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Unresolved gustatory, olfactory and auditory adverse drug reactions to antibiotic drugs: a survey of spontaneous reporting to Eudravigilance

§Sara Ferraro[1], §Irma Convertino[1], Luca Leonardi[1], Corrado Blandizzi[1,2], Marco Tuccori[1, 2]

[1]Unit of Pharmacology and Pharmacovigilance, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[2]Unit of Adverse Drug Reaction Monitoring, University Hospital of Pisa, Pisa, Italy

§ co-first authors

Corresponding author:

Marco Tuccori,

Unit of Adverse Drug Reactions Monitoring, University Hospital of Pisa, Tuscan Regional Centre of Pharmacovigilance, Via Roma, 55, I-56126 Pisa, Italy

Tel.: +39-050-992071

Fax: +39-050-2218758

Email: m.tuccori@ao-pisa.toscana.it; marco.tuccori@gmail.com

Abstract

Objectives: Sensory adverse drug reactions (ADRs) are generally expected to be transient in nature. However, spontaneous reports describe frequently these events as long-lasting or unresolved. In this study, the authors reviewed the Eudravigilance publicly accessible database to describe the volume and expectedness of potentially unresolved outcomes for gustatory, olfactory and auditory (GOA) suspected ADRs associated with antibiotics for systemic use.

Methods: "Overall" and "GOA" suspected ADRs were extracted from Eudravigilance, to estimate the distribution of their outcomes among different antibiotic groups. Then, the authors identified the drugs contributing to at least 15% of all suspected GOA ADRs observed for the antibiotic groups, and evaluated the expectedness.

Results: The frequency of persistent/permanent outcomes was higher for GOA suspected ADRs, as compared to the overall ones. Unresolved and undetermined outcomes for antibiotic-associated GOA ADRs in Eudravigilance might hide a large number of events with underestimated clinical consequences. Several persistent/permanent antibiotic-associated GOA reactions could be classified as serious and unexpected.

Conclusion: Potential long-lasting or irreversible GOA reactions are often reported for all antibiotics drugs. Further studies are warranted to clarify whether this is an actual safety issue or simply it reflects a general difficulty in outcomes assessment for such reactions.

Key words: antibiotic, quinolone, sensory, gustatory, olfactory, auditory, unresolved, adverse drug reaction

1 Introduction

Irreversible or persistent mild to moderate disabilities can be an important consequence of adverse drug reactions (ADRs) that strongly affect the quality of life. In 2017, the European Medicine Agency (EMA) started a review of the safety of fluoroquinolone and quinolone antibiotics, with a particular focus on the rare disabling, long-lasting and potentially permanent ADRs, mainly involving muscles, tendons, bones and the nervous system, including sensory ADRs. In November 2018, this review culminated with the recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) to suspend the marketing authorization of medicines containing quinolones (cinoxacin, flumequine, nalidixic acid and pipemidic acid) and to restrict the use of fluoroquinolones[1].

Although some sensory alterations are labelled for several antibiotic drugs, these reactions are commonly known to be transient in nature. However, an analysis of taste and smell alterations, performed on the Italian spontaneous ADR reporting database and published in 2011, revealed that the reports for these reactions described frequently long-lasting or unresolved outcomes, not only for fluoroquinolones, but also for other drug classes, including macrolide antibiotics[2]. Furthermore, irreversible auditory adverse reactions are labelled only for few antibiotic drugs, such as gentamycin and vancomycin, for which literature evidence about their ototoxicity is consistent[3–5].

In this study, publicly accessible data collected in the Eudravigilance database were reviewed to describe the extent and expectedness of unresolved outcomes for gustatory, olfactory and auditory (GOA) suspected ADRs reported for antibiotics for systemic use. In particular, this study is aimed at identifying the antibiotics groups that could show a remarkable frequency of potentially persistent or permanent GOA reactions, taking into account the frequency of the same outcomes reported for overall suspected ADRs. Finally, we checked the expectedness of the observed GOA reactions, in order to evaluate whether other classes, besides quinolones, should deserve greater attention by health authorities, due to a possible underestimation of the clinical and social impact of such reactions.

2 Methods

2.1 Data source

In the present study, publicly accessible data of Eudravigilance database of spontaneously reported suspected ADRs (http://www.adrreports.eu/en/search_subst.html), collected up to February 2019, were used.

2.2 Dictionary creation

A dictionary of GOA ADRs, through the selection of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) referring to sensory adverse reactions related to gustatory, olfactory and auditory alterations, was created (Supplementary Table 1 a-c). We excluded those conditions that can cause indirectly gustatory, olfactory and auditory disorders (e.g. traumatic events), and selected PTs that refer to drug-related impairments of impulses from mechanoreceptors (for audition sense) and chemoreceptors (for gustation and olfaction senses) to specific brain areas responsible for signal processing. The dictionary of the drugs of interest (n=137) included every drug of the Anatomical Therapeutic Chemical (ATC) class J01 (antibacterial drugs for systemic use), for which at least a report of ADR was present in the Eudravigilance database (Supplementary Table 2).

2.3 Data extraction

The tool "Online access to suspected side-effect reports", available at www.adrreports.eu, was used to extract drug-event pairs of interest. For each antibiotic drug, the total number of "overall" ADRs as well as the total number and specific events for GOA suspected ADRs were extracted in accordance with PTs reported in the dictionary, as defined above. Each GOA drug-event pair was classified according to its outcome ("fatal", "not recovered/not resolved", "not specified", "recovered/resolved", "recovered/resolved with sequelae", "recovering/resolving", and "unknown"). Fatal outcomes were associated to a lack of detention of resolution of GOA reactions. The outcomes were then organized in three larger groups: defined outcomes ("recovered/resolved"), persistent or permanent outcomes ("not recovered/not resolved", "recovered/resolved with sequelae" and "recovering/resolving") and undetermined outcomes ("not specified", "unknown" and "fatal").

2.4 Data analysis

The extracted data were organized in accordance with third and fourth level of ATC classification and a descriptive analysis was performed. Firstly, we assessed the distribution of defined, persistent/permanent and undetermined outcomes of drug-event pairs (both overall and GOA reactions) associated with third-level ATC classes (pharmacological subgroups). In particular, GOA reactions were analyzed further, allocating them into the three subcategories: gustatory reactions, auditory reactions and olfactory reactions. Pharmacological subgroups that resulted with less than 50 GOA reactions after data extraction were excluded from the analysis, and the distribution of

defined, persistent/permanent and undetermined outcomes, related to overall and GOA reactions were assessed. Then, the antibiotics drugs that contributed with more than 50 GOA reactions to at least 15% of total GOA reactions, extracted for their respective antibiotic groups, were identified. For these drugs, the expectedness of the extracted suspected GOA ADRs was finally evaluated through examination of their respective EMA Summary of Product Characteristics (SPC), or Italian Medicine Agency (AIFA) SPC (when the SPC was not available in the first source). When more than one SPC was available, the SPC of the originator medicinal product was used as reference source. The events included in the "undesirable effects" section (4.8) of SPCs were then compared to the adverse events' PTs found in Eudravigilance. In particular, each PT was defined as "listed" if it was exactly indexed in the SPC of the active compound of interest, while it was defined as "linked" if it was related, for clinical features and severity, to another PT already listed in the reference SPC. All the extracted PTs that were not identified either as listed or as linked were classified as "unlabelled". Any disagreement about this classification was resolved by discussion among the authors. A flowchart of data extraction and allocation is showed in figure 1.

3 Results

According to the selection criteria, 748,798 overall drug-event pairs were extracted. Supplementary Table 3 shows the number of drug-event pairs extracted from Eudravigilance for antibiotics belonging to the therapeutic group J01, according to third- and fourth- levels of ATC classification. Drug-event pairs were classified as overall, GOA, gustatory, olfactory and auditory reactions. Table 1 displays the number of overall reactions for the most reported antibiotics groups, organized by frequency of GOA reactions with details of their outcomes. Seven groups have a percentage of GOA reactions ≥ 1%. Aminoglycosides and macrolides show 5.6% and 4,2%, respectively, followed by imidazole derivatives (2.4%), lincosamides (2%), tetracyclines (1.6%), fluoroquinolones (1.5%) and glycopeptide antibiotic drugs (1%). As shown in Table 1, the frequency of persistent/permanent outcomes of GOA reactions (ranged between 36.3% and 56.1%) results greater than that of the overall ADRs (ranged between 15.4% and 33.9%), except for quinolones, that show the lowest frequency of persistent/permanent overall reactions, but no persistent/permanent GOA reactions. Moreover, among the overall ADRs, persistent/permanent reactions are always less than the undetermined and the defined ones, except for nitrofuran derivatives. The other two outcome categories of

overall reactions are distributed among the drug classes in a quite balanced way. On the contrary, persistent/permanent GOA reactions are often more than the undetermined and the defined ones, except for aminoglycoside (44.1% of persistent/permanent versus 49% of undetermined reactions) and the second generation of cephalosporins, which show the lowest rate of persistent/permanent GOA reactions (36% of persistent/permanent versus 49.2% of undetermined reactions).

