



Drug-Induced Anaphylaxis in a Vietnamese Pharmacovigilance Database: Trends and Specific Signals from a Disproportionality Analysis

Khac-Dung Nguyen^{1,2} · Hoang-Anh Nguyen¹ · Dinh-Hoa Vu¹ · Thi Thuy-Linh Le¹ · Hoang-Anh Nguyen Jr.¹ · Bich-Viet Dang¹ · Trung-Nguyen Nguyen³ · Dang-Hoa Nguyen¹ · Thanh-Binh Nguyen⁴ · Jean-Louis Montastruc² · Haleh Bagheri²

© Springer Nature Switzerland AG 2018

Abstract

Introduction Despite the numerous studies investigating drug-induced anaphylaxis (DIA), understanding and quantitative data analysis in developing countries remain limited. The aim of our study is to describe and quantify DIA using the National Pharmacovigilance Database of Vietnam (NPDV).

Methods Spontaneous reporting of adverse drug reactions (ADRs) recorded between 2010 and 2016 were retrospectively analysed to identify DIA reports. The trend and characteristics of DIA cases were described. Multivariate disproportionality analysis was used for signal generation.

Results Overall, 4873 DIA cases (13.2% of total ADRs) were recorded in the NPDV, 111 of which resulted in death (82% of total ADR-induced deaths) over a 7-year period. There was a remarkable increase in DIA reporting over time ($p < 0.001$). The incidence rates of DIA reporting per total ADRs and per 100,000 inhabitants remained high (mean rates [95% CI] of 12.06 [9.88–14.24] and 0.77 [0.33–1.20], respectively). Concerning suspected drugs, systemic antibiotics ($n = 3318$, 68%) were mostly reported with a reporting odds ratio (ROR) and 95% CI of 2.35 [2.20–2.51]. In the case of antibiotic-induced anaphylaxis, the third-generation cephalosporins were predominant ($n = 1961$, 40.2%, ROR 2.39 [2.24–2.55]). We also noted drugs generally associated with DIA such as contrast agents (ROR 2.43 [2.04–2.88]) and anaesthetics (ROR 4.02 [3.30–4.89]). Furthermore, unexpected signals were observed for alpha-chymotrypsin (ROR 1.75 [1.23–2.44]) and amoxicillin/sulbactam (ROR 1.59 [1.18–2.10]), uncommonly reported in western countries.

Conclusion In recent years, cases of drug-induced DIA have increased in Vietnam, mostly due to antibiotics and third-generation cephalosporins. The inappropriate use of these drugs should be taken into account. Our findings also highlighted typical Vietnamese signals for alpha-chymotrypsin- and amoxicillin/sulbactam-induced anaphylaxis, which may relate to a specific sociological context in resource-limited countries.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40264-018-0758-8>) contains supplementary material, which is available to authorized users.

✉ Haleh Bagheri
haleh.bagheri@univ-tlse3.fr

Extended author information available on the last page of the article

Key Points

This study is the first Vietnamese population-based research using the National Pharmacovigilance Database of Vietnam to describe the specific characteristics and generated signals of drug-induced anaphylaxis in a developing context.

Antibiotics related to approximately two-thirds of drug-induced anaphylaxis reporting, in which third-generation cephalosporins were predominant.

Signals were generated for some drugs used to a lesser extent in other countries, highlighting the issues relating to healthcare management and policy in a developing context and suggesting the need to consider benefits/risks and the rational use of these drugs.

1 Introduction

Anaphylaxis is a severe, life-threatening, systemic hypersensitivity reaction that can appear in two forms: IgE-mediated allergic anaphylaxis (immunological cause) and non-allergic anaphylaxis (non-immunological cause) [1]. A brief definition was proposed at the Second Symposium on the Definition and Management of Anaphylaxis: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death” [2]. Considered a common cause of anaphylaxis, drug-induced anaphylaxis (DIA) is classified as a type-B reaction as it is mostly an unpredictable and dose-independent event that occurs suddenly after the patient comes into contact with the causative drug [3, 4].

Data on the incidence and quantitative analysis of DIA remain limited. The true incidence of DIA is still unknown despite the incidence of anaphylaxis being estimated at 8–50 cases per 100,000 person-years in western countries [5]. Antibiotics, contrast agents and non-steroidal anti-inflammatory drugs (NSAIDs) seem to be the most common causes of anaphylaxis leading to hospitalisation, with incidence rates of about 1 in 5000 exposures and a predominantly female risk factor (65%) [3, 6]. To date, only a few quantitative population-based studies have focused on DIA and knowledge of anaphylaxis in developing countries remains limited. Because of different incidence rates, potential bias and under-reporting, Mertes et al. also highlighted concerns that studies from one country could not be extrapolated to other countries [7]. Hence, population-specific studies are ultimately required in order to address this serious global issue.

Recently in Vietnam, anaphylaxis has emerged as a concern, thereby highlighting the need to record DIA data to promote risk-related dialogue amongst healthcare

practitioners [8–10]. With the significant increase in Individual Case Safety Reports (ICSRs) in the National Pharmacovigilance Database of Vietnam (NPDV) [11], use of the cumulative database and generation of anaphylactic signals could highlight the specific drug safety issues faced by the Vietnamese population. Therefore, research based on the 7-year period of NPDV was carried out in order to describe the characteristics and trends of DIA reporting in Vietnam and generate DIA signals in a country with limited resources.

2 Materials and Methods

2.1 Setting and Data Source

Despite being a member of the WHO Program for International Drug Monitoring in 1999, the NPDV was officially developed and maintained by the National Drug Information and Adverse Drug Reaction Monitoring Centre (NDI-ADRM) from 2009 onwards. Since 2010, the NPDV has been used systematically to provide feedback to the reporter by NDIADRM staff [11]. The structure and management of the NPDV comply with international safety reporting guidelines (ICH E2B, E2D) [12]. From 2010 to 2016, NPDV included 40,031 Individual Case Safety Reports (ICSRs, referred to as adverse drug reactions [ADRs] in this study) [11]. The data were collected from 13,617 healthcare units (including 1153 public hospitals) across the country and from pharmaceutical companies (officially included in NPDV in 2012). Most of the reports were generated by national and provincial hospitals and spontaneously reported by healthcare workers (HCWs). The contribution of ADR reporting from private pharmacies and patients does not apply to this period. In order to be validated and recorded in the NPDV, every ADR submitted to pharmacovigilance centres had to be recorded on an official ADR form stating the following essential information: patient’s characteristics (age, gender), suspected drugs, description of the ADR and reporter’s details [13]. Suspected drugs were classed according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. The coding of ADR terminologies was carried out using World Health Organisation Adverse Reaction Terms (WHO-ART) [14]. ADR causality was assessed (using the WHO—Uppsala Monitoring Centre Causality Assessment) by trained NDIADRM personnel and/or one or two members of the Technical Expert Committee, depending on the severity of the ADR [11, 15]. The three afore-mentioned activities are normally performed for all ADRs reported to the DIADRM within a set time limit (from several weeks to several months, depending on the severity of the ADRs) [11].

2.2 Study Design

All ADRs that met the following criteria were included in this study: (i) spontaneously reported by HCWs; (ii) received between 01 January 2010 and 31 December 2016; (iii) no missing data in terms of patient characteristics (age and gender), drugs suspected and ADR description; (iv) ADR causality for suspected drugs with a ‘certain’, ‘probable’ or ‘possible’ assessment. The original ADRs were thoroughly reviewed and, to identify the anaphylaxis reports (cases), satisfied anaphylaxis criteria proposed by the Second Symposium on the Definition and Management of Anaphylaxis [2]. According to this definition, anaphylaxis is an acute serious systemic reaction fulfilling at least one of the following three clinical criteria:

- rapid skin manifestation with either cardiovascular or respiratory system involvement;
- at least two cutaneous, respiratory, gastrointestinal or cardiovascular symptoms shortly after exposure to a likely allergen;
- reduced systolic blood pressure (< 90 mmHg or > 30% decrease) following exposure to known allergen.

Cases also included the ADRs, the narrative description of which included reports of ‘anaphylactic shock’ or ‘anaphylactic reaction’ with no mention of clinical manifestations. Regarding time correlation, only cases with time-to-onset (TTO, calculated by the time interval from administration of the last dose and the onset of anaphylactic symptoms) within 24 h were chosen for analysis, including cases with time descriptions expressed in ‘minutes’, ‘hours’, ‘shortly’, ‘during infusion/injection’ or ‘immediately’ after drug exposure or with a narrative description corroborating the fact that the TTO did not exceed 24 h. ADRs including anaphylactic symptoms whose TTOs exceeded 2 days or were undistinguishable, were excluded. Furthermore, all ADRs with non-anaphylactic symptoms were deemed as non-cases in this study (Fig. 1). Drug exposure was investigated in cases and non-cases.

