 chapters	Description	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	Total (%)
E	E150	(0.00)	(2.04)	(0.00)	(14.86)	(11.67)	(7.48)
	E160	1 (1.85)	1 (2.04)	43 (34.68)	51 (34.46)	48 (40.00)	144 (29.09)
	E273	0 (0.00)	0 (0.00)	1 (0.81)	0 (0.00)	0 (0.00)	1 (0.20)
G	G253	1 (1.85)	2 (4.08)	4 (3.23)	0 (0.00)	2 (1.67)	9 (1.82)
	G409	1 (1.85)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.20)
	G958	0 (0.00)	0 (0.00)	1 (0.81)	1 (0.67)	0 (0.00)	2 (0.40)
I	I427	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.83)	1 (0.20)
	I952	0 (0.00)	0 (0.00)	1 (0.81)	0 (0.00)	0 (0.00)	1 (0.20)
K	K711	3 (5.56)	4 (8.16)	12 (9.67)	10 (6.76)	9 (7.50)	38 (7.68)
L	L270	5 (9.26)	1 (2.04)	9 (7.25)	10 (6.76)	7 (5.83)	32 (6.46)
O	O689	0 (0.00)	0 (0.00)	1 (0.81)	0 (0.00)	0 (0.00)	1 (0.20)
Total		54	49	124	148	120	495

4.2. Incidence of ADRs related hospitalizations using spontaneous database

Table 4.10 shows that the number of ADRs related to hospitalization and incidences of ADRs-related hospitalization, identified from the hospital spontaneously

reported adverse drug reactions, during the 5-year study period. As shown in the table, there were 283,070 hospitalizations and 2,003 hospitalizations with spontaneous reported of ADRs (0.71%).

Table 4.10; Total number and incidence of ADRs-related hospitalization during 2007-2011 using spontaneous database

Year	2007	2008	2009	2010	2011	total	% change 2007-2011
Total number of hospitalization	52,955	55,764	55,309	57,041	62,001	283,070	17.08
Total number of ADRs-related hospitalization	263	363	496	418	463	2003	76.05
Incidence of ADRs-related hospitalization (%)	0.50	0.65	0.90	0.73	0.75	0.71	50.00

4.3. Estimating total patients with ADRs related hospitalizations using capture-recapture method

Source 1: hospital administrative database

Source 2: hospital spontaneously reported

4.3.1 Estimating total patients with ADR related hospitalizations during 2007 to 2011 using capture-recapture method

As shown in table 4.11, the total number of ADR related hospitalization identified from both source (a) was 850. The total number of ADR-related hospitalizations identified from hospital database was 7,756 (a+b) while the

total number of ADR-related hospitalization identified from spontaneous reported (a+c) was 2,003.

Table 4.11: Total patients with ADR related hospitalizations during 2007 to 2011 using capture-recapture method

Hospital administrative database	Spontaneously reported		Total
	Yes	No	
Yes	850	6,906 (7,756-850)	7,756
No	1,153 (2,003-850)	x	
Total	2,003		N

N = $\frac{(a+b+1)\,(a+c+1)}{(a+1)}$ -1
= ((7,757* 2,004)/851) – 1)
= 18,266

x = N – (a+b+c)
= 18,266- (850+6,906+1,153)
= 9,357

% Completeness of spontaneous report = $\frac{(a+c)}{N}$*100%
= (2,003/18,266)*100
= 10.97%

% Completeness of electronic database = (7,756/18,266)*100
= 42.46%

% Completeness of both sources = ((7,756+1,153) / 18,266)*100
= 48.77%

According to capture-recapture method, the total number of patients with ADRs related hospitalizations during 2007-2011 was estimated at 18,267.

During the 5-year of study period, there were 283,070 hospitalizations. Then, incidences of ADRs-related hospitalization estimated from two data sources using Capture-Recapture (CR) Methods was 6.45%.

4.3.2 Total patients with ADR related hospitalizations in 2011 using capture-recapture method

As shown in table 4.12, the total number of ADR related hospitalization identified from both source (a) was 181. The total number of ADR-related hospitalizations identified from hospital database was 2,149 (a+b) while the total number of ADR-related hospitalization identified from spontaneous reported (a+c) was 463.

Table 4.12: Estimating total patients with ADR related hospitalizations in 2011 using capture-recapture method

Hospital administrative database	Spontaneously reported		Total
	Yes	No	
Yes	181	1,968 (2,149-181)	2,149
No	282 (463-181)	x	
Total	463		N

$$N = \frac{(a+b+1)\,(a+c+1)}{(a+1)} - 1$$
$$= ((2{,}150 * 464)/182) - 1)$$
$$= 5{,}481$$

$$x = N - (a+b+c)$$
$$= 5{,}481 - (181+282+1{,}968)$$
$$= 3{,}050$$

$$\% \text{ Completeness of spontaneous report} = \frac{(a+c)}{N} * 100\%$$
$$= (463/5{,}481) * 100$$

= 8.45%

% Completeness of electronic database = (2,149/5,481)*100
= 39.21%

% Completeness of both sources = ((2,149+282) / 5,481)*100
= 44.35%

According to capture-recapture method, the total number of patients with ADRs related hospitalizations during 2011 was estimated at 5,481.

During 2011, there were 62,001 hospitalizations. Using capture-recapture method, incidences of ADRs-related hospitalization was estimated at 8.84%.

CHAPTER V
DISCUSSION

From 283,070 hospitalizations during the year 2007 to 2011, 7,756 ADRs were detected through hospital database, representing 2.74% of total hospitalization. Our findings are in line with that of the previous review in which the rate of ADRs ranged from 0.16% to 15.7% depending on the method of detection (3). Our findings are also in line with previous studies that use similar method to identify ADR but slightly higher: Spain 1.69% (18), England 0.5% to 0.9% (17, 37), Portugal 1.26% (38). However, it should be noted that previous studies were conducted nationwide while our study was conducted in one tertiary care hospital so the rate might be higher due to the use of more complex medications compared to other types of hospital. Nevertheless, when compared our results with those of the previous studies in Thailand (7-11), which found that incidence of ADRs among hospitalized patients varied widely ranging between 0.07% to 38.64% our detection rate was relatively low. Difference in method used to identify ADR may account for this difference. It should be noted that method used in the previous studies were chart review while in this study administrative database was employed. Nevertheless, we believed that the detection rate in our study may still under-estimated due to under-recognition and under-reporting of ADRs in routine hospital activity. However, when compared with the spontaneous report, our study found confirmed that administrative database yield higher detection rate of ADRs than spontaneous report (26). To yield more accurate estimate, when using data from both hospital database and spontaneous report, the incidence of ADR related hospitalization during 2007 to 2011 estimated using both hospital database and spontaneous report was 6.45%. Our study indicates the potential use of routine administrative database and spontaneous report to estimate the incidence of ADRs.

Similar to the previous studies (18) we found that incidences of ADR related with admissions were increasing. Beside it may be the result of actual increase in rate of ADRs it may probably due to the improved diagnostic as well.

