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Analysis of Adverse Events Reports Submitted to the Food and Drugs Administration of the United States of America (2007-2012)

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Many nations collect data on adverse events (AEs) associated with the use of drugs using what is generally referred to as the Spontaneous Reporting System (SRS) [1,2,3]. Analysis of such data is important in discovering hitherto unknown problems associated with drug use and in understanding the features of the variables related to the problem of adverse drug reactions (ADRs) [4,5,6]. The SRS of the Food and Drugs Administration (FDA) of the United States of America (US), known as the FDA Adverse Event Reporting System (FAERS) [3], is probably the largest system for collecting data on AEs associated with drug use.
Objectives: (i) Find any trends in the variables associated with the problem of adverse events in drug use, (ii) Elucidate some of the issues raised in the literature by way of the evidence provided by the data, (iii) Find the drugs that were most cited as principal suspect in adverse events and (iv) Examine the data for any other notable attributes.
Methods: Quarterly Extracts from the FAERS database covering the period 2007 to 2012, which is publicly available on the website of the Food and Drugs Administration (FDA, US), were analysed. Out of the over fifty (50) variables contained in the extracts, fourteen (14) of them, which were thought to be relevant to the objectives of the study, were examined. Owing to the nature of the data, the tools of frequencies, proportions and averages were used in the analysis of it.

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Results: The results of the analysis revealed that for the period 2007 – 2012, the reported cases of adverse events almost tripled (2.7 times), with annual growth rate of 22.1%. Reports on female subjects dominated throughout the period, accounting for a little over two-thirds of the reported cases annually and in the overall number of reports for the period. The proportion of cases that resulted in death appeared to be increasing over time. Non-health professionals are almost as likely as health professionals to report adverse events. Expedited reports (concerning events that are unexpected, from the perspective of the known pharmacology of the suspect drug(s)) accounted for the highest number of cases throughout the period. A large proportion of the cases were reported electronically with an indication of increasing trend over the period under review and in the years following. The age group most involved in adverse events associated with drug use is 45 – 64, followed by the age groups 65 and over, 45 – 59, 18 – 44 and 0 – 17 in descending order of involvement when looked at from the point of view of number of reported cases. However the results of the analysis show that susceptibility to adverse events increases with age; the older one gets the more vulnerable one becomes to adverse events involving drug use. The analysis also revealed that some of the problems that prevent the best use of SRS data, such as missing values for age and sex, mentioned in the literature, existed during the period under consideration [7,8,9].

Conclusion: It is essential to encourage reporting of adverse events, especially accurate and prompt reporting. This is indispensable in dealing with the problem of adverse events in medication use comprehensively; as it not easy to obtain data on the variables involved with the problem through other means and SRS data provide useful insights, especially when keying out factors that contribute to the occurrence of adverse events associated with drug use.

Keywords: Drugs; Adverse Event (AE); Adverse Drug Reaction (ADR); Spontaneous Reporting System (SRS).

1. INTRODUCTION

It is common knowledge that drug use come with some potential dangers, especially if not used according to the recommended dose regimen. Many countries have therefore setup systems to track harmful events (adverse events (AEs)) and other irregularities that occur during the use of medications. One of such system is the FDA Adverse Event Reporting System (FAERS, previously known as the AERS) of the Food and Drugs Administration (FDA) of the United States of America (US) [3]. Among other things, the FAERS helps the FDA of US to determine whether an AE that occurred during the use of a medication is really an adverse reaction occasioned by the use of the drug. This is particularly helpful in circumstances where the adverse reaction is hitherto unknown, as it gives the FDA (US) (and for that matter other drug regulatory agencies) the opportunity to address the problem as early as possible to eliminate or curtail further harm to consumers of such medication. This paper will not go into what spontaneous reporting systems or the associated broader field of pharmacovigilance are about; there are several papers that can serve as teasers in this regard [1,2,3,10,11,12]. In this article, we present the results of a study into FAERS data covering the period from 2007 to 2012. The objectives of the study were to (i) find any trends in the variables associated with the problem of adverse events in drug use, (ii) elucidate some of the issues raised in the literature by way of the evidence provided by the data (iii) find some of the drugs that were most cited as principal suspect in adverse events, and (iv) examine the data for any other notable attributes.

2. METHODS

2.1 Data: Nature and Processing

The data which is the subject of this study were obtained from the website of the FDA (US), which publishes anonymised quarterly extracts of data on adverse events from the FAERS database [7]. This study concerns quarterly extracts covering the period from 2007 to 2012, which were downloaded between October 1, 2018 and December 31, 2018. Each quarterly extract is made up of seven ASCII (American Standard Code for Information Exchange) data files together with their metadata – which further explains the attributes of the seven data files and the variables they hold. The seven data files are Demographic, Drugs, Reaction, Outcome, Report Source, Therapy and Indication [7]. There are altogether over fifty (50) variables (including link

or key variables) in the seven data files. However only fourteen (14) of these variables thought to be concerned with the objectives of the study were examined.

It is possible to have multiple records of the same adverse event episode in the data. This was particularly prominent up to the third quarter of 2012. The FDA (US) reorganised the collection process of adverse event data, transitioning from an old adverse event reporting system (now known as the Legacy Adverse Event Reporting System, LAERS) which was Individual-Safety-Report (ISR)-based to a new adverse event reporting system (known as the FDA Adverse Event Reporting System, FAERS) which is Case/Version-based [7], making the new system less prone to the existence of duplicate reports of the same adverse event episode. All duplicate records were removed, leaving only the latest versions of the adverse event cases, which have the most up-to-date information about the cases [7].

To make the data as homogeneous as possible, records of adverse events occurring outside the US were excluded. By the same token records of events reported in studies of sponsors or in the literature were removed. Moore et al. [13] note that records from such sources bring in additional variation as they may not be aptly described as 'spontaneous'.