At the top of the list, tetracyclines show a percentage of 56.1% of persistent/permanent outcomes, followed by the third generation of cephalosporins and nitrofuran derivatives (50.8% and 50.6%, respectively), imidazole derivatives (50.4%), macrolides and fluoroquinolones (49.4% and 49.3%, respectively). The remaining classes gradually deviate from the 50% (range 39.4 - 46.9%). Almost all the antibiotic groups show the same outcome's trend of GOA reactions: the highest frequency is usually associated with persistent/permanent outcome (36.3 - 56.1%), followed by the undetermined one (28.6 – 40.0%) and last by the defined outcome, (6.7% - 29.7%) with the lowest frequencies.

The distribution of persistent/permanent, undetermined and defined reactions among the three different category of GOA reactions (gustatory, olfactory and auditory) is shown in Supplementary Table 4. All the three categories of GOA reactions show the same trend of outcome distribution: persistent/permanent reactions are the most frequent ADRs, followed by the undetermined and the defined ones. When comparing gustatory reactions to the overall ones, we found that among the antibiotic classes, persistent/permanent gustatory reactions (12.0 - 53.9%) are often more frequent than overall ones (20.6 - 33.9%). Only sulfonamides and trimethoprim class and glycopeptide antibacterials show an opposite state. The distribution analysis of olfactory reactions, shows that all the antibiotic classes are associated with a greater frequency of persistent/permanent reactions (57.1 - 100.0%) than overall ones (20.6 - 33.9%). Any olfactory reaction was observed for glycopeptide antibiotics. Likewise, persistent/permanent auditory reactions are always more frequent (33.3 - 53.7%) than the overall ones (16.8 - 33.9%). In general, olfactory reactions show the highest rate of persistent/permanent outcomes, followed by auditory and gustatory reactions.

Among antibiotic classes, twenty drugs were selected for the expectedness assessment of GOA reactions, in agreement with inclusion criteria. The following antibiotics are representative of the antibiotic class they belong to: doxycycline and minocycline (tetracyclines); ceftriaxone (third generation of cephalosporins); nitrofurantoin

(nitrofuran derivatives); metronidazole (imidazole derivatives); ciprofloxacin, levofloxacin and moxifloxacin (fluoroquinolones); clarithromycin and azithromycin (macrolides); vancomycin (glycopeptide antibacterials); amoxicillin/clavulanic acid (penicillins); amikacin, gentamycin and tobramycin (aminoglycosides); clindamycin (lincosamides); meropenem and imipenem/ciclastatin (carbapenems); linezolid (other antibacterials NEC); cefuroxime (third generation of cephalosporins). More detailed information is provided in Supplementary Table 5(a-n) that shows the amount of persistent/permanent, undetermined and defined GOA reactions associated with drugs belonging to the analyzed antibiotic groups.

Table 2 shows that all selected antibiotics have a greater frequency of persistent/permanent GOA reactions compared to the overall reactions. Eight antibiotics (i.e. azithromycin, tobramycin, doxycycline, metronidazole, moxifloxacin levofloxacin, minocycline and ceftriaxone) have a percentage of persistent/permanent reactions ranged between 50.4 % and 60.9%. Ten drugs (amikacin, gentamicin, clarithromycin, clindamycin, ciprofloxacin, vancomycin, imipenem/cilastatin, minocycline, meropenem and amoxicillin/clavulanic acid) show a frequency of persistent/permanent GOA reactions ranged between 40.1% and 48.1%. Only linezolid and cefuroxime have a percentage of persistent/permanent GOA reaction under 40% (34.8% and 34.4%, respectively).

All the above-mentioned antibiotic drugs were evaluated for the expectedness, and the results of the analysis are listed in Table 3, which shows labelled ADRs reported in the originator's SPC as compared to the listed, linked and unlabelled suspected ADRs reported in Eudravigilance for each drug. Ciprofloxacin, clarithromycin, azithromycin are the only three drugs that do not show any unlabelled suspected GOA reaction, while all the other drugs have at least one unlabelled GOA reaction. In particular, unexpected gustatory, olfactory and auditory reactions were reported in Eudravigilance for 13, 14 and 13 antibiotic drugs, among the twenty included in this analysis.

4 Discussion

In the present analysis, the distribution of persistent/permanent, undetermined and defined outcomes recorded for the antibiotic groups showed a general trend toward a high proportion of persistent/permanent suspected ADRs in the GOA group as compared to the overall suspected ADRs. Indeed, persistent/permanent suspected ADRs represented less than one third of the overall reactions in every subgroup, and more than a half of the GOA

reactions in most of the antibiotic classes. The proportion of undetermined GOA reactions resulted almost similar to that of undetermined overall ones across the different antibiotics.

The detailed data about gustatory, olfactory and auditory reactions, showed that among the classes under evaluation, olfactory reactions were generally the least frequently reported. This could depend on an actual low occurrence of olfactory adverse events or perhaps, patients or healthcare professionals might detect this kind of reactions more hardly. However, among the antibiotics groups, the percentage of persistent/permanent olfactory reactions was higher than that of persistent/permanent gustatory and auditory reactions. Carbapenems and tetracyclines were the antibiotics with the higher percentage of persistent/permanent olfactory reactions, followed by cephalosporins and nitrofuran derivatives. Of note, olfactory adverse reactions are not expected for these antibiotics. Data supporting drug-related events of olfactory impairment have been reported for tetracyclines[6–8] but not for the other antibiotics. Furthermore, to the best of our knowledge, there is no evidence in medical literature supporting an association between these drug classes and permanent olfactory effects.

The distribution of outcomes related to gustatory reactions was quite homogeneous throughout the antibiotic classes. In particular, for most groups, persistent/permanent gustatory reactions were more than 40%. Even for gustatory reactions, tetracyclines were the most frequently reported with persistent/permanent outcomes, although other classes (aminoglycosides, fluoroquinolones and imidazole derivatives) displayed quite similar frequencies. Notably, gustatory reactions are generally unexpected for tetracyclines and aminoglycosides, but labelled for fluoroquinolones[2] and imidazole derivatives[9]. However, evidence about permanent gustatory reactions for these drugs are not documented in the literature, with a possible exception for fluoroquinolones[1].

Persistent/permanent auditory reactions represented about half of the total auditory suspected reactions for almost all antibiotic classes, with exception carbapenems, lincosamides and second generation cephalosporins. Nitrofuran derivatives, third generation of cephalosporins, tetracyclines and imidazole derivatives showed the highest percentage of persistent/permanent outcomes. Auditory reactions are unlabelled for nitrofuran derivatives, cephalosporins and imidazole derivatives, while are expected for tetracyclines. Notably, drug-related auditory impairments attributed to metronidazole assumption are described in literature[9,10], while some tetracyclines are well known to cause tinnitus, a specific hearing disorder[11,12].

These findings can be explained by an actual long-lasting or irreversible effect of antibiotics on nerves involved in gustatory, olfactory and auditory perception, or simply by a general difficulty in assessing the resolution of such adverse events. When biologic plausibility for these reactions is considered, auditory ADRs after aminoglycosides, such as deafness, are often described as a consequence of the degeneration of cochlear sensory hair cells. In particular, the damage to cochlear hair cells seems to occur due to oxidative stress, which begins in the basal area of the cochlea. However, differentiated hair cells can not be replaced by regeneration once they are lost, and thus a severe damage likely results in an irreversible hearing loss[13,14]. Contrary to the mechanisms of permanent auditory disorders caused by drugs, those related to gustatory or olfactory permanent impairments are less known, even though a similar pharmacodynamic detrimental effect on nerves could be hypothesized[15]. However, since these adverse events appear as a general issue of all antibiotics, it is unlikely that a unique common biological mechanism can explain these observations. Therefore, the general difficulty in assessing the ultimate outcome of GOA reactions remains the most likely hypothesis.