When looking at the major drugs groups most frequently associated with ADR, we found that hormones and their synthetic substitutes and antagonists (Y42 glucocorticoid, thyroid hormones, antithyroids, insulin, oral hypoglyceamics, oral contraceptives, oestrogen and progestogen, anti-gonadotrophines, anti-oestrogens, antiprogestogen, androgens; 23.77%) Systemic antibiotics (Y40 sulphonamides, other anti-mycobacterial, anti-malarials, anti-protozoal, anti-helminthics, anti-virals; 13.23%), Agent primarily affecting blood constituents (Y44 iron preparations, anti-megaloblastic anemia preparation, anticoagulants antagonists, antithrombotic drugs, thrombolytic drugs, blood products, plasma substitutes; 12.60%), and Analgesics, antipyretics and anti-inflammatory drugs (Y45 opioids and related analgesics, salicylates, propionic acid derivatives, nonsteroidal anti-inflammatory drugs, antirheumatics, 4 aminophenol derivatives; 6.46%) were the most involved drug groups. When looking at the primary diagnosis, drug induced hypoglycemia, drug induced neutropenia, drug induced hypotension, toxic liver disease, and skin eruption due to drugs were identified as the leading diagnosis related to ADR. According to our result, caution should be made to monitor safety among patients who were prescribed with those drugs or drugs related with those ADRs. Our findings are broadly similar to the previous studies (27), which found that systematic agents particularly neoplastic drugs (Y43), analgesic (Y45), cardiovascular drug (Y52), antibiotic (Y40), water-balance, mineral and uric acid (Y54), hormones and their synthetic substitute and antagonist (Y42) were the most common drug class associated with ADRs. However, it should be noted that the total number of drug prescribed was not available so direct comparison of the number of ADR associated with the class of drugs may not be appropriated.

When looking at the most common diagnoses, we found that anemia is the most common diagnosis the case of ADR-related hospitalization. This is similar to the previous study (27), which found that drug induced hemolytic anemia and aplastic anemia were ranked as the fastest growing diagnosis related to ADRs (3, 13, 17, 38). Incidence of ADR-related hospitalization was quite high among elderly. The high rate

among elderly may probably due to the fact that elderly are more likely to receive multiple medication and there is age-associated change in pharmacokinetic and pharmacodynamics (3, 50).

When looking at gender, consistent with the previous studies (13, 37), we found that ADRs occurred more frequent in female than male. Further research to elucidate whether this relationship occurs because women are more likely to develop adverse drug reactions or because women are more likely to report adverse drug reactions is needed. It is widely known that women tend to present more to their doctors for treatment and consequently would be expected to experience more ADRs, Redemaker has suggested that pharmacological, immunological and hormonal differences and the fact that women take more medications may explain some gender differences (51).

Limitations of study

1. Our study is limited in that the proportion of ADR-related hospitalizations is probably an underestimation of the real situation. With regard to underreporting, this can be attributed to different cause such as under-recognition and under-reporting of ADRs in routine hospital activity. Nevertheless, we found that the use of administration database resulting in the higher rate of ADR detection than spontaneous reporting. Kongkaew, et al. found that studies that employed multiple ADR detection methods reported higher ADR admission rates compared with studies that used medical record review alone (3) so using combination of methods may yield more accurate incidence of ADRs. Nevertheless, administrative database offered moderate detection rate with relatively low resources required, when compared with medical record review (26).

2. We do not have details on the number of drugs prescribed so the analysis by comparing the numbers of drugs class involve with ADRs might be misleading.

3. Our study was conducted in one tertiary care hospital in Thailand. Generalization of the findings to other settings may be made with caution.

4. Another limitation is inherent to the use of administration database, which often contain inaccurate coding, and incomplete information on ADR as they are used primarily for administrative purposes, they may be less concerned with accurate recording of ICD.

Although, medical record review or intensive monitoring might be considered as a valid method, they are too resource-consuming to be utilized in a nationwide or to be used continuously.

This study was the first study in developing country examining trend of ADR-related hospitalization at one tertiary care hospital using hospital routinely administration database and using 2 sources (administrative database and spontaneous report). We confirmed that administrative database is useful and easily accessible method to determine proportion of the adverse drug events caused by drug in hospital and that capture-recapture method can be applied to estimate incidence of ADR related hospitalization. Our study supports the innovative approach of using hospital routine data and spontaneous report to monitor ADR as it yields moderate ADR detection rate with relatively low resources needed. However, improvement in the completeness, accuracy and standardization of coding should be promote.

CHAPTER VI
CONCLUSION

We found that ADR related hospitalizations were an increasing important public health problem. Incidence of ADRs related hospitalization varied from 0.71% (spontaneous report) to 2.47% (hospital administrative database) and 6.45% (capture-recapture method) of total hospitalization. As the result, awareness of harms associated with ADR should be raised while policies aims at increasing patient safety should be promoted.

Although lower detection rate compared to intensive review or chart review {Kongkaew, 2008 #33;Miguel, 2013 #50}, administrative database offered moderate detection rate with relatively low resources required. Therefore, it was recommended as an effective methodology of pharmacovigilance and appropriate to be routinely applied a national level for developed countries {Miguel, 2013 #78}. Our study is the first study to confirm that the use of administration database to routinely monitoring drug safety in the hospital is also feasible in less developing countries and also the first study applying capture-recapture method using data from spontaneous report and hospital database to estimate the incidence of ADR-related hospitalization.

Future integration of computer systems within hospitals and the expansion of electronic prescribing and electronic health records may make ICD codes a more useful practical tool. Hospitals should also consider interventions such as developing educational interventions and mechanisms to provide feedback on recording of ADR to hospital physicians and to improve the identifications and coding of admissions linked to ADR. However, in the future it would be necessary to develop coding and reporting systems independently of treating physicians that are usually not specially trained to code diagnoses.

In addition, evidence on economic burden of ADR related hospitalization is clearly needed to bring attention of hospital administrators and health care policy makers to improve patient safety as well as to save such the unnecessary cost.

