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Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009

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DECLARATIONS

Competing interests

None declared

Funding

The Dr Foster Unit is funded by Dr Foster Intelligence.

Imperial College London is grateful for support from the NIHR Biomedical Research Centre scheme and the NIHR Collaboration for Leadership in Applied Health Research & Care (CLAHRC) scheme.

MM is funded by an NIHR postdoctoral award and is an investigator for the EU-ADR FP7 and Serious Adverse Events Consortium (SAEC) projects on adverse drug reactions

Summary

Objectives Adverse drug reactions (ADR) are an important cause of morbidity and mortality. We analysed trends in hospital admissions associated with ADRs in English hospitals between 1999 and 2008.

Design Data from the Hospital Episode Statistics database were examined for all English hospital admissions (1999–2008) with a primary or secondary diagnosis of an ADR recorded.

Setting All NHS (public) hospitals in England.

Main outcome measures The number of admissions and in-hospital mortality rate with a 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) were obtained and analysed. Further analysis for the year 2008–2009 was performed with regard to age, gender, proportion aged >65 yrs and total bed-days.

Results Between 1999 and 2008, there were 557,978 ADR-associated admissions, representing 0.9% of total hospital admissions. Over this period the annual number of ADRs increased by 76.8% (from 42,453 to 75,076), and in-hospital mortality rate increased by 10% (from 4.3% to 4.7%). In 2008, there were 6,830,067 emergency admissions of which 75,076 (1.1%) were drug-related. Systemic agents were most commonly implicated (19.2%), followed by analgesics (13.3%) and cardiovascular drugs (12.9%). There has been a near two-fold increase in nephropathy and cardiovascular consequences secondary to drugs and a 6.8% fall in mental and behavioural disorders due to drugs.

Conclusions ADRs have a major impact on public health. Our data suggest the number of ADR admissions has increased at a greater rate than the increase in total hospital admissions; some of this may be due to improved diagnostic

Ethical Approval

We have approval from St Mary's Hospital Local Research Ethics Committee to use routinely collected hospital administrative data for research. Also, we have been granted permission by the Patient Information Advisory Group under Section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001) to use routinely collected hospital administrative data to provide measures of quality of delivery of healthcare by provider.

Guarantors
T-YW and AM

Contributorship
T-YW extracted the relevant ICD-10 codes, carried out the literature review and drafted the manuscript. M-HJ and AB obtained and analysed the data and prepared the

coding. However, in-hospital mortality due to ADR admissions also increased during the period. Our findings should prompt policymakers to implement further measures to reduce ADR incidence and their associated in-hospital mortality, and methods to improve the recording of ADRs.

Introduction

An adverse drug reaction (ADR) is an undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use,¹ and is one of the major causes of iatrogenic disease.² ADRs cause significant morbidity and mortality and increase the length of hospital stays. The economic burden of ADRs on the British NHS is also high, accounting for considerable extra NHS costs.³

ADRs may be on target (where there is a clear dose relationship) and may be reversible on reducing or withdrawing the drug,^{1,4} or off target (where there is uncertain dose response relationship). Idiosyncratic ADRs which are largely unpredictable, can depend on the genetic susceptibility of the individual and are often more serious (sometimes fatal). The benefit-harm relationships of ADRs are complex and should always be taken into account when prescribing.

From the patients' perspective, ADRs affects quality of life, confidence in treatment, influence adherence to medications, and increase costs of care.¹ The manifestation of ADRs may also mimic a disease process and, therefore, lead to further investigations and treatments.

Older people or those with multiple long-term diseases are more susceptible to ADRs.⁵ As comorbidity increases with increasing age, polypharmacy (use of more than four prescription drugs⁶) is seen more frequently in older patients.^{7,8} Moreover, between 14 and 24% of older adults receive potentially inappropriate medications.⁹ For example, long-acting benzodiazepines have a high potential for severe adverse outcomes in older patients, according to Beers criteria (a list of inappropriate medications for the elderly).¹⁰ Polypharmacy increases the likelihood of drug-drug interaction and adverse drug reactions.¹¹ ADRs then in turn prompt the patient to seek further medical help and multiple primary and secondary care visits may ensue.¹²

Despite the clinical impact of adverse drug reactions, methods for monitoring them remained limited. Databases derived from electronic health records such as the General Practice Research

Database (GPRD) or QResearch are also being increasingly used to monitor ADRs. Other approaches include: clinical trials, prescription event monitoring, spontaneous reporting, and linked administrative databases. However, where an ADR is rare, clinical trials lack power to detect associations. Prescription event monitoring examines risk in newly-marketed drugs but has a relatively short follow-up and difficulty in selecting appropriate controls. Spontaneous reporting is done through pharmacovigilance reporting such as the MHRA (Medicines and Healthcare Products Regulatory Agency) Yellow Card Scheme in the UK, although under-reporting remains a significant issue.