When expectedness is considered for the antibiotics most frequently associated with GOA reactions, we found that unexpected gustatory, olfactory and auditory reactions were reported in Eudravigilance for most of the listed drugs. In addition, only two drugs had information about the duration or severity of the adverse event in their SPC. Particularly, the gentamicin label reports the auditory ADR “irreversible deafness”, and the vancomycin label reports the auditory ADR “permanent hearing loss”. Of note, the duration of an ADR is a relevant information that might suggest a condition of irreversibility of the adverse event, and consequently a different attribution of seriousness. Accordingly to EMA guidelines on Good Pharmacovigilance Practices (GVP)[16], the definition of serious adverse drug reaction includes those adverse reactions resulting in persistent or significant disability or incapacity. GOA persistent and permanent ADRs can significantly affect quality of life[17], and patients should be alerted about the potential irreversibility of adverse events caused by treatments. Considering that about 40-50% of GOA reactions reported in Eudravigilance for antibiotic drugs are potentially classifiable as persistent/permanent, we can hypothesize that several of these reactions meet the criteria for being classified as serious and unexpected. However, it is reasonable to suppose that these reactions have not been managed as such by both regulatory authorities and marketing authorization holders. It is important to note that the MedDRA dictionary reports the PT code “deafness permanent”, while similar coding are not listed for olfactory and gustatory reactions. This

could represent an important limitation for the identification of related signals in spontaneously reported ADR databases. Of note, a revision of the codification system would be warranted, since drug-related permanent gustatory and olfactory reactions are actually described in literature[18–20].

Quinolones and fluoroquinolones have been analyzed separately. Indeed, we observed only one GOA reaction for quinolones among the few overall reactions (just 421) reported for this antibiotic class. On the contrary, fluoroquinolones had a greatest amount of GOA reactions (2628), with a percentage of 1.5% out of the large amount of overall reactions extracted for this antibiotic class. Notably, fluoroquinolones showed the same trend of most antibiotic classes. Among the GOA suspected ADRs, the persistent/permanent reactions covered the 49.1%, making fluoroquinolones take the fourth position with macrolides, after imidazole derivatives (50.4%), nitrofuran derivatives, third generation of cephalosporins (50.6 and 50.8%, respectively) and tetracyclines (56.1%). These results, confirm the possible association of permanent/persistent GOA reactions with fluoroquinolones exposure, but also highlight that other antibiotic classes could be further investigated.

The wide distribution of permanent/persistent GOA reactions compared to the overall ones among the analyzed antibiotic groups, and the extracted suspected GOA ADRs which were showed to be unexpected for some antibiotics, suggest that additional studies are needed to master these findings. Moreover, the extent of unresolved and undetermined outcomes for GOA reactions reported for antibacterial drugs in Eudravigilance might potentially hide a large number of events with underestimated clinical consequences. Indeed, apparently mild and transient reactions can strongly affect the quality of life when their outcomes become persistent. In general, when assessing the expectedness of a reported ADR, the persistence of signs and symptoms should be followed up carefully and improving the collaboration with patients in this process is essential, particularly with subjective ADRs, like GOA ones.

The study has some limitations. The most important one is the level of details available on publicly accessible Eudravigilance data. A consequence of this condition is the difficulty in the identification and exclusion of duplicates and in performing a causality assessment. Furthermore, the lack of information about the time to outcome after drug discontinuation would have been important to identify unresolved outcomes assessed after long time (potential permanent events). Therefore, we can not exclude of having misclassified some suspected ADRs as persistent/permanent simply because these were

reported soon after their onset and there was no indication on the time of recovery. Moreover, we tried to include only PTs associated with gustatory, olfactory and auditory damages that are likely caused by direct neurological drug-related injury, however we cannot exclude that some codes could refer to traumatic damage, which could emerge only if the narrative of cases was available.

5 Conclusion

The study's findings showed that adverse reactions classified as persistent/permanent represent a wide proportion of total GOA reactions for all antibiotics drugs. The distribution of such outcomes is undoubtedly higher for GOA ADR reports as compared to the overall ones across the different antibiotic classes. This could mean that such reactions can be sometimes long-lasting or irreversible for several antibiotics. However, this finding might reflect also an intrinsic difficulty in assessing the resolution of these events as compared to other kinds. Further studies should be implemented to clarify this issue.

Author contributions

SF, IC, LL and MT were involved in the conception, design, analysis and interpretation of the data. CB and MT revised critically the manuscript, and SF, IC, LL, CB and MT reviewed the final version. All authors agree to be accountable for all aspects of the work.

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Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

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Example of studies (together with reference 2) that evaluated the persistence of gustatory, auditory and olfactory adverse drug reactions to antibiotics

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Examples of studies (together with reference 2) that evaluated the persistence of gustatory, auditory and olfactory adverse drug reactions to antibiotics

Table 1.

Antibiotic group	Overall Reactions (n)	GOA reactions (n, % of overall reactions)	Persistent/Permanent (%)		Undetermined (%)		Defined (%)	
			Overall	GOA	Overall	GOA	Overall	GOA
Aminoglycosides	20,405	1150 (5.6)	21.8	44.1	49.1	49.2	29.1	6.7
Macrolides	76,807	3215 (4.2)	23.1	49.4	41.3	30.5	35.6	20.1
Imidazole derivatives	22,130	538 (2.4)	29.0	50.4	36.4	23.6	34.6	26.0
Lincosamides	17,205	344 (2.0)	23.3	39.8	37.8	30.5	38.9	29.7
Tetracyclines	28,905	458 (1.6)	26.4	56.1	38.6	30.1	35.0	13.8
Fluoroquinolones	174,611	2628 (1.5)	25.7	49.3	43.3	33.4	31.0	17.3
Glycopeptide antibacterials	36,219	354 (1.0)	20.6	46.9	40.2	36.4	39.2	16.7
Other antibacterials (NEC)	29,719	254 (0.9)	21.9	39.4	46.5	34.3	31.6	26.3
Sulfonamides	6,833	61 (0.9)	30.6	45.9	34.8	29.5	34.6	24.6

and trimethoprim								
Cephalosporins (Second generation)	23,545	160 (0.7)	16.8	36.3	45.5	40.0	37.7	23.7
Penicillins	168,213	995 (0.6)	23.8	45.9	35.6	30.4	40.6	23.7
Carbapenems	24,582	153 (0.6)	21.3	39.9	43.0	36.6	35.7	23.5
Nitrofuran derivatives	14,413	89 (0.6)	33.9	50.6	29.6	31.5	36.5	17.9
Cephalosporins (Third generation)	71,387	238 (0.3)	29.5	50.8	31.5	28.6	39.0	20.6
Quinolones	*421*	*1 (-)*	*15.4*	-	*53.7*	-	*30.9*	-

NEC: not elsewhere classified

Table 2.

Abtibiotic	Overall Reactions (n)	GOA reactions (n, %of overall reactions)	Persistent/Permanent (%)		Undetermined (%)		Defined (%)	
			Overall	GOA	Overall	GOA	Overall	GOA
amikacin	4698	347 (7.4)	21.1	42.4	46.8	51.9	32.1	5.7
gentamicin	8868	536 (6.0)	24.3	42.0	42.7	52.1	33.0	5.9
clarithromycin	36033	1684 (4.7)	23.9	47.7	40.7	28.1	35.4	24.2
azithromycin	22206	949 (4.3)	25.1	56.4	41.6	29.0	33.3	14.6
tobramycin	6549	249 (3.8)	18.8	50.6	59.3	39.4	21.9	10.0
doxycycline	13199	335 (2.5)	29.2	60.9	37.7	25.1	33.1	14.0
metronidazole	21519	523 (2.4)	29.1	50.7	36.5	22.8	34.4	26.5
clindamycin	16815	342 (2.0)	23.4	40.1	37.7	30.1	38.9	29.8
moxifloxacin	38110	720 (1.9)	19.3	50.4	48.6	29.6	32.1	20.0
ciprofloxacin	56653	880 (1.6)	27.3	46.9	43.3	36.5	29.4	16.6
levofloxacin	63575	719 (1.1)	28.2	53.8	41.6	30.2	30.2	16.0
vancomycin	28308	310 (1.1)	20.6	48.1	42.3	35.8	37.1	16.1
linezolid	17244	184 (1.1)	23.1	34.8	44.9	35.9	32.0	29.3

cefuroxime	14214	131 (0.9)	17.0	34.4	43.9	40.5	39.1	25.1
imipenem and cilastatin	8597	77 (0.9)	22.2	44.2	39.0	41.5	38.8	14.3
minocycline	9788	80 (0.8)	23.0	42.5	38.3	40.0	38.7	17.5
nitrofurantoin	14371	89 (0.6)	34.0	50.6	29.6	31.4	36.4	18.0
meropenem	11400	54 (0.5)	21.6	44.4	45.6	33.3	32.8	22.3
amoxicillin, clavulanic acid	112703	105 (0.3)	25.2	48.0	34.4	30.2	40.4	21.8
ceftriaxone	39144	287 (0.3)	28.8	55.2	30.6	21.0	40.6	23.8

Table 3.