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APPENDIX

Table A.1: ICD-10 codes (Y40-Y59) for drugs, medicaments and biological substances causing adverse effects in therapeutic use

ICD-10	External cause mortality/ morbidity by:
Y40	**Systematic antibiotics:** Penicillins, cefalosporins and other beta-lactam antibiotics, macrolides, tetracyclines, aminoglycosides, rifamycin, antifungals, others
Y41	**Other systematic anti-infectives and antiparasitics:** Sulphonamides, other anti-mycobacterial, anti-malarials, anti-protozoal, anti-helminthics, anti-virals
Y42	**Hormones and substitutes:** Glucocorticoids, thyroid hormones, anti-thyroids, insulin, oral hypoglyceamics, oral contraceptives, oestrogen and progestogen, anti-gonadotrophins,anti-oestrogens, anti- progestogen, androgens
Y43	**Systemic agents:** anti-allergic and anti-emetic drugs, anti-neoplastic and immunosuppressive drugs, acidifying/ alkalizing agents
Y44	**Agents affect blood constituents:** Iron preparations, anti-megaloblastic-anemia preparations, anticoagulants antagonists, antithrombotic drugs, thrombolytic drugs, blood products, plasma substitutes
Y45	**Analgesics, anti-pyretics and anti-inflammatory drugs:** Opioids and related analgesics, salicylates, propionic acid derivatives, nonsteroidal anti-inflammatory drugs, antirheumatics, 4-aminophenol derivatives
Y46	**Anti-epileptics and anti-parkinsonism drugs:** Succinimides, oxazolidinediones, hydatoin derivatives, deoxybarbiturates, iminostibenes, valproic acid, anti- parkinsonism drugs, anti-spasticity drugs
Y47	**Sadatives, hypnotics and anti-anxiety drugs:** Barbiturates,

Table A.1: ICD-10 codes (Y40-Y59) for drugs, medicaments and biological substances causing adverse effects in therapeutic use

ICD-10	External cause mortality/ morbidity by:
Y47	benzodiazepines, cloral derivatives, paraldehyde, bromine compounds, sedative, hypnotics and anti-anxiety drugs, unspecified
Y48	**Anaesthetics and therapeutic gases:** Inhaled/ parenteral anaesthetics, local anaesthetics, therapeutic gases
Y49	**Psychotropic drugs:** Tricyclic and tetracyclic antidepressants, monoamine-oxidase-inhibitor, phenothiazine antipsychotics and neuroleptics, butyrophenone and thioxanthene neuroleptics, other antidepressants, antipsychotics and neuroleptics
Y50	**Central nervous system stimulants**: Analeptics, opioid receptor antagonists, , methylxanthines, other central nervous system stimulants
Y51	**Drugs primarily affecting the autonomic nervous system:** Anticholinesterase agents, cholinergics, ganglionic blocking drugs, anti cholinergics, antimuscarinics, spasmolytics, alpha-adrenoreceptor agonists/ antagonists, beta-adrenoreceptor agonists/ antagonists, centrally acting and adrenergic-nervous-blocking agents
Y52	**Agents affecting the cardiovascular system:** Cardiac-stimulant glycosides, calcium-channel blockers, other anti-dysrhythmic drugs, other coronary vasodilators, angiotensin-converting-enzyme inhibitors, other anti-hypertensives, anti-hyperlipidaemic and anti-arteriosclerotic drugs, peripheral vasodilators, anti-varicose drugs
Y53	**Agents affecting the gastrointestinal system:** Antacids, anti-gastric-secretion drugs, laxatives, anti-diarrhoeal, emetics
Y54	**Agents affecting water-balance and mineral and uric metabolism:** Mineralocorticoids, mineralocorticoids antagonists, carbonic-anhydrase inhibitors, benzothaidiazine derivatives, other diuretics, electrolytic, caloric and water-balance agents, agents affecting calcification, agents affecting uric acid metabolism

Table A.1: ICD-10 codes (Y40-Y59) for drugs, medicaments and biological substances causing adverse effects in therapeutic use

ICD-10	External cause mortality/ morbidity by:
Y55	**Agents acting on smooth and skeletal muscles and the respiratory system:** Oxytocic drugs, skeletal muscles relaxants, anti-tussives, expectorants, anti-common-cold drugs, anti-asthmatics
Y56	**Topical agents primarily affecting skin and mucous membrane:** Local anti-fungal, anti-infective, anty-inframmatory drugs, anti-pruritics, local detergents, emollients, keratolytics, ophthalamological drugs,otrhinolaryngological drugs, dental drugs
Y57	**Other and unspecified drugs:** Appetite depressants, lipotropic drugs, antidotes and chelating agents, alcohol deterrents, X-ray contrast media, vitamin
Y58	**Bacterial vaccines**
Y59	**Other vaccines**: Viral/ rickettsial/ protozoal vaccines, immunoglobulin

Table A.2: ICD-10 codes (primary diagnosis codes) for 'adverse drug reaction', 'drug-induced', 'due to drug', 'due to medicament' or 'drug allergy' causing adverse effects in therapeutic use

ICD-10 chapter	ICD-10 codes	Primary cause mortality/ morbidity by:
D	D52.1	Drug-induced folate deficiency anaemia
	D59.0	Drug-induced autoimmune haemolytic anaemia
	D59.2	Drug-induced nonautoimmune haemolytic anaemia
	D61.1	Drug-induced aplastic anaemia
	D64.2	Secondary sideroblastic anaemia due to drugs and toxins

Table A.2: ICD-10 codes (primary diagnosis codes) for 'adverse drug reaction', 'drug-induced', 'due to drug', 'due to medicament' or 'drug allergy' causing adverse effects in therapeutic use

ICD-10 chapter	ICD-10 codes	Primary cause mortality/ morbidity by:
D	D70	Agranulocytosis
		Agranulocytic angina
		Infantile genetic agranulocytosis
		Kostmann's disease
		Neutropenia:
		• drug-induced
E	E06.4	Drug-induced thyroiditis
	E15	Nondiabetic hypoglycaemic coma
		Drug-induced insulin coma in nondiabetic
	E16.0	Drug-induced hypoglycaemia without coma
	E23.1	Drug-induced hypopituitarism
	E24.2	Drug-induced Cushing's syndrome
	E03.2	Hypothyroidism due to medicaments and other exogenous substances
	E27.3	Drug-induced adrenocortical insufficiency
	E66.1	Drug-induced obesity
G	G24.0	Drug-induced dystonia
	G25.1	Drug-induced tremor
	G25.3	Drug-induced myoclonus
	G25.4	Drug-induced chorea
	G25.6	Drug-induced tics and other tics of organic origin
	G44.4	Drug-induced headache, not elsewhere classified
	G62.0	Drug-induced polyneuropathy

Table A.2: ICD-10 codes (primary diagnosis codes) for 'adverse drug reaction', 'drug-induced', 'due to drug', 'due to medicament' or 'drug allergy' causing adverse effects in therapeutic use

ICD-10 chapter	ICD-10 codes	Primary cause mortality/ morbidity by:
G	G71.1	Myotonic disorders
		Dystrophia myotonica [Steinert]
		Myotonia:
		• drug-induced
	G72.0	Drug-induced myopathy
	G95.8	Other specified diseases of spinal cord
		Cord bladder NOS
		Myelopathy:
		• drug-induced
H	H26.3	Drug-induced cataract
I	I42.7	Cardiomyopathy due to drugs and other external agents
	I95.2	Hypotension due to drugs
J	J70.2	Acute drug-induced interstitial lung disorders
	J70.3	Chronic drug-induced interstitial lung disorders
	J70.4	Drug-induced interstitial lung disorders, unspecified
K	K71	Toxic liver disease
		Includes: drug-induced:
		• idiosyncratic (unpredictable) liver disease
		• toxic (predictable) liver disease
	K71.1	Toxic liver disease with hepatic necrosis Hepatic failure (acute)(chronic) due to drugs
	K85.3	Drug-induced acute pancreatitis