Consequently, when a drug is first marketed, there is often limited information about its safety in routine clinical use,¹³ although under the black triangle scheme new medicines are intensively monitored by the Commission on Human Medicines (CHM) and the MHRA. Drug safety assessment should be considered an integral part of everyday clinical practice,¹ as well as necessity for phase IV (post-marketing surveillance) trials. Under such post-marketing surveillance, drugs continue to be withdrawn from the market due to safety concerns; for example, the withdrawal of rofecoxib in 2004¹⁴ due to concerns about cardiovascular safety (MI and stroke) and, more recently, efalizumab in 2009, a recombinant humanized monoclonal antibody used to treat psoriasis, due to potential risk of progressive multifocal leukoencephalopathy (PML).

We analysed hospital admissions associated with ADRs in all NHS (public) English hospitals in the past 10 years, using the Hospital Episode Statistics database. We examined the epidemiology of hospital admissions for ADRs including temporal trends, in-hospital mortality, the age and gender distribution of these admissions, and differences in ADR rates between individual hospitals.

Methods

Hospital Episode Statistics (HES) is an administrative database produced by the Department of

tables and figure. AM, PA, DB and MM conceived the study, mentored the other authors and made critical contributions to the manuscript at each stage

Acknowledgements

None

Reviewer

David Henry

Health for England.¹⁵ It is available for every year from 1989 onwards and comprises data gathered locally from each NHS hospital's Patient Administration System or Hospital Information System.⁴ It covers all inpatient and day-case activity delivered by NHS hospitals in England, and contains demographic, administrative and clinical information. The data-set contains over 300 fields including age, gender, admission method, primary and secondary diagnosis fields, length of stay, and method of discharge (including in-hospital death). The basic unit of the data-set is the consultant episode, covering the continuous period of time during which a patient was under the care of one consultant. Episodes of care were linked into admissions and those ending in transfer to another hospital were linked together to avoid multiple counting. The 10th International Classification of Diseases (ICD-10) is used for diagnosis coding.

For each financial year from 1999–2000 to 2008–2009, we obtained HES records in which there was an ICD-10 code containing the following keywords: 'adverse drug reaction', 'drug-induced', 'due to drug', 'due to medicament' or 'drug allergy'. For comprehensiveness, we also searched for ICD-10 codes relevant to ADRs containing the word 'immunization', since vaccines were considered as a form of medication. We then divided the main diagnostic codes into chapters based on ICD-10, as shown in Appendix 1 online (see <http://jrsm.rsmjournals.com/cgi/content/full/103/6/239/DC1>). We also analysed codes in the range Y40–59, which are known as 'external cause' codes or 'secondary diagnoses'. In this way, we excluded accidental or intentional poisoning due to drugs. We analysed those codes that explicitly stated that the admission was caused by a certain drug.

HES records contain one main diagnosis code and 13 (six up to 2000) secondary diagnosis codes. We flagged all the emergency admissions with ADR-related ICD-10 codes in either the primary diagnoses or secondary diagnoses fields. We calculated the frequency of each three-digit external Y codes and of related ADRs ICD-10 codes of each chapter for each financial year. We excluded possible duplications in coding; an admission coding both ADR-related primary and secondary diagnoses is only counted once, as shown in Table 1. When analysed by individual ICD-10 chapters or categories in Tables 2–5, these admissions might be counted twice or more. However, the majority of the

admissions (99.5% for year 2008–2009) only had one ADR-related ICD-10 code in their diagnosis.

For the latest year, 2008–2009, we examined the number of admissions by age, gender, proportion of older people (age >65 yrs), total bed-days and in-hospital mortality of each category of ADR. We showed the distribution of hospital-level ADR rates on a funnel plot. Statistical analysis was performed with SAS software (version 9.2). For all analyses, only data for emergency (unplanned) admissions were used.