2.3 Statistical Analysis

A descriptive analysis of the main features of the anaphylactic cases was carried out. Continuous variables were summarised as mean or median with a 95% confidence interval (CI) or interquartile ranges (IQRs) to suit the data distribution method selected. Categorical variables were described as frequencies and percentages. Comparisons in terms of gender, age, reporter’s job and fatal outcome between cases and non-cases were analysed using the Mann–Whitney *U* non-parametric test or *t* test

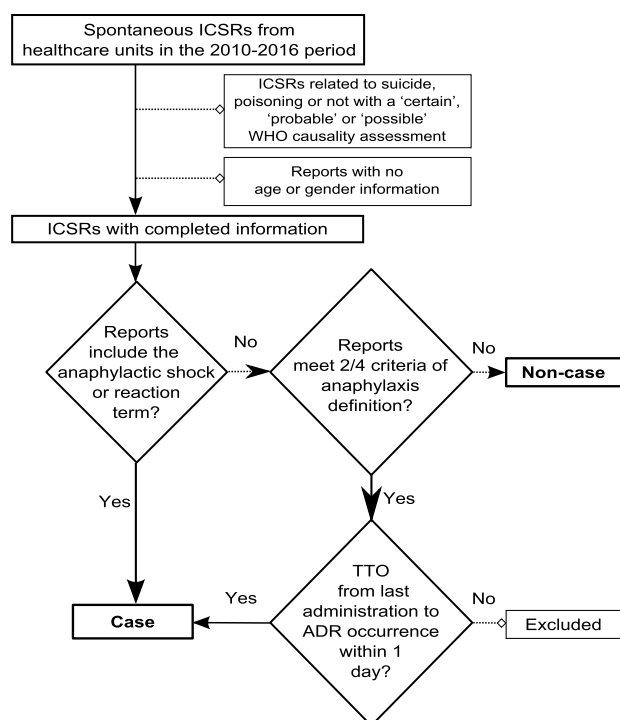


Fig. 1 Flowchart of anaphylaxis cases and non-cases selected from the Vietnamese database. *ICSR* individual case safety report

for continuous variables and the Fisher’s exact test or the chi-squared test for categorical variables. Probabilities (*p* values) of < 0.05 were considered significant.

The association between drugs and anaphylaxis was analysed using the ADR reporting odds ratio (ROR) as a measure of disproportionality (a case/non-case method) [16–18]. The calculation of ROR together with its 95% CI is similar to the calculation of an odds ratio from a case-controlled study, using the multivariate generalised linear regression model:

$$\log(\text{Odd}) = \beta_0 + \beta_1 Y + \beta_2 G + \beta_3 A$$

where *Y* is the reporting year, *G* is gender, and *A* is patient’s age in ADRs.

In our study, RORs were calculated for specific suspected drugs or pharmacological classes with at least three anaphylactic cases. A signal is generated with a specific drug (or pharmacological class) if the lower threshold of the ROR 95% CI is > 1. For ROR values > 2, the signal was considered ‘robust’ [19]. The trend analysis of age group, gender and year with DIA incidence rates was assessed using the Poisson regression model adjusted for the overall Vietnamese population [20]. Statistical analyses were completed using R statistical software (version 3.4.0, issued 21 April 2017) [21].

3 Results

3.1 Trend Reporting and Demographic Characteristics

During the 7-year study, the NPDV acknowledged 4873 (13.2%) anaphylactic cases and 32,061 (86.8%) non-cases (Fig. 2). Based on the Vietnamese population census [22], the annual incidence rate of DIA reporting ranged from 1.85 to 18.25 (with a mean [95% CI] of 7.6 [03.3–12.0]) cases per million population-years. There was a remarkable trend towards increased reporting over time, and more than 50% of all DIA cases were highlighted during the last 2 years of the study period. The results of Poisson regression, adjusted in line with the variation in the Vietnamese population and the total number of ADRs, suggested that the DIA reporting trend had a significant tendency to increase during the study period ($p < 0.001$) (see Electronic Supplementary Material 1). In addition, the incidence rates of reported DIA per

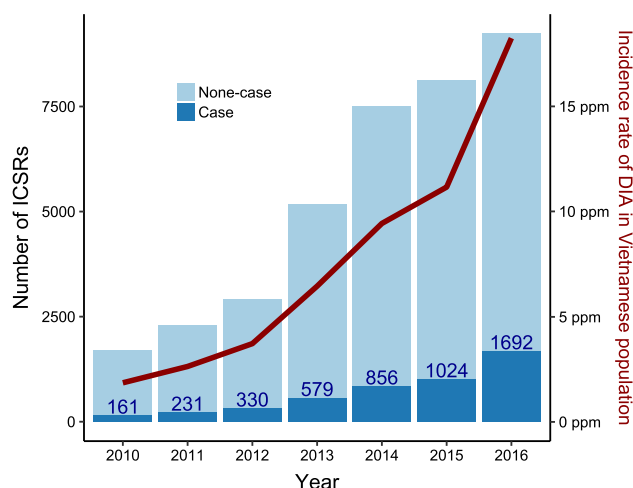


Fig. 2 Reporting trend of drug-induced anaphylaxis in Vietnam. ICSR individual case safety report, DIA drug-induced anaphylaxis

total ADRs and per 100,000 population increased annually ($p < 0.001$) and remained high (mean rates [95% CI] of 12.06 [9.88–14.24] and 0.77 [0.33–1.20], respectively). Among the overall 135 ADR-induced deaths in the same period, 111 cases (2.3%) were related to DIA. This figure is significantly higher than that recorded in the non-case group ($n = 24$, 0.1%, $p < 0.001$) (Table 1).

Despite the fact that anaphylaxis can occur at any age, the majority of patients were adults (51.8% patients between 20 and 60 years old) and these patients were statistically older than their non-case peers ($p < 0.001$). We also found that over half of DIA cases involved patients in the 20–59 years age group (51.19%). In the 0–19 years age group, reports focused primarily on male patients ($p = 0.02$), whereas females were mostly affected in the 20–39 years age group ($p < 0.001$). Gender was relatively balanced in the other age groups (Fig. 3). Incidence rates involving patients aged 60 years or over differed statistically according to gender. During the period of the study, the total DIA spontaneous reporting increased each year corresponding to a higher reporting rate by pharmacists, accounting for 40% of overall DIA cases; those of medical doctors or nurses also increased, albeit to a considerably lesser degree than pharmacists (Fig. 4).

3.2 Drug Trigger Factors and Quantitative Signals

Although numerous suspected drugs were reported, the top eight pharmacotherapeutic groups (number of reports > 30) included systemic antibiotics in pole position ($n = 3318$, 68%), followed by NSAIDs ($n = 226$, 4.6%), blood substitutes and perfusion solutions ($n = 198$, 4.1%), contrast agents ($n = 189$, 3.9%), anaesthetic drugs ($n = 160$, 3.3%) and finally antipyretics and drugs containing paracetamol ($n = 129$, 2.6%) (Fig. 5).

Systemic antibiotics were the main cause of DIA with an annual increase in terms of trend (Fig. 6). β -lactams were the most widely reported subgroup. More than half of DIA cases (Fig. 7) involved cephalosporins and carbapenems (J01D)

Table 1 Case and non-case demographic characteristics

Characteristics	Non-case ($N = 32,073$)	Case ($N = 4877$)	p value
Median age (IQR)	35.0 (23.0–54.0)	42.0 (23.0–61.0)	< 0.001
Age group, years; n (%)			< 0.001
0–19 ^a	6374 (19.9)	1055 (21.6)	
20–39	11,890 (37.1)	1233 (25.3)	
40–59	7824 (24.4)	1295 (26.6)	
60–79	4842 (15.1)	1013 (20.8)	
80+	1143 (3.6)	281 (5.8)	
Gender, male; n (%)	14,563 (45.4)	2282 (46.8)	0.073
Mortality; n (%)	24 (0.1)	111 (2.3)	< 0.001

IQR interquartile range

^aIncluding 395 cases of DIA in children between 0 and 2 years of age

Fig. 3 Age group and gender distribution in drug-induced anaphylaxis. **a** Distribution according to number of cases. **b** Distribution according to incidence per 100,000 inhabitants

