Original Research Article

Assessment of the Post-Marketing "Drug Ineffective" Reports Received by the Saudi Vigilance System

ABSTRACT

Aim: Drug Ineffective (DI) reports are Adverse Drug Events (ADE) important for post-marketing surveillance (PMS). Currently drug safety information from the DI reports received by the Saudi Food and Drug Authority (SFDA) via the Saudi Vigilance System (SVS) is undetermined. The study aims to describe the DI reports received by the SVS from different stakeholders.

Methods: DI reports received by the SVS between January 2020 to December 2021 were retrieved and characterized based on patients' demographics, reporter type and suspected drug type and group in comparison to non-DI reports. Potential determinants of the DI reports were screened to estimate odds ratios (OR) and the 95% confidence intervals (CI) for these reports.

Results: The total number of DI reports was 1885. Adults constituted the major age group (67.6 %), and male gender dominated most DI reports (80.2%) compared to equal percentages of males and females in non-DI reports. Most of the DI reports were reported by pharmacists (68.9%), and the most frequently reported drugs associated with DI and non-DI reports were Metformin (16.3%) and Atorvastatin (5.30%) respectively. Adjustment of potential confounding variables showed that gender (AOR = 2.285, 95% CI = 1.921–2.719) and age (AOR = 1.005, 95% CI = 1.002– 1.007) were significantly associated with the DI reports.

Conclusion: DI reports were frequently associated with adult male patients, and were more frequently reported by pharmacists. Most of the DI reports did not indicated the seriousness criteria, and the most frequently reported drug associated with DI reports was Metformin.

KEYWORDS

adverse drug events, drug ineffective, pharmacovigilance, post-marketing surveillance, Saudi Vigilance System

1 INTRODUCTION

"Drug Ineffective" (DI) is a standardized medical terminology based on the Medical Dictionary for Regulatory Activities (*Med*DRA) preferred terms (PTs) developed by the International Council for Harmonization (ICH) for medical products used by humans [1]. DIis one aspect of Adverse Drug Event (ADE) that is unanticipated and potentially hazardous if it went undetected or unreported[2-4]. DI reflects the performance of medicine in real-life population, and hence the unexpected or unexplained ineffectiveness can be potentially vital reportable event in pharmacovigilance and pharmacoepidemiological studies[5-7]. It might increase the risk of disease or ineffective drug related morbidity and mortality, and raisehealthcare costs [8-10].

Pharmacovigilance supports the regulation of the pharmaceutical market by focusing on the safety, quality, and effectiveness of these products[11, 12]. Post-Marketing Surveillance (PMS) keeps track of a drug's safety after it has been approved for sale and its clinical studies have been successfully investigated[13, 14]. The goal of many pharmaceutical regulatory bodies is to monitor drugs through rigorous testing and post-marking reports for ADE after they went through the clinical trial phases[13-16]. In the Kingdom of Saudi Arabia, pharmacovigilance has been strongly initiated by the Saudi Food and Drug Authority (SFDA)to monitor the safety of drugs through the establishment of the National Pharmacovigilance Center (NPC) in 2009. The SFDA is the 92nd member of the Uppsala Monitoring Center (UMC) established World Health Organization to receiveADE reports from the subscribing countries [17, 18].

The NPC is responsible for collecting, analyzing, and evaluating ADE reports from across the Kingdom, as well as fostering a culture of reporting; identifying and rectifying the causes of ADE [19, 20]. The NPC receives information about ADE from stakeholders via the SFDA unified call center (19999), email and online reporting forms that can be accessed via the SFDA web site[21]. In September of 2018 the SFDA developed a user-friendlyonline reporting interface known as the Saudi Vigilance System (SVS), updated the reporting forms and currently is very active in receiving ADE including DI reports from different types of reporters [19, 21, 22]. Data received by the SVS spontaneous reporting system can be utilized by the SFDA to easily conduct drug safety assessments and risk management improvement studies to aid in the decision-making processes [5, 20].