Results

Overall hospital admissions for ADRs

Table 1 summarizes the annual number of total hospital admissions, the number of admissions associated with ADRs and in-hospital mortality rates. In our 10-year study period, there were 59,718,694 total emergency hospital admissions and 557,978 admissions with a diagnostic code indicative of ADRs (0.9%). Of these, 188,024 were primary diagnoses and 444,780 were of 'external cause'. There were 26,399 in-hospital deaths in ADR admissions, a case-fatality rate of 4.7%.

Ten-year trends in hospital admissions for ADRs

Between 1999 and 2008, the total number of hospital admissions increased by 28.3%, but the total number of admissions due to ADRs increased by 76.8%. The majority of the latter was due to an increase in external cause codes. The in-hospital mortality rate of ADR admissions increased by 10%, from 4.3% to 4.7%, although this stabilized from 2004 onwards (Table 1).

Tables 2 and 3 describe the burden of ADRs according to ICD-10 code. The number of ADRs with a primary diagnosis increased by 36.8% during this study. Nephropathy due to drugs (from 109 to 303 admissions), cardiovascular consequences (from 1238 to 3399 admissions) and drug-induced lung disorders (from 64 to 157 admissions) were the three fastest growing ADRs as a primary diagnosis (Table 2). Mental and behavioural disorders due to drugs decreased 6.8% during the 10-year period, although the category bore the highest admission burden (57,096 diagnoses in the study period). Drug-induced anaemia (–21.8%) and complications following injection,

immunization or anaesthesia (−7.0%) declined during the years 2004–2008.

The number of ADRs recorded in any secondary diagnosis field increased 105.8% during the study period (Table 3). The three fastest growing ADRs as external causes were drugs related to: gastrointestinal system (from 302 to 854 admissions); water-balance (from 2081 to 5789 admissions); and systemic agents (from 5146 to 12,667 admissions). In contrast, the only reported rate which showed a decrease was under the category of bacterial vaccines (from 297 to 153 admissions).

General description for year 2008–2009

In 2008–2009, the total number of emergency admissions in England was 6,830,067, of which 75,076 (1.1%) were drug-related (Table 1). The total admission rate in England was 13,726 per 100,000 person-years and the ADR admission rate in England was 146 per 100,000 person-years (data not shown). Mental and behavioural disorders due to drugs (24.5%), cardiovascular consequences (15.1%) and complications following injection, immunization or anaesthesia (14.8%) were the most frequent manifestations of ADRs (Table 4). Systemic agents were the most implicated class (Y43, 19.2%), followed by analgesics, antipyretics and anti-inflammatory drugs (Y45, 13.3%) and cardiovascular drugs (Y52, 12.9%) (Table 5). Systemic agents (Y43) were primarily antineoplastic or immunosuppressive drugs.

The admission burden was highest for mental and behavioural disorders due to drugs (94,579 total bed-days), but in-hospital mortality rate was highest for lung disorders due to drugs (17.2%) (Table 4). The highest admission burden was associated with systemic agents (Y43, 112,667 total bed-days), but the in-hospital mortality rate was highest among ADR due to agents affecting blood constituents (Y44, 9.4%).

Age distribution for year 2008–2009

Most hospital admissions associated with adverse drug reactions occurred in older patients. In 2008–2009, 58.5% of hospital admissions in which there was an external ICD-10 code for ADR occurred in people aged 65 years and over. The median age of ADRs with an external code was 70 (Table 5). ADRs due to bacterial vaccines (Y58) usually occurred in

Table 1 Total number of emergency admissions for which there was a primary diagnosis or 'external cause' of ADR from 1999 to 2008

Year	Change (%)											
	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	1999–2008	2004–2008
Total number of admissions	5,321,796	5,319,791	5,337,034	5,494,066	5,818,057	6,116,507	6,423,646	6,496,945	6,560,785	6,830,067	28.3	11.7
Number with drug-induced codes	16,434	16,237	17,151	16,645	18,307	19,652	20,465	20,009	20,685	22,439	36.5	14.2
Number with external cause codes	31,486	32,641	33,842	36,617	41,722	44,745	50,063	53,198	56,883	63,583	101.9	42.1
Total admissions due to ADRs	42,453	43,288	45,518	47,455	53,218	56,629	61,931	64,536	67,874	75,076	76.8	32.6
In-hospital mortality of ADR admissions	1816	1879	2259	2480	2672	2679	2878	3013	3189	3534	94.6	31.9
In-hospital mortality rate of ADR admissions	4.3	4.3	5.0	5.2	5.0	4.7	4.6	4.7	4.7	4.7	10.0	−0.5