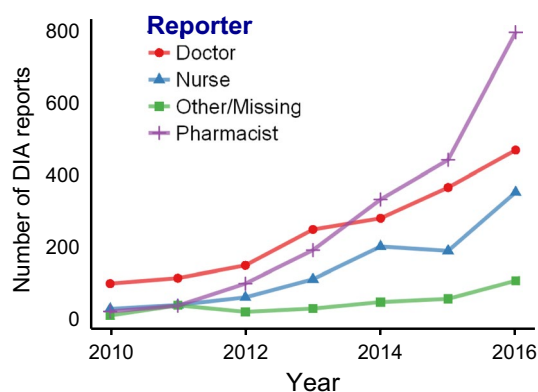
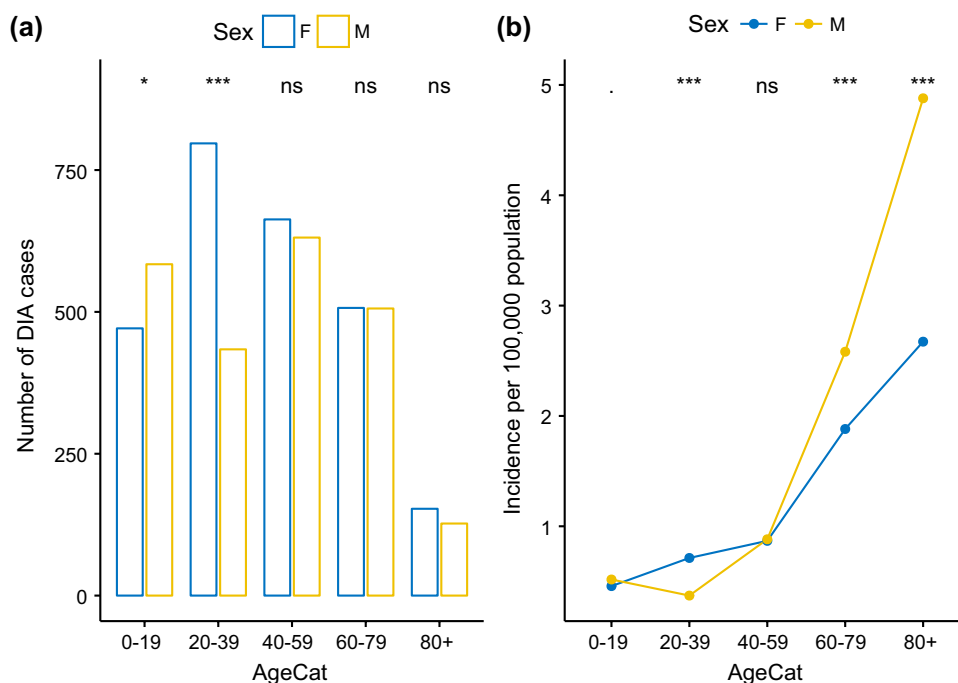


Fig. 4 Trends in reporter distribution in Vietnamese drug-induced anaphylaxis

($n = 2482$, 50.9%), followed by penicillins (J01C) ($n = 470$, 9.6%) and quinolones (J01B) ($n = 227$, 4.7%). Furthermore, we found that third-generation cephalosporins (C3G) were the primary cause of DIA ($n = 1961$, 40.2%) and the top three most reported drugs were cefotaxime ($n = 875$, 18.0%), ceftriaxone ($n = 461$, 9.5%) and ceftazidime ($n = 381$, 7.8%). Among cephalosporins, signals were generated with the third-generation cephalosporins (J01DD) ROR 2.39 [95% CI 2.24–2.55] followed by first-generation (J01DB) ROR 1.85 [95% CI 1.57–2.16] and fourth-generation cephalosporins (J01DE) ROR 2.22 [95% CI 1.71–2.85]. The anaphylactic signals relating to specific antibiotics (> 20 cases) were generated with C3G (cefotaxime, ceftriaxone, ceftazidime, cefoperazone, ceftizoxim, cefoperazone/sulbactam), penicillins (amoxicillin/sulbactam, amoxicillin, amoxicillin/clavulanic acid, ampicillin,

benzyl penicillin, phenoxymethyl penicillin), first-generation cephalosporins (cephalexin, cefadroxil, cefazolin, cefradin), second-generation cephalosporins (cefuroxime), fourth-generation cephalosporins (cefepim) and carbapenems (imipenem/cilastatin) (see Electronic Supplementary Material 2).

Signals were also found for anaesthetic drugs (ROR 4.02 [95% CI 3.30–4.89]) with lidocaine, bupivacaine, fentanyl, propofol, sufentanil; contrast agents (ROR 2.43 [95% CI 2.04–2.88]) comprising iobitridol, iopromide, iohexol, iopamidol and omeprazole in the proton pump inhibitor (PPI) group with ROR 1.61 [95% CI 1.11–2.29]. Although no signals were generated for NSAIDs, we found 296 (6.1%) DIA cases related to this second most widely reported pharmacological group, mainly involving diclofenac ($n = 192$, 3.9%). This was followed by blood substitutes and infusion solutions (ROR 1.64 [95% CI 1.39–1.91]) involving glucose and/or electrolyte solutions (ROR 1.97 [95% CI 1.43–2.67]). Finally, significant signals were recorded for alpha-chymotrypsin (ROR 1.75 [95% CI 1.23–2.44]), amoxicillin/sulbactam (ROR 1.59 [95% CI 1.18–2.10]) and tranexamic acid (ROR 3.62 [95% CI 2.01–6.08]) (Table 2).

4 Discussion

4.1 Trends and Specific Characteristics of Drug-Induced Anaphylaxis (DIA) and the Impact of a Resource-Limited Setting

To our knowledge, this is the first DIA analysis in a health-care unit setting based on spontaneous reporting of ADRs

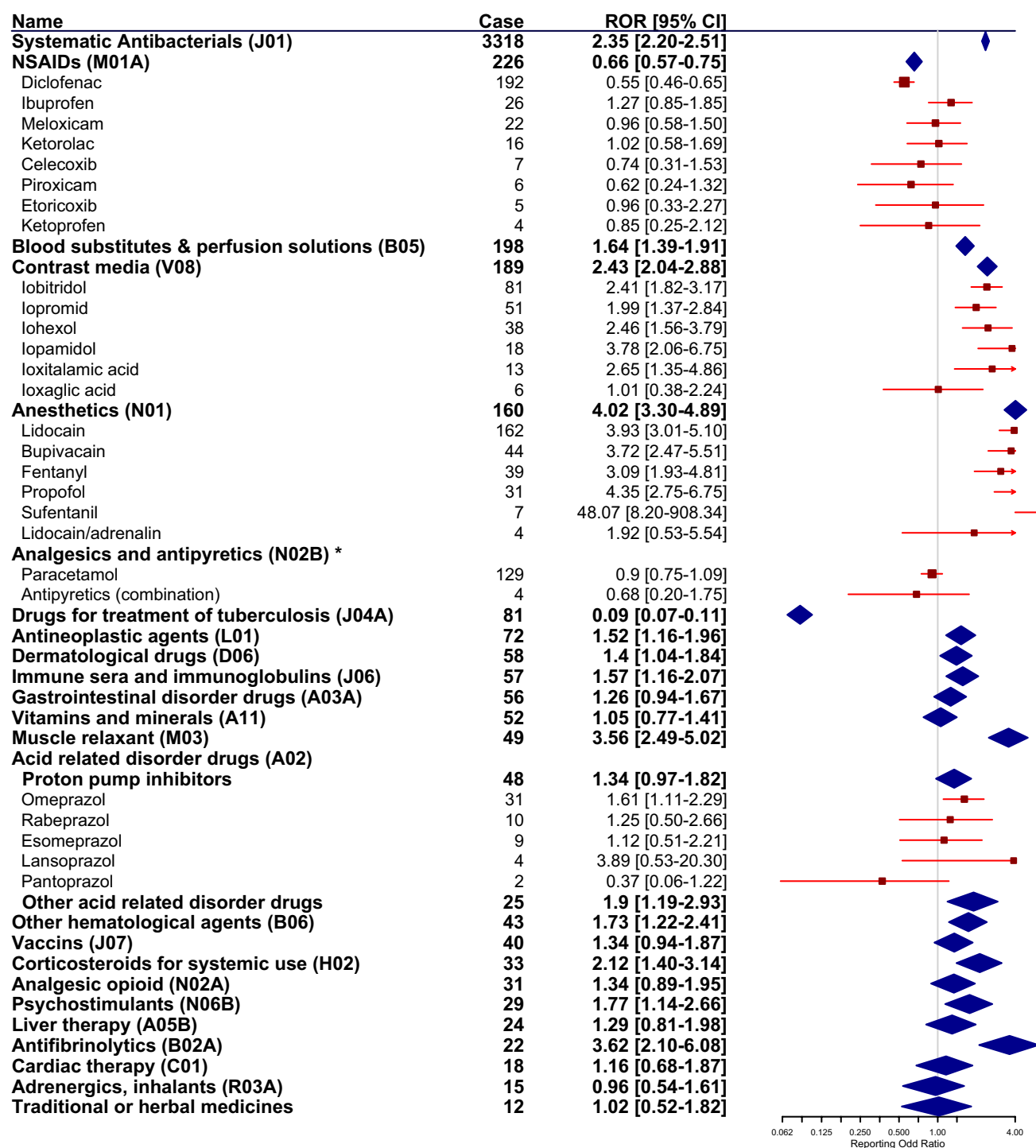


Fig. 5 Distribution of pharmacological groups in drug-induced anaphylaxis. *Including all paracetamol-containing combinations

in Vietnam. We recorded an overall annual incidence of 5.18 DIA cases per 100,000 Vietnamese inhabitants during this study period. Globally, the annual incidence of anaphylaxis, taking all causes into account, ranged from 3.2 to 49.8 cases per 100,000 people, with medication proving a major trigger factor [23, 24]. Taking into consideration that

under-reporting was about 5–10% [25] and even lower in a developing context, the incidence of DIA estimated in reality could be even higher in other countries. We also observed an increasing trend towards DIA reporting over time. The DIA reporting rate (accounting for >10% of all ADRs) was higher than that recorded in Portugal, the UK and some western