Table A.2: ICD-10 codes (primary diagnosis codes) for 'adverse drug reaction', 'drug-induced', 'due to drug', 'due to medicament' or 'drug allergy' causing adverse effects in therapeutic use

ICD-10 chapter	ICD-10 codes	Primary cause mortality/ morbidity by:
L	L10.5	Drug-induced pemphigus
	L23.3	Allergic contact dermatitis due to drugs in contact with skin
	L24.4	Irritant contact dermatitis due to drugs in contact with skin
	L25.1	Unspecified contact dermatitis due to drugs in contact with skin
	L27.0	Generalized skin eruption due to drugs and medicaments
	L27.1	Localized skin eruption due to drugs and medicaments
	L64.0	Drug-induced androgenic alopecia
M	M10.2	Drug-induced gout
	M32.0	Drug-induced systemic lupus erythematosus
	M80.4	Drug-induced osteoporosis with pathological fracture
	M81.4	Drug-induced osteoporosis
	M83.5	Other drug-induced osteomalacia in adults
M	M87.1	Osteonecrosis due to drugs
O	O68	Labour and delivery complicated by fetal stress [distress]
		Includes: fetal distress in labour or delivery due to drug administration

Table A.2: ICD-10 codes (primary diagnosis codes) for 'adverse drug reaction', 'drug-induced', 'due to drug', 'due to medicament' or 'drug allergy' causing adverse effects in therapeutic use

ICD-10 chapter	ICD-10 codes	Primary cause mortality/ morbidity by:
P	P58.4	Neonatal jaundice due to drugs or toxins transmitted from mother or given to newborn
	P93	Reactions and intoxications due to drugs administered to fetus and newborn
		Grey syndrome from chloramphenicol administration in newborn
R	R50.2	Drug-induced fever

Table A.3: Number of hospitalizations with an 'external cause' code for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y40	Systemic antibiotics	32 (15.84)	19 (19.20)	13 (12.62)	2 (11.11)	17 (22.08)	13 (12.16)	16.28
Y41	Other systemic anti-infectives and antiparasitics	8 (3.96)	6 (6.06)	2 (1.94)	1 (5.56)	4 (5.19)	3 (2.80)	3.38
Y42	Hormones and their synthetic substitutes and antagonists	12 (5.94)	3 (3.03)	9 (8.74)	0 (0.00)	3 (3.90)	9 (8.41)	3.25

Table A.3: Number of hospitalizations with an 'external cause' code for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y43	Primarily systemic agents	8 (3.96)	1 (1.01)	7 (6.80)	2 (11.11)	3 (3.90)	3 (2.80)	7
Y44	Agents primarily affecting blood constituents	51 (25.25)	27 (27.27)	24 (23.30)	0 (0.00)	17 (22.08)	34 (31.78)	4.61
Y45	Analgesics, antipyretics and anti-inflammatory drugs	11 (5.45)	7 (7.07)	4 (3.88)	5 (27.77)	3 (3.90)	3 (2.80)	3.55
Y46	Antiepileptics and anti-Parkinsonism drugs	11 (5.45)	5 (5.05)	6 (5.83)	1 (5.56)	7 (9.09)	3 (2.80)	5.66
Y47	Sedatives, hypnotics and anti-anxiety drugs	7 (3.47)	5 (5.05)	2 (1.94)	3 (16.66)	2 (2.59)	2 (1.87)	4.14
Y48	Anaesthetics and therapeutic gases	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0

Table A.3: Number of hospitalizations with an 'external cause' code for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y49	Psychotropic drugs, not elsewhere classified	2 (0.99)	1 (1.01)	1 (0.97)	0 (0.00)	1 (1.30)	1 (0.93)	1
Y50	Central nervous system stimulants, not elsewhere classified	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Y51	Drugs primarily affecting the autonomic nervous system	2 (0.99)	1 (1.01)	1 (0.97)	0 (0.00)	0 (0.00)	2 (1.87)	1
Y52	Agents primarily affecting the cardiovascular system	18 (8.91)	8 (8.08)	10 (9.71)	0 (0.00)	5 (6.49)	13 (12.16)	14.89
Y53	Agents primarily affecting the Gastrointes-tinal system	1 (0.50)	1 (1.01)	0 (0.00)	1 (5.56)	0 (0.00)	0 (0.00)	1

Table A.3: Number of hospitalizations with an 'external cause' code for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	4 (1.98)	2 (2.02)	2 (1.94)	0 (0.00)	1 (1.30)	3 (2.80)	17.75
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	1 (0.49)	1 (1.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.93)	12
Y56	Topical agent primarily affecting skin/mucous membranes and opth/ot-rhlary/dental drugs	1 (0.49)	0 (0.00)	1 (0.97)	0 (0.00)	1 (1.30)	0 (0.00)	11
Y57	Other and unspecified drugs and medicaments	32 (15.84)	11 (11.11)	21 (20.39)	2 (11.11)	13 (16.88)	17 (15.90)	12

Table A.3: Number of hospitalizations with an 'external cause' code for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y58	Other and unspecified drugs and medicaments	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Y59	Other and unspecified vaccines and biological substance	1 (0.49)	1 (1.01)	0 (0.00)	1 (5.56)	0 (0.00)	0 (0.00)	2
Total		202	99	103	18	77	107	8.72

Table A.4: Number of hospitalizations with an 'external cause' code for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y40	Systemic antibiotics	61 (16.14)	25 (15.92)	36 (16.29)	6 (18.75)	35 (22.00)	20 (10.70)	9.10
Y41	Other systemic anti-infectives and anti-parasitics	11 (2.91)	5 (3.18)	6 (2.72)	0 (0.00)	9 (5.66)	2 (1.07)	7.36

Table A.4: Number of hospitalizations with an 'external cause' code for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y42	Hormones and their synthetic substitutes and antagonists	11 (2.91)	4 (2.55)	7 (3.18)	0 (0.00)	3 (1.89)	8 (4.28)	4.82
Y43	Primarily systemic agents	11 (2.91)	3 (1.91)	8 (3.62)	2 (6.25)	9 (5.66)	0 (0.00)	5.27
Y44	Agents primarily affecting blood constituents	100 (26.46)	42 (26.75)	58 (26.24)	0 (0.00)	33 (20.75)	67 (35.83)	6.08
Y45	Analgesics, antipyretics and anti-inflam-matory drugs	18 (4.76)	9 (5.73)	9 (4.08)	2 (6.25)	6 (3.77)	10 (5.35)	2.89
Y46	Antiepileptics and anti-Parkinsonism drugs	19 (5.03)	11 (7.00)	8 (3.62)	3 (9.38)	8 (5.03)	8 (4.28)	7.68
Y47	Sedatives, hypnotics and anti-anxiety drugs	4 (1.06)	0 (0.00)	4 (1.81)	1 (3.12)	1 (0.63)	2 (1.07)	4.5