Table 2
Annual number of emergency admissions with a primary diagnosis for an ADR

ICD-10 chapters	Description	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	Change (%) 1999–2008	Change (%) 2004–2008
D	Drug-induced anaemia	155	138	145	162	143	316	259	178	194	247	59.4	-21.8
E	Drug-induced metabolic disorders	857	824	821	954	1014	1125	1184	1218	1316	1561	82.1	38.8
F	Mental and behavioural disorders due to drugs	5937	5466	5517	5703	5905	6044	5989	5603	5399	5533	-6.8	-8.5
G	Drug-induced neuromuscular disorders	889	873	864	812	933	1042	1188	1266	1304	1578	77.5	51.4
H	Drug-induced cataract and hearing loss	27	12	10	10	21	28	31	40	22	42	55.6	50.0
I	Cardiovascular consequences due to drugs	1238	1387	1438	1483	1776	2076	2374	2492	2996	3399	174.6	63.7
J	Drug-induced lung disorders	64	48	53	88	80	103	101	123	110	157	145.3	52.4
K	Toxic liver disease	438	446	438	487	549	493	578	530	533	614	40.2	24.5
L	Dermatitis due to drugs	1870	1829	1866	1935	2183	2392	2719	2713	2842	3213	71.8	34.3
M	Drug-induced immune disorders	1946	2222	3307	2338	2298	2329	2361	2380	2497	2564	31.8	10.1
N	Nephropathy due to drugs	109	134	163	149	183	208	207	202	298	303	178.0	45.7
T	Complications following injection, immunization or anaesthesia	2956	2930	2614	2608	3322	3593	3589	3357	3289	3343	13.1	-7.0
Total		16,486	16,309	17,236	16,729	18,407	19,749	20,580	20,102	20,800	22,554	36.8	14.2

Table 3
Annual number of emergency admissions with an 'external code' for an ADR

ICD-10 codes	Description	1999-2000	2000-2001	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009 (%)	Change 2008	Change 2009 (%)	Change 2004-2008
Y40	Systemic antibiotics	3364	3510	3439	3719	4446	5065	5738	5976	6297	6996	108.0	108.0	38.1
Y41	Other systemic anti-infectives and antiparasitics	635	712	676	757	843	967	1064	1205	1241	1364	114.8	114.8	41.1
Y42	Hormones and their synthetic substitutes and antagonists	2089	2154	2064	2371	2632	2785	3041	2101	3496	4352	108.3	108.3	56.3
Y43	Primarily systemic agents	5143	5268	6162	6663	6892	7332	8447	9789	11,175	12,667	146.2	146.2	72.8
Y44	Agents primarily affecting blood constituents	2939	2973	3083	3363	4003	2904	2993	2992	3055	3171	7.9	7.9	9.2
Y45	Analgesics, antipyretics and anti-inflammatory drugs	4364	4385	4302	4788	5328	6078	7054	7375	7857	8747	100.4	100.4	43.9
Y46	Antiepileptics and anti-Parkinsonism drugs	962	927	1004	1025	1106	1222	1296	1316	1354	1492	55.1	55.1	22.1
Y47	Sedatives, hypnotics and anti-anxiety drugs	293	352	346	356	450	462	519	561	598	624	113.0	113.0	35.1
Y48	Anaesthetics and therapeutic gases	185	194	151	167	208	206	265	248	289	350	89.2	89.2	69.9
Y49	Psychotropic drugs, not elsewhere classified	1373	1563	1485	1469	1798	1935	1962	2133	2256	2422	76.4	76.4	25.2
Y50	Central nervous system stimulants, not elsewhere classified	52	64	56	58	63	71	111	68	83	88	69.2	69.2	23.9
Y51	Drugs primarily affecting the autonomic nervous system	1698	1834	1981	2135	2559	2866	3164	3178	3331	3591	111.5	111.5	25.3
Y52	Agents primarily affecting the cardiovascular system	3587	4040	4164	4524	5147	5949	6588	7100	7723	8518	137.5	137.5	43.2
Y53	Agents primarily affecting the gastrointestinal system	302	338	293	321	411	457	579	584	670	854	182.8	182.8	86.9
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	2081	2258	2613	3115	3833	4316	4946	5109	5115	5789	178.2	178.2	34.1
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	292	308	270	272	329	352	383	405	416	485	66.1	66.1	37.8
Y56	Topical agent primarily affecting skin/mucous membranes and ophth/ot-rh-lary/dental drugs	784	639	719	705	743	808	864	909	873	1020	30.1	30.1	26.2
Y57	Other and unspecified drugs and medicaments	1297	1280	1346	1368	1448	1738	2115	2329	2543	2892	123.0	123.0	66.4
Y58	Bacterial vaccines	297	218	160	172	311	250	172	178	163	153	-48.5	-48.5	-38.8
Y59	Other and unspecified vaccines and biological substance	329	266	222	217	340	359	380	331	336	412	25.2	25.2	14.8
Total		32,069	33,283	34,536	37,565	42,890	46,122	51,681	53,887	58,871	65,987	105.8	105.8	43.1