Currently, PMS studies focusing on the assessment of DI reports worldwide are scarce and similarly PMS studies on those reports that are received by the Saudi NPC are lacking. One of the earliest studies focusing on the adverse event reports received by the regional Center for Drug Safety Monitoring (CDSM) in Astrakhan, Russia for the period of 2010 to 2014 found that 1% of ADEs were associated with ineffectiveness of drugs[23]. In 2018 Misu et.al reported thatDI (6.4%) was the most frequently reported ADE through the United States Food & Drug Administration Adverse Reporting System (FAERS) database [24], and in South Korea, DI constituted about 1.0 to 1.3% of the ADEs reported to the Korean Adverse Event Reporting System (KAERS) database between 2013 to 2016[4]. The aim of this study was to describe the

DI reports received by the SFDAthrough the SVS from different stakeholders in comparison to the non-DI reports from January 2020 to December 2021, and explore the trends associated with patients' demographics, reporter types and type of medications that are frequently associated with the DIreports.

2 METHODS

A retrospectiveanalysis was conducted to assess the DI reports received through the SFDA's SVS in comparison to the non-DI reports from January 2020 to December 2021.The study protocol was approved by the Institutional Review Board of Riyadh Elm University with IRB Number: FPGRP/2021/672/734/763 in June 18, 2022 and was conducted in collaboration with the SFDA.

2.1 Data source

The NPC established ADE spontaneous reporting system that receives reports directly from public users,HCPs, and Qualified Person Responsible for Pharmacovigilance (QPPV) via different methods of reporting, including traditional phone, fax and verbal communication method, email, paperand online reporting forms[19]. The NPC through feedback from stakeholders continues to update and modify the reporting forms to enhance the compliance of the public and HCPs in submitting ADE reports [19, 20].

Our study used the data of the SVS online reporting system submitted ADEs to the SFDA – NPC database.The Saudi Vigilance website can be accessed through the link: ade.sfda.gov.sa [22]. All DI reports received from patients, consumers, HCPs, and QPPV were included. ADEs related to vaccines, herbal products, cosmetics, veterinary medication and non-medical products (Contrast Media, Medical devices, etc.) were excluded.

A total of 239,088 ADE reports accrued by the NPC database between January 2018 and December 2021, and 2,716 of which were DI reports. All DI and non-DI reports by the SVS from January 2020 and December 2021 were retrieved and provided for evaluation and characterization in this study.

2.2 Definition of drug ineffectiveness

All DI reports that were eligible for drug ineffectiveness were identified and extracted from the SVSusingthe following key words defined by the *Med*DRA PTs:therapeutic failure, lack of efficacy, drug ineffective, ineffective, treatment failure or drug failure[1].

2.3 ADE reporting form description

The report form is composed of eight sections; the first two sections are mandatory: contact information (reporter email and mobile phone number) and request information, and

the later fields are optional to be filled by the reporter; suspected drug information, patient information, product details, side effect, concomitant drugs and contact information (name, profession, and region)

In each of these sections the requested information is either selected from a list of options, provided a yes or no answers, or filled as in a free narrative space by the reporter. Because of the voluntary nature of the reporting process, a number of data fieldsin the collected data forms were empty. In case the report was deemed significant for follow up by the NPC the reporter can be contacted through the provided mandatory contact information.

It is worth mentioning that since the beginning of 2022 the ADE reporting form was updated by the NPC. A copy of the ADE reporting form from which the data presented in this study was retrieved; is provided as supplementary and can be accessed by clicking the link Supplementary I.

2.4 Datacollection

To compare the characteristics of the DI and non-DI reports, the following categories received by theNPC data file were utilized: report date, age group, gender, reporter type (profession), drug generic name, WHO Top Group, and seriousness criteria.