Table A.4: Number of hospitalizations with an 'external cause' code for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y48	Anaesthetics and therapeutic gases	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Y49	Psychotropic drugs, not elsewhere classified	4 (1.06)	2 (1.27)	2 (0.90)	0 (0.00)	3 (1.89)	1 (0.53)	3.25
Y50	Central nervous system stimulants, not elsewhere classified	1 (0.26)	1 (0.64)	0 (0.00)	0 (0.00)	1 (0.63)	0 (0.00)	2
Y51	Drugs primarily affecting the autonomic nervous system	8 (2.12)	3 (1.91)	5 (2.26)	3 (9.38)	3 (1.89)	2 (1.07)	4
Y52	Agents primarily affecting the cardiovascular system	25 (6.61)	7 (4.46)	18 (8.14)	0 (0.00)	3 (1.89)	22 (11.76)	5.08

Table A.4: Number of hospitalizations with an 'external cause' code for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y53	Agents primarily affecting the gastrointestinal system	1 (0.26)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	1 (0.53)	3
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	13 (3.44)	4 (2.55)	9 (4.07)	0 (0.00)	3 (1.89)	10 (5.35)	6
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	1 (0.26)	1 (0.64)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.53)	2
Y56	Topical agent primarily affecting skin/mucous membranes and opth/ot-rhlary/dental drugs	2 (0.53)	1 0.64)	1 (0.45)	0 (0.00)	2 (1.26)	0 (0.00)	8

Table A.4: Number of hospitalizations with an 'external cause' code for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y57	Other and unspecified drugs and medicaments	84 (22.22)	37 (23.57)	47 (21.27)	12 (37.50)	39 (24.53)	33 (17.65)	9.18
Y58	Other and unspecified drugs and medicaments	2 (0.53)	1 (0.64)	1 (0.45)	2 (6.25)	0 (0.00)	0 (0.00)	1.5
Y59	Other and unspecified vaccines and biological substance	2 (0.53)	1 (0.64)	1 (0.45)	1 (3.12)	1 (0.63)	0 (0.00)	3
Total		378	157	221	32	159	187	6.94

Table A.5: Number of hospitalizations with an 'external cause' code for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y40	Systemic antibiotics	156 (15.32)	86 (18.22)	70 (12.82)	12 (18.75)	107 (22.86)	37 (7.61)	16.81
Y41	Other systemic	57 (5.60)	29 (6.14)	28 (5.13)	2 (3.13)	37 (7.91)	18 (3.70)	8.60

Table A.5: Number of hospitalizations with an 'external cause' code for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y41	anti-infectives and antiparasitics							
Y42	Hormones and their synthetic substitutes and antagonists	226 (22.20)	73 (15.47)	153 (28.02)	3 (4.68)	91 (19.44)	132 (27.16)	10.79
Y43	Primarily systemic agents	82 (8.06)	34 (7.21)	48 (8.79)	16 (25.00)	45 (9.62)	21 (4.32)	11.52
Y44	Agents primarily affecting blood constituents	112 (11.00)	59 (12.50)	53 (9.71)	2 (3.13)	51 (10.91)	59 (12.14)	5.88
Y45	Analgesics, antipyretics and anti-inflammatory drugs	76 (7.47)	38 (8.06)	38 (6.96)	9 (14.06)	37 (7.91)	30 (6.17)	7.08
Y46	Antiepileptics and anti-Parkinsonism drugs	37 (3.63)	25 (5.30)	12 (2.19)	2 (3.13)	20 (4.27)	15 (3.09)	11.76

Table A.5: Number of hospitalizations with an 'external cause' code for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y47	Sedatives, hypnotics and anti-anxiety drugs	14 (1.38)	6 (1.28)	8 (1.47)	4 (6.25)	3 (0.64)	7 (1.44)	5.86
Y48	Anaesthetics and therapeutic gases	2 (0.20)	1 (0.21)	1 (0.18)	1 (1.56)	1 (0.21)	0 (0.00)	8
Y49	Psychotropic drugs, not elsewhere classified	15 (1.47)	7 (1.48)	8 (1.47)	1 (1.56)	6 (1.28)	8 (1.65)	4.2
Y50	Central nervous system stimulants, not elsewhere classified	1 (0.10)	1 (0.21)	0 (0.00)	0 (0.00)	1 (0.21)	0 (0.00)	37
Y51	Drugs primarily affecting the autonomic nervous system	36 (3.54)	15 (3.18)	21 (3.85)	0 (0.00)	9 (1.92)	27 (5.55)	5.58
Y52	Agents primarily affecting the cardiovascular system	72 (7.07)	29 (6.14)	43 (7.88)	2 (3.13)	18 (3.85)	52 (10.70)	6.65

Table A.5: Number of hospitalizations with an 'external cause' code for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y53	Agents primarily affecting the gastrointestinal system	5 (0.49)	1 (0.21)	4 (0.73)	0 (0.00)	2 (0.43)	3 (0.62)	4.4
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	58 (5.70)	29 (6.14)	29 (5.31)	0 (0.00)	13 (2.78)	45 (9.26)	5.28
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	6 (0.59)	5 (1.06)	1 (0.18)	1 (1.56)	0 (0.00)	5 (1.03)	5.5
Y56	Topical agent primarily affecting skin/mucous membranes and opth/ otrhlary/	5 (0.49)	2 (0.42)	3 (0.55)	0 (0.00)	4 (0.85)	1 (0.21)	5.8

Table A.5: Number of hospitalizations with an 'external cause' code for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y56	dental drugs							
Y57	Other and unspecified drugs and medicaments	51 (5.01)	29 (6.14)	22 (4.03)	3 (4.68)	23 (4.91)	25 (5.14)	7.82
Y58	Other and unspecified drugs and medicaments	4 (0.39)	1 (0.21)	3 (0.55)	4 (6.25)	0 (0.00)	0 (0.00)	2.25
Y59	Other and unspecified vaccines and biological substance	3 (0.29)	2 (0.42)	1 (0.18)	2 (3.13)	0 (0.00)	1 (0.21)	1.33
Total		1018	472	546	64	468	486	9.64

Table A.6: Number of hospitalizations with an 'external cause' code for an ADR in year 2010; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y40	Systemic antibiotics	147 (12.92)	85 (16.86)	62 (9.78)	12 (20.34)	85 (17.17)	50 (8.56)	14.64
Y41	Other systemic anti-infectives and antiparasitics	66 (5.80)	37 (7.34)	29 (4.58)	5 (8.47)	41 (8.28)	20 (3.42)	8.73
Y42	Hormones and their synthetic substitutes and antagonists	324 (28.47)	111 (22.02)	213 (33.60)	1 (1.69)	112 (22.64)	211 (36.13)	8.73
Y43	Primarily systemic agents	125 (10.98)	47 (9.33)	78 (12.30)	15 (25.42)	73 (14.76)	37 (6.34)	11.04
Y44	Agents primarily affecting blood constituents	112 (9.84)	58 (11.51)	54 (8.52)	0 (0.00)	41 (8.28)	71 (12.16)	7.12
Y45	Analgesics, antipyretics and anti-inflammatory drugs	82 (7.21)	37 (7.34)	45 (7.10)	3 (5.09)	41 (8.28)	38 (6.51)	6.99
Y46	Antiepileptics and anti-Parkinsonism	26 (2.28)	11 (2.18)	15 (2.37)	2 (3.39)	12 (2.42)	12 (2.05)	20.27