Table 4
Number of HES emergency admissions with a primary diagnosis for an ADR in 2008–09: median age of admissions, old age and gender distribution of admissions, total bed-days and mortality

ICD-10 chapters	Description	Total (%)	Men (%)	Median age	Age 65+(%)	Total bed-days	In-hospital mortality rate
D	Drug-induced anaemia	1.1	44.1	68	57.1	2898	7.7
E	Drug-induced metabolic disorders	6.9	44.8	72	62.5	19,078	6.2
F	Mental and behavioural disorders due to drugs	24.5	68.9	33	3.5	94,579	1.0
G	Drug-induced neuromuscular disorders	7.0	44.4	70	60.7	32,389	6.7
H	Drug-induced cataract and hearing loss	0.2	42.9	52	28.6	454	4.8
I	Cardiovascular consequences due to drugs	15.1	46.5	78	80.5	36,430	3.8
J	Drug-induced lung disorders	0.7	55.4	73	68.2	2130	17.2
K	Toxic liver disease	2.7	42.7	43	24.4	10,430	11.4
L	Dermatitis due to drugs	14.2	41.2	60	41.9	42,801	4.2
M	Drug-induced immune disorders	11.4	56.4	69	60.9	31,518	12.5
N	Nephropathy due to drugs	1.3	58.1	66	55.8	4632	9.6
T	Complications following infection, immunization or anaesthesia	14.8	40.9	57	30.2	26,717	2.9
Total	22,554	100.0	51.4	59	41.5	302,574	4.8

Table 5
Annual number of emergency admissions with an 'external code' for an ADR in 2008–09: median age of admissions, old age and gender distribution of admissions, total bed-days and mortality

ICD-10 codes	Description	Total (%)	Men (%)	Median age	Age 65+ (%)	Total bed-days	In-hospital mortality rate
Y40	Systemic antibiotics	10.6	40.5	64	47.4	82,684	4.3
Y41	Other systemic anti-infectives and antiparasitics	2.1	30.6	64	49.1	15,620	2.8
Y42	Hormones and their synthetic substitutes and antagonists	6.6	44.5	67	54.6	53,065	6.9
Y43	Primarily systemic agents	19.2	42.5	61	38.2	112,667	5.4
Y44	Agents primarily affecting blood constituents	4.8	46.2	76	75.9	45,865	9.4
Y45	Analgesics, antipyretics and anti-inflammatory drugs	13.3	44.0	69	57.1	93,656	4.4
Y46	Antiepileptics and anti-Parkinsonism drugs	2.3	48.0	64	49.2	22,488	2.1
Y47	Sedatives, hypnotics and anti-anxiety drugs	0.9	44.6	66	49.7	8875	4.5
Y48	Anaesthetics and therapeutic gases	0.5	44.9	44	27.7	2861	2.9
Y49	Psychotropic drugs, not elsewhere classified	3.7	38.1	72	61.6	36,767	3.5
Y50	Central nervous system stimulants, not elsewhere classified	0.1	53.4	49	35.7	822	3.4
Y51	Drugs primarily affecting the autonomic nervous system	5.4	49.6	78	81.8	27,746	1.8
Y52	Agents primarily affecting the cardiovascular system	12.9	53.1	78	81.3	80,570	3.3
Y53	Agents primarily affecting the gastrointestinal system	1.3	37.2	75	62.2	8790	3.9
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism	8.8	35.6	80	86.8	71,974	5.4
Y55	Agents primarily act smooth and skeletal muscle and respiratory system	0.7	34.6	51	30.9	3282	3.3
Y56	Topical agent primarily affecting skin/mucous membranes and oph/ot-rh-lary/dental drugs	1.5	41.7	58	39.6	8061	3.8
Y57	Other and unspecified drugs and medicaments	4.4	43.3	69	55.6	33,866	4.5
Y58	Bacterial vaccines	0.2	54.9	<1	7.2	623	0.0
Y59	Other and unspecified vaccines and biological substance	0.6	47.1	57	17.0	2070	1.5
Total	65,987	100	42.9	70	58.5	680,833	4.6