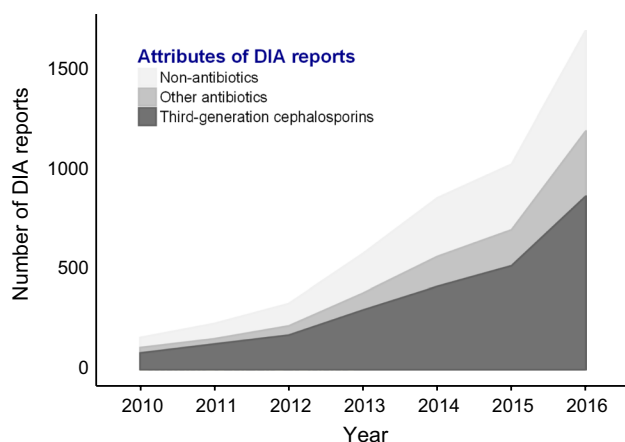


Fig. 6 Reporting trends of antibiotic-induced anaphylaxis. *DIA* drug-induced anaphylaxis

countries [3, 24, 26] and similar to the result reported by Zhao et al. in China [27]. The DIA incidence rate varies from one population to another because of a lack of consensus in terms of the definition of anaphylaxis and analysis of different cohorts. The highest incidence of DIA in our study was observed in patients over 60 years of age (2–3 and 3–5/100,000 males and females, respectively), which

correlates well to findings in an Australian study [24, 28]. In addition, the higher incidence rate in older patients is consistent with increased co-morbidity and greater sensitivity to allergic reactions, as evidenced in earlier studies [28, 29].

The high rate of DIA reporting in Vietnam could be partly explained by the early stages in the development of the pharmacovigilance system as well as improved knowledge of and attitudes towards ADR reporting in the HCW community. In addition, the spontaneous reporting database in Vietnam mostly contains easily detectable ADRs such as anaphylaxis (rapid TTO after drug administration). This could account for the high reporting incidence rate and contribute to a disproportionate database structure and subsequent dilution of signals [26, 30].

Despite the fact that the real DIA-induced mortality rate cannot be calculated from the present data, estimates suggest approximately 2.5% of total ADRs and 0.17 deaths per million inhabitants/year, which does not differ substantially from earlier results in other countries [5, 28, 31]. Besides, delays in the use of epinephrine (noted in many DIA reports, data not shown), and an inconsistent approach to anaphylaxis management prior to the publication of an official guideline, recently led to difficult DIA handling issues in Vietnam [8]. The aforementioned features highlight the major public health issues and the striking differences between

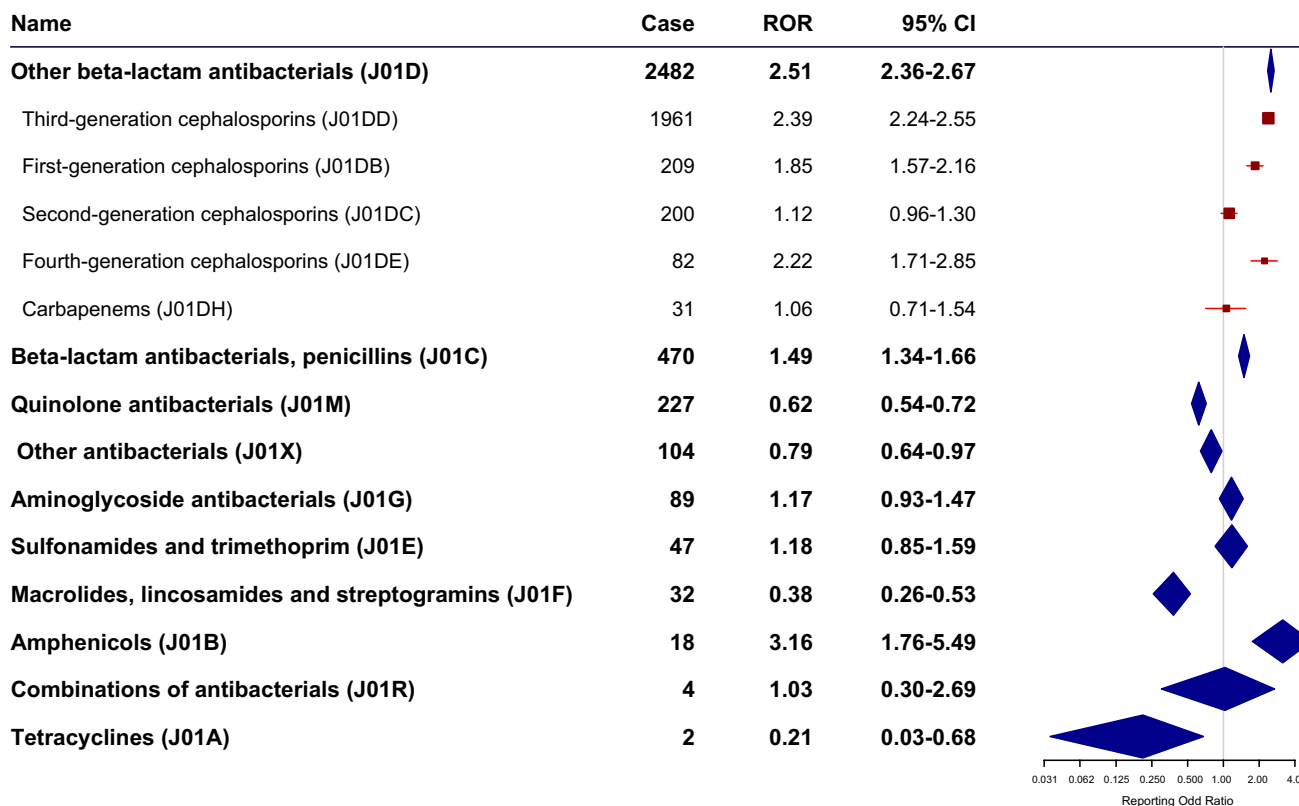


Fig. 7 Antibiotics and predominance of cephalosporins involved in drug-induced anaphylaxis

Table 2 Some drugs and anaphylactic signals typical for Vietnam or developing countries

Drug	Cases	ROR	95% CI
Amoxicillin/sulbactam	65	1.59	1.18–2.10
Glucose and/or electrolyte solution	59	1.97	1.43–2.67
Alpha-chymotrypsin	43	1.75	1.23–2.44
L-ornithine-l-aspartate	40	1.47	0.92–2.26
Tranexamic acid	22	3.62	2.10–6.08

CI confidence interval, ROR reporting odds ratio

developing and developed pharmacovigilance systems. Vietnam continues to differ from other countries in terms of HCW knowledge and practices [32]. The increasing trend towards pharmacist-reported DIA suggests that pharmacists play a key role in DIA notification. The contribution of pharmacists to the NPDV could be a potential catalyst in developing pharmacovigilance systems [33, 34], especially the new pharmacovigilance system in Vietnam.

According to a worldwide study, DIA can occur at any age, with women being more affected than men [35]. This may be due to a gender-related variation in drug consumption. However, our findings showed a gender ratio variation in DIA between age groups. For example, males were affected even more frequently than females ($p < 0.05$) in the specific 0–19 years age group.

4.2 Drug-Induced Anaphylaxis Through High-Volume Consumption

Overuse of antibiotics is still a major health issue in Vietnam [36–38]. Patients can easily buy over-the-counter antibiotics in the community pharmacies—hence the incidence of community DIA cannot be estimated. Data used for health insurance refunds (in-house data) and the number of marketing authorisations for imported antibiotics show a significant trend towards high-volume antibiotic consumption amongst the Vietnamese population [39]. In the context of popular use or even overuse in community and hospital settings, prevention of ADRs seems impossible. There is an obvious link between the use of antibiotics and the high rate of drug-related anaphylaxis in Vietnam. Given the vast number of drugs with marketing authorisations and active substance overlap in Vietnam, it seems difficult to identify and manage specific antibiotics [39]. In this study, systemic antibiotics, especially β -lactams, were responsible for the majority of DIA reports, and three pharmacological classes generating significant signals (J01B, J01C, J01D) were also widely used by the Vietnamese population. Whereas penicillins were mostly reported in relation to DIA in developed countries [3, 40], C3G use was the main cause of DIA in Vietnam, with signal generation. This finding is consistent

with results recorded in China, confirming the higher risks related to these drugs [27].

