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The impact of a changed legislation on reporting of adverse drug reactions in Sweden, with focus on nurses' reporting

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Abstract

Purpose: In March 2007~~,~~ a legislative amendment was issued in Sweden compelling nurses to report~~, which included all nurses as reporters of~~all suspected adverse drug reactions (ADRs) to the national pharmacovigilance system. The aim of this study is ~~was~~ to describe the status of ADR reporting ~~in Sweden~~, before and after the implementation of the legislative changes ~~in the legislation~~ and to describe the general characteristics of ~~the~~ suspected ADRs reported by nurses.

Methods: The Swedish pharmacovigilance system ~~in Sweden~~ during the study period constituted of six regional centres that ~~, which handled~~responsible for the handling of all spontaneous ADR reports within their region. In this study we identified all individual ADR reports from 2005 and 2010 ~~were identified, reports from~~, analysed in depth the ADR reports from two regional centres ~~were scrutinised,~~ and collated information about the reporter and the nature of the reported ADR ~~was analysed~~.

Results: From the two regional centres, a total of ~~In total~~ 898 ~~reports were submitted in 2005~~ and 1074 reports ~~in 2010~~were submitted in 2005 and 2010 respectively. Nurses submitted 31% (275 reports) of the reports in 2005 and 24% (260 reports) in 2010. ~~Reporting from nurses~~Nurses' reporting of serious ADRs was 3% (7 reports) in 2005 and 7% (17 reports) in 2010 ~~and~~ with reporting of unlabelled ADRs ~~was~~at 4% (11 reports) in 2005 and 17% (45 reports) in 2010. Most of the serious and/or unlabelled reactions were related to vaccine administration ~~s~~ (14 reports in 2005 and 36 reports in 2010).

Conclusions: The overall ADR reporting by nurses ~~after the legislative amendment~~ did not appear to increase after the change in ~~the~~reporting legislation. The proportion of serious and/or unlabelled ADR ~~reports from~~reported by nurses did however appear to increase during the same period. Taken together our data suggests that f~~F~~urther pro-active measures ~~actions~~ should be considered in order to involve nurses in ~~nurses more effectively in~~ the reporting of

suspected ADRs.

Keywords: adverse drug reaction, spontaneous reporting, pharmacovigilance, nurses.

Introduction

Adverse drug reactions (ADRs) are one of the most common causes of morbidity and mortality and constitute a major problem both in medical and economical terms [1-5]. Post marketing, spontaneous reporting of suspected ADRs is an essential part of an effective pharmacovigilance systems. The goal of ADR reporting systems is to increase patient safety by collecting information about suspected ADRs in order to detect previously unknown ADRs or obtain new information on known ADRs. Underreporting is however a major challenge prolonging the time to identify new informationin the identification and characterization ofn suspected ADRs. A review article from 2006 showed that the underreporting is a serious problem with reporting rates of reporting varying ied from between 0 and 94%, with an overall average reporttting rate of 6% [6]. Several reasons for the One reason underreporting of ADRs have been suggested including why only a small proportion of ADRs are reported a has been discussed, such as is lack of knowledge on how to report ADRs, misconception that absolute confidence in the diagnosis of an ADR is necessary and lack of time among healthcare professionals [7].

In Sweden, reporting of suspected ADRs has been mandatory since 1975 for physicians, dentists, and nurses with prescription privileges[8]. Nurses in particular have close contact with patients and they are commonly generally responsible for the administration of drug therapy in inpatientshospitalised patientscases patients. As a result of their role in patient care, nurses have the potential to play a valuable role in the enhancement ofing pharmacovigilance systems. Previous studies on ADR reporting have shown that the quantity, quality and information gained from ADR reports is markedly increased if nurses are included in the reporting system by nurses have shown that the reporting rate increases if nurses are included as reporters of suspected ADRs [8-11], the quality of the reported ADRs

reporting has been shown to be adequate and their reports contribute with new information [12, 13]. In Sweden, reporting of suspected ADRs has been mandatory since 1975 for physicians, dentists, and nurses with prescription privileges [14]. Among nurses with prescription privileges in Sweden, the proportion of nurses reporting ADRs has increased from 2-3% in the 1990s to 12% in 2004 [11]. In order to increase the overall reporting of ADRs, a legislative amendment was issued in Sweden in March 2007, where all nurses were included as reporters of suspected ADRs [15]. The effects of the new legislation on suspected ADR reporting hasve, however, not been evaluated. The aim of this study was therefore to describe the ADR reporting from healthcare professionals in Sweden, before and after the change in the legislation and to describe the characteristics of the reported suspected ADRs by nurses.