Age groups were classified into the following subgroups: Neonates (<28 days); Infants (>28 days–24 months); Children (>24 months–12 years); Adolescents (>12–19 years); Adults (>19–65 years); Elderly (>65 years). Reporter type was classified into: Physicians, Pharmacists, QPPV, Nurses and Patients. The ADE seriousness criteria included the following classifications: death, life threatening, permanent disability, hospitalization, prolonged hospitalization more than 24 hours, congenital anomaly,required intervention to prevent permanent impairment/damage, or otherSupplementary I.

2.5Statistical analysis

Data received through the SVSwere collected in Microsoft Excel sheets and appropriately revised. Data were transferred to the Statistical Package for Social Sciences (SPSS) version 26 for statistical analysis. In descriptive statistics, continuous variables were presented as means and standard deviations, while categorical variables were described as frequencies and percentages. Correlations between categorical variables were tested using Chi-square statistics. Comparing means of continuous variable were tested by independent samples t-test. Univariate and multivariate binary logistic regression were used to calculate crude and adjusted odds ratios(OR) and their 95% confidence intervals (CI). P-value of< 0.05 was considered to be statistically significant.

3 RESULTS

The total number of ADE reportsreceived by the SVS between January 2020 and December 2021 was 104,455 reports, of which 1,885 (1.8%) were reports coded with “drug ineffective” PT. Comparison of the number of reports received over the two years of the study period indicated that the ADE reports are increasing over time (Table 1).Although the majority of the DI reports did not indicate the reporter type (75.8%), pharmacistswere the major reporter group reporting about 23% and 69.8% of the DI and non-DI ADE reports respectively. While the seriousness criteria for most of the DI reports (82%) was not indicated, most of the non-DI ADEs were not serious (88.6%).

Analysis of patients’ demographics involved in the reported ADE indicated that most patients with DI were males (80%) compared to an approximately equal proportion of males and females in ADE with non-DI reports (49.4% and 50.6% respectively) (Table 2). Adults between the age of more than 19 to 65 years were more frequently associated with ADE in both DI and non-DI reports (67.6% and 72.4% respectively) compared to other age groups (Table 2).

To investigate whether patients’ demographics are factors that are associated with the reported DI, logistic regression model was applied. The analysis indicated that male subjects were 2.285 times more likely to have drug ineffectiveness than female subjects. One-year increment in age was associated with 1.005 times more likely to have drug ineffectiveness (significant but has very small effect) (Table 3).

Table 4 shows the top 20 drug names that were frequently reported as the suspected drugs associated with the reported DI and non-DI ADEs. Metformin (16.34%) and valsartan (10.45%) were the top two drugs during the study period that were associated with DI reports.Atorvastatin (5.30%) followed by metformin (4.90%) were the top two drugs associated with non-DI reports. Many of the suspected drugs in the DI reports were those used for the treatment of hypertension and heart failure (e.g.Valsartan, Perindopril, Bisoprolol, Furosemide, Spironolactone, Amlodipine and Indapamide) and type 1 and type 2 diabetes (e.g. Metformin, Insulin, Vildagliptin and Pioglitazone).

Characterizing the frequency of DI and non-DI reports based on the WHO top pharmacological groups of suspecteddrugs showed that biguanides (16.34%), statins and angiotensin II receptor antagonists (10.72%) were more frequently associated with DI reports. For the non-DI reports, statins (6.31%),biguanides (4.93%), and analgesia producing opioids (4.54%) were the most frequently reported WHO top pharmacological groups (Table 5).

Table 6 indicates the frequency at which drugs suspected of the DI and non-DI ADEs were associated with seriousness criteria. Insulin was reported to have serious consequences in 17 out of 169 total reports (10%), compared to other drugs in the DI category which were less frequently reported but with high percentage of seriousness categorization such as vincristine (9 out of 10 reports (90%)) (Table 6).Prolongation of existing hospitalization and requirement of inpatient hospitalizationwere the highest two seriousness criteria associated with suspected drugs of the reported drug ineffectiveness (Supplementary Table 1).