infants (median age <1), and younger patients tended to have ADRs from anaesthetics and therapeutic gases (Y48, median age 44) or CNS stimulants (Y50, median age 49). Older patients (>65 yrs) tended to have ADRs due to water-balance drugs (Y54, median age 80), drugs affecting the autonomic nervous system (Y51, median age 78) or the cardiovascular system (Y52, median age 78). Agents primarily affecting water-balance and mineral and uric acid metabolism (Y54) included mineralocorticoids, diuretics, agents affecting calcification or uric acid metabolism, and mineral salts.

Younger people tended to manifest ADRs as mental and behavioural disorders (median age 33) or toxic liver disease (median age 43). By contrast, those aged >65 yrs tended to have a clinical picture of cardiovascular consequences (median age 78), lung disorders (median age 73) or metabolic disorders (median age 72) (Table 4).

Gender distribution for year 2008–2009

There was little gender difference in admissions with a primary code of ADR (51.4% men) (Table 4). However, female patients predominate in admissions with an external cause code of ADR (42.9% men) (Table 5). Men were more likely to suffer from mental and behavioural disorders (68.9% men) and women were more likely to suffer from complications following injection, immunization or anaesthesia (40.9% men) (Table 4). Women appear more likely to be affected by ADRs due to systemic anti-infectives and antiparasitics (Y41, 30.6% men), agents primarily acting on smooth and skeletal muscle and respiratory system (Y55, 34.6% men) or water-balance agents (Y54, 35.6% men) (Table 5).

Socioeconomic status and ADR

We analysed ADR rate per 1000 admissions by population-weighted quintiles based on the Carstairs deprivation index allocated via the postcode to a small geographical area ('output area'). However, there was no simple socioeconomic gradient in ADR rates per 1000 admissions, which were 9.9, 10.7, 10.4, 9.9 and 9.1 from quintile 1 (least deprived) through quintile 5 (most deprived).

Individual performance of NHS acute hospital trusts

We analysed the relationship between total emergency admissions and the percentage of ADR-related admissions for NHS acute hospital trusts, as shown in Figure 1. There were two trusts with unusually high rates: one with the proportion of 12% (3393 admissions) and the other with 34% (1134 admissions). Both of them were not included in the funnel plot. However, there was still wide variation in ADR-related admission percentages between individual NHS trusts, with many rates lying outside the control limits despite excluding these two trusts.

Discussion

Characteristics of this study

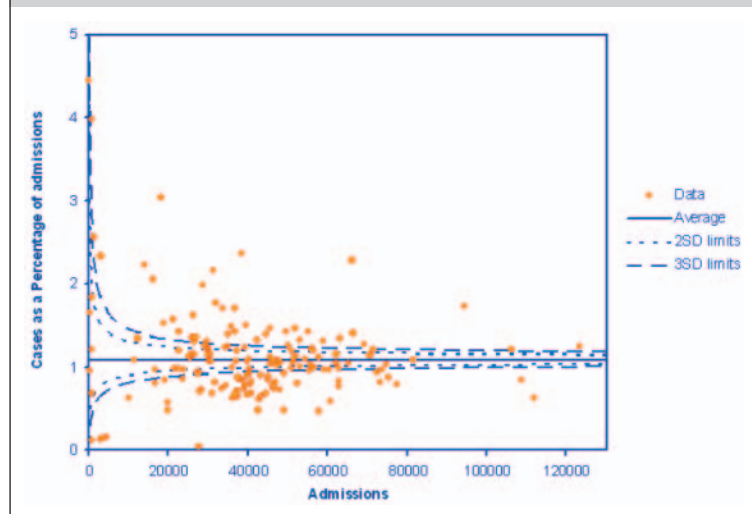
This study on hospital admissions for adverse drug reactions is unique in several aspects. The strengths of this study included its comprehensiveness in covering all NHS hospital admissions in England and its time trends.