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
Tetracyclines	Doxycycline*	Gustatory	-	-	-	Ageusia; Dysgeusia; Hypogeusia
		Olfactory	-	-	-	Anosmia; Hyposmia; Parosmia
		Auditory	Tinnitus	Tinnitus	Auditory disorder	Deafness; Deafness bilateral; Deafness unilateral; Auditory hallucination; Hyperacusis; Hypoacusis; Ototoxicity; Sudden hearing loss
	Minocycline[§]	Gustatory	-	-	-	Ageusia; Dysgeusia; Hypogeusia
		Olfactory	-	-	-	Parosmia
		Auditory	Hypoacusis; Tinnitus	Hypoacusis; Tinnitus	-	Deafness; Deafness neurosensory; Deafness transitory; Deafness unilateral; Auditory hallucination; Hyperacusis; Ototoxicity
Cephalosporins (3rd generation)	ceftriaxone[§]	Gustatory	-	-	-	Ageusia; Dysgeusia
		Olfactory	-	-	-	Anosmia; Parosmia
		Auditory	-	-	-	Deafness; Deafness bilateral; Deafness

continued

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
						neurosensory; Deafness transitory; Deafness unilateral; Hallucination, auditory; Hyperacusis; Hypoacusis; Ototoxicity; Sudden hearing loss; Tinnitus; Presbyacusis
Nitrofuran derivatives	nitrofurantoin[§]	Gustatory	-	-	-	Ageusia; Dysgeusia; Hypogeusia
		Olfactory	-	-	-	Anosmia; Parosmia
		Auditory	-	-	-	Auditory disorder; Deafness; Deafness bilateral; Deafness unilateral; Hallucination, auditory; Hyperacusis; Hypoacusis; Inner ear disorder; Sudden hearing loss; Tinnitus
Imidazole derivatives	metronidazole[§]	Gustatory	Taste disorders	-	Ageusia; Dysgeusia; Hypogeusia	-
		Olfactory	-	-	-	Anosmia; Parosmia.
		Auditory	-	-	-	Auditory disorder; Deafness; Deafness bilateral; Deafness

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
						neurosensory; Deafness unilateral; Auditory hallucination; Hyperacusis; Hypoacusis; Ototoxicity; Sudden hearing loss; Tinnitus
Fluoroquinolones	ciprofloxacin[§]	Gustatory	Taste disorders	-	Ageusia; Dysgeusia; Hypergeusia; Hypogeusia	-
		Olfactory	Olfactory nerve disorders	-	Anosmia; Hyposmia; Parosmia	-
		Auditory	Hearing loss; Hearing impaired; Tinnitus	Deafness; Tinnitus	Auditory disorder; Deafness bilateral; Deafness neurosensory; Deafness transitory; Deafness unilateral; Dysacusis; Auditory hallucination; Hyperacusis; Hypoacusis; Inner ear disorder; Mixed deafness; Ototoxicity; Sudden hearing loss	-
	levofloxacin[*]	Gustatory	Dysgeusia	Dysgeusia	Ageusia;	-

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
					Hypergeusia; Hypogeusia	
		Olfactory	Hyposmia	Hyposmia.	-	Anosmia; Olfactory hallucination; Parosmia
		Auditory	Hearing loss; Tinnitus	Deafness; Tinnitus	Auditory disorder; Deafness bilateral; Deafness neurosensory; Deafness transitory; Deafness unilateral; Mixed deafness; Hypoacusis; Inner ear disorder; Ototoxicity; Presbyacusis; Sudden hearing loss	-
	moxifloxacin[$]	Gustatory	Taste disorders; Ageusia	Ageusia	Dysgeusia; Hypogeusia	-
		Olfactory	Smell disorders; Anosmia	Anosmia	Hyposmia; Parosmia	-
		Auditory	Hearing loss; Deafness transitory; Tinnitus	Deafness; Deafness transitory; Tinnitus	Auditory disorder; Deafness bilateral; Deafness neurosensory; Deafness unilateral;	Auditory hallucination; Hyperacusis

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
					Hypoacusis; Inner ear disorder; Mixed deafness; Ototoxicity; Presbyacusis; Sudden hearing loss	
Macrolides	clarithromycin[§]	Gustatory	Ageusia; Dysgeusia	Ageusia; Dysgeusia	Hypogeusia	-
		Olfactory	Anosmia; Hyposmia; Parosmia	Anosmia; Hyposmia; Parosmia	Olfactory nerve disorder	-
		Auditory	Auditory disorders; Deafness; Tinnitus	Auditory disorders; Deafness; Tinnitus	Auditory hallucination; Deafness bilateral; Deafness neurosensory; Deafness transitory; Deafness unilateral; Sudden hearing loss; Hyperacusis; Hypoacusis; Neurosensory hypoacusis; Otoacoustic emissions test abnormal; Ototoxicity; Presbyacusis	-

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
	azithromycin[§]	Gustatory	Ageusia; Dysgeusia	Ageusia; Dysgeusia	Hypogeusia	-
		Olfactory	Anosmia; Parosmia	Anosmia; Parosmia	Hyposmia; Olfactory hallucination	-
		Auditory	Auditory disorder; Deafness; Tinnitus	Auditory disorder; Deafness; Tinnitus	Auditory hallucination; Deafness bilateral; Deafness neurosensory; Deafness unilateral; Sudden hearing loss; Hyperacusis; Hypoacusis; Inner ear disorder; Neurosensory hypoacusis; Ototoxicity	-
Glycopeptide antibacterials	Vancomycin[*]	Gustatory	-	-	-	Ageusia; Dysgeusia
		Olfactory	-	-	-	-
		Auditory	Ototoxicity; Permanent hearing loss; Tinnitus; Transitory hearing loss	Ototoxicity; Tinnitus	Auditory disorder; Auditory hallucination; Deafness; Deafness bilateral; Deafness neurosensory; Deafness unilateral; Hyperacusis;	-

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
					Hypoacusis; Neurosensory hypoacusis; Sudden hearing loss	
Penicillins	amoxicillin, clavulanic acid*	Gustatory	-	-	-	Ageusia; Dysgeusia; Hypogeusia
		Olfactory	-	-	-	Anosmia; Hyposmia; Parosmia
		Auditory	-	-	-	Acoustic neuritis; Auditory disorder; Deafness; Deafness bilateral; Deafness neurosensory; Deafness transitory; Deafness unilateral; Hallucination, auditory; Hyperacusis; Hypoacusis; Mixed deafness; Ototoxicity; Sudden hearing loss; Tinnitus
Aminoglycosides	amikacin[§]	Gustatory	-	-	-	Dysgeusia
		Olfactory	-	-	-	-
		Auditory	Deafness; Deafness neurosensory; Hypoacusis; Tinnitus	Deafness; Deafness neurosensory; Hypoacusis; Tinnitus	Audiogram abnormal; Auditory disorder; Auditory nerve disorder; Deafness bilateral;	-

continued

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
					Deafness unilateral; Mixed deafness; Neurosensory hypoacusis; Ototoxicity; Presbyacusis; Sudden hearing loss	
	gentamicin[§]	Gustatory	-	-	-	Dysgeusia
		Olfactory	-	-	-	Anosmia; Parosmia
		Auditory	Auditory disorders; Deafness; Hypoacusis; Irreversible Deafness; Tinnitus	Auditory disorder; Deafness; Deafness permanent; Hypoacusis; Tinnitus	Acoustic stimulation tests abnormal; Auditory hallucination; Deafness bilateral; Deafness neurosensory; Deafness transitory; Deafness unilateral; Hyperacusis; Neurosensory hypoacusis; Otoacoustic emissions test abnormal; Ototoxicity; Presbyacusis; Sudden hearing loss; VIII nerve	-

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
					lesion	
	tobramycin*	Gustatory	-	-	-	Dysgeusia
		Olfactory	-	-	-	Parosmia
		Auditory	Hearing loss; Tinnitus	Deafness; Tinnitus	Auditory disorder; Deafness bilateral; Deafness neurosensory; Deafness transitory; Deafness unilateral; Hypoacusis; Inner ear disorder; Neurosensory hypoacusis; Ototoxicity; Presbyacusis; Sudden hearing loss	Auditory hallucination
Lincosamides	clindamycin[§]	Gustatory	Dysgeusia	Dysgeusia	Hypogeusia; Ageusia	-
		Olfactory	-	-	-	Anosmia; Hallucination, olfactory; Parosmia
		Auditory	-	-	-	Deafness; Deafness bilateral; Deafness neurosensory; Deafness unilateral; Hallucination, auditory; Hypoacusis;