Some of the variables can assume more than one value per subject. One is therefore compelled to dichotomise such variables under certain circumstances when analysing these variables. For instance the outcome of an adverse event (Outcome) for a given case may be Disability, Life-threatening and Hospitalization. Thus Outcome for this case has three values. One is therefore forced to look upon Outcome as Death and all other outcomes or Life-threatening and all other outcomes et cetera as the situation may require. The sum of the percentages corresponding to these 'responses' is expected to be more than 100% as the values Outcome can assume are not mutually exclusive.

Reports of adverse events come in three forms: direct, expedited and periodic. Direct reports are those that are sent to the FDA without recourse to the manufacturer (sponsor). Expedited reports concern reports from sponsors on adverse events that are unexpected or not described in the product information – the event has "not been previously observed" [14] per the indications for the use of the drug as documented in the product information. Sponsors are obliged by law to report such events to the FDA within 15 days. Periodic reports are done on quarterly basis; they concern serious events that are recognised as bona fide reactions to the medication(s) in question and are captured in the product information [14].

One could report the age of a subject of an adverse event in hours, days, weeks, months, years or decades and there is evidence that some ages were expressed in seconds [7]. Ages expressed in units other than years were converted to years to ensure a single unit of measurement for age, and was then recoded into four groups as 0-17, 18-44, 45-64 and 65 and over. Grouping age this way allows one to assess how the non-active segment of the population compares with the active segment.

The sex of a subject is required to be specified as F for female and M for male. In situations where the sex is not specified or unknown (or cannot be determined) – such as in the case of a fetus – the codes NS and UNK are used respectively [7]. Sex values other than F and M were recoded as missing for the purposes of this study.

Indeed a frequency display of the various variables revealed some anomalies in the coding at the data entry stage. Variables with such anomalies in the coding where recoded as appropriate or as missing as the situation may require.

The data which is the subjects of the study reported herein is secondary. One can, therefore, not understand the data to the same degree as the compilers of the data. As noted in the literature on SRS [4,7,8,9], SRS data are associated with some challenges, of which missing values is perhaps the most notable. Some of the variables have missing values for a considerable number of the cases. One is nevertheless compelled to assess the situation of the problems associated with the use of drugs using this data as the data come with unique information that are hard to obtain otherwise; at any rate such information helps deepen our understanding of the problems associated with drug use and their reporting [15].

2.2 Tools

The analysis of the data was done using the tools of frequencies, proportions and averages.

The averages of the numerical variables were found using the geometric mean owing to its ability to rein in the effect of extreme values. The SAS software [16], the R statistical software [17] and the MS Excel [18] were used to analyse the data. The SAS software was helpful in addressing database and data processing concerns while the R software was mainly used to produce the graphics. The MS Excel was used to compute the averages of the variables. The organisation of the data described herein is such that it is almost impossible to analyse it without any knowledge of a data base management software such as MS Access or a software with SQL capability such as SAS.

3. RESULTS OF ANALYSIS AND DISCUSSION

3.1 Results

3.1.1 Trend in the number of reports over time

A total of 2,483,936 adverse event cases remained after removing cases coming from outside of the US or occurring in the literature or in studies, for the period 2007 to 2012 (Table 1). Number of cases received annually almost tripled (2.7 times) from 241,640 in 2007 to 655,568 in 2012, accounting for an average increase of 22.1 percent annually.

Figure 1 shows the trend in the number of cases reported per million people per year. The trend presented by the figure and the average annual increase in the number of cases indicate that the number of adverse events reported annually to the FDA (US) is growing at a rate faster than the annual growth rate of the US population. This could be due to increasing incidence of adverse events or increasing awareness amongst the populace of the importance of reporting adverse events.

3.1.2 Patient outcomes

As much as 959,934 (38.6%) of the total of 2,483,936 (Table 2a) cases that remained, after taking out cases coming from outside of the US or occurring in the literature or in studies, had missing patient outcome values for the period under consideration. The remainder of 1,524,002 (61.4%) cases has the following breakdown: Deaths 258,449 (17%), Life-threatening 82,457 (5.4%), Hospitalisation - initial or prolonged stay 614,662 (40.3%), Disability 66,418 (4.4%), Congenital Anomaly 12,835 (0.8%), Required Intervention to Prevent Permanent Impairment/Damage 26,339 (1.7%) and Other Outcomes 828,353 (54.4%) (Table 2b). The sum of the percentages exceed 100 owing to that fact that these outcomes are not mutually exclusive; a subject can experience more than one of these outcomes at the same time as alluded to early on. The proportion of cases of adverse events that resulted in an outcome of deaths in the US for the non-missing cases assumed a low value of 11.6% in 2007 and a high value of 20.2% in 2012 with the average for the period under consideration being 15.9% (Table 2c). The figures come to 7.6 (2007), 11.6 (2011) and 9.9% respectively when the denominator is changed to number of all cases (Table 2d), assuming none of the missing outcome values is death. Of course this assumption is hardly possible, and so is the assumption that all the missing outcomes are deaths, which would result in higher estimates than has been reported above. However, this manner of looking at the situation permits us to appreciate what conservative estimates look like [15].

The trend in the number of deaths (Table 1) suggest an increase over time. Figure 2a presents a comparison of the trends in the annual number of deaths, other outcomes and all non-missing cases. The figure suggest an

Table 1. Yearly and overall values for death, other outcomes and all reported adverse events

Year	Total (All events)	Number of deaths	Deaths %	Other outcomes %	Total (Excluding cases with missing death values)	Deaths %	Other outcomes %
2007	241,640	18,389	7.6	92.4	157,965	11.6	88.4
2008	285,622	25,988	9.1	90.9	180,287	14.4	85.6
2009	313,461	32,309	10.3	89.7	211,369	15.2	84.8
2010	458,212	48,319	10.5	89.5	275,275	17.5	82.5
2011	529,433	61,346	11.6	88.4	342,992	17.8	82.2
2012	655,568	72,098	11.0	89.0	356,114	20.2	79.8
Total	2,483,936	258,449	10.4	89.6	1,524,002	17.0	83.0