Methods

Since 1965 Sweden has a spontaneous reporting system for suspected ADRs. Until 2012 the Pharmacovigilance system in Sweden consisted of six regional centres, which handled the spontaneous ADR reports within their region. Within the Pharmacovigilance system all suspected serious, uncommon or otherwise unexpected ADRs were supposed to be reported. Moreover, reporting of all ADRs was encouraged during the first 2 years after drug approval. Information from each individual report was stored in the national database; the Swedish Drug Information System (SWEDIS). Data stored in the database consisted of information about the patient, drugs used, suspected ADRs, outcome, causality assessment, the reporter, origin of the report and administrative data. Until 2012 the WHO definition of an ADR, "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function", was used within the Swedish spontaneous reporting system [16].

In SWEDIS drugs can be listed as being suspected of having caused or contributed to the reaction, as interacting with another prescribed drug, or as concomitant medication not related to the ADR. Drugs were coded according to the WHO Collaborating Centre for Drug Statistics Methodology International Anatomical Therapeutic Chemical (ATC) classification [17]. The ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology [18]. Each report may include more than one ADR and/or drug. Each ADR was classified with respect to its causality using the WHO definitions [16]; ~~Certain: plausible time relationship to drug exposure, positive de- and rechallenge. Probable: reasonable time sequence to drug exposure, positive dechallenge, other explanations are unlikely. Possible: reasonable time sequence to drug exposure, dechallenge may be lacking other possible explanations may exists. Unlikely: unreasonable time sequence to drug exposure and other plausible explanations exists. Unclassified: more data are essential for a proper assessment or additional data are being examined. Unclassifiable: insufficient or contradictory information that cannot be supplemented or verified. Moreover, each ADR was classified as serious if leading to death, required hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening and not serious if the reaction was transient and managed without the need for hospitalization~~and seriousness [19]. The reported ADRs were classified as unlabelled if the reported reactions were not included in the ADR section of the Summary of Product Characteristics (SPC) at the time when the ADR was reported.

All individual ADR reports from 1st of January to 31st of December of 2005 and 2010 were identified in SWEDIS. The ADR reports from the Southeast regional Pharmacovigilance centre and the Northern regional Pharmacovigilance centre in Sweden were collected and

scrutinised. The population living in the two regions comprised 21% (1,860,582 individuals) in 2005 and 20% (1,877,255 individuals) in 2010 of the Swedish population and included a population with similar age and gender distribution as Sweden in total [20]. ~~was.~~ Information on the reporter (~~age,~~ sex and profession) and the reported ADR (MedDRA classification, administered drugs, seriousness, labelling in the SPC and causality assessment) were extracted from the ADR reports. Reporters were categorized as nurse (working in primary care, in hospital or in school healthcare), physician (working in primary care or in hospital) and other (dentist). The category other also included reports submitted from other healthcare professionals not obligated to report ADRs, including reports from dental hygienists, pharmacists and laboratory technicians. Information about the physicians' level of education, medical specialists training were identified in a register of all physicians in Sweden.

The data were analysed descriptively. For each reporter category (physician, nurse and other), the proportions of reported ADRs, serious and/or unlabelled ADRs were calculated. ~~Moreover~~Furthermore, serious and/or unlabelled ADRs reported by nurses were described in more detail.

Results

In total 4065 reports were submitted to the Swedish pharmacovigilance system in 2005 and 5159 reports in 2010. Of these 22% (898 reports) in 2005 and 21% (1074 reports) in 2010 were submitted to the Northern and the Southeast regional pharmacovigilance centres. Most of the reporters were physicians (67% in 2005 and 75% in 2010), and female (58% in 2005 and 60% in 2010) (table 1). Among nurses 98% were female in 2005 and 93% in 2010. Among the physicians 40% were female in 2005 and 49% in 2010.