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
						Ototoxicity; Sudden hearing loss; Tinnitus
Carbapenems	meropenem[§]	Gustatory	-	-	-	Ageusia; Dysgeusia
		Olfactory	-	-	-	Anosmia; Parosmia
		Auditory	Hearing hallucination	-	-	Deafness; Deafness neurosensory; Deafness unilateral; Hypoacusis; Neurosensory hypoacusis; Ototoxicity; Tinnitus
	imipenem, ciclastatin*	Gustatory	Taste alteration	-	Ageusia	Dysgeusia; Hypogeusia
		Olfactory	-	-	-	Parosmia
		Auditory	Hearing impaired	-	Hallucination, auditory; Hypoacusis; Inner ear disorder; Tinnitus	Deafness; Deafness bilateral; Deafness neurosensory; Deafness unilateral
Other antibacterials NEC	linezolid[§]	Gustatory	Taste alteration	-	Dysgeusia; Hypogeusia	Ageusia
		Olfactory	-	-		Anosmia; Parosmia
		Auditory	Tinnitus	Tinnitus	Auditory disorder	Deafness; Deafness bilateral; Deafness neurosensory; Deafness unilateral;

Antibiotic group	Drug	Reaction category	Labelled GOA ADRs	GOA suspected ADRs reported in EV		
				Listed	Linked	Unlabelled
						hallucination auditory; Hypoacusis; Mixed deafness; Ototoxicity
Cephalosporins (2nd Generation)	cefuroxime§	Gustatory	-	-	-	Ageusia; Dysgeusia
		Olfactory	-	-	-	Anosmia; Hyposmia; Parosmia
		Auditory	-	-	-	Auditory disorder; Deafness; Deafness neurosensory; Hallucination, auditory; Hyperacusis; Hypoacusis; Sudden hearing loss; Tinnitus

*: EMA source; §: AIFA source; NEC: not elsewhere classified

Supplementary Table 5 a Tetracyclines and GOA reactions: outcomes and proportions (% value) of each drug.

Tetracyclines	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
doxycycline	204	84	47	335	**73.1**
chlortetracycline	0	0	0	0	0
lymecicline	2	4	0	6	1.3
metacycline	0	0	0	0	0
oxitetracycline	0	2	0	2	0.4
tetracycline	9	7	1	17	3.7
minocycline	34	32	14	80	**17.5**
tigecycline	8	9	1	18	4.0
all drugs	257	138	63	458	100

Supplementary Table 5 b Cephalosporins (third generation) and GOA reactions: outcomes and proportions (% value) of each drug.

Cephalosporins (third generation)	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
cefcapene	3	0	0	3	1.3
cefdinir	2	3	1	6	2.5
cefditoren	0	1	1	2	0.8
cefixime	8	6	4	18	7.6
cefodizime	0	0	0	0	0
cefoperazone	0	0	0	0	0
cefoperazone, sulbactam	7	0	1	8	3.4
cefotaxime	9	3	6	18	7.6
cefpiramide	0	0	0	0	0
cefpodoxime	15	7	2	24	10.1
cefsulodin	0	0	0	0	0
ceftazidime	15	15	7	37	15.5
ceftazidime, avibactam	0	0	0	0	0

cefteram	0	0	0	0	0
ceftibuten	4	10	1	15	6.3
ceftizoxime	0	1	1	2	0.8
ceftriaxone	58	22	25	105	**44.1**
all drugs	121	68	49	238	100

Supplementary Table 5 c Nitrofuran derivatives and GOA reactions: outcomes and proportions (% value) of each drug.

Nitrofuran derivatives	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
nitrofurantoin	45	28	16	89	**100**
nitrofurantoin, pyridoxine hydrochloride	0	0	0	0	0
all drugs	45	28	16	89	100

Supplementary Table 5 d Imidazole derivatives and GOA reactions: outcomes and proportions (% value) of each drug.

Imidazole Derivatives	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
metronidazole	265	119	139	523	**97.2**
tinidazole	4	7	1	12	2.2
ornidazole	2	1	0	3	0.6
all drugs	271	127	140	538	100

Supplementary Table 5 e Fluoroquinolones and GOA reactions: outcomes and proportions (% value) of each drug.

Fluoroquinolones	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%

ofloxacin	88	102	32	222	8.4
ciprofloxacin	413	321	146	880	**33.5**
pefloxacin	0	0	0	0	0
enoxacin	1	2	2	5	0.2
norfloxacin	18	13	9	40	1.5
lomefloxacin	6	1	1	8	0.3
rufloxacin	0	1	0	1	0
grepafloxacin	6	4	4	14	0.5
levofloxacin	387	217	115	719	**27.4**
trovafloxacin	10	1	1	12	0.5
moxifloxacin	363	213	144	720	**27.4**
prulifloxacin	4	3	0	7	0.3
all drugs	1296	878	454	2628	100

Supplementary Table 5 f Macrolides and GOA reactions: outcomes and proportions (% value) of each drug.

Macrolides	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
erythromycin	58	59	57	174	5.4
spiramycin	9	4	12	25	0.8
roxithromycin	146	164	15	325	10.1
clarithromycin	803	474	407	1684	**52.4**
azithromycin	535	275	139	949	**29.5**
telithromycin	36	5	17	58	1.8
all drugs	1587	981	647	3215	100

Supplementary Table 5 g Glycopeptide antibacterials and GOA reactions: outcomes and proportions (% value) of each drug.

Glycopeptide antibacterials	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
vancomycin	149	111	50	310	**87.6**
teicoplanin	17	15	7	39	11.0
telavancin	0	3	2	5	1.4
dalbavancin	0	0	0	0	0
oritavancin	0	0	0	0	0
all drugs	166	129	59	354	100

Supplementary Table 5 h Sulfonamides and trimethoprim and GOA reactions: outcomes and proportions (% value) of each drug.

Sulfonamides and trimethoprim	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
trimethoprim	22	13	14	49	80.4
sulfafurazole	0	0	0	0	0
sufamethizole	0	0	0	0	0
sulfanilamide	0	1	0	1	1.6
sulfamethoxazole	6	4	1	11	18.0
sulfametrole, trimethoprim	0	0	0	0	0
all drugs	28	18	15	61	100

Supplementary Table 5 i Penicillins and GOA reactions: outcomes and proportions (% value) of each drug.

Penicillins	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
ampicillin	3	8	2	13	1.3
pivampicillin	0	0	0	0	0
carbenicillin	1	0	0	1	0.1

amoxicillin	230	108	91	429	**43.2**
bacampicillin	1	0	0	1	0.1
pivmecillinam	7	0	2	9	0.9
mezlocillin	0	1	0	1	0.1
piperacillin	6	3	5	14	1.4
ticarcillin	0	2	0	2	0.2
temocillin	0	0	0	0	0
benzathine benzylpenicillin	1	2	1	4	0.4
benzathine benzylpenicillin, lidocaine hydrochloride	0	0	0	0	0
benzathine benzylpenicillin, procaine benzylpenicillin monohydrate	0	1	0	1	0.1
benzathine phenoxymethylpenicillin	0	0	1	1	0.1
benzylpenicillin	4	4	7	15	1.5
penamecillin	0	0	0	0	0
phenoxymethylpenicillin	25	15	13	53	5.3
procaine benzylpenicillin	4	7	8	19	1.9
cloxacillin	4	3	1	8	0.8
dicloxacillin	4	0	0	4	0.4
flucloxacillin	27	5	6	38	3.8
oxacillin	0	0	0	0	0
ampicillin, sulbactam	7	3	7	17	1.7
amoxicillin, clavulanic acid	114	108	65	287	**28.9**
sultamicillin	3	8	4	15	1.5
piperacillin, tazobactam	14	24	23	61	6.1
ampicillin trihydrate, flucloxacillin sodium	2	0	0	2	0.2
ampicillin, cloxacillin	0	0	0	0	0
all drugs	457	302	236	995	100

Supplementary Table 5 j Aminoglycosides and GOA reactions: outcomes and proportions (% value) of each drug.

Aminoglycosides	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
amikacin	147	180	20	347	**30.2**
gentamicin	225	279	32	536	**46.6**
neomycin	9	9	0	18	1.5
tobramycin	126	98	25	249	**21.7**
all drugs	507	566	77	1150	100

Supplementary Table 5 k Lincosamides and GOA reactions: outcomes and proportions (% value) of each drug.