4 DISCUSSION

DI reports are received spontaneously by the SVS platform since it was initiated in 2018. Our results show that ADE and DI reports received by the NPC were reported mostly by pharmacists. The seriousness criteria of most of the DI report was not indicated by the reporters. Most of the DI reports were involving male patients and adults as the most prominent age group. Based on the guidelines of good pharmacovigilance practice (GVP) set forth by the SFDA, reports on ADE should be submitted on a regular basis by the Marketing Authorization Holders (MAH) to the NPC within the legal timeframe. The SFDA coordinates the monitoring of medicinal products and provides advice on the measures necessary to ensure their safe and effective use[25]. The NPC provided the Pharmacovigilance Electronic Reporting Service SVS as an online spontaneous reporting system for ADEs and pharmaceutical products defects to facilitate the reporting by the public and the HCPs[22] .

ADEs tend to have different manifestations depending on the region, and patients' demographic factors and genetic background [23].In our study, the drugs that were most frequently associated with DI were medications used to treat type 1 and type 2 diabetes (e.g. Metformin, Insulin, Vildagliptin and Pioglitazone)andhypertension and heart failure (e.g. Valsartan, Perindopril, Bisoprolol, Furosemide, Spironolactone, Amlodipine and Indapamide). Classification of the most reported medication based on the WHO top pharmacological group showed that DI reports were most frequently associated biguanides, angiotensin II receptor antagonists, and statins. These findings correlate with the adult age group that was frequently associated with the reported DI in ourthe current study, and alignwith the documented high prevalence of chronic diseases e.g. hypertension[26], diabetes[27] and hypercholesterolemia [28]among adults in the Kingdome of Saudi Arabia.

Several studies had characterized the post-marketing drug ineffective reports received by the regulatory authority database in their respective countries. In 2018, Misu et al. reported that the DI reports received by the US FAERS database were received mainly from female adult consumers, and much of these DI reports did not have serious criteria. They reported that the most frequentdrugs associated with the reported DI were medications used for management of

symptomatic conditions (e.g. adalimumab, etanercept, naproxen and loratadine)[24].Similarly, in 2019, Kim et al. reported the DI reports received by the Korean KAERS database were received from adults age group consumers, with females as the most frequently involved gender in these reports, and indicated that most of the DI reports did not have serious ADE. They also reported that the most reported drugs associated with DI were Ciclopirox as antifungal, Escitalopram for mood disorders, and Teriparatide to treat osteoporosis[4].

Throughout the study period, the DI reports received by the NPC in Saudi Arabia are increasing with time, indicating good pharmacovigilance practice in the country, and awareness of stakeholders of the importance of ADE reporting. Overall, the DI reports analyzedin our study were missing important information that could have maximized the benefit sought from them. The current practice by the NPC is that for any DI report of interestreported, the missing information can be retrieved by contacting the reporter through the provided contact information in the report form. We recommend that the NPC increasesthe mandatory fields and adds additional PTs to the ADE form to increase the chance of signaling significant reports and prioritizing the investigation of suspected DI reports that might have potentially useful post-marketing drug safety information.

Efforts from the NPC to increase the awareness of HCPs and consumers of the importance of filling narrative fields in the ADE reports is crucial[9, 19]. The narrative description of the ADE and patients experience of the reported event will improve the yield of potentially useful DI reports and support the PMS efforts. The advancement of artificial intelligence (AI) tools can be utilized by the NPC to identify important narrative features in the ADE reports[29, 30], which then can aid in signaling potentially significant reports and prioritize them to be reviewed by the SFDA.