The proportion of reports submitted by nurses was 31% in 2005 (275 reports) and 24% (260 reports) in 2010. The proportion of reports from hospital nurses was 0.4% (4 reports) in 2005 and 2% (25 reports) in 2010 and from nurses in primary care 6% (~~55~~ 57 reports) in 2005 and 9% (96 reports) in 2010. The proportion of reports from nurses working in the school healthcare in the Northern regional Pharmacovigilance Centre was 14% (46 reports) in 2005 and 12% (49 reports) in 2010. In the Southeast regional Pharmacovigilance centre 30% (168 reports) of the reports was from nurses working in the school healthcare in 2005 compared with 13% (88 reports) in 2010. In 2005 100 reporters submitted more than 1 report compared to 172 reporters in 2010.

The majority of the reported ADRs were non-serious (66% in 2005 and 61% in 2010) and labelled reactions (76% in 2005 and 74% in 2010) that had at least a possible causal relationship to the suspected drug(s) (table 2). The reporting of unlabelled ADRs among nurses was 4% in 2005 and 17.3% in 2010, and among physicians 32% in 2005 and 29% in 2010. The reporting of serious reactions among nurses was 3% in 2005 and 7% in 2010, and among physicians 48% in 2005 and 49% in 2010.

The majority of substances reported by nurses as suspected to have caused an ADR were anti-infectives for systemic use (such as antibiotics, vaccines and antivirals) 95% (262 reports) in 2005. Although reports containing anti-infectives for systemic use appeared to decrease in 2010 among nurses, this category still accounted for more than 80% (231 reports) of all reports. Vaccines accounted for most of these reports. Vaccines also constituted the largest drug group that was assessed as causing serious and/or unlabelled ADRs reported by nurses in 2005 and 2010 (table 3). In 2010, the spectrum of suspected drugs among serious

and/or unlabelled ADRs also included reports from e.g. anti-bacterials, nervous system drugs, contrast media and drugs for treatment of bone disease and obstructive airways.

Discussion

This retrospective study indicates that the proportion of ~~adverse drug reactions~~ADRs reported by nurses in the Southeast and Northern Pharmacovigilance Centres in Sweden did not increase after the legislative amendment that included all nurses as reporters of suspected ADRs. There did ~~however appeared~~however appear to be an increase in~~of~~ number of ADR reports from nurses working outside the school healthcare and in~~. T~~ the proportion of serious and/or unlabelled ADRs from nurses in general.~~ did however appear to increase~~ This~~,~~ suggest~~s~~ing~~ a shift after the legislative amendment towards nurses reporting more ADRs that add new information within the Pharmacovigilance system~~ after the legislative amendment~~.

~~Despite including all nurses as reporters of suspected ADRs,~~In this study, the number of ADR reports from~~s reported by~~ nurses seemed to decrease in 2010 ~~appeared to decrease~~ compared to~~with~~ 2005~~ in this study~~. The main decrease was observed among nurses working in~~ the~~ school healthcare, where a 50% reduction occurred. These nurses administer vaccinations within the Swedish childhood vaccination programme~~ to children in school~~ and a large part of their reports concern vaccine-related ADRs ~~related to vaccines~~ [11]. Due to changes in the vaccines included in ~~In October~~ 2003 and 2005, the Swedish Medical Products Agency~~ (MPA)~~ requested ~~issued a letter to~~ nurses/physicians working in~~ the~~ school healthcare~~ with a request~~ to report all ADRs~~, including those listed in the ADR section of the SPC,~~ suspected to be caused by vaccines, including those listed in the SPC ~~, in order to increase the knowledge of these ADRs~~ [21]~~. The same procedure was performed~~ requested in ~~2005 when a new vaccine was introduced to the program of childhood vaccinations in~~

~~Sweden~~ ~~Sweden and the MPA encouraged nurses/physicians working in the school healthcare to report all ADRs observed related to this vaccine~~ [21, 22]. These two events might explain the high number of reports from nurses working in ~~the~~ school healthcare in 2005. I~~n fact, i~~f excluding reports from nurses working in ~~the~~ school healthcare, an increase in reports from~~by~~ nurses in this study was ~~indicated~~ observed in 2010 (11%) compared to ~~between~~ 2005 ~~and 2010 in this study ((~~7%~~) of reports in 2005 vs 11% in 2010)~~.