Lincosamides	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
clindamycin	137	103	102	342	**99.4**
lincomycin	0	2	0	2	0.6
all drugs	137	105	102	344	100

Supplementary Table 5 l Carbapenems and GOA reactions: outcomes and proportions (% value) of each drug.

Carbapenems	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
meropenem	24	18	12	54	**35.3**
ertapenem	2	6	12	20	13.1
doripenem	1	0	1	2	1.3
imipenem and cilastatin	34	32	11	77	**50.3**
all drugs	61	56	36	153	100

Supplementary Table 5 m Other antibacterials and GOA reactions: outcomes and proportions (% value) of each drug.

Other Antibacterials (NEC)	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)	%
fosfomycin	19	6	10	35	13.8
clofoctol	0	0	0	0	0
methenamine	0	2	0	2	0.8
nitroxoline	1	0	0	1	0.4
linezolid	64	66	54	184	**72.4**
daptomycin	14	12	3	29	11.4
bacitracin	2	1	0	3	1.2
all drugs	100	87	67	254	100

NEC: not elsewhere classified

Supplementary Table 5 n Cephalosporins (Second generation) and GOA reactions: outcomes and proportions (% value) of each drug.

Cephalosporins (Second Generation)	Persistent/permament	Undetermined	Defined	Total	%

	(n)	(n)	(n)	(n)	
cefaclor	7	9	4	20	12.5
cefamandole	0	0	0	0	0
cefminox	0	0	0	0	0
cefonicid	0	0	0	0	0
cefotiam	2	0	1	3	1.9
cefoxitin	3	1	0	4	2.5
cefprozil	1	1	0	2	1.2
cefuroxime	45	53	33	131	**81.9**
all drugs	58	64	38	160	100

Supplementary Table 2. Dictionary of drugs belonging to the ATC class J01 (Antibacterials for systemic use) for which at least a report of suspected ADR was reported in the Eudravigilance database.

ATC code level four, class name	ATC code level three, class name	Drugs
J01A **TETRACYCLINES**	**J01AA** *Tetracyclines*	chlortetracycline; doxycycline; lymecicline; metacycline; minocycline; oxitetracycline; tetracycline; tigecycline
J01B **AMPHENICOLS**	**J01BA** *Amphenicols*	chloramphenicol; thiamphenicol
J01C **β-LACTAM ANTIBACTERIALS, PENICILLINS**	**J01CA** *Penicillins with extended spectrum*	amoxicillin; ampicillin; bacampicillin; carbenicillin; mezlocillin; piperacillin; pivampicillin; pivmecillinam; temocillin; ticarcillin
	J01CE *β-lactamase sensitive penicillins*	benzathine benzylpenicillin; benzathine benzylpenicillin, lidocaine hydrochlorid; benzathine benzylpenicillin, procaine benzylpenicillin monohydrate; benzathine phenoxymethylpenicillin; benzylpenicillin; penamecillin; phenoxymethylpenicillin; procaine benzylpenicillin
	J01CF *β-lactamase resistant penicillins*	cloxacillin; dicloxacillin; flucloxacillin; oxacillin
	J01CR *Combinations of penicillins, including*	amoxicillin, acid clavulanic; ampicillin, sulbactam; ampicillin trihydrate, flucloxacillin sodium; ampicillin, cloxacillin; piperacillin, tazobactam; sultamicillin

	β-lactamase inhibitors	
J01D **OTHER β-LACTAM** **ANTIBACTERIALS**	**J01DB** *First-generation cephalosporins*	cefadroxil; cefalexin; cefalotin; cefapirin; cefatrizine; cefazolin; cefradine; ceftezole
	J01DC *Second-generation cephalosporins*	cefaclor; cefamandole; cefminox; cefonicid; cefotiam; cefoxitin; cefprozil; cefuroxime
	J01DD *Third-generation cephalosporins*	cefcapene; cefdinir; cefditoren; cefixime; cefodizime; cefoperazone; cefoperazone, sulbactam; cefotaxime; cefpiramide; cefpodoxime; cefsulodin; ceftazidime; ceftazidime, avibactam; cefteram; ceftibuten; ceftizoxime; ceftriaxone
	J01DE *Fourth-generation cephalosporins*	cefepime; cefpirome
	J01DF *Monobactams*	aztreonam
	J01DH *Carbapenems*	ertapenem; meropenem; doripenem; imipenem, cilastatin
	J01DI *Other cephalosporins and penems*	ceftobiprole; ceftaroline;
J01E **SULFONAMIDES AND** **TRIMETHOPRIM**	**J01EA** *Trimethoprim and derivatives*	trimethoprim
	J01EB *Short-acting sulfonamides*	sulfafurazole; sufamethizole; sulfanilamide
	J01EC *Intermediate-acting sulfonamides*	sulfamethoxazole
	J01EE *Combinations of sulfonamides and trimethoprim, including derivatives*	sulfametrole, trimethoprim
J01F **MACROLIDES,** **LINCOSAMIDES AND**	**J01FA** *Macrolides*	azithromycin; clarithromycin; erythromycin; roxithromycin; spiramycin; telithromycin
	J01FF	clindamycin; lincomycin

STREPTOGRAMINS	*Lincosamides*	
	J01FG *Streptogramins*	pristinamycin; daflopristin, quinupristin
J01G AMINOGLYCOSIDE ANTIBACTERIALS	**J01GB** *Other aminoglycosides*	amikacin; gentamicin; neomycin; tobramycin
J01M QUINOLONE ANTIBACTERIALS	**J01MA** *Fluoroquinolones*	ciprofloxacin; enoxacin; grepafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin; trovafloxacin
	J01MB *Other quinolones*	cinoxacin; flumequine; nalidixic acid; pipemidic acid
J01R COMBINATIONS OF ANTIBACTERIALS	**J01RA** *Combinations of antibacterials*	spiramycin/metronidazole
J01X OTHER ANTIBACTERIALS	**J01XA** *Glycopeptide antibacterials*	vancomycin; teicoplanin; telavancin; dalbavancin; oritavancin
	J01XB *Polymyxins*	polymyxin b
	J01XC *Steroid antibacterials*	fusidic acid
	J01XD *Imidazole derivatives*	metronidazole; tinidazole; ornidazole
	J01XE *Nitrofuran derivatives*	nitrofurantoin; nitrofurantoin, pyridoxine hydrochloride
	J01XX *Other antibacterials*	fosfomycin; clofoctol; methenamine; nitroxoline; linezolid; daptomycin; bacitracin; tedizolid phosphate

ATC: Anatomical Therapeutic Chemical

Supplementary Table 3. Number of overall and GOA reactions associated with antibiotic classes according to third- and fourth-levels of ATC classification.

ATC CLASS NAME	Third-level ATC class	Fourth-level ATC class	Overall reactions	GOA reactions	Gustatory reactions	Olfactory reactions	Auditory reactions
TETRACYCLINES	**J01A**	J01AA	**28,905**	**458**	**158**	**62**	**238**
AMPHENICOLS	**J01B**	J01BA	**1,368**	**25**	**21**	**0**	**4**
β-LACTAMS and PENICILLINS	**J01C**	J01CA	56,626	470	243	58	168
		J01CE	12,663	93	33	2	59
		J01CF	9,651	50	24	2	24
		J01CR	89,273	382	165	41	176
			168,213	**995**	**465**	**103**	**427**
OTHER β -LACTAMS ANTIBACTERIALS	**J01D**	J01DB	15,347	42	14	5	23
		J01DC	23,545	160	74	20	66
		J01DD	71,387	238	69	27	142
		J01DE	6,653	14	3	2	9
		J01DI	755	1	0	0	1
		J01DF	1,365	5	0	0	5
		J01DH	24,582	153	26	6	121
			143,634	**613**	**186**	**60**	**367**
SULFONAMIDES and TRIMETHOPRIM	**J01E**	J01EA	5,751	49	14	6	**29**
		J01EB	126	1	0	0	**1**
		J01EC	897	11	1	0	**10**
		J01EE	59	0	0	0	**0**
			6,833	**61**	**15**	**6**	**40**
MACROLIDES, LINCOSAMIDES and STREPTOGRAMINS	**J01F**	J01FA	76,807	3,215	1,409	591	1,215
		J01FF	17,205	344	259	21	64
		J01FG	3,990	12	5	4	3
			98,002	**3,571**	**1,673**	**616**	**1,282**
AMINOGLYCOSIDES	**J01G**	J01GB	**20,405**	**1,150**	**16**	**5**	**1,129**
QUINOLONES	**J01M**	J01MA	174,611	2,628	758	448	1,422
		J01MB	421	1	0	0	1
			175,032	**2,629**	**758**	**448**	**1,423**
COMBINATIONS OF ANTIBACTERIALS	**J01R**	J01RA	**928**	**11**	**5**	**0**	**6**
OTHER ANTIBACTERIALS	**J01X**	J01XA	36,219	354	25	0	329
		J01XB	232	2	0	0	2
		J01XC	2,766	12	6	1	5
		J01XD	22,130	538	353	16	169
		J01XE	14,413	89	41	7	41
		J01XX	29,719	254	71	6	177
			105,479	**1,249**	**496**	**30**	**723**

GOA: gustatory, olfactory and auditory; ATC: Anatomical Therapeutic Chemical

Supplementary Table 4 a Number of overall and gustatory reactions reported for the listed antibiotic groups and organized by frequency of gustatory reactions according to their outcomes.