In terms of specific drugs, cefotaxime, ceftriaxone and ceftazidime were the main three causes of DIA. The use of these C3Gs could reflect the severity of antibiotic resistance in the country. In addition, the anaphylactic signals generated by fourth-generation cephalosporins and carbapenems paint an alarming picture and should act as a significant ‘wake-up call’ in terms of antibiotic use in Vietnam [41]. Furthermore, the irrational use of these drugs was commonly observed in clinical practice in Vietnam [42]. Steps should therefore be taken to promote the knowledge, attitude and practice of HCWs vis-à-vis anaphylaxis, rational antibiotic use and ADR reporting, thereby ensuring the sustainable development of pharmacovigilance in Vietnam.

4.3 Assumed Impact of Medication Error and Drug Quality on Anaphylactic Issues in Resource-Limited Countries

Apart from exposing the ‘allergenic’ role of active substances in suspect drugs, anaphylaxis could potentially stem from medication errors or drug-quality issues. The unexplained signals generated for glucose or electrolyte solutions could corroborate the above hypothesis. In addition, many anaphylaxis cases were included in the list of ADRs suspected in conjunction with Vietnamese drug-quality issues [11]. Drug quality continues to be a significant problem around the globe, especially in developing countries, and could cause serious ADRs including anaphylaxis [43]. Recent studies have shown that the generation of signals from a pharmacovigilance database could be a valuable tool in addressing the issue [44, 45]. Medication errors, on the other hand, remain another significant problem that has recently emerged in Vietnam [46]. Basically, anaphylactic symptoms could rapidly appear following incorrect administration of intravenous medication (‘speed shock’) [47, 48]. Given limited nursing experience and the hospital over-load situation in Vietnam, medication errors are unlikely to be prevented [49–51].

The overlap of medication error, drug quality and adverse reactions poses a real challenge in any assessment to establish precise causality [52]. Despite appropriate diagnosis of anaphylaxis by determining several markers to confirm or rule out drug-related causes [53], routine application seems more complex in a developing context. Hence, the specific generation of anaphylactic signals in this study could distinguish the Vietnamese pharmacovigilance system from other developed systems.

4.4 Special Signals Unique to Low- and Middle-Income Countries

Compared with worldwide DIA studies involving the use of global pharmacovigilance databases, our findings highlighted some unique characteristics and typical signals in other developing countries [26, 27]. In addition to common causes of anaphylaxis involving NSAIDs and anaesthetics, we also detected interesting signals relating to drugs that are not commonly used outside developing countries. At the time of this study, alpha-chymotrypsin is no longer marketed in western countries, and drug-related safety profiles are very limited. Alpha-chymotrypsin is only used in some developing countries (mostly Vietnam and China) and its robust anaphylactic signal shows that the risk intensified recently regardless of therapeutic efficacy *per se*. The finding was consistent with the emerging signal of alpha-chymotrypsin-related anaphylactic shock established by WHO-UMC [54].

Moreover, although the signal related to l-ornithine-l-aspartate was not statistically generated, we found 40 DIA cases related to this drug. The literature search did not reveal much information about this drug and the *VigiBase*[®] outcome shows that related ICSRs were not commonly reported outside developing countries [55]. Consequently, this raises the question as to whether some drugs are withdrawn from western countries and ‘reintroduced’ in developing countries. The finding highlighted the need for systematic re-evaluation of the benefit/risk ratio in order to safeguard public health [56, 57].

4.5 Other Drugs with Notable Comments

The high frequency and signals related to contrast agents and drugs used in anaesthesia are well documented and our results showed similar results [26, 58]. The findings also indicate that the anaphylactic risk associated with non-ionic contrast agents is higher than that linked to ionic agents [59, 60]. In anaesthesia and a perioperative setting, patients are normally given a number of drugs and the exact cause is difficult to identify [61]. Hence, greater attention to detail and continuous training in anaphylaxis and related risks are essential for radiologists and anaesthetists. In addition, the signal generation for PPIs (omeprazole) in our study is similar to the results recorded by Montañez et al. [62]. The appropriate use of this group can help to reduce severe risks amongst the general population [63]. Despite its rare occurrence with only several case reports being highlighted in the literature [64, 65], tranexamic acid-induced anaphylaxis showed a relatively high ROR in our study. We highlighted the uncommon anaphylactic risks associated with tranexamic acid and omeprazole through a population-based database, which reflects some differences in a social context

and confirms the capacity of proactive signal generation in Vietnam. Furthermore, anaphylaxis could be recorded and managed by clinical-based networks in western countries [66–68]. However, spontaneous reporting via the unique hospital-based registry was used for recording anaphylactic issues in Vietnam. Hence, NPVD findings contributed significantly to the understanding of anaphylaxis and related risk management in this country.

4.6 Strengths and Limitations

The study has some limitations. Firstly, under-reporting and missing information could not always be avoided due to the spontaneous nature of the reports. Since real adverse drug reactions within the community are not always reported in full to pharmacovigilance centres, risks may be underestimated. Secondly, the considerable increase in total ADRs reported to NDIADRMV could partly contribute to the significant increasing trend in DIA between 2010 and 2016. Besides, some factors relating to the resource-limited context in Vietnam and potentially influencing the disproportionality analysis were not taken into account in this study [11]. Similarly, the fact that real data for specific drug consumption were not available proved to be a major obstacle in interpreting the signals. However, we used the commonly accepted definition of anaphylaxis (given at the Second Symposium on the Definition and Management of Anaphylaxis) to evaluate cases of anaphylaxis. Furthermore, a case-by-case evaluation with narrative description enhanced the accuracy of the analysis and eliminated classification bias. The missing data were eliminated and multivariate case/non-case analysis was also applied to generate the signals. Therefore, these findings and the follow-up signals could be indicative of further strengthening of anaphylaxis management in this country.

5 Conclusion

Our study shows an overall picture of DIA in Vietnam from a pharmacovigilance perspective coupled with distinguishing features from developed countries. These results also show that some factors could considerably influence the incidence of DIA in a developing context, namely high antibiotic consumption, safety concerns relating to drugs not marketed in developed countries, drug quality and medication error. Antibiotics (especially C3G) were shown to be the main cause of DIA. Radio contrast agents, NSAIDs, PPIs and anaesthetic drugs were also implicated in DIA in Vietnam. The data gleaned from our study and signals generated by certain drugs can be considered in assessing their benefit/risk ratio in order to preclude serious ADRs and proactively protect public health in Vietnam. Signal follow-up and greater correlation with other medical data should be

applied in order to identify, manage and reduce the drug-related risks more effectively in Vietnam.

Author contributions Study designed by H-AN, D-HN, T-BN. Research carried out by K-DN, TT-LL, H-AN (Jr), B-VD, T-NN. Data analysed by K-DN. New methods or models contributed by K-DN, H-AN, HB, D-HV. Paper written by K-DN, H-AN, D-HV, J-LM, HB.

Compliance with Ethical Standards

Funding The National Centre for Drug Information and Adverse Drug Reaction Monitoring acknowledges support from the National WHO Office in Vietnam (involved in signal detection: WHO Reference 2017/716670-0; PO Number 201735388). Khac-Dung Nguyen acknowledges the French Embassy in Hanoi and the Pierre Fabre Foundation for their financial support of his doctoral studies at the UMR 1027 INSERM–University Toulouse III, France, in close collaboration with the National Centre for Drug Information and Adverse Drug Reaction Monitoring, Hanoi University of Pharmacy, Hanoi, Vietnam. No other sources of funding were used to assist in the preparation of this article.

Conflict of interest Khac-Dung Nguyen, Hoang-Anh Nguyen, Dang-Hoa Nguyen, Thanh-Binh Nguyen, Dinh-Hoa Vu, Thi Thuy-Linh Le, Hoang-Anh Nguyen (Jr), Bich-Viet Dang, Trung-Nguyen Nguyen, Jean-Louis Montastruc, and Haleh Bagheri have no conflicts of interest that are directly relevant to the content of this manuscript.