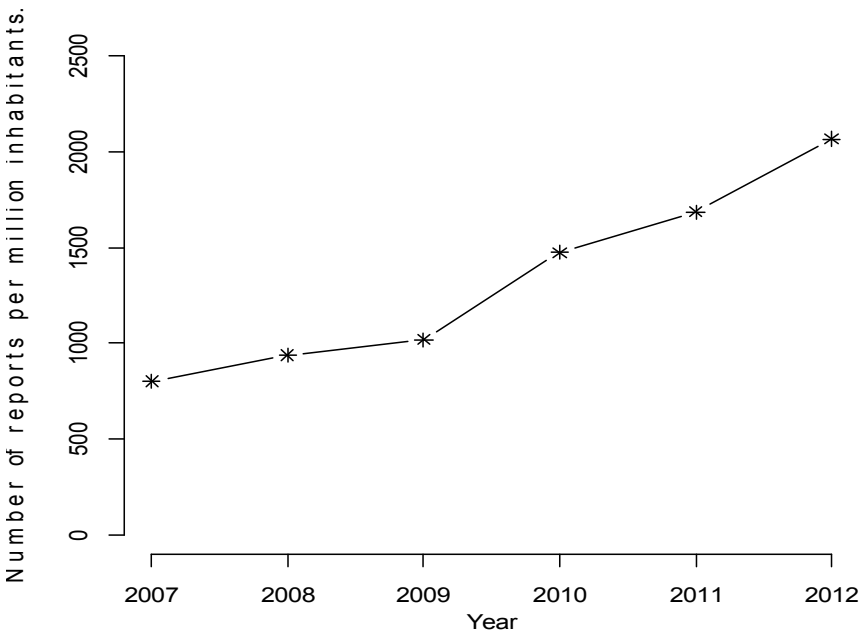

Fig. 1. Line chart showing the number of reports per million inhabitants against time, 2007 – 2012

Table 2a. Patient outcomes, 2007 – 2012

Cases					
Valid		Missing		Total	
Count	%	Count	%	Count	%
1,524,002	61.4	959,934	38.6	2,483,936	100

Table 2b. Patient outcomes, 2007 – 2012

Outcome	Cases	Percentage (%)
Death (DE)	258,449	17.0
Life-Threatening (LT)	82,457	5.4
Hospitalization - Initial or Prolonged stay (HO)	614,662	40.3
Disability (DS)	66,418	4.4
Congenital Anomaly (CA)	12,835	0.8
Required Intervention to Prevent Permanent Impairment/Damage (RI)	26,339	1.7
Other (OTH)	828,353	54.4

increasing trend in the annual number of deaths, other outcomes and all non-missing cases. Figure 2b shows a comparison of the trends in the annual number of deaths, other outcomes and all cases and Figure 3 shows the annual percentage deaths for all the cases and for non-missing cases. The pattern presented by Figure 2b parallels that of Figure 2a; suggesting an increasing trend in the annual number of deaths, other outcomes and all cases. Can the issue of missing values of Outcome affect the trend in the number of deaths over time? An attempt was made to answer this question by the use of Figure 2b and Figure 3.

The trend in the bars plotted with percentages determined from the number of all annual non-missing cases (mistyrose colour) compares with that in the bars plotted with percentages determined from the number of all annual cases (lightblue colour) except that of 2012 where there is a dip in the bar for the percentage determined from the number of all annual cases relative to that of 2011 (Figure 3). Thus the issue of missing values appear not to have had any serious effect on the proportion of deaths reported, overall.

As was indicated above the proportion of cases in which the subject was hospitalised (initial or resulting in prolongation of hospital stay) stood at

Table 2c. Percentages for patient outcomes calculated with number of non-missing cases as denominator, 2007-2012

	Patient outcomes						
Year	**DE**	**LT**	**HO**	**DS**	**CA**	**RI**	**OTH**
2007	11.6	6.3	41.0	4.8	0.6	2.3	56.8
2008	14.4	7.0	40.4	4.1	1.0	2.9	52.9
2009	15.2	6.3	41.1	4.0	0.7	2.8	52.9
2010	17.5	5.1	39.3	3.5	0.8	1.7	54.4
2011	17.8	4.7	41.2	5.1	0.7	1.1	55.8
2012	20.2	4.4	39.3	4.2	0.9	0.6	53.2
Average	15.9	5.6	40.4	4.3	0.8	1.7	54.3

Table 2d. Percentages for patient outcomes calculated with number of all cases as denominator, 2007- 2012

	Patient outcomes						
Year	**DE**	**LT**	**HO**	**DS**	**CA**	**RI**	**OTH**
2007	7.6	4.2	26.8	3.2	0.4	1.6	37.1
2008	9.1	4.4	25.5	2.6	0.7	1.9	33.4
2009	10.3	4.2	27.8	2.7	0.5	1.9	35.8
2010	10.5	3.1	23.6	2.2	0.5	1.0	32.7
2011	11.6	3.1	26.7	3.3	0.5	0.8	36.2
2012	11.0	2.4	21.4	2.3	0.5	0.4	28.9
Average	9.9	3.5	25.2	2.7	0.5	1.1	33.9