Antibiotic group	Overall reactions (n)	Gustatory reactions (n)	Persistent/Permanent reactions (%)		Undetermine reactions (%	
			Overall	Gustatory	Overall	Gu
Aminoglycosides	**20,405**	16	21.8	50.0	49.1	
Macrolides	**76,807**	1409	23.1	46.0	41.3	
Imidazole derivatives	**22,130**	353	29.0	49.6	36.4	
Lincosamides	**17,205**	259	23.3	39.8	37.8	
Tetracyclines	**28,905**	158	26.4	53.8	38.6	
Fluoroquinolones	**174,611**	758	25.7	49.6	43.3	
Glycopeptide antibacterials	**36,219**	25	20.6	12.0	40.2	
Other antibacterials (NEC)	**29,719**	71	21.9	31.0	46.5	
Sulfonamides and trimethoprim	**6,833**	15	30.6	26.7	34.8	
Cephalosporins (Second generation)	**23,545**	74	16.8	27.0	45.5	
Penicillins	**168,213**	465	23.8	47.1	35.6	
Carbapenems	**24,582**	26	21.3	42.3	43.0	

Nitrofuran derivatives	**14,413**	41	33.9	53.9	29.6
Cephalosporins (Third generation)	**71,387**	69	29.5	42.0	31.5

NEC: not elsewhere classified

Supplementary Table 4 b Number of overall and olfactory reactions reported for the listed antibiotic groups and organized by frequency of olfactory reactions according to their outcomes.

Antibiotic group	**Overall reactions (n)**	**Olfactory reactions (n)**	**Persistent/Permanent reactions (%)**		**Undetermine reactions (%**	
			Overall	Olfactory	Overall	O
Aminoglycosides	**20,405**	5	21.8	57.1	49.1	
Macrolides	**76,807**	591	23.1	60.9	41.3	
Imidazole derivatives	**22,130**	16	29.0	62.5	36.4	
Lincosamides	**17,205**	21	23.3	57.1	37.8	
Tetracyclines	**28,905**	62	26.4	80.6	38.6	
Fluoroquinolones	**174,611**	448	25.7	60.9	43.3	
Glycopeptide antibacterials	**36,219**	-	20.6	-	40.2	
Other antibacterials (NEC)	**29,719**	6	21.9	66.7	46.5	
Sulfonamides and trimethoprim	**6,833**	6	30.6	66.7	34.8	
Cephalosporins	**23,545**	20	16.8	80.0	45.5	

(Second generation)					
Penicillins	**168,213**	103	23.8	60.2	35.6
Carbapenems	**24,582**	6	21.3	100.0	43.0
Nitrofuran derivatives	**14,413**	7	33.9	71.4	29.6
Cephalosporins (Third generation)	**71,387**	27	29.5	66.7	31.5

NEC: not elsewhere classified

Supplementary Table 4 c Number of overall and auditory reactions reported for the listed antibiotic groups and organized by frequency of auditory reactions according to their outcomes.

Antibiotic group	**Overall reactions (n)**	**Auditory reactions (n)**	**Persistent/Permanent reactions (%)**		**Undetermine reactions (%**	
			Overall	Auditory	Overall	A
Aminoglycosides	**20,405**	1129	21.8	43.9	49.1	
Macrolides	**76,807**	1215	23.1	47.7	41.3	
Imidazole derivatives	**22,130**	169	29.0	50.9	36.4	
Lincosamides	**17,205**	64	23.3	34.4	37.8	
Tetracyclines	**28,905**	238	26.4	51.3	38.6	
Fluoroquinolones	**174,611**	1422	25.7	45.5	43.3	
Glycopeptide antibacterials	**36,219**	329	20.6	49.5	40.2	

Other antibacterials (NEC)	**29,719**	177	21.9	41.8	46.5
Sulfonamides and trimethoprim	**6,833**	40	30.6	50.0	34.8
Cephalosporins (Second generation)	**23,545**	66	16.8	33.3	45.5
Penicillins	**168,213**	427	23.8	41.2	35.6
Carbapenems	**24,582**	121	21.3	34.7	43.0
Nitrofuran derivatives	**14,413**	41	33.9	53.7	29.6
Cephalosporins (Third generation)	**71,387**	142	29.5	52.1	31.5

NEC: not elsewhere classified

Supplementary Table 5 o Tetracyclines and GOA reactions: outcomes and proportions (% value) of each drug.

Tetracyclines	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
doxycycline	204	84	47	335
chlortetracycline	0	0	0	0
lymecicline	2	4	0	6
metacycline	0	0	0	0
oxitetracycline	0	2	0	2
tetracycline	9	7	1	17
minocycline	34	32	14	80

tigecycline	8	9	1	18
all drugs	257	138	63	458

Supplementary Table 5 p Cephalosporines (third generation) and GOA reactions: outcomes and proportions (% value) of each drug.

Cephalosporins (third generation)	**Persistent/permanent (n)**	**Undetermined (n)**	**Defined (n)**	**Total (n)**
cefcapene	3	0	0	3
cefdinir	2	3	1	6
cefditoren	0	1	1	2
cefixime	8	6	4	18
cefodizime	0	0	0	0
cefoperazone	0	0	0	0
cefoperazone, sulbactam	7	0	1	8
cefotaxime	9	3	6	18
cefpiramide	0	0	0	0
cefpodoxime	15	7	2	24
cefsulodin	0	0	0	0
ceftazidime	15	15	7	37
ceftazidime, avibactam	0	0	0	0
cefteram	0	0	0	0
ceftibuten	4	10	1	15
ceftizoxime	0	1	1	2
ceftriaxone	58	22	25	105
all drugs	121	68	49	238

Supplementary Table 5 q Nitrofuran derivatives and GOA reactions: outcomes and proportions (% value) of each drug.

Nitrofuran derivatives	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
nitrofurantoin	45	28	16	89
nitrofurantoin, pyridoxine hydrochloride	0	0	0	0
all drugs	45	28	16	89

Supplementary Table 5 r Imidazole derivatives and GOA reactions: outcomes and proportions (% value) of each drug.

Imidazole Derivatives	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
metronidazole	265	119	139	523
tinidazole	4	7	1	12
ornidazole	2	1	0	3
all drugs	271	127	140	538

Supplementary Table 5 s Fluoroquinolones and GOA reactions: outcomes and proportions (% value) of each drug.

Fluoroquinolones	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
ofloxacin	88	102	32	222
ciprofloxacin	413	321	146	880
pefloxacin	0	0	0	0
enoxacin	1	2	2	5

norfloxacin	18	13	9	40
lomefloxacin	6	1	1	8
rufloxacin	0	1	0	1
grepafloxacin	6	4	4	14
levofloxacin	387	217	115	719
trovafloxacin	10	1	1	12
moxifloxacin	363	213	144	720
prulifloxacin	4	3	0	7
all drugs	1296	878	454	2628

Supplementary Table 5 t Macrolides and GOA reactions: outcomes and proportions (% value) of each drug.

Macrolides	**Persistent/permament (n)**	**Undetermined (n)**	**Defined (n)**	**Total (n)**
erythromycin	58	59	57	174
spiramycin	9	4	12	25
roxithromycin	146	164	15	325
clarithromycin	803	474	407	1684
azithromycin	535	275	139	949
telithromycin	36	5	17	58
all drugs	1587	981	647	3215

Supplementary Table 5 u Glycopeptide antibacterials and GOA reactions: outcomes and proportions (% value) of each drug.

Glycopeptide antibacterials	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
vancomycin	149	111	50	310
teicoplanin	17	15	7	39
telavancin	0	3	2	5
dalbavancin	0	0	0	0
oritavancin	0	0	0	0
all drugs	166	129	59	354

Supplementary Table 5 v Sulfonamides and trimethoprim and GOA reactions: outcomes and proportions (% value) of each drug.