The total ~~number~~proportion of ADR reports from nurses in this study, 31% in 2005 and 24% in 2010, are higher that what was observed in Sweden in 2004 ~~might appear to be low, 30.6% in 2005 and 24% in 2010. These numbers are however higher than 2004 (12%) and the 90s (2-3%) [11],. The nurses reporting rate in this study was similar to~~and in ~~-~~Italy (23,6% during 2004-2010) [8] but lower than in Portugal (54% during 2001-2010) [23]. In Portugal, nurses have been included as reporters since the start of the Portuguese pharmacovigilance system in 1992 and ~~-~~have therefore ~~have~~ a longer tradition of reporting ADRs. In a~~A~~ Swedish survey from 2010 [9], a random sample of 753 nurses was ~~included~~performed on , members from~~in~~ ~~-~~a random sample of nurses who were members in one of two trade unions, the Swedish Association of Health Professionals (engaged 75,300 Swedish nurses at the time)~~, that engaged 75300 nurses in Sweden at the time~~. Of the 453 nurses that responded to the survey, 58% reported that they were aware of their role as reporters of suspected ADRs but only 14% stated that they had reported an ADR. Nurses' involvement in Pharmacovigilance activities in Sweden could ~~could~~ hence be further encouraged ~~even further~~.

~~The main purpose of spontaneous ADR reporting is to detect previously unknown ADRs and unknown information about known ADRs.~~ Although the number of ADR reports~~s reported~~

~~by~~ from nurses in this study appeared to decrease during the study period, there ~~appeared~~seemed to be an increase~~d in~~ reporting of serious and/or unlabelled reactions. Similar results have~~This has also~~ been shown in an Italian study [8], where the reporting rate of serious reactions from Italian nurses increased from 13% in 2004 to 26% in 2010 [8]. ~~The proportion of serious ADRs in our study is however low compared with a previous Swedish study [11] where 8% of nurses' reports were assessed as serious in 2003 and 2004. Previous studies [10, 13, 24] have shown that education has led to increased the reporting of serious and/or unlabelled suspected ADRs by nurses. This might may be due to the fact that because due to that emphasis is put on the importance of reporting serious and unlabelled ADRs is emphasised during thi during these education and training programss education.. In two Swedish studies nurses at departments of internal medicines [13], orthopaedic [13] and geriatric medicine [25] received information on ADRs and on how to report ADRs. During the one year follow up 23 reports were submitted from the departments of internal medicines and orthopaedics of which 74% were assessed as serious and 20% as unlabelled [13]. The nurses inFrom the department of geriatric medicine submitted 18 reports were submitted during the one year follow up, of which 39% were assessed as serious and 33% as unlabelled [25]. These results show that education in fact may lead to increased reporting of serious and/or unlabelled reactions. In a study from the UK [12] nurses received information on how to report ADRs. During the follow up of 13, 17 and 21 months, 177 reports were submitted and 36% of the reports submitted by nurses were assessed as serious.~~

~~Vaccines have for long constituted the majority of reported drugs from nurses in Sweden [11] as well as in the UK [12].~~ A closer observation of all serious and/or unlabelled ADRs reported by nurses in this study showed a broadened spectrum of suspected drugs in 2010 compared to 2005, even if vaccines still accounted for the majority of suspected drug

reactions. ~~causing the serious and/or unlabelled reactions.~~ In addition to vaccines, nurses' reports on serious ADRs also included ~~such as~~ anti-bacterials and ~~,~~ anti-epileptics and drugs for treatment of bone disease and obstructive airways. ~~In the study where nursing reporting was introduced in clinical departments~~ [13]~~, neurological, gastrointestinal, psychiatric reactions were most commonly reported.~~

This study shows that the reporting of~~ed~~ ADRs by~~from~~ physicians ~~-~~was not negatively affected by the inclusion of nurses as ADR reports, since ~~appeare~~the number of ADR reports from physicians increased ~~d to be higher~~ in 2010 compared to ~~that of~~ 2005. In a ~~Thus including nurses as reporters of ADRs does not seem to have a negative effect on ADR reporting by physicians. This has also been shown in a~~Swedish pilot study of nursing reporting in Sweden [13], ~~where~~ 89% of the physicians stated that their own willingness to report was not affected by nurses reporting. Moreover, in a Swedish~~one~~ survey [26] the~~a~~ majority of hospital physicians in Sweden reported that they were positive or neutral to nurses reporting. Further studies are however needed to assess the effect on physicians reporting.