Table A.6: Number of hospitalizations with an 'external cause' code for an ADR in year 2010; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y46	drugs							
Y47	Sedatives, hypnotics and anti-anxiety drugs	8 (0.70)	8 (1.59)	0 (0.00)	2 (3.39)	1 (0.20)	5 (0.86)	1.75
Y48	Anaesthetics and therapeutic gases	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Y49	Psychotropic drugs, not elsewhere classified	13 (1.14)	6 (1.19)	7 (1.10)	4 (6.78)	5 (1.01)	4 (0.68)	2.62
Y50	Central nervous system stimulants, not elsewhere classified	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Y51	Drugs primarily affecting the autonomic nervous system	33 (2.90)	17 (3.37)	16 (2.52)	0 (0.00)	5 (1.01)	28 (4.79)	4.15

Table A.6: Number of hospitalizations with an 'external cause' code for an ADR in year 2010; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y52	Agents primarily affecting the cardiovascular system	63 (5.54)	32 (6.35)	31 (4.89)	2 (3.39)	22 (4.44)	39 (6.68)	5.29
Y53	Agents primarily affecting the gastrointestinal system	4 (0.35)	2 (0.40)	2 (0.32)	0 (0.00)	1 (0.20)	3 (0.52)	5.5
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	66 (5.80)	20 (3.97)	46 (7.26)	0 (0.00)	25 (5.05)	41 (7.02)	3.26
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	3 (0.27)	1 (0.20)	2 (0.31)	1 (1.69)	0 (0.00)	2 (0.34)	17.67
Y56	Topical agent primarily affecting skin/mucous	3 (0.27)	1 (0.20)	2 (0.31)	0 (0.00)	0 (0.00)	3 (0.52)	2.33

Table A.6: Number of hospitalizations with an 'external cause' code for an ADR in year 2010; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y56	membranes and opth/ otrhlary/ dental drugs							
Y57	Other and unspecified drugs and medicaments	51 (4.48)	24 (4.76)	27 (4.26)	3 (5.09)	30 (6.06)	18 (3.08)	13.12
Y58	Other and unspecified drugs and medicaments	4 (0.35)	1 (0.20)	3 (0.47)	3 (5.09)	1 (0.20)	0 (0.00)	3
Y59	Other and unspecified vaccines and biological substance	8 (0.70)	6 (1.19)	2 (0.31)	6 (10.17)	0 (0.00)	2 (0.34)	1.38
Total		1138	504	634	59	495	584	9.08

Table A.7: Number of hospitalizations with an 'external cause' code for an ADR in year 2011; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y40	Systemic antibiotics	130 (10.48)	72 (13.51)	58 (8.20)	14 (23.73)	82 (15.27)	34 (5.28)	14.89
Y41	Other systemic anti-infectives and antiparasitics	75 (6.05)	44 (8.26)	31 (4.38)	2 (3.39)	49 (9.12)	24 (3.73)	10.25
Y42	Hormones and their synthetic substitutes and antagonists	381 (30.73)	140 (26.27)	241 (34.09)	1 (1.69)	127 (23.66)	253 (39.28)	7.26
Y43	Primarily systemic agents	142 (11.45)	57 (10.69)	85 (12.02)	13 (22.03)	91 (16.95)	38 (5.90)	15.07
Y44	Agents primarily affecting blood constituents	126 (10.16)	58 (10.88)	68 (9.62)	1 (1.69)	40 (7.45)	85 (13.20)	7.05
Y45	Analgesics, antipyretics and anti-inflammatory drugs	70 (5.65)	26 (4.88)	44 (6.22)	4 (6.78)	42 (7.82)	24 (3.73)	4.57
Y46	Antiepileptics and anti-Parkinsonism	39 (3.15)	20 (3.75)	19 (2.69)	4 (6.78)	20 (3.72)	15 (2.33)	6.62

Table A.7: Number of hospitalizations with an 'external cause' code for an ADR in year 2011; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y46	drugs							
Y47	Sedatives, hypnotics and anti-anxiety drugs	12 (0.97)	6 (1.12)	6 (0.85)	2 (3.39)	5 (0.93)	5 (0.78)	6.17
Y48	Anaesthetics and therapeutic gases	2 (0.16)	1 (0.19)	1 (0.15)	0 (0.00)	1 (0.19)	1 (0.15)	8.5
Y49	Psychotropic drugs, not elsewhere classified	15 (1.21)	10 (1.88)	5 (0.71)	0 (0.00)	8 (1.49)	7 (1.09)	5.67
Y50	Central nervous system stimulants, not elsewhere classified	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Y51	Drugs primarily affecting the autonomic nervous system	36 (2.90)	14 (2.63)	22 (3.11)	0 (0.00)	13 (2.42)	23 (3.57)	5.81

Table A.7: Number of hospitalizations with an 'external cause' code for an ADR in year 2011; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y52	Agents primarily affecting the cardiovascular system	60 (4.84)	22 (4.13)	38 (5.37)	1 (1.69)	16 (2.98)	43 (6.68)	3.48
Y53	Agents primarily affecting the gastrointestinal system	3 (0.24)	1 (0.19)	2 (0.28)	1 (1.69)	2 (0.37)	0 (0.00)	2
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	76 (6.13)	25 (4.69)	51 (7.21)	1 (1.69)	10 (1.86)	65 (10.09)	3.64
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	4 (0.32)	1 (0.19)	3 (0.42)	2 (3.39)	2 (0.37)	0 (0.00)	2

Table A.7: Number of hospitalizations with an 'external cause' code for an ADR in year 2011; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
Y56	Topical agent primarily affecting skin/mucous membranes and opth/ otrhlary/ dental drugs	1 (0.08)	0 (0.00)	1 (0.15)	0 (0.00)	1 (0.19)	0 (0.00)	0
Y57	Other and unspecified drugs and medicaments	63 (5.08)	31 (5.82)	32 (4.53)	9 (15.25)	28 (5.21)	26 (4.04)	7.48
Y58	Other and unspecified drugs and medicaments	2 (0.16)	2 (0.36)	0 (0.00)	2 (3.39)	0 (0.00)	0 (0.00)	1
Y59	Other and unspecified vaccines and biological substance	3 (0.24)	3 (0.56)	0 (0.00)	2 (3.39)	0 (0.00)	1 (0.15)	1.67
Total		1240	533	707	59	537	644	8.42