OurThisstudy has some limitations. We did not include all MedDRA PT “Drug ineffective” reports received by the NPC database. The retrieval of the ADE reports collected by different sources (phone, fax, email, and paper forms) and stored on different platforms, was labor intensive. Hence our study period was limited to the duration where most of the ADE reports can be retrieved directly from the SVS database. Another limitation is the small data size and incomplete reports fields which limited our ability to accurately assess the characteristics of the data subsets of these reports; such as whether the reported drugs were used for an approved indication or not. Also, the analysis did not include some factors such as causality assessments and time to onset. Finally, the SVS; like other PMS databases; lacks some variables such as risk factors affecting drug effectiveness and patient's medical history, which were addressed by SFDA in early 2023 by developing mandatory fields in ADE reports that originate from feedback the NPC received from healthcare professionals.We hope that the findings of this study will direct future research focusing on PMS and

pharmacoepidemiologicalanalysis utilizing the SVS database, and analyze the collected data at the national level to enhance the Kingdom of Saudi Arabi drug safety efforts.

5 CONCLUSION

DI reports received by the Saudi NPC – SVS during the study period were reported mostly by pharmacists and did not indicate the seriousness criteria of the ADE. Adults and males were the most frequently associated groups in the DI reports. Medications used to treat chronic diseases such as hypertension, diabetes and hypercholesterolemia were the most frequently reported suspected drugs in the DI reports. Awareness of HCPs and consumers of the importance of filling the narrative sections of the ADE report is important to enhance the usefulness of drug safety signals utilized for post-marketing surveillance efforts.

DECLARATIONS

ETHICS APPROVAL
Ethics approval to conduct the study was received from the Institutional Review Board of Riyadh Elm University with IRB Number: FPGRP/2021/672/734/763 in June 18, 2022.

CONSENT TO PARTICIPATE
Not applicable as all data available to the study team were anonymous.

CONSENT FOR PUBLICATION
Not applicable as all data available to the study team were anonymous.

AVAILABILITY OF DATA AND MATERIALS
The datasets generated during and/or analyzed during the current study are available from the data custodian in the SFDAby request. Supplementary file for the ADE form and supplementary table 1 indicating the frequency of seriousness criteria for suspected drugs with high frequency of the reported seriousness are shown in the Online Supplement.
Supplementary material is available on the publisher's website along with the published article.

CODE AVAILABILITY
Not applicable

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TABLE 1 Characteristics of "drug ineffective and non-drug ineffective" adverse drug event reports received by the Saudi Vigilance System during the study period.

Characteristic	DI Reports (*N* = 1,885)		Non- DI Reports (*N* = 102,750)		Total ADE Reports (N=104,455)	
	N	%	*N*	%	*N*	%
Number of reports / Year						

2020	181	9.6	16,432	15.99	16,613	15.91
2021	1,704	90.4	86,138	83.83	87,842	84.09
Reporter type						
Physicians	4	0.2	73	0.1	77	0.1
Pharmacists	434	23	71,587	69.8	72,021	68.9
Nurses	2	0.1	10	0.01	12	0.01
QPPV	13	0.7	0	0	13	0.01
Patients	3	0.2	74	0.1	77	0.1
Missing	1,429	75.8	30,826	30.1	32,255	30.9
Seriousness criteria						
Not Serious	252	13.4	90,921	88.6	91,173	87.3
Death	0	0	94	0.1	94	0.1
Life threatening	6	0.3	42	0.04	48	0.05
Permanent disability	2	0.1	19	0.02	21	0.02
Hospitalization	31	1.6	439	0.4	470	0.4
Prolonged hospitalization > 24 hr.	34	1.8	382	0.4	416	0.4
Congenital anomaly	0	0	12	0.01	12	0.01
Required intervention to prevent permanent impairment/damage	6	0.3	2804	2.7	2,810	2.7
Other serious	9	0.5	524	0.5	533	0.5
Missing	1,545	82.0	7,333	7.1	8,878	8.5

ADE adverse drug event, DI drug ineffective, QPPV Qualified Person responsible for Pharmacovigilance