The main limitation of this study, however, ~~-~~is that we were not able to take other factors into consideration ~~other factors~~ that might~~ay~~ have affected the reporting rate during the study period, such as media attention on specific ADRs. ~~Another limitation was the generalizability of the results to other regions in Sweden and outside of Sweden, since. In this study only ADR reports received by two of six regional pharmacovigilance centres in Sweden hav~~was~~e been scrutinized. Moreover, we only compared the reporting of suspected ADRs in 2005 and 2010. and o~~O~~ther difference might have been observed if including other years in the study.~~

Conclusions

The overall ADR reporting from nurses was in the same order of magnitude after the inclusion of all nurses as ~~ADR~~ reporters. There was an increase in reports from ~~other~~ nurses ~~than those~~ working in ~~school healthcare~~primary care and hospitals, and~~,~~ there also appeared to be an increase of serious and/or unlabelled ADR reports from nurses in general after the legislative amendment. Most of the nurses ~~nurses'~~ ADR reports that w~~a~~ere classified ~~s~~~~ere~~ ~~assessed~~ as serious and/or unlabelled reactions were related to vaccine administration~~s~~. Taken together our data suggests that further pro-active measures should be considered in order to involve nurses in the reporting of suspected ADRs.~~Based on our studies we suggest that fFurther actions should be considered in order to involve nurses more effectively in the reporting of suspected ADR.~~

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Contributors

AKJ was the principal investigator. IJ, MDB, SAK collected data. SAK drafted the manuscript. All authors contributed to the study design, and interpretation of the results and commented on the draft. All authors had full access to the data. AKJ is the guarantor of the study.

Ethical statement

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later

amendments or comparable ethical standards. For this type of study formal consent is not required by law.

Conflict of interest statement:

The authors declare that they have no conflict of interest.

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Table 1. Characteristics of healthcare professionals reporting ADRs in the Southeast and Northern pharmacovigilance region in 2005 and 2010.

	All reporters		Reports from the Southeast pharmacovigilance region		Reports from the Northern pharmacovigilance region	
	2005	2010	2005	2010	2005	2010
	Number of reports (%) N = 898	Number of reports (%) N=1074	Number of reports (%) N=560	Number of reports (%) N=680	Number of reports (%) N=338	Number of reports (%) N=394
Female reporter[s]	524 (58)	641 (60)	340 (61)	404 (59)	184 (54)	237 (60)
All nurses[b]	275 (31)	260 (24)	208 (37)	176 (26)	67 (20)	84 (21)
Nurses working in primary care	57 (6)	96 (9)	38 (7)	68 (10)	19 (6)	28 (7)
Nurses working in hospital	4 (0.4)	25 (2)	2 (0.4)	19 (3)	2 (1)	6 (2)
Nurses working in school healthcare	214 (24)	137 (13)	168 (30)	88 (13)	46 (14)	49 (12)
All physicians[b]	601 (67)	803 (75)	342 (61)	498 (73)	259 (77)	305 (77)
Physicans working as General practitioner	207 (23)	161 (15)	99 (18)	84 (12)	108 (32)	77 (20)
Physicans working in Hospital	394 (44)	640 (60)	243 (43)	412 (61)	151 (45)	228 (58)
Others[c]	22 (2)	11 (1)	10 (2)	6 (1)	12 (4)	5 (1)

[a] The sex of the reporter was unknown in 0 reports in 2005 and 16 reports in 2010.

[b] The workplace of the reporter was unknown in 0 reports in 2005 and 2 reports in 2010.

[c] The profession of the reporter were unknown in 5 reports in 2005 and 4 reports in 2010.

Table 2. Characteristics of the suspected ADRs reported in relation to the profession of the reporter.

	All reporters		Nurse		Physician		Others	
	2005 Number of reports (%) N=898	2010 Number of reports (%) N=1074	2005 Number of reports (%) N=275	2010 Number of reports (%) N=260	2005 Number of reports (%) N=601	2010 Number of reports (%) N=803	2005 Number of reports (%) N=22	2010 Number of reports (%) N=11
Serious ADRs	301 (34)	413 (39)	7 (3)	17 (7)	286 (48)	393 (49)	8 (36)	3 (27)
Fatal ADRs	24 (3)	16 (2)	1(0.4)	0 (0)	23 (4)	16 (2)	0 (0)	0 (0)
ADRs unlabelled in the SPC[a]	210 (23)	281 (26)	11 (4)	45 (17)	194 (32)	232 (29)	5 (23)	4 (36)
Causality assessed as at least possible[b]	842 (94)	1010 (94)	272 (99)	254 (98)	548 (91)	745 (93)	22 (100)	11 (100)

Abbreviations: ADR, adverse drug reaction; SPC, Summary of Product Characteristics.