Building on previous work using HES,^{4,16} we have tried to be systematic in capturing all ADR-related ICD-10 codes. We had access to mortality data associated with hospital admissions, which gave us a further insight into the severity of ADR-related admissions and we accessed patient-level rather than aggregate data. A prior study conducted by Pirmohamed and colleagues analysed admissions due to ADRs in two North-West English hospitals.³ However, their sample size (18,820 admissions) was substantially less than in this nationwide survey.

Limitations of this study

The main limitation of our study is that Hospital Episode Statistics data have the weaknesses associated with all routinely collected data; namely missing, incomplete or inaccurate data. Differences in coding practice between hospitals or populations covered make comparisons at hospital level difficult and will be one key explanation of the variation seen in Figure 1. We were also unable to rule out changes in coding as a result of behavioural or policy change as an explanation for our findings. If such variation occurs between hospitals, it is also

Figure 1
Funnel plot of the relationship between the total emergency admissions and the cases of ADRs as percentage of total emergency admissions for NHS acute hospital trusts



likely within hospitals over time, which is a possible explanation for some of the trends observed. Nevertheless, HES represents one of several important resources for monitoring ADRs because of its size, national coverage and relatively standardized recording regulations.

We do not have data on the pre-hospital utilization of drugs (or over-the-counter drug usage), nor do we have details on the number of drugs prescribed or taken by patients before admission. There is no indication on the HES record whether the recorded ADRs were present on admission, or occurred during a patient's stay in hospital. If given as a primary diagnosis, in the first episode of care, then it is perhaps more likely that the ADR occurred prior to admission, and if given as a secondary diagnosis, then perhaps more likely to have occurred in hospital. However, this interpretation is limited, as there will be some considerable blurring between these two scenarios.

We do not have data from general practice or outpatient visits, and we are unable to link ADRs to consultations.¹² Minor ADRs which might affect the patient's quality of life but not to the extent of hospital admission were not covered by our study. We were also unable to obtain data regarding risk benefit calculations of ADRs. Hence, given the limitations of our data, we must interpret the results with caution.

Overall trends

Our study showed that the number of admissions due to ADRs has increased significantly over the time period examined. The reported increase of ADR admissions by 76.8% may be due to improved record keeping and increased public awareness. Population ageing also added to this trend,¹⁷ since ADRs are most frequently encountered in older people with multiple long-term conditions.

In this study, we included immunization as part of our analysis. Complications following injection, immunization or anaesthesia accounted for 31,601 admissions in the study decade, 26,717 bed days in year 2008–2009, and an in-hospital mortality rate of 2.9%. Most of the admissions occurred in infants.

The majority of the increase in ADR admissions was due to increases in admissions with an ADR-related external code (105.8% change in the study period). These are most likely to have developed as a result of treatments in hospital, in contrast to admissions with a primary diagnosis of ADR, which may be due to drugs prescribed in the community or from a previous hospital admission.

Comparison with other studies

Pirmohamed *et al.* estimated that in England, ADRs were responsible for 6.5% of all emergency hospital admissions in adults and at least 5000 deaths per year.³ However, this study excluded some categories of patients. Howard *et al.* suggested that the percentage of preventable drug-related admissions to hospitals was 3.7%.^{18,19} In our study, ADR admissions accounted for only 0.8–1.1% of all annual admissions for 1999–2008, and the in-hospital mortality for ADR admissions for 2008–2009 was 3534, which was substantially less than suggested in previous literature. There are two possible explanations for this inconsistency. First, this may suggest a suboptimal recording of ADRs in the HES database because of under-recognition and under-reporting of ADRs in routine hospital activity data.¹⁶ Conversely, our study is based on a comprehensive nationwide data-set, which might also be more close to the reality than previous extrapolations from smaller scale studies.

Contradictory to some prior expectations,⁴ the introduction of the Quality and Outcome Framework

(QOF) on 1 April 2004 in England did not seem to aggravate the burden of ADRs. Instead, the in-hospital mortality in ADR admissions stabilized at 4.7% from 2004 onwards. Drug-induced anaemia and complications following injection, immunization or anaesthesia increased for the years 1999–2004, culminated in year 2004–2005, and then decreased thereafter.

There is an association between increasing age and ADR risk,²⁰ and elderly people are more susceptible to ADRs. Previous studies suggested that diuretics and antiplatelets are often used in elderly patients and accounted for 5.3% and 4.0%, respectively, of all primary care prescriptions in England.¹⁸ This study also showed similar findings, in which agents primarily affecting water-balance (Y54) and cardiovascular system (Y52) are the most implicated categories in ADRs in older people.