TABLE 2 Demographic characteristics of the patients involved in the “drug ineffective and non-drug ineffective” adverse drug event reports

		DI	Non-DI	*P*-Value
Age in years	Mean (SD)	52.9 (19.7)	50.4 (21.9)	0.002
Age categories*	Neonates	0.3 %	0.2 %	< 0.001
	Infants	1.3 %	0.6 %	

	Children	3.6 %	1.8 %	
	Adolescents	2.0 %	3.1 %	
	Adults	67.6 %	72.4 %	
	Elderly	25.2 %	21.9 %	
Gender	Male	80.2 %	49.4 %	< 0.001
	Female	19.8 %	50.6 %	

DI drug ineffective, Neonates (<28 days); Infants (>28 days–24 months); Children (>24 months–12 years); Adolescents (>12–19 years); Adults (>19–65 years); Elderly (>65 years). p value for age was calculated using independent samples t-test while p values for age categories and gender were of the Chi-Square test. SD standard deviation. Missing answers were excluded.

TABLE 3 Logistic regression model to predict factors associated with drug ineffectiveness such as age and gender

		Crude		**Adjusted**	
		Odds ratio	**95% CI**	**Odds ratio**	**95% CI**
Gender	Female	Ref.	Ref.	Ref.	Ref.
	Male	0.241	0.215-0.270*	2.285	1.921-2.719*
Age		0.966	0.993- 0.999*	1.005	1.002-1.007*

Ref. reference category. * significant results. Crude odds ratios were calculated using univariate binary logistic regression analyses. Adjusted odds ratios were calculated using multivariate binary logistic regression analysis.

TABLE 4 Frequently reported drugs with ineffectiveness and non-ineffectiveness

DI			**Non-DI**		
Drug name	**Frequency**	**Percentage**	**Drug name**	**Frequency**	**Percentage**
Metformin	308	16.34%	Atorvastatin	5423	5.30%
Valsartan	197	10.45%	Metformin	5049	4.90%

Perindopril	188	9.97%	Furosemide	4238	4.20%
Insulin	169	8.97%	Piperacillin/ Tazobactam	3843	3.7%
Atorvastatin	150	7.96%	Perindopril	2953	2.90%
Bisoprolol	148	7.85%	Amlodipine	2313	2.30%
Furosemide	135	7.17%	Meropenem	2306	2.20%
Rosuvastatin	52	2.76%	Valsartan	2186	2.10%
Levetiracetam	41	2.18%	Bisoprolol	2109	2.10%
Vildagliptin	38	2.02%	Vancomycin	2032	2.00%
Spironolactone	37	1.96%	Insulin	1737	1.70%
Pioglitazone	21	1.11%	Ferrous sulfate	1677	1.60%
Omeprazole	20	1.06%	Enoxaparin	1661	1.60%
Aripiprazole	18	0.95%	Dexamethasone	1639	1.60%
Amlodipine	15	0.80%	Fentanyl	1562	1.50%
Ceftriaxone	14	0.74%	Morphine	1508	1.50%
Indapamide	11	0.58%	Acetylsalicylic acid	1468	1.40%
Escitalopram	10	0.53%	Favipiravir	1307	1.30%
Heparin	10	0.53%	Warfarin	1137	1.10%
Vincristine	10	0.53%	Tamsulosin	1103	1.10%
Others*	293	15.54%	Others*	55319	53.9%

DI drug ineffective, * Combined drugs with low frequency.