[a] At least one ADR diagnosis was classified as not labelled in the SPC.

[b] All ADR diagnosis of one case classified as certain, probable and/or possible.

Table 3. All serious or unlabelled ADRs in relation to the suspected substance reported by nurses in 2005 and 2010.

Year	(ATC code) Drug group (Number of reports)	Reported ADR[a,b] (Number of reports)
2005		
	(A10) Drugs used in diabetes (1)	Reproductive system and breast disorders[c] (1)
	(G03) Sex hormones and modulators of the genital system (2)	Skin and subcutaneous tissue disorders[c] (1), general disorders and administration site conditions[c] (1), cardiac disorders[c] (1)
	(J07) Vaccines (14)	Skin and subcutaneous tissue disorders[c,d] (9), general conditions and administration site conditions[c,d] (3), respiratory, thoracic and mediastinal disorders[c] (2), eye disorders[c] (1), nervous system disorders[d] (1), psychiatric disorders[c] (1), gastrointestinal disorders[d] (1)
	(N06) Psychoanaleptics (1)	Psychiatric disorders[d] (1)
2010		
	(A02) Drugs for acid related disorders (1)	General disorders and administration site conditions[c] (1)
	(C08) Calcium channel blockers (1)	Psychiatric disorders[c] (1)
	(C09) Agents acting on the renin-angiotensin system (1)	Respiratory, thoracic and mediastinal disorders[c] (1)
	(G02) Other gynaecologicals (1)	Respiratory, thoracic and mediastinal disorders[c] (1), gastrointestinal disorders[c] (1)
	(G03) Sex hormones and modulators of the genital system (1)	Psychiatric disorders[c] (1), general disorders and administration site conditions[c] (1)
	(H01) Pituitary and hypothalamic hormones and analogues (1)	Nervous system disorders[c] (1)
	(J01) Antibacterials (2)	Skin and subcutaneous tissue disorders[c,d] (1), general disorders and administration site conditions[d] (1)
	(J07) Vaccines (36)	General disorders and administration site conditions[c,d] (24),

		nervous system disorders[c,d] (5), psychiatric disorders[c,d] (4), skin and subcutaneous tissue disorders[c] (3), gastrointestinal disorders[c,d] (3), respiratory, thoracic and mediastinal disorders[c,d] (2), blood and lymphatic tissue disorders[c] (2), musculoskeletal and connective tissue disorders[c,d] (1), reproductive system and breast disorders[c,d] (1)
	(L02) Endocrine therapy (1)	Skin and subcutaneous tissue disorders[c] (1)
	(M01) Anti-inflammatory and antirheumatic products (1)	Skin and subcutaneous tissue disorders[c] (2)
	(M05) Drugs for treatment of bone disease (1)	Respiratory, thoracic and mediastinal disorders[d] (1), general disorders and administration site conditions[c,d] (1)
	(N03) Antiepileptics (1)	Congenital, familial and genetic disorders[d] (2)
	N07) Other nervous system drug (1)	General disorders and administration site conditions[d] (1)
	(R03) Drugs for obstructive airways (1)	Reproductive system and breast disorders[c,d] (1)
	(V08) Contrast media (5)	Respiratory, thoracic and mediastinal disorders[c,d] (4), gastrointestinal disorders[d] (2), general disorders and administration site conditions[d] (2), skin and subcutaneous tissue disorders[d] (2)