References

- Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J. Allergy Clin. Immunol.* 2004;113:832–6.
- Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J. Allergy Clin. Immunol.* 2006;117:391–7.
- Ribeiro-Vaz I, Marques J, Demoly P, Polónia J, Gomes ER. Drug-induced anaphylaxis: a decade review of reporting to the Portuguese Pharmacovigilance Authority. *Eur. J. Clin. Pharmacol.* 2013;69:673–81.
- Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ.* 2003;327:1222–5.
- Tang MLK, Osborne N, Allen K. Epidemiology of anaphylaxis. *Curr. Opin. Allergy Clin. Immunol.* 2009;9:351–6.
- Bochner BS, Lichtenstein LM. Anaphylaxis. *N. Engl. J. Med.* 1991;324:1785–90.
- Mertes PM, Guttormsen AB, Harboe T, Johansson SGO, Florvaag E, Husum B, et al. Can spontaneous adverse event reporting systems really be used to compare rates of adverse events between drugs? *Anesth. Analg.* 2007;104:471–2.
- Ministry of Health. Circular 51/2017/TT-BYT Guidelines on prevention, diagnosis and management of anaphylaxis. 2017. <http://canhgiacduoc.org.vn/SiteData/3/UserFiles/Thong%20tu%20Huong%20dan%20phong,%20chan%20doan%20va%20xu%20tri%20soc%20phan%20ve%202017.pdf>.
- Le TTL. Evaluation of signal detection and management of anaphylactic reactions from spontaneous reporting database in Vietnam [Thesis in Vietnamese]. Hanoi University of Pharmacy. 2015.
- Dang BV, Nguyen TB, Nguyen HA, Tran TN, Vo TTT, Pham PL. Analysis of antibiotic-associated anaphylaxis in Vietnam in the period of 2010 – 2015 [in Vietnamese]. *Pharmacology Research and Drug Information Journal* (ISSN 1859-364X). http://www.hup.edu.vn/cpbdv/pqlkh/noidung/Lists/TapchiNCDTTT/View_Detail.aspx?ItemID=22. Accessed 15 May 2018.
- Nguyen K-D, Nguyen P-T, Nguyen H-A, Roussin A, Montastruc J-L, Bagheri H, et al. Overview of pharmacovigilance system in Vietnam: lessons learned in a resource-restricted Country. *Drug Saf.* 2018;41:151–9.
- ICH. Efficacy Guidelines: E2A-E2F Pharmacovigilance. 2018. <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>. Accessed 29 Jun 2018.
- Ministry of Health. National Guideline of Pharmacovigilance. According to Decision 2111/QĐ-BYT from Ministry of Health (Vietnam). 2015. http://canhgiacduoc.org.vn/SiteData/3/UserFiles/HDQCGD%20Final%2029_05_2015.pdf. Accessed 24 Dec 2016.
- WHO Collaborating Centre for International Drug Monitoring. WHO Adverse Reaction Terminology (WHO-ART). 2012. <http://www.unc-products.com/>. Accessed 18 Sep 2017.
- Olsson S. The role of the WHO programme on international drug monitoring in coordinating worldwide drug safety efforts. *Drug Saf.* 1998;19:1–10.
- Moore N, Kreft-Jais C, Haramburu F, Noblet C, Andrejak M, Ollagnier M, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol.* 1997;44:513–8.
- van Puijtenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol. Drug Saf.* 2002;11:3–10.
- Faillie J-L. Case-non case studies: principles, methods, bias and interpretation [Article in French]. *Therapie.* 2018;73:247–55.
- EMA. Screening for adverse reactions in EudraVigilance (EMA/849944/2016). 2016. https://www.ema.europa.eu/documents/other/screening-adverse-reactions-eudravigilance_en.pdf.
- General Statistics Office of Vietnam. Population and employment : area, population and population density by province. www.gso.gov.vn2017. https://www.gso.gov.vn/default_en.aspx?tabid=774. Accessed 10 Oct 2017.
- CRAN. R: The R Project for Statistical Computing. 2017. <https://www.r-project.org/>. Accessed 30 Aug 2017.
- US Department of Commerce. US Census Bureau: Population. 2017. <https://www.census.gov/data-tools/demo/idb/region.php?N=%20Results%20&T=3&A=separate&RT=0&Y=2010,2011,2012,2013,2014,2015,2016&R=-1&C=VM>. Accessed 28 Jun 2018.
- Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J. Allergy Clin. Immunol.* 2008;122:1161–5.
- Thong BY-H, Tan T-C. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol.* 2011;71:684–700.
- Hazell L, Shakir SAW. Under-reporting of adverse drug reactions : a systematic review. *Drug Saf.* 2006;29:385–96.
- Leone R, Conforti A, Venegoni M, Motola D, Moretti U, Meneghelli I, et al. Drug-induced anaphylaxis : case/non-case study based on an italian pharmacovigilance database. *Drug Saf.* 2005;28:547–56.
- Zhao Y, Sun S, Li X, Ma X, Tang H, Sun L, et al. Drug-induced anaphylaxis in China: a 10 year retrospective analysis of the

- Beijing Pharmacovigilance Database. *Int J Clin Pharm*. 2017. <https://doi.org/10.1007/s11096-017-0535-2>.
28. Liew WK, Williamson E, Tang MLK. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol*. 2009;123:434–42.
29. Park H-K, Kang M-G, Yang M-S, Jung J-W, Cho S-H, Kang H-R. Epidemiology of drug-induced anaphylaxis in a tertiary hospital in Korea. *Allergol Int*. 2017;66:557–62.
30. Moore N, Kreft-Jais C, Haramburu F, Noblet C, Andrejak M, Ollagnier M, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol*. 1997;44:513–8.
31. Wang DY, Forslund C, Persson U, Wiholm BE. Drug-attributed anaphylaxis. *Pharmacoepidemiol Drug Saf*. 1998;7:269–74.
32. Trinh HT, Nguyen HTL, Pham VTT, Ba HL, Dong PTX, Cao TTB, et al. Hospital clinical pharmacy services in Vietnam. *Int J Clin Pharm*. 2018;20:33. <https://doi.org/10.1007/s11096-018-0633-9>.
33. van Grootheest K, van Puijenbroek EP, de Jong-van den Berg LTW. Do pharmacists' reports of adverse drug reactions reflect patients' concerns? *Pharm World Sci*. 2004;26:155–9.
34. van Grootheest AC, de Jong-van den Berg LTW. The role of hospital and community pharmacists in pharmacovigilance. *Res Social Adm Pharm*. 2005;1:126–33.
35. Montastruc J-L, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. *Fundam Clin Pharmacol*. 2002;16:343–6.
36. Nguyen KV, Thi Do NT, Chandna A, Nguyen TV, Pham CV, Doan PM, et al. Antibiotic use and resistance in emerging economies: a situation analysis for Viet Nam. *BMC Public Health*. 2013;13:1158.
37. Phu VD, Wertheim HFL, Larsson M, Nadjm B, Dinh Q-D, Nilsson LE, et al. Burden of Hospital Acquired Infections and Antimicrobial Use in Vietnamese Adult Intensive Care Units. *PLoS One*. 2016;11:e0147544.
38. Thu TA, Rahman M, Coffin S, Harun-Or-Rashid M, Sakamoto J, Hung NV. Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *Am J Infect Control*. 2012;40:840–4.
39. Chu QT. Trends on imported medicine and associated factors during 2006–2014 [Doctoral Thesis in Vietnamese Code 62.72.04.12]. 2017.
40. Salvo F, Polimeni G, Cutroneo P, Leone R, Confortic A, Moretti U, et al. Allergic reactions to oral drugs: a case/non-case study from an Italian spontaneous reporting database (GIF). *Pharmacol. Res.* 2008;58:202–7.
41. Minh NT, Tuyền NT, Thắng TN, Hùng DD, Nga CT, Phương NT, et al. Survey on the consumption of carbapenem in Bach Mai Hospital in the period 2012–2016 [in Vietnamese]. *Vietnam Pharm. J*. 2017;57:63–6.
42. Mao W, Vu H, Xie Z, Chen W, Tang S. Systematic review on irrational use of medicines in China and Vietnam. *PLOS One*. 2015;10:e0117710.
43. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. *Br J Clin Pharmacol*. 2014;78:218–43.
44. Trippe ZA, Brendani B, Meier C, Lewis D. Identification of substandard medicines via disproportionality analysis of individual case safety reports. *Drug Saf*. 2017;40:293–303.
45. Juhlin K, Karimi G, Andér M, Camilli S, Dheda M, Har TS, et al. Using VigiBase to identify substandard medicines: detection capacity and key prerequisites. *Drug Saf*. 2015;38:373–82.
46. Cheema RK. Seven people die after dialysis treatment in Vietnam. 2017. <https://today.mims.com/seven-people-die-after-dialysis-treatment-in-vietnam>. Accessed 21 May 2018.
47. Milbert AH. Infusion reactions with special reference to “speed shock”. *Am J Surg*. 1934;26:479–85.
48. Hirshfeld S, Hyman HT, Wanger JJ. Influence of velocity on the response to intravenous injections. *Arch Intern Med (Chic)*. 1931;47:259–87.
49. Van Tuong P, Phuong TTM, Anh BTM, Nguyen THT. Assessment of injection safety in Ha Dong General Hospital, Hanoi, in 2012. *F1000Res*. 2017 <https://doi.org/10.12688/f1000research.11399.4>.
50. Nguyen H-T, Nguyen T-D, van den Heuvel ER, Haaijer-Ruskamp FM, Taxis K. Medication errors in Vietnamese Hospitals: prevalence, potential outcome and associated factors. *PLOS One*. 2015;10:e0138284.
51. Fahimi F, Ariapanah P, Faizi M, Shafaghi B, Namdar R, Ardakani MT. Errors in preparation and administration of intravenous medications in the intensive care unit of a teaching hospital: an observational study. *Aust Crit Care*. 2008;21:110–6.
52. Ralph Edwards I. Causality assessment in pharmacovigilance: still a challenge. *Drug Saf*. 2017;40:365–72.
53. Tomasiak-Łozowska MM, Klimek M, Lis A, Moniuszko M, Bodzenta-Łukaszyk A. Markers of anaphylaxis—a systematic review. *Adv Med Sci*. 2018;63:265–77.
54. Grundmark B, Isah AO. Chymotrypsin and anaphylactic shock, a continuing safety issue. *Upps. Monit. Cent.—WHO Signal*. 2016:5–7.
55. The Uppsala Monitoring Centre. VigiBase®. 2018. <https://www.who-umc.org/vigibase/vigibase/>. Accessed 18 Jul 2018.
56. Rågo L, Santoso B. Drug regulation: history, present and future. In: *Drug benefits and risks: international textbook of clinical pharmacology*. IOS Press and Uppsala Monitoring Centre. 2008. http://www.who.int/medicines/technical_briefing/tbs/Drug_Regulation_History_Present_Future.pdf. Accessed 18 Sep 2018.
57. National Assembly of Vietnam. Law on pharmacy revised. 2016. <http://vbpl.vn/TW/Pages/vbpqen-toanvan.aspx?ItemID=11099>. Accessed 1 Jul 2016.
58. Caimmi S, Caimmi D, Bernardini R, Caffarelli C, Crisafulli G, Pingitore G, et al. Perioperative anaphylaxis: epidemiology. *Int J Immunopathol Pharmacol*. 2011;24:S21–6.
59. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology*. 1990;175:621–8.
60. Maddox TG. Adverse reactions to contrast material: recognition, prevention, and treatment. *Am Fam Physician*. 2002;66:1229–34.
61. Mertes PM, Volcheck GW, Garvey LH, Takazawa T, Platt PR, Guttormsen AB, et al. Epidemiology of perioperative anaphylaxis. *Presse Méd*. 2016;45:758–67.
62. Montañez MI, Mayorga C, Bogas G, Barrionuevo E, Fernandez-Santamaria R, Martin-Serrano A, et al. Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis. *Front Immunol*. 2017;8:614.
63. Nghiem TTL. La prophylaxie d'ulcère de stress par les inhibiteurs de la pompe à protons: Étude de bon usage à l'hôpital Thanh Nhan, Hanoi. 2015. <http://canhgiacduoc.org.vn/SiteData/3/UserFiles/LV%202015%20Nghien%20Thi%20Thuy%20Linh-%20Mekong.pdf>. Accessed 18 July 2018.
64. Chiem J, Ivanova I, Parker A, Krengel W, Jimenez N. Anaphylactic reaction to tranexamic acid in an adolescent undergoing posterior spinal fusion. *Paediatr Anaesth*. 2017;27:774–5.
65. Li PH, Trigg C, Rutkowski R, Rutkowski K. Anaphylaxis to tranexamic acid—a rare reaction to a common drug. *J Allergy Clin Immunol Pract*. 2017;5:839–41.