TABLE 5 Frequently reported WHO top pharmacological groups with ineffectiveness and non-ineffectiveness

DI			Non-DI		
WHO group	**Frequency**	**Percentage**	**WHO group**	**Frequency**	**Percentage**
Biguanides	308	16.34%	Statins	6472	6.31%

Statins	202	10.72%	Biguanides	5058	4.93%
Angiotensin II receptor antagonists	202	10.72%	Analgesia producing opioids	4653	4.54%
Antiarrhythmics, class Ib	192	10.19%	Loop or high-ceiling diuretics	4238	4.13%
Insulins and analogues	169	8.97%	Beta-lactamase inhibitors	3845	3.75%
Adrenergic receptor antagonists	155	8.22%	Corticosteroids	3792	3.70%
Loop or high-ceiling diuretics	135	7.16%	Vitamins and probiotics	3289	3.21%
Biologics and immunomodulators for ulcerative colitis	44	2.33%	Angiotensin converting enzyme inhibitors	3118	3.04%
Dipeptidyl peptidase-4 inhibitors	41	2.18%	Angiotensin II receptor antagonists	3038	2.96%
Mineralocorticoid receptor antagonist	38	2.02%	Glycopeptide antibacterial	2769	2.70%
Antipsychotics	35	1.86%	Carbapenems	2688	2.62%
Proton pump inhibitors	29	1.54%	Weak CYP3A inhibitors	2523	2.46%
Selective serotonin reuptake inhibitors	21	1.11%	P-gp substrates	2517	2.45%
Thiazolidinediones	21	1.11%	Adrenergic receptor antagonists	2468	2.41%
Dihydropyridine derivative calcium channel blockers	18	0.95%	Platelet aggregation inhibitors, excluding heparin	1824	1.78%
Nonsteroidal anti-inflammatory drugs	15	0.80%	Insulins and analogues	1728	1.68%
Cephalosporins, third-generation	15	0.80%	Heparin	1662	1.62%
Antineoplastic pyrimidine analogues	11	0.58%	Nonsteroidal anti-inflammatory drugs	1609	1.57%
Monoclonal antibodies - non-antineoplastic	11	0.58%	Monoclonal antibodies - non-antineoplastic	1520	1.48%
Low-ceiling diuretics, excluding thiazides	11	0.58%	P-gp inhibitors	1476	1.44%
Others*	212	11.25%	Others*	42283	41.22%

DI drug ineffective. * Combined groups with low frequency.

TABLE 6 The most frequently reported drugs with serious criteriawith ineffectiveness and non-ineffectiveness

DI			Non-DI		
Drug name	**Frequency (Total)***	**Percentage**	**Drug name**	**Frequency (Total)***	**Percentage**

Insulin	17 (169)	10%	Metformin	241 (4757)	5%
Vincristine	9 (10)	90%	Atorvastatin	209 (4649)	4%
Methotrexate	6 (6)	100%	Denosumab	202 (212)	95%
Cytarabine	4 (4)	100%	Insulin	154 (1458)	11%
Heparin	4 (10)	40%	Evolocumab	123 (133)	92%
Etoposide	3 (3)	100%	Levothyroxine	103 (810)	13%
Levetiracetam	3 (41)	7%	Liraglutide	87 (307)	28%
Furosemide	3 (135)	2%	Perindopril	85 (2550)	3%
Doxorubicin	2 (2)	100%	Furosemide	84 (4080)	2%
Tocilizumab	2 (2)	100%	Valsartan	81 (1840)	4%
Denosumab	2 (4)	50%	Vancomycin	76 (1977)	4%
Peg asparaginase	2 (4)	50%	Amlodipine	67 (2004)	3%
Vancomycin	2 (7)	29%	Interferon beta-1a	64 (75)	85%
Metformin	2 (308)	1%	Methotrexate	63 (823)	8%
Amikacin	1 (1)	100%	Spironolactone	57 (956)	6%
Amoxicillin/ clavulanic acid	1 (1)	100%	Heparin	56 (587)	10%
Belimumab	1 (1)	100%	Paracetamol	54 (948)	6%
Bnt162b2	1 (1)	100%	Warfarin	53 (1094)	5%
Cytosine arabinoside	1 (1)	100%	Linagliptin	52 (192)	27%
Eculizumab	1 (3)	33%	Ceftriaxone	49 (868)	6%

DI drug ineffective. * Total reports of the same drug