~~Year~~	~~Drug group (ATC code)~~	~~Suspected substance (Number of reports)~~	~~Reported ADR[a,b] (Number of reports)~~
~~2005~~			
	~~Drugs used in diabetes (A10)~~	~~insulin detemir (1)~~	~~menometorrhagia[c] (1)~~
	~~Sex hormones and modulators of the genital system (G03)~~	~~ethinylestradiol (1), etonogestrel (1)~~	~~chloasma[c] (1), feeling cold[c] (1), palpitations[c] (1)~~
	~~Vaccines (J07)~~	~~pertussis, purified antigen, combinations with toxoids (6), diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus (3), measles, combinations with mumps and rubella, live attenuated (3), tetanus toxoid,~~	~~skin reaction[d] (4), skin mass[c] (2), application site reaction[c] (2), angioedem[d] (1), nasal congestion[c] (1), dizziness[c] (1), eyelid oedema[c] (1), febrile convulsion[d] (1),~~

		combinations with diphtheria toxoid (2)	hypersensitivity[d] (1), irritability[e] (1), nasal pruritus[e] (1), pyrexia[d] (1), vomiting[d] (1)	
	Psychoanaleptics (N06)	venlafaxine (1)	completed suicide[d] (1)	
2010				
	Drugs for acid related disorders (A02)	omeprazol (1)	drug ineffective[e] (1)	
	Calcium channel blockers (C08)	felodipine (1)	depressed mood[e] (1)	
	Agents acting on the renin-angiotensin system (C09)	candesartan (1)	dyspnoea[e] (1)	
	Other gynaecologicals (G02)	levonogestrel (1)	dyspnoea[e] (1), vomiting[e] (1)	
	Sex hormones and modulators of the genital system (G03)	etonogestrel (1)	obsessive thoughts[e] (1), decreased appetite[e] (1)	
	Pituitary and hypothalamic hormones and analogues (H01)	oxytocin (1)	sensory disturbance[e] (1)	
	Antibacterials (J01)	cefotaxim (1), nitrofurantoin (1)	erythema multiforme[e,d] (1), hypersensitivity[d] (1)	
	Vaccines (J07)	influenza, inactivated, split virus or surface antigen (13), diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus (6), measles, combinations with mumps and rubella, live attenuated (6), pertussis, purified antigen, combinations with toxoids (4), pneumococcus, purified polysaccharides antigen conjugated (4), hepatitis B, purified antigen (1), encephalitis, tick borne, inactivated, whole virus (1), papillomavirus (human types 6, 11, 16, 18) (1)	aluminium allergy[e] (5), hypersensitivity[e] (4), dizziness[e,d] (3), pyrexia[d] (3), syncope[e,d] (3), dyspnoea[e,d] (2), skin mass[e] (2), abdominal pain[d] (1), amnesia[e] (1), apathy[e,d] (1), balance disorder[e] (1), convulsion [e,d] (1), crying[d] (1), decreased appetite[e] (1), ecchymosis[e] (1), dysgeusia[e] (1), gingivitis[e] (1), haematoma[e] (1), headache[d] (1), influenza like illness[e] (1), lethargy[e] (1), lymphadenopathy[e] (1), muscle	

			contractions involuntary[c,d] (1), narcolepsy[c,d] (1), nausea[d] (1), oedema[c] (1), pain[d] (1), petit mal epilepsy[c] (1), paraesthesia[c] (1), testicular pain[c,d] (1)
	Endocrine therapy (L02)	leuprorelin (1)	skin mass[c] (1)
	Anti-inflammatory and antirheumatic products (M01)	etoricoxib (1)	angioedema[c] (1), dermatitis bullos[c] (1)
	Drugs for treatment of bone disease (M05)	zoledronic acid (1)	asthma[d] (1), influenza like illness[c,d] (1)
	Antiepileptics (N03)	topiramat (1)	cleft palate[d] (1), heart disease congenital[d] (1)
	Other nervous system drug (N07)	disulfiram (1)	potentiating drug interaction[d] (1)
	Drugs for obstructive airways (R03)	formoterol (1)	abortion[c,d] (1)
	Contrast media (V08)	ioversol (3), iomeprol (1), iohexol (1)	anaphylactic shock[d] (1), cough[d] (1), dermatitis bullous[d] (1), dizziness[d] (1), nasal congestion[c] (1), pharyngeal oedema[d] (2), sneezing[c,d] (2), urticaria[d] (1)

Abbreviations: ADR, adverse drug reaction; ATC, Anatomic Therapeutic Chemical classification system; MedDRA, Medical Dictionary for Regulatory Activities

[a] One report can contain multiple ADR diagnoses, not all of them within the same system organ class.

[b] The ADRs are classified according to the System organ class within the MedDRA terminology.

[c] Unlabelled reaction in at least one of the reports

[d] Serious reaction in at least one of the reports