Table A.8; Number of hospitalizations with a primary diagnosis for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
D	Drug-induced anaemia	303 (63.26)	143 (61.64)	160 (64.78)	64 (82.05)	182 (69.20)	57 (41.30)	15.62
E	Drug-induced metabolic disorders	48 (10.02)	19 (8.19)	29 (11.74)	0 (0.00)	14 (5.32)	34 (24.64)	4.08
G	Drug-induced neuromuscular disorders	10 (2.09)	6 (2.59)	4 (1.62)	1 (1.28)	6 (2.28)	3 (2.18)	11.7
H	Drug-induced cataract and hearing loss	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
I	Cardiovascular consequences due to drugs	19 (3.96)	8 (3.45)	11 (4.45)	0 (0.00)	6 (2.28)	13 (9.42)	3.053
J	Drug-induced lung disorders	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
K	Toxic liver disease	25 (5.22)	15 (6.46)	10 (4.05)	0 (0.00)	16 (6.08)	9 (6.52)	13.88
L	Dermatitis due to drugs	72 (15.03)	41 (17.67)	31 (12.55)	13 (16.67)	37 (14.08)	22 (15.94)	10.07
M	Drug-induced immune	2 (0.42)	0 (0.00)	2 (0.81)	0 (0.00)	2 (0.76)	0 (0.00)	7.5

Table A.8; Number of hospitalizations with a primary diagnosis for an ADR in year 2007; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
M	disorders							
O	Pregnancy, childbirth and the puerperium due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
P	Certain conditions originating in the perinatal period due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
R	Drug-induced symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Total		479	232	247	78	263	138	12.92

Table A.9; Number of hospitalizations with a primary diagnosis for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
D	Drug-induced anaemia	324 (63.91)	150 (64.38)	174 (63.50)	77 (92.78)	173 (67.31)	74 (44.31)	13.10
E	Drug-induced metabolic disorders	58 (11.44)	15 (6.44)	43 (15.69)	0 (0.00)	15 (5.84)	43 (25.75)	2.93
G	Drug-induced neuromuscular disorders	24 (4.73)	16 (6.87)	8 (2.92)	1 (1.20)	16 (6.23)	7 (4.19)	5.46
H	Drug-induced cataract and hearing loss	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
I	Cardiovascular consequences due to drugs	18 (3.55)	7 (3.00)	11 (4.01)	0 (0.00)	6 (2.33)	12 (7.19)	2.89
J	Drug-induced lung disorders	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
K	Toxic liver disease	39 (7.69)	19 (8.15)	20 (7.30)	0 (0.00)	23 (8.95)	16 (9.58)	9
L	Dermatitis due to drugs	44 (8.68)	26 (11.16)	18 (6.58)	5 (6.02)	24 (9.34)	15 (8.98)	9.60
M	Drug-induced immune	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0

Table A.9; Number of hospitalizations with a primary diagnosis for an ADR in year 2008; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
M	disorders							
O	Pregnancy, childbirth and the puerperium due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
P	Certain conditions originating in the perinatal period due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
R	Drug-induced symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Total		507	233	274	83	257	167	10.60

Table A.10; Number of hospitalizations with a primary diagnosis for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
D	Drug-induced anaemia	405 (45.92)	198 (48.53)	207 (43.67)	90 (86.54)	207 (47.92)	108 (31.21)	12.52
E	Drug-induced metabolic disorders	209 (23.70)	67 (16.42)	142 (29.95)	3 (2.88)	78 (18.05)	128 (37.00)	12.96
G	Drug-induced neuromuscular disorders	39 (4.42)	21 (5.14)	18 (3.80)	0 (0.00)	18 (4.17)	21 (6.07)	16.23
H	Drug-induced cataract and hearing loss	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
I	Cardiovascular consequences due to drugs	52 (5.90)	35 (8.58)	17 (3.59)	0 (0.00)	19 (4.40)	33 (9.54)	8.58
J	Drug-induced lung disorders	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
K	Toxic liver disease	59 (6.69)	29 (7.11)	30 (6.33)	3 (2.88)	37 (8.56)	19 (5.49)	12.54
L	Dermatitis due to drugs	117 (13.26)	58 (14.22)	59 (12.45)	7 (6.74)	73 (16.90)	37 (10.69)	16.29

Table A.10; Number of hospitalizations with a primary diagnosis for an ADR in year 2009; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
O	Pregnancy, childbirth and the puerperium due to drugs	1 (0.11)	0 (0.00)	1 (0.21)	1 (0.96)	0 (0.00)	0 (0.00)	7
P	Certain conditions originating in the perinatal period due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
R	Drug-induced symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
Total		882	408	474	104	432	346	13.05

Table A.11; Number of hospitalizations with a primary diagnosis for an ADR in year 2010; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
D	Drug-induced anaemia	392 (39.08)	183 (40.49)	209 (37.93)	133 (89.27)	170 (38.90)	89 (21.34)	12.92
E	Drug-induced metabolic disorders	387 (38.58)	151 (33.41)	236 (42.83)	1 (0.67)	148 (33.87)	238 (57.07)	9.67
G	Drug-induced neuromuscular disorders	28 (2.79)	11 (2.43)	17 (3.09)	7 (4.70)	8 (1.83)	13 (3.12)	14.89
H	Drug-induced cataract and hearing loss	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
I	Cardiovascular consequences due to drugs	38 (3.79)	23 (5.09)	15 (2.72)	0 (0.00)	12 (2.74)	26 (6.24)	3.18
J	Drug-induced lung disorders	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
K	Toxic liver disease	42 (4.19)	26 (5.75)	16 (2.90)	0 (0.00)	27 (6.18)	15 (3.60)	7.07
L	Dermatitis due to drugs	107 (10.67)	52 (11.50)	55 (9.98)	4 (2.68)	69 (15.79)	34 (8.15)	15.60
M	Drug-induced immune disorders	1 (0.10)	0 (0.00)	1 (0.18)	0 (0.00)	1 (0.23)	0 (0.00)	7

Table A.11; Number of hospitalizations with a primary diagnosis for an ADR in year 2010; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
O	Pregnancy, childbirth and the puerperium due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
P	Certain conditions originating in the perinatal period due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
R	Drug-induced symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	8 (0.80)	6 (1.33)	2 (0.37)	4 (2.68)	2 (0.46)	2 (0.48)	3.75
	Total	1003	452	551	149	437	417	11.31