66. Renaudin J-M, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin D-A. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy*. 2013;68:929–37.
67. González-Pérez A, Aponte Z, Vidaurre CF, Rodríguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J. Allergy Clin. Immunol.* 2010;125(1098–1104):e1.
68. Takazawa T, Oshima K, Saito S. Drug induced anaphylaxis in the emergency room. *Acute Med Surg.* 2017;4:235–45.

Affiliations

Khac-Dung Nguyen^{1,2} · Hoang-Anh Nguyen¹ · Dinh-Hoa Vu¹ · Thi Thuy-Linh Le¹ · Hoang-Anh Nguyen Jr.¹ · Bich-Viet Dang¹ · Trung-Nguyen Nguyen³ · Dang-Hoa Nguyen¹ · Thanh-Binh Nguyen⁴ · Jean-Louis Montastruc² · Haleh Bagheri²

¹ The National Drug Information and Adverse Drug Reaction Monitoring Centre, Hanoi University of Pharmacy, Hanoi, Vietnam

² Laboratoire de Pharmacologie Médicale et Clinique, Faculté de Médecine de l'Université Paul-Sabatier (Medical and Clinical Pharmacology Laboratory, Faculty of Medicine, Paul-Sabatier University) and Centre Hospitalier Universitaire de Toulouse (Toulouse University Hospital Centre), Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacoépidémiologie et d'Information sur le Médicament (Midi-Pyrenees Centre for Pharmacovigilance,

Pharmacoepidemiology and Drug Information), UMR INSERM 1027, Toulouse, France

³ Poison Control Centre, Bach Mai Hospital, Hanoi, Vietnam

⁴ Department of Pharmacy Management and Pharmacoeconomics, Hanoi University of Pharmacy, Hanoi, Vietnam

Title: Drug-Induced Anaphylaxis in a Vietnamese Pharmacovigilance Database: Trends and Specific Signals from a Disproportionality Analysis

Journal: Drug Safety

Authors: Khac-Dung Nguyen ^{a,b}, Hoang-Anh Nguyen ^a, Dinh-Hoa Vu ^a, Thi Thuy-Linh Le ^a, Hoang-Anh Nguyen (jr) ^a, Bich-Viet Dang ^a, Trung-Nguyen Nguyen ^c, Dang-Hoa Nguyen ^a, Thanh-Binh Nguyen ^d, Jean-Louis Montastruc ^b, Haleh Bagheri ^b

Author affiliation: ^a The National Centre of Drug Information and Adverse Drug Reaction Monitoring, Hanoi University of Pharmacy, Hanoi, Vietnam. ^b Laboratoire de Pharmacologie Médicale et Clinique, Faculté de Médecine de l'Université Paul-Sabatier (Medical and Clinical Pharmacology Laboratory, Faculty of Medicine, Paul-Sabatier University) and Centre Hospitalier Universitaire de Toulouse (Toulouse University Hospital Centre), Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacoépidémiologie et d'Information sur le Médicament (Midi-Pyrenees Centre for Pharmacovigilance, Pharmacoepidemiology and Drug Information), UMR INSERM 1027, Toulouse, France. ^c Poison Control Centre, Bach Mai Hospital, Hanoi, Vietnam. ^d Department of Pharmacy Management and Pharmacoeconomics, Hanoi University of Pharmacy

Email of Corresponding author: haleh.bagheri@univ-tlse3.fr

Electronic Supplementary Material 1: Codes and results of Poisson regression

1 Code for Poisson regression model adjusted for the overall Vietnamese population

```
(model.poisson = anaph.rate.pop %>% glm(formula=DIACase ~ as.numeric(Year),
offset = log(Vietnam.pop), family = poisson(link="log"))) %>%summary()

##
## Call:
## glm(formula = DIACase ~ as.numeric(Year), family = poisson(link = "log"),
##      data = ., offset = log(Vietnam.pop))
##
## Deviance Residuals:
##      1       2       3       4       5       6       7
## -0.4062 -0.8457 -1.5267  2.2503  2.9214 -3.3779  0.5771
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)   -13.54108    0.04774 -283.66  <2e-16 ***
## as.numeric(Year)  0.37368    0.00847  44.12  <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 2321.006  on 6  degrees of freedom
## Residual deviance:   28.553  on 5  degrees of freedom
## AIC: 89.222
##
## Number of Fisher Scoring iterations: 3
```

```
exp(model.poisson$coef)
```

```
##      (Intercept) as.numeric(Year)
##      1.315782e-06      1.453079e+00
```

2 Code for Poisson regression model adjusted for the total ADR reports

```
(model.poisson = anaph.rate.pop %>% glm(formula = DIACase ~ as.numeric(Year),
offset = log(totalADR), family = poisson(link = "log"))) %>% summary()
```

```
##
## Call:
## glm(formula = DIACase ~ as.numeric(Year), family = poisson(link = "log"),
##      data = ., offset = log(totalADR))
##
## Deviance Residuals:
##      1      2      3      4      5      6      7
##  2.0100  1.6672  2.0056 -0.5418 -3.5715 -4.4934  4.7731
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)   -2.64048    0.05051  -52.28  <2e-16 ***
## as.numeric(Year)  0.11787    0.00901   13.08  <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 247.992  on 6  degrees of freedom
## Residual deviance:  66.864  on 5  degrees of freedom
## AIC: 127.53
##
## Number of Fisher Scoring iterations: 4
```

```
exp(model.poisson$coef)
```

```
##      (Intercept) as.numeric(Year)
##      0.07132668      1.12509442
```