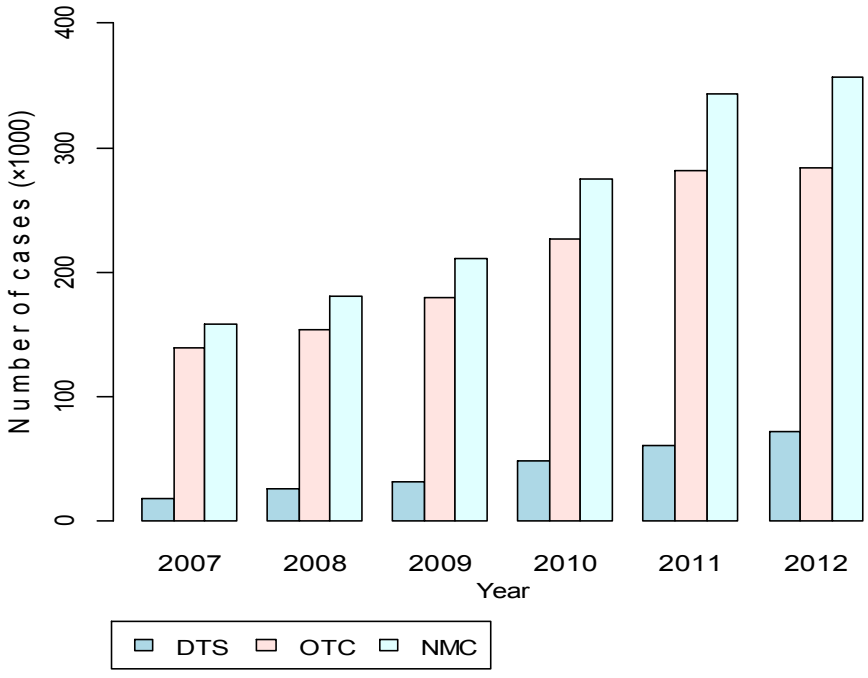

Fig. 2a. Multiple bar chart comparing the Trends in Deaths (DTS), Other Outcomes (OTC) and Non-missing Cases (NMC)

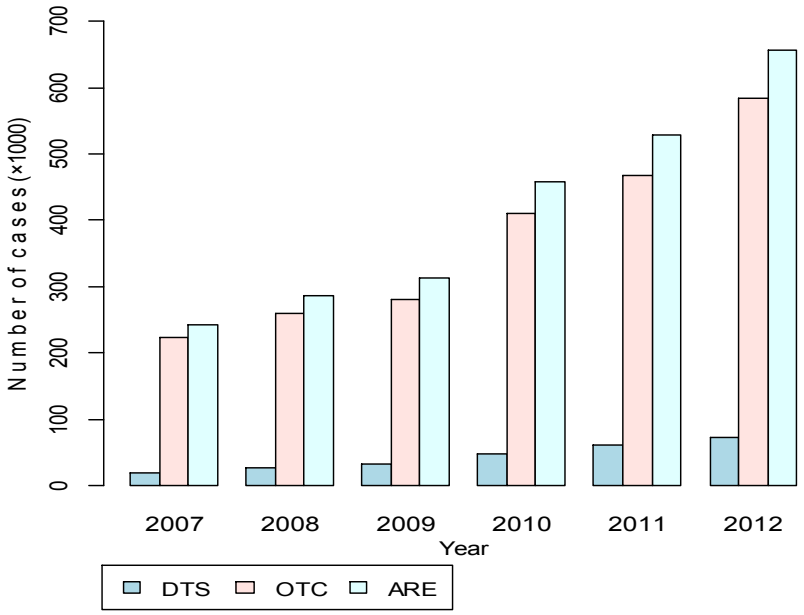

Fig. 2b. Multiple bar chart comparing the Trends in Deaths (DTS), Other Outcomes (OTC) and All Events (ARE)

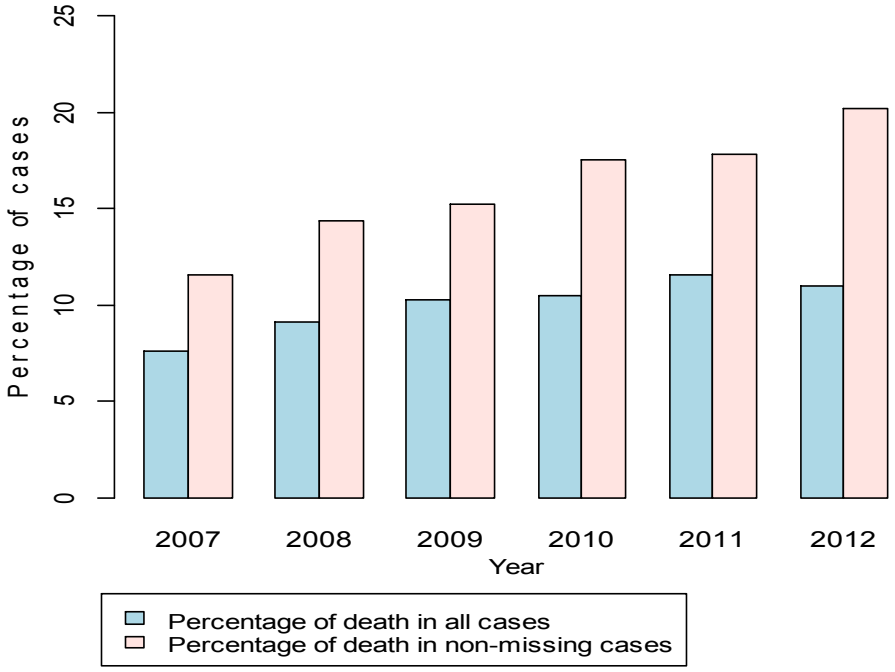

Fig. 3. Multiple bar chart comparing the trends in the percentage of deaths for all events and for the non-missing cases

40.3% (excluding missing cases) for the period under consideration. This relatively high figure is indicative of the likelihood of spontaneous reports involving serious adverse events. The maximum for the period is 41.2% (2011) and the minimum is 39.3% (2010, 2012) with 40.4% as the average for the period under consideration. The respective values when the number of all

cases is used as the denominator instead of number of non-missing cases, as was done for death, are 27.8 (2009), 21.4 (2012) and 25.2%. Tables 2c and 2d provide the values for other outcomes.

3.1.3 Occupation of reporters

Original reporters of cases of adverse events are required to specify their occupation whether or not the report was submitted directly. Of the total number of 2,483,936 cases that were examined for the period under consideration, 213,040 (8.6%) of them had the occupation of the reporter to be missing (Table 3a). The remaining cases were split almost evenly between health professionals (HP: Physicians, Pharmacists, Other Health-Professionals; 50.2%) and non-health professionals (NHP: Legal Representatives, Consumers; 49.8%) (Table 3b). An examination of the annual values shows moderate differences (of about 6% maximum) between number of reports submitted by health professionals and non-health professionals except in 2009 where the HP source contributed more than the NHP source by about 13% (Figure 4), with the NHP source dominating in three (2007, 2011, 2012) of the six years and the other three years (2008, 2009, 2010) going to the HP source.