Table A.12; Number of hospitalizations with a primary diagnosis for an ADR in year 2011; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
D	Drug-induced anaemia	346 (38.06)	169 (39.21)	177 (37.03)	104 (87.39)	176 (40.74)	66 (18.44)	15.54
E	Drug-induced metabolic disorders	346 (38.06)	145 (33.64)	201 (42.05)	1 (0.84)	130 (30.09)	215 (60.05)	9.36
G	Drug-induced neuromuscular disorders	30 (3.30)	15 (3.48)	15 (3.14)	2 (1.69)	14 (3.24)	14 (3.91)	9.13
H	Drug-induced cataract and hearing loss	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
I	Cardiovascular consequences due to drugs	32 (3.52)	15 (3.48)	17 (3.56)	0 (0.00)	14 (3.24)	18 (5.03)	3.94
J	Drug-induced lung disorders	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
K	Toxic liver disease	47 (5.17)	28 (6.50)	19 (3.97)	1 (0.84)	31 (7.18)	15 (4.19)	11.26
L	Dermatitis due to drugs	105 (11.56)	58 (13.46)	47 (9.83)	10 (8.40)	65 (15.05)	30 (8.38)	14.41
M	Drug-induced immune disorders	1 (0.11)	0 (0.00)	1 (0.21)	0 (0.00)	1 (0.23)	0 (0.00)	5

Table A.12; Number of hospitalizations with a primary diagnosis for an ADR in year 2011; median age of admissions, old age and gender distribution of admissions and length of hospital stay

ICD-10 chapters	Description	Total (%)	Male (%)	Female (%)	Age			LOS
					≤16	17-59	≥60	
O	Pregnancy, childbirth and the puerperium due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
P	Certain conditions originating in the perinatal period due to drugs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0
R	Drug-induced symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2 (0.22)	1 (0.23)	1 (0.21)	1 (0.84)	1 (0.23)	0 (0.00)	9.5
Total		909	431	478	119	432	358	12.19

Details of number of admissions with an each of primary diagnosis for an ADR in year 2007-11

Table A.13; Number of admissions with an each of primary diagnosis for an ADR in year 2007-2011

ICD-10 chapters	ICD-10 codes	Description	2007	2008	2009	2010	2011	Total
D	D52.1	Drug-induced folate deficiency anaemia	0	0	0	0	0	0
	D59.0	Drug-induced autoimmune haemolytic anaemia	0	0	1	1	0	2
	D59.2	Drug-induced nonautoimmune haemolytic anaemia	0	0	0	0	0	0
	D61.1	Drug-induced aplastic anaemia	1	2	2	2	8	15
	D64.2	Secondary sideroblastic anaemia due to drugs and toxins	0	1	0	0	0	1
	D70	Drug-induced neutropeni	302	321	402	389	338	1752
E	E03.2	Hypothyroidism due to medicaments and other exogenous substances	0	0	2	2	1	5
	E06.4	Drug-induced thyroiditis	0	0	0	0	0	0

Table A.13; number of admissions with an each of primary diagnosis for an ADR in year 2007-2011

ICD-10 chapters	ICD-10 codes	Description	2007	2008	2009	2010	2011	Total
E	E15	Nondiabetic hypoglycaemic coma Drug-induced insulin coma in nondiabetic	3	3	21	63	62	152
	E16.0	Drug-induced hypoglycaemia without coma	42	53	176	316	282	869
	E23.1	Drug-induced hypopituitarism	0	0	0	0	0	0
	E24.2	Drug-induced Cushing's syndrome	0	0	3	1	0	4
	E27.3	Drug-induced adrenocortical insufficiency	3	2	7	5	1	18
	E66.1	Drug-induced obesity	0	0	0	0	0	0
G	G24.0	Drug-induced dystonia	1	0	0	1	1	3
	G25.1	Drug-induced tremor	1	0	0	1	0	2
	G25.3	Drug-induced myoclonus	2	10	25	12	18	67
	G25.4	Drug-induced chorea	0	0	0	0	0	0

Table A.13; number of admissions with an each of primary diagnosis for an ADR in year 2007-2011

ICD-10 chapters	ICD-10 codes	Description	2007	2008	2009	2010	2011	Total
	G25.6	Drug-induced tics and other tics of organic origin	0	0	0	0	0	0
G	G44.4	Drug-induced headache, not elsewhere classified	1	1	0	0	0	2
	G62.0	Drug-induced polyneuropathy	0	0	1	0	1	2
	G71.1	Drug-induced myotonic disorders	0	0	0	0	0	0
	G72.0	Drug-induced myopathy	2	2	3	2	4	13
	G95.8	Drug-induced other specified diseases of spinal cord	3	11	10	12	6	42
H	H26.3	Drug-induced cataract	0	0	0	0	0	0
I	I42.7	Cardiomyopathy due to drugs and other external agents	0	0	0	1	2	3
	I95.2	Hypotension due to drugs	19	18	52	37	30	156

Table A.13; number of admissions with an each of primary diagnosis for an ADR in year 2007-2011

ICD-10 chapters	ICD-10 codes	Description	2007	2008	2009	2010	2011	Total
J	J70.2	Acute drug-induced interstitial lung disorders	0	0	0	0	0	0
	J70.3	Chronic drug-induced interstitial lung disorders	0	0	0	0	0	0
	J70.4	Drug-induced interstitial lung disorders, unspecified	0	0	0	0	0	0
K	K71	Drug-induced toxic liver disease	0	0	0	0	0	0
	K71.1	Toxic liver disease with hepatic necrosis	25	39	58	42	47	211
	K85.3	Drug-induced acute pancreatitis Hepatic failure (acute)(chronic) due to drugs	0	0	1	0	0	1
L	L10.5	Drug-induced pemphigus	0	0	0	0	0	0
	L23.3	Allergic contact dermatitis due to drugs in contact with skin	0	1	0	0	0	1

Table A.13; number of admissions with an each of primary diagnosis for an ADR in year 2007-2011

ICD-10 chapters	ICD-10 codes	Description	2007	2008	2009	2010	2011	Total
L	L24.4	Irritant contact dermatitis due to drugs in contact with skin	0	0	0	0	0	0
	L25.1	Unspecified contact dermatitis due to drugs in contact with skin	0	1	0	4	6	11
	L27.0	Generalized skin eruption due to drugs and medicaments	71	42	112	98	95	418
	L27.1	Localized skin eruption due to drugs and medicaments	1	0	5	5	4	15
	L64.0	Drug-induced androgenic alopecia	0	0	0	0	0	0
M	M10.2	Drug-induced gout	0	0	0	0	0	0
	M32.0	Drug-induced systemic lupus erythematosus	2	0	0	0	0	2
	M80.4	Drug-induced osteoporosis with pathological fracture	0	0	0	0	0	0

Table A.13; number of admissions with an each of primary diagnosis for an ADR in year 2007-2011

ICD-10 chapters	ICD-10 codes	Description	2007	2008	2009	2010	2011	Total
M	M81.4	Drug-induced osteoporosis	0	0	0	0	0	0
	M83.5	Other drug-induced osteomalacia in adults	0	0	0	0	0	0
	M87.1	Osteonecrosis due to drugs	0	0	0	1	1	2
O	O68	Includes: fetal distress in labour or delivery due to drug administration	0	0	1	0	0	1
P	P58.4	Neonatal jaundice due to drugs or toxins transmitted from mother or given to newborn	0	0	0	0	0	0
	P93	Reactions and intoxications due to drugs administered to fetus and newborn	0	0	0	0	0	0
R	R50.2	Drug-induced fever	0	0	0	8	2	10

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