Title: Drug-Induced Anaphylaxis in a Vietnamese Pharmacovigilance Database: Trends and Specific Signals from a Disproportionality Analysis

Journal: Drug Safety

Authors: Khac-Dung Nguyen ^{a,b}, Hoang-Anh Nguyen ^a, Dinh-Hoa Vu ^a, Thi Thuy-Linh Le ^a, Hoang-Anh Nguyen (jr) ^a, Bich-Viet Dang ^a, Trung-Nguyen Nguyen ^c, Dang-Hoa Nguyen ^a, Thanh-Binh Nguyen ^d, Jean-Louis Montastruc ^b, Haleh Bagheri ^b

Author affiliation: ^a The National Centre of Drug Information and Adverse Drug Reaction Monitoring, Hanoi University of Pharmacy, Hanoi, Vietnam. ^b Laboratoire de Pharmacologie Médicale et Clinique, Faculté de Médecine de l'Université Paul-Sabatier (Medical and Clinical Pharmacology Laboratory, Faculty of Medicine, Paul-Sabatier University) and Centre Hospitalier Universitaire de Toulouse (Toulouse University Hospital Centre), Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacoépidémiologie et d'Information sur le Médicament (Midi-Pyrenees Centre for Pharmacovigilance, Pharmacoepidemiology and Drug Information), UMR INSERM 1027, Toulouse, France. ^c Poison Control Centre, Bach Mai Hospital, Hanoi, Vietnam. ^d Department of Pharmacy Management and Pharmacoeconomics, Hanoi University of Pharmacy

Email of Corresponding author: haleh.bagheri@univ-tlse3.fr

Electronic Supplementary Material 2: List of drugs suspected and signal calculation (number of DIA reports>5)

Drug	Cases	ROR	95% CI
Cefotaxime	939	1.98	1.82-2.15
Ceftriaxone	486	2.06	1.84-2.29
Ceftazidime	421	1.94	1.72-2.18
Diclofenac	192	0.55	0.46-0.65
Lidocaine	162	3.93	3.01-5.10
Ciprofloxacin	161	0.71	0.59-0.84
Cefuroxime	143	1.08	0.89-1.29
Paracetamol	129	0.89	0.75-1.09
Amoxicillin	121	1.25	1.08-1.43
Cefoperazone	114	2.19	1.83-2.62
Cefalexin	106	2.02	1.60-2.54
Amoxicillin/clavulanic acid	88	1.26	0.97-1.62
Iobitridol	81	2.41	1.82-3.17
Gentamicin	77	1.43	1.08-1.86
Levofloxacin	77	0.48	0.37-0.62

Cefoperazone/sulbactam	73	2.6	1.91-3.50
Metronidazole	72	1.17	0.90-1.51
Amoxicillin/sulbactam	65	1.59	1.18-2.10
Cefepime	60	2.21	1.61-3.00
Glucose and/or electrolytes IV solution	59	1.97	1.43-2.67
Ceftizoxime	57	1.83	1.34-2.46
Ampicillin	56	1.42	1.14-1.75
Ampicillin/sulbactam	55	1.21	0.88-1.65
Sulfamethoxazole/trimethoprim	55	1.19	0.86-1.61
Iopromide	51	1.99	1.37-2.84
Vancomycin	50	0.62	0.45-0.83
Streptomycin	48	0.14	0.10-0.18
Cefazolin	45	1.75	1.24-2.41
Bupivacaine	44	3.72	2.47-5.51
Alphachymotrypsin	43	1.75	1.23-2.44
L-ornithine-l-aspartate	40	1.47	0.92-2.26
Fentanyl	39	3.09	1.93-4.81
Iohexol	38	2.46	1.56-3.79
Cefadroxil	37	1.94	1.31-2.80
Amikacin	36	1.56	1.03-2.28
Blood products	35	1.71	1.14-2.50
Penicillin V	35	6.54	3.81-11.28
Tetanus antitoxin	35	0.98	0.66-1.41
Propofol	31	4.35	2.75-6.75
Omeprazole	31	1.61	1.11-2.29
Oxaliplatin	31	2.23	1.37-3.51
Methylprednisolone	29	2.19	1.43-3.25
Oxytocin	28	1.64	1.06-2.46
Cefamandole	28	1.4	0.89-2.11
Cefpirome	26	2.19	1.38-3.37
Ibuprofen	26	1.27	0.85-1.85
Piracetam	25	1.88	1.18-2.90
Vitamins and/or minerals	24	1.01	0.63-1.56

Rifampicin/isoniazid/pyrazinamide	24	0.15	0.10-0.21
Atracurium	23	16.39	7.91-36.41
Tranexamic acid	22	3.62	2.10-6.08
Meloxicam	22	0.96	0.58-1.50
Ranitidine	22	2.52	1.39-4.33
Tobramycin	22	1.07	0.61-1.78
Chloramphenicol	21	3.01	1.68-5.20
Ethambutol	21	0.11	0.07-0.16
Salbutamol	19	0.96	0.54-1.61
Ofloxacin	19	0.63	0.54-0.72
Cefaclor	18	1.8	1.04-2.98
Iopamidol	18	3.78	2.06-6.75
Ticarcilin/clavulanic acid	18	2.18	1.22-3.72
Piperacillin/tazobactam	17	1.41	0.79-2.39
Paclitaxel	17	1.42	0.72-2.61
Amino acids	16	1.68	0.96-2.78
Ketorolac	16	1.02	0.58-1.69
Cefixime	16	0.5	0.28-0.83
Clindamycin	16	0.21	0.11-0.38
Meropenem	16	1.23	0.58-2.34
Rifampicin	15	0.11	0.08-0.15
Imipenem/cilastatin	15	0.76	0.42-1.29
Benzylpenicillin	14	2.38	1.26-4.22
Cefmetazole	14	1.21	0.65-2.08
Cefradine	14	1.75	0.94-3.04
Drotaverine	14	0.77	0.40-1.34
Ioxitalamic acid	13	2.65	1.35-4.86
Hyoscine N-Butylbromide	13	2.27	1.04-4.59
Glutathione	12	3.65	1.70-7.56
Oxacillin	12	1.47	0.86-2.39
Terpin/codeine	12	2.88	1.40-5.56
Vaccines	12	1.34	0.94-1.87
Clarithromycin	12	0.55	0.23-1.12

Cefalotin	11	1.49	0.73-2.83
Misoprostol	11	0.47	0.24-0.82
Carboplatin	11	1.26	0.57-2.49
Chloramphenicol	10	1.93	0.91-3.71
Nefopam	10	1.1	0.53-2.06
Penicillin (no classification)	10	2.99	2.20-4.01
Azithromycin	10	0.78	0.36-1.47
Diazepam	10	0.35	0.16-0.67
Midazolam	10	10.58	3.66-32.23
Tinidazole	10	0.85	0.38-1.68
Rifampicin/isoniazid/pyrazinamide/ethambutol	10	0.13	0.05-0.25
Rabeprazole	10	1.25	0.50-2.66
Albumin	9	1.56	0.85-2.68
Esomeprazole	9	1.12	0.51-2.21
Floctafenine	9	3.8	1.61-8.39
Hydrocortisone	9	5.62	2.12-14.43
Pethidine	9	1.84	0.73-4.04
Acetylleucin	8	3.36	1.34-7.79
Suxamethonium	8	7.23	2.71-18.98
Ceftazole	8	0.86	0.35-1.79
Domperidone	8	1.16	0.44-2.56
Celecoxib	7	0.74	0.31-1.53
Furosemide	7	0.76	0.32-1.56
Immunoglobulin	7	13.78	4.71-45.26
Piperacillin	7	1.78	1.10-2.78
Rocuronium bromid	7	5.69	1.93-16.78
Alverine	7	1.35	0.55-2.85
Cefpodoxime	7	0.48	0.18-1.00
Sufentanil	7	48.07	8.20-908.34
Ioxaglic acid	6	1.01	0.38-2.24
Cefoxitin	6	0.94	0.36-2.09
Fluorescein	6	3.26	1.11-8.65
Fosfomycin	6	0.68	0.26-1.47

Imipenem	6	1.1	0.66-1.74
Metoclopramide	6	1.9	0.76-4.13
Piroxicame	6	0.62	0.24-1.32
Pyrazinamide	6	0.09	0.06-0.13