3.1.4 Types of report

For the period under discussion, 174,725 (7.0%) of the reports were of the direct type, 1,299,712 (52.3%) were of the expedited type and 1,009,499 (40.6%) were periodic ones (Table 4). Apart from 2008 when there was an increase in the percentage of direct reports over that of 2007, percentage of direct reports have been declining, with expedited reports accounting for the highest number of reports annually, followed by reports of the periodic type. The percentage of expedited and periodic reports kept fluctuating (Figure 5) over the period under consideration.

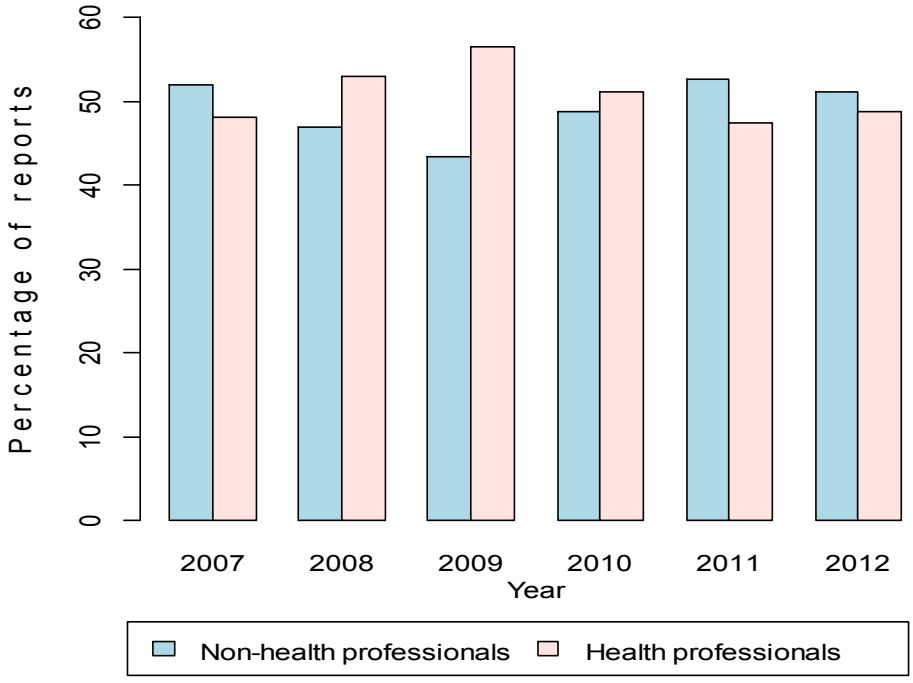

Fig. 4. Percentage of non-health professional and health professionals reports from 2007-2012

Table 3a. Occupation of original reporters, 2007 – 2012

Cases					
Valid		Missing		Total	
Count	%	Count	%	Count	%
2,270,896	91.4	213,040	8.6	2,483,936	100

Table 3b. Occupation of original reporters, 2007-2012

Occupation	Cases	Percentage (%)
Physician	601,585	26.5
Pharmacist	132,614	5.8
Other Health-Professionals	405,591	17.9
Lawyer	71,571	3.2
Consumer	1,059,535	46.7

Table 4. Report types, 2007 – 2012

Type of report	Cases	Percentage (%)
Direct	174,725	7.0
Expedited	1,299,712	52.3
Periodic	1,009,499	40.6

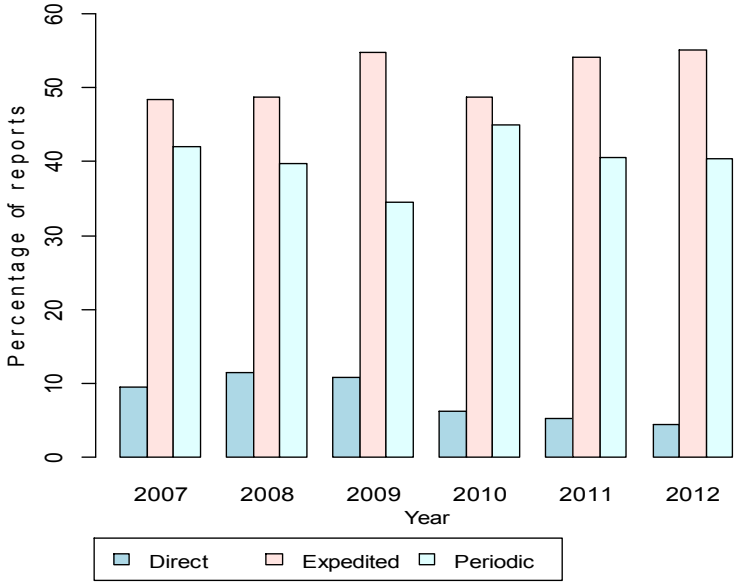

Fig. 5. Percentage of report types from 2007-2012

3.1.5 Mode of submission of reports

Only one report had the mode of submission to be missing (Table 5a). In all, 2,082,062 (83.8%) of the reports were submitted via the internet, with the remaining 401,873 (16.2%) in hard copy (Table 5b). The annual figures shows that submission via the internet is increasing over time while submission in hard copy is declining; the former rose from 66.39% in 2007 to 91.55% in 2012, an increase of 25.16 percentage points.

3.1.6 Sex of subjects

As shown in Table 6a, the sex of 219,240 (8.8%) of the subjects reported on for the period under consideration were unaccounted for – the sex was not specified or is missing. Of the 2,264,696 (91.2%) remaining cases, 852,820 (37.7%) were male and 1,411,876 (62.3%) were female. The higher number of female cases is in consonance with what was reported by Wysowski and Swartz [19], and exemplifies the annual sex structure of the cases reported on, with females subjects accounting for a little over three-fifth of the total number of reports annually (Figure 6).