Pirmohamed *et al.* reported that 59% of the patients admitted with an ADR were female.³ Our study also showed that 57% of hospital admissions with a secondary code of ADR are female. The pharmacokinetics and pharmacodynamics of drug metabolism differ between the two sexes and are influenced by gender-specific factors such as body build, hormonal transitions, or medical-seeking behaviour.²¹ We cannot tell from this study if these differences are due to true discrepancies in ADR occurrence rates or are consequences of gender differences in prescription, consultation and usage patterns.

As to the drug types most implicated in ADR, our study showed that systemic agents are responsible for one-fifth of total ADR admissions in year 2008–2009, followed by analgesics and cardiovascular drugs. Systemic agents are also the third fastest growing agent in ADR-related admissions during the study period. These findings are similar to previous works by Waller *et al.*,¹⁶ but other studies also showed that low-dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs were the most commonly implicated drugs in ADR.^{3,8,18} Our results differed from this, and this can be explained by the different classification system of the drugs we used. We examined ICD-10 external cause codes to infer to the drug class, instead of individual generic name drugs. Broad groupings of drugs are used in this study, as exemplified by the systemic agent category, which includes antineoplastic drugs, immunosuppressive agents, enzymes, anti-allergic and anti-emetic drugs.

Conclusions

The advent of modern medicine has brought hope to many people with previously untreatable diseases, such as the use of penicillin to treat syphilis, or combination therapy to treat HIV infection. Nevertheless, ADRs are unwanted events following drug prescription and should be considered as part of a risk-benefit approach when prescribing medicines, particularly in vulnerable groups. Although ADRs continue to be a major public health problem resulting in a considerable use of NHS hospital resources and a significant number of deaths, their impact is often overlooked. Hospital admissions showed an apparent rise in relation to ADRs; however, this may be a consequence of improved recording.

There are several initiatives exploring susceptibility to ADRs through international collaborations (such as FP7-funded EU-ADR, The Serious Adverse Event Consortium, among others). Spontaneous reporting is important in identifying previously undetected ADRs, mostly type-B reactions, to allow appropriate drug regulatory action to be taken but frequently is unable to detect rare events until after years of patient use, with less than 10% reported.² It is also a passive reporting policy and would benefit from being linked to other databases. More active drug surveillance schemes might be a potential strategy to address the high mortality associated with ADR admissions (4.7% in this study).

Other current strategies to improve drug safety include stringent safety testing; nationwide implementation of updated prescribing software to reduce prescribing errors;^{22,23} medicines reconciliation on admission and discharge from hospital to minimize polypharmacy;²⁴ financial incentives for clinicians to report ADRs to address under-recording; and funding for research to decipher the complex multifactorial pathogenesis of idiosyncratic ADRs.²⁵

Because of the wide range of medications available, ADRs vary in manifestations and organ system. Heightened awareness of pharmacovigilance by clinicians in diagnosing ADRs is crucial for continued drug safety monitoring. Over 70% of adverse drug reactions were possibly avoidable³ and preventable through simple improvements in prescribing, e.g. increased awareness of warning prompts of possible drug interactions and high-risk patient groups, prescribing a drug at the lowest dose necessary to achieve the therapeutic target.

Developed countries worldwide tend to have progressively older populations. In the UK, the number of people age 65 years and over is estimated to increase by 53% between 2001 and 2031.¹⁷ This increase will result in a rise in the number of people at higher risk of suffering from ADRs, which are more likely to be severe in this group.²⁶ In our study, we also noticed that most ADR increases occur in those over the age of 65.

In this study, systemic agents were the most implicated and the third fastest growing agent in ADR-related admissions. This is also correlated with the rapid ageing of the English population, since systemic anti-cancer therapy (SACT) is targeted at malignancies whose risk increases with age. According to NCEPOD report 2008,²⁷ 43% of cancer cases suffered from clinically significant treatment-related toxicities.

Our data suggest that the number of ADR admissions may have increased at a greater rate than the increase in total hospital admissions, but it is unclear whether this could also be due to increased recording. Also, the percentage of ADR-related admissions varied considerably between individual NHS trusts. This study should prompt policy-makers toward implementing further measures to reduce ADR incidence and their associated in-hospital mortality; and to make greater use of routinely collect NHS data, such as Hospital Episode Statistics, to monitor the epidemiology of ADRs and identify potentially avoidable aetiological factors, and to improve the completeness, accuracy and standardization of coding across hospitals.

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