Sulfonamides and trimethoprim	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
trimethoprim	22	13	14	49
sulfafurazole	0	0	0	0
sufamethizole	0	0	0	0
sulfanilamide	0	1	0	1
sulfamethoxazole	6	4	1	11
sulfametrole, trimethoprim	0	0	0	0
all drugs	28	18	15	61

Supplementary Table 5 w Penicillins and GOA reactions: outcomes and proportions (% value) of each drug.

Penicillins	Persistent/permament	Undetermined	Defined (n)	Total

	(n)	**(n)**		**(n)**
ampicillin	3	8	2	13
pivampicillin	0	0	0	0
carbenicillin	1	0	0	1
amoxicillin	230	108	91	429
bacampicillin	1	0	0	1
pivmecillinam	7	0	2	9
mezlocillin	0	1	0	1
piperacillin	6	3	5	14
ticarcillin	0	2	0	2
temocillin	0	0	0	0
benzathine benzylpenicillin	1	2	1	4
benzathine benzylpenicillin, lidocaine hydrochloride	0	0	0	0
benzathine benzylpenicillin, procaine benzylpenicillin monohydrate	0	1	0	1
benzathine phenoxymethylpenicillin	0	0	1	1
benzylpenicillin	4	4	7	15
penamecillin	0	0	0	0
phenoxymethylpenicillin	25	15	13	53
procaine benzylpenicillin	4	7	8	19
cloxacillin	4	3	1	8
dicloxacillin	4	0	0	4
flucloxacillin	27	5	6	38
oxacillin	0	0	0	0
ampicillin, sulbactam	7	3	7	17
amoxicillin, clavulanic acid	114	108	65	287
sultamicillin	3	8	4	15
piperacillin, tazobactam	14	24	23	61
ampicillin trihydrate,	2	0	0	2

flucloxacillin sodium				
ampicillin, cloxacillin	0	0	0	0
all drugs	457	302	236	995

Supplementary Table 5 x Aminoglycosides and GOA reactions: outcomes and proportions (% value) of each drug.

Aminoglycosides	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
amikacin	147	180	20	347
gentamicin	225	279	32	536
neomycin	9	9	0	18
tobramycin	126	98	25	249
all drugs	507	566	77	1150

Supplementary Table 5 y Lincosamides and GOA reactions: outcomes and proportions (% value) of each drug.

Lincosamides	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
clindamycin	137	103	102	342
lincomycin	0	2	0	2
all drugs	137	105	102	344

Supplementary Table 5 z Carbapenems and GOA reactions: outcomes and proportions (% value) of each drug.

Carbapenems	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
meropenem	24	18	12	54
ertapenem	2	6	12	20
doripenem	1	0	1	2
imipenem and cilastatin	34	32	11	77
all drugs	61	56	36	153

Supplementary Table 5 aa Other antibacterials and GOA reactions: outcomes and proportions (% value) of each drug.

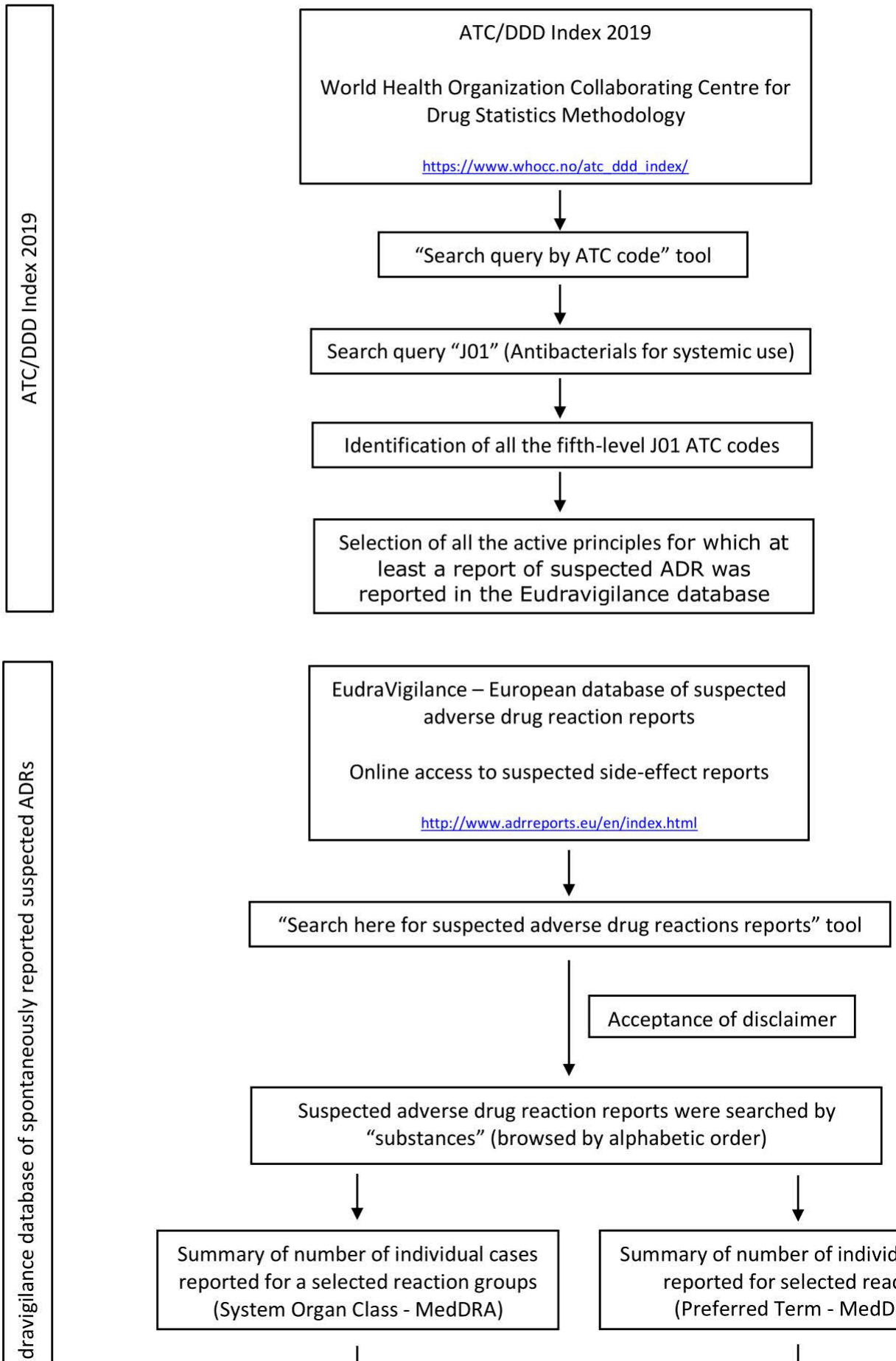
Other Antibacterials (NEC)*	Persistent/permament (n)	Undetermined (n)	Defined (n)	Total (n)
fosfomycin	19	6	10	35
clofoctol	0	0	0	0
methenamine	0	2	0	2

nitroxoline	1	0	0	1
linezolid	64	66	54	184
daptomycin	14	12	3	29
bacitracin	2	1	0	3
all drugs	100	87	67	254

Supplementary Table 5 bb Cephalosporins (Second generation) and GOA reactions: outcomes and proportions (% value) of each drug.

Cephalosporins (Second Generation)	**Persistent/permament (n)**	**Undetermined (n)**	**Defined (n)**	**Total (n)**
cefaclor	7	9	4	20
cefamandole	0	0	0	0
cefminox	0	0	0	0
cefonicid	0	0	0	0
cefotiam	2	0	1	3
cefoxitin	3	1	0	4
cefprozil	1	1	0	2
cefuroxime	45	53	33	131
all drugs	58	64	38	160

Figure 1.


ATC/DDD Index 2019
ATC/DDD Index 2019
World Health Organization Collaborating Centre for Drug Statistics Methodology
https://www.whocc.no/atc_ddd_index/
"Search query by ATC code" tool
Search query "J01" (Antibacterials for systemic use)
Identification of all the fifth-level J01 ATC codes
Selection of all the active principles for which at least a report of suspected ADR was reported in the Eudravigilance database
EudraVigilance – European database of suspected adverse drug reaction reports
Online access to suspected side-effect reports
http://www.adrreports.eu/en/index.html
"Search here for suspected adverse drug reactions reports" tool
Acceptance of disclaimer
Suspected adverse drug reaction reports were searched by "substances" (browsed by alphabetic order)
Summary of number of individual cases reported for a selected reaction groups (System Organ Class - MedDRA)
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