3.1.7 Age of subjects

As much as 1,035,326 (41.8%) of the reports had the age of the subject to be missing (Table 7a). The remaining 1,448,610 cases have the following distribution: the groups 0 – 17, 18 – 44, 45 – 64 and 65 and over accounted for 81,107

(5.6%), 366,673 (25.3%), 562,735 (38.9%) and 438,095 (30.3%) of the cases respectively (Table 7b).

The age distribution structure of the annual non-missing cases was quite stable from year to year with minor shift in the proportion of the cases accounted for by each age group and have a comparable structure as the overall age distribution of the non-missing cases for the period under consideration; with the proportions of the various age groups occurring in descending order of magnitude as 45 – 64, 65 and over, 18 – 44 and 0 – 17 for all the years under consideration as depicted by Figure 7.

3.1.8 Age and sex load of adverse events

A cross classification of the number of cases reported, on the basis of age and sex, is presented in Table 8. The table also presents percentage values of the size of the age groups in the overall US population, an adjustment (expected) of the percentage sizes of the age groups in the overall US population for likelihood of drug use and the 'proportion' (*p*) of each of these age groups in the overall number of non-missing cases relative to the size of these age groups in the overall US population. The 'proportion' for a given age group for a particular year was found by first multiplying by 10,000 the quotient obtained by dividing the number of non-missing cases for the age group for that year by the number of people in the age group in the US population for that year. This yields the age group specific 'proportion' for that year. The geometric mean of the annual 'proportions' for a given age group gives the value of *p* for the age group for period under review [15].

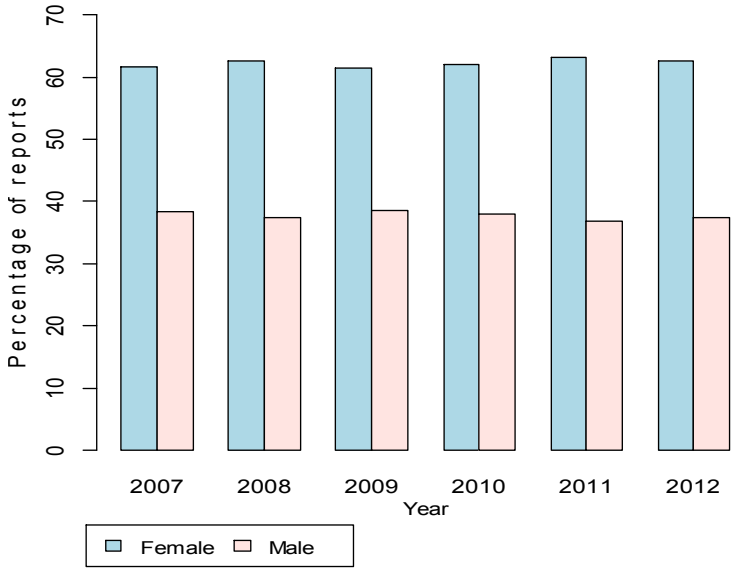

Fig. 6. Percentage of reports on male and female subjects from 2007-2012

Table 5a. Report submission mode, 2007 – 2012

Cases					
Valid		Missing		Total	
Count	%	Count	%	Count	%
2,483,936	100.0	1	0.0	2,483,936	100

Table 5b. Report submission mode, 2007 – 2012

Electronic submission	Cases	Percentage (%)
No	401,873	16.2
Yes	2,082,062	83.8

Table 6a. Sex of subjects, 2007 – 2012

Cases					
Valid		Missing		Total	
Count	%	Count	%	Count	%
2,264,696	91.2	219,240	8.8	2,483,936	100

Table 6b. Sex of subjects, 2007 - 2012

Sex	Cases	Percentage (%)
Female	1,411,876	62.3
Male	852,820	37.7

Table 7a. Age of subjects, 2007 – 2012

Cases					
Valid		Missing		Total	
Count	%	Count	%	Count	%
1,448,610	58.2	1,035,326	41.8	2,483,936	100

Table 7b. Age of subjects, 2007 – 2012

Age range	Cases	%
≤ 17	81,107	5.6
18 – 44	366,673	25.3
45 – 64	562,735	38.9
≥ 65	438,095	30.3

Table 8 shows that even though the number of female cases in the various age groups and in the overall number of non-missing cases is more than that of the males, the situation is the reverse for the age group 0 – 17; the male cases are more than the female cases. The percentage of the cases in the age range 0 – 44 (combining the groups 0 – 17 and 18 – 44) is less than that of the percentage of this age group in the overall US population, even when the latter percentage has been adjusted (expected cases) for potential drug use. For the age range 45 and over (combining the groups 45 – 64 and 65 and over) the reverse is the case for the above observation; percentage of the cases in the age group is more than that of the percentage of this age group in the overall US population even when the latter percentage has been adjusted (expected cases) for potential drug use.

The percentage of cases in the 'active' age group (combining the age groups 18 – 44 and 45 – 64) is slightly more than that of the overall US population (1.5 percentage point difference Figure 8) and almost on par with the corresponding value for the adjusted (expected cases, 0.5 difference). The above observed patterns are quite consistent with results obtained by Moore et al [13].

The value of the 'proportion' (p), increases with age (down Table 8). Figure 9 shows a graphical rendition of the pattern in the values of p over the period under review; the values of p for the various age groups appear to increase over time.

3.1.9 'Active ingredients' (Drugs) most cited as suspect in adverse events

Table 9 presents a list of the top twenty (20) 'active ingredients' (drugs), in descending order of frequency, most cited as suspect in causing adverse events for the period under consideration. In generating the above list, all medicinal forms (proprietary or brand products) that contain the same active ingredients (drugs) were recoded into the respective generic names.

3.2 Discussion

The results of the analysis show that the number of AE reports (excluding cases coming from outside of the US or occurring in the literature or in studies) submitted to the FDA (US) almost trebled (2.7 times) over the period under consideration with an annual growth rate of 22.1%. For a population which is growing at a rate 0.93% per annum (using 2000 and 2010 census figures) [22], the annual growth rate of

22.1 percent in the number of reports submitted is relatively fast. This suggest two possibilities: the number of adverse events is growing at an increasing rate or the populace is becoming more aware of the need to further the course of pharmacovigilance by reporting adverse events, when one considers the well-known phenomenon of under-reporting [11,23] of AEs or both. The trend in the number of reports per million people as depicted by Figure 1 reinforces the view that the number of reported cases will continue to rise in the foreseeable future.

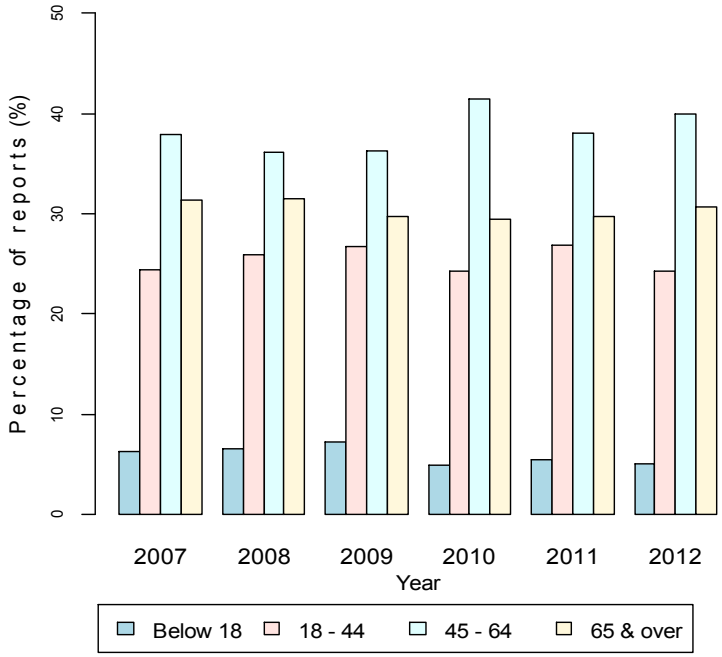

Fig. 7. Percentage of reports for the various age groups for the period 2007 - 2012

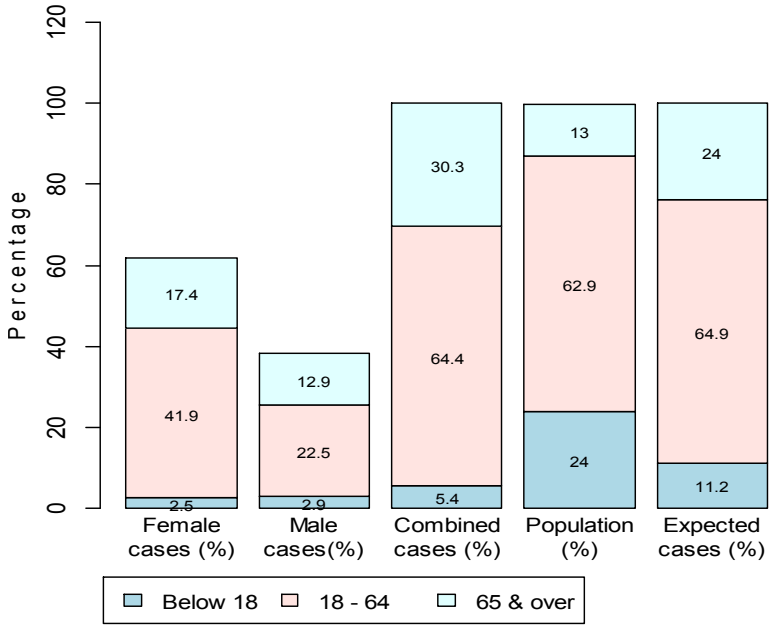

Fig. 8. Age and gender load of reported adverse events associated with drug use for the period 2007 - 2012

Table 8. Age and sex load of adverse events, 2007-2012

Age group	Female		Male		Total		US Pop'n Estimate [ς]	Exp'ed cases [ξ]	Prop'n*p*
	Cases	%	Cases	%	Cases	%	%	%	
≤ 17	35,894	2.5	40,730	2.9	915,890	5.4	24.0	11.2	1.7
18 – 44	252,540	17.7	109,216	7.7	361,215	25.4	36.5	28.3	4.8
45 – 64	344,801	24.2	211,732	14.8	555,746	39.0	26.4	36.6	10.1
≥ 65	248,214	17.4	184,103	12.9	431,845	30.3	13.0	24.0	16.3
Total	881,449	61.8	545,781	38.2	2,264,696	100.0	100.0	100.0	

[ς] Estimated from US population census values [20]. [ξ] Population adjusted for potential drug use based on the 2007-2010 and 2011-2014 data on prescription drug use [21]

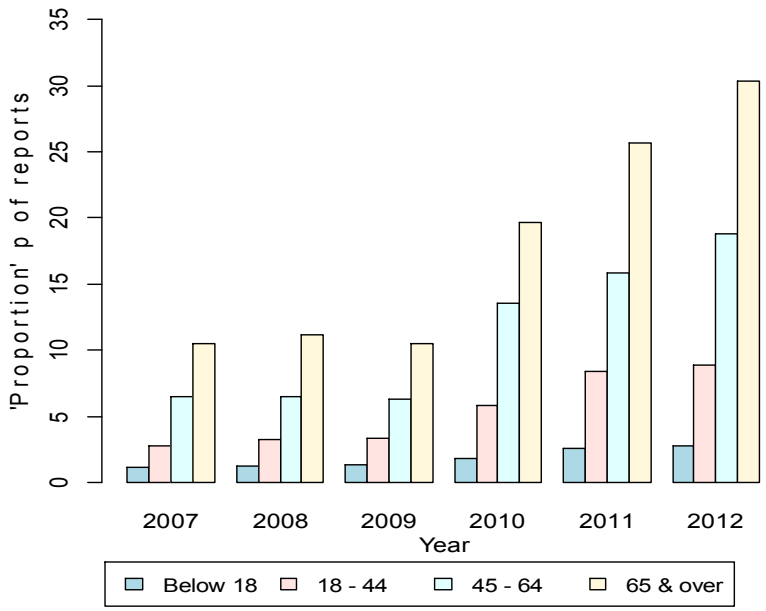

Fig. 9. The 'proportion' p of the various age groups reported on for the period 2007-2012

The number of cases with an outcome of death appear to be increasing over time as the overall number of reported cases increase over time (Figures 2a and 2b). However, the number of deaths appear to grow faster than the number of cases reported as Figure 3 shows a rise in the proportion of cases that result in death over time relative to both the overall number of reports and the non-missing cases, except for 2012 when there was dip in the proportion of deaths in the non-missing cases relative to that of 2011. What could account for the relatively higher increase in number of deaths compared to the increase in the number of cases reported? Are fatal adverse events becoming more prevalent? This calls for further investigation.

The results on Outcome (of the adverse events) suggest that, of the reported cases of adverse events for the period 2007 to 2012, at least 7.6% had an outcome of death and 21.4 resulted in hospitalization (including prolongation of hospital stay).

It could be inferred from the results that, on the whole, the level of awareness of non-health professionals on the need to contribute to pharmacovigilance by reporting cases of AEs compares favourably with that of health professionals as the percentage of reports coming from the two groups are almost on par and reports from non-professionals were in the majority in three of the years with the remaining three years dominated by reports from professionals.

By definition, expedited report concern adverse events that are unexpected or not described in the product information [14]. Their dominance, therefore, of the overall number of reports submitted for the period under consideration and the reports submitted annually points to the persistence of the problem of uncommon but serious adverse events, and makes the need to find unknown but bona fide adverse drug reactions and eliminate or reduce them all the more pressing.

The preponderance of electronically submitted reports echoes the increasing importance of the internet in information exchange in general and in pharmacovigilance in particular. Electronic submission holds a lot of promise owing to the advantage of speed, if reporting could be done accurately, as imprecise description of adverse events, drugs and other variables tends to hamper speedy and optimal use of this important source of information [15]. Cleaning spontaneous reports data for regulatory purposes is an arduous and time consuming task, even when experts are involved [24], so the best approach to having quality data is to encourage accurate reporting.

Table 9. Top twenty (20) active ingredients (drugs) most cited as suspect for causing adverse events, 2007-2012

Drug name	Rank
Etanercept	1
Adalimumab	2
Natalizumab	3
Levonorgestrel	4
Varenicline	5
Interferon Beta-1a	6
Infliximab	7
Quetiapine	8
Rosiglitazone	9
Niacin	10
Esomeprazole	11
Lenalidomide	12
Pregabalin	13
Exenatide	14
Dianeal	15
Zoledronic Acid	16
Naproxen	17
Tiotropium Bromide	18
Teriparatide	19
Dabigatran	20

According to the 2010 US census, males and females constitute 49.2% and 50.8% respectively of the US population [22], a ratio of roughly 1:1. What then could explain the finding that for reports of cases with known sex, the ratio of male to female is roughly 2:3 (37.7% male and 62.3% female, Table 7b). It is inconceivable that the phenomenon of missing sex values will affect males more than females. Are females predisposed to adverse events more than males? Perhaps this question is answered in part by the information that the female segment of the US population had a higher propensity for drug use than the male segment (at least one prescription drug use in the last 30 days: male 43.35%, female 53.85% [21] for the period under consideration). In spite of the fact that, overall, female cases out number male cases, for the age group 0 – 17, male cases out number female cases. Are males below the age of 18 more susceptible to adverse events associated with drug use than their female counterparts, given the fact that the likelihood of drug use is the same (22.74%) [21] for males and females within this age group? If so, what could account for this? This calls for further investigation.

From Table 8, p increases with age (down the table) suggesting that the older segment of the population are more vulnerable to adverse events associated with drug use than the younger segment of the population. This observation is reinforced by the fact that for the age group 0 – 17 the percentage of reported cases is less than the percentage of the group in the overall US population, even when the latter has been adjusted (expected) for potential drug use. For the age group 65 and over the percentage of reported cases is greater than the percentage of the group in the overall US population even when it has been adjusted (expected) for potential drug use. The increasing trend in the values of p over the period under review suggest that the number of reports that were coming from the various age groups were increasing from year to year; an indication that awareness of the need to report adverse events associated with drug use is increasing, resulting more reports from the various age groups when one considers the issue of under-reporting [11,23] or adverse events are on the increase which is having corresponding effect on the rate of reporting or both.

It must be underscored that if an adverse event occurs during the use of a medication, it does not necessarily follow that the cause of the event is the medication. The occurrence of the adverse event may be a coincidence or the event is related to the disease being treated or is a symptom of an unidentified disease. Another medication being taken simultaneously with the suspect medication or drug-drug interaction may be the cause of the event [11,25]. Thus due diligence, through examination of the data on a medication in respect of an adverse event by experts, must be done before one could conclude that the medication caused the adverse event. That said, the foregoing does not take away the fact that most drugs have side-effects. Indeed some drugs, by the way they work, produce few but quite deleterious adverse reactions, while others produce several but less serious adverse reactions. Both types of drugs can make it to a list like Table 9 by virtue of the seriousness of the adverse events they cause or the multiplicity of less serious adverse events that occur concurrently during the use of a medication, that, to the user, portends a possible sinister outcome; which most probably motivate the reportage of such cases, given the notorious fact of under-reporting of adverse events occurring during the use of drugs [11,23].

4. CONCLUSION

The results of the analysis show that very useful insight can be gained from the analysis of SRS

data, which can be helpful in understanding the problem of adverse events in medication use, as the results of the analysis confirm that age and sex are potential contenders when trying to discover factors that are associated with the occurrence of adverse events. Further research is required to answer the questions raised in the discussions and it is essential to encourage reporting of adverse events, especially accurate and prompt reporting if the questions raised are to be answered comprehensively and the society is to derive maximum benefit from SRS data.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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