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Prevalence of antibiotic allergy labels in a tertiary referral center in Belgium

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Abstract

Background: Antibiotic (AB) allergies are amongst the most frequently occurring adverse drug reactions. In US literature, AB allergy labels (AAL) are reported in 10-15% of patients' charts, however, large-scale European analyses are scarce.

Objectives: To retrospectively assess the prevalence of AAL in a tertiary referral hospital in Belgium between 2010 and 2018.

Methods: Patients that consulted and/or were hospitalized during the study period, who had been labeled with an AB allergy were selected for further analysis.

Results: Out of 1 009 598 unique patients, 28 147 patients (3%) were registered with one or more AAL, being 1% of out- (n= 9 562) and 7% of inpatients (n= 18 585). Women were more likely to carry an AAL (68%) compared with men (32%, $p<0.001$). In patients with an AAL, 9% had multiple labels and 5% had labels for multiple AB classes. Most frequently, betalactams were involved (84% of AAL), followed by quinolones (7%) and sulfonamides and macrolides (both 3%). Moreover, 88% of the reactions were self-reported, mostly being an unspecified rash (53%), whereas only 3% were considered confirmed AAL.

Conclusion: With an overall prevalence of 3%, the burden of AAL is less in our Western European center compared with US reports. However, this prevalence most likely still represents an overestimation of genuine AB allergic patients since most labels lack confirmation and/or specifications. Our work indicates knowledge on the local epidemiology of AAL is necessary to estimate the impact of better allergy labeling and delabeling strategies.

Highlights

What is already known about this topic? Antibiotic allergy labels (AAL) appear in 10 to 15% of US patients' charts and subsequently affect future health care decisions. However, large-scale analyses on the prevalence and characteristics in European centers are scarce.

What does this article add to our knowledge? With an overall prevalence of 3% of patients that consulted our center, being 1% of outpatients and 7% of those hospitalized, AAL are reported less when compared to literature.

How does this study impact current management guidelines? Varying prevalences of AAL might impact the outcome of delabeling strategies that should be tailored to the local AAL 'epidemic'. Improved documentation of AAL can help minimizing the burden of incorrect AAL.

Keywords

Allergy labeling; Allergy registration; Antibiotics; Betalactam allergy; Delabeling strategies; Drug allergy; Drug hypersensitivity

Abbreviations

AAL, antibiotic allergy labels; AB, antibiotic; ATC, anatomical therapeutic chemical; BL, beta-lactam; BLI, betalactamase inhibitor; DDD, defined daily dose; EPR, Electronic Patient Record; ICD, International Classification of Disease codes; MDAS, multiple drug allergy syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; SJS, Stevens-Johnson syndrome; US, United States of America; UZ Leuven, University Hospitals Leuven, Belgium; VRE, vancomycin-resistant *Enterococcus spp.*

Introduction

Antibiotic (AB) allergies, particularly due to beta-lactams (BL), are amongst the most frequently occurring adverse drug reactions (1). Indeed, many patients have an AB allergy reported in their medical file, hereafter referred to as an antibiotic allergy label (AAL). Studies in United States of America (US) centers indicate that 10 to 15% of hospitalized and outpatients, respectively, carry one or more AAL (2–5). However, large-scale European analyses are scarce and primarily focus on penicillin (6–11).

Delabeling studies have indicated that a large part of AAL, especially for BL, are incorrect (12,13), while AAL themselves are associated with increased use of suboptimal AB, a higher cost, and use of AB that generally cover a broader antimicrobial spectrum (14). AAL are also associated with increased odds of (colonization with) AB resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA)(15), and vancomycin-resistant *Enterococcus spp.*(VRE)(16). Moreover, these are associated with worse clinical outcomes, such as an increased length of hospital stay and a higher likelihood of ICU admission (5,17). Charneski *et al.* even report a higher in-hospital mortality (5). However, delabeling studies indicated that a varying fraction of AAL are genuine and re-exposure to the culprit can re-elicite symptoms of a hypersensitivity reaction. This balance between the indirect harm due to an unjust AAL and potential harm due to iatrogenic re-exposure in case of a legitimate AAL needs to be carefully considered for each individual patient and for the population when implementing delabeling strategies (18).

Therefore, an in-depth knowledge on the local epidemiology of AAL is pivotal to guide strategies to improve AAL and/or delabeling. The aim of this study is to evaluate AAL recorded in the electronic patient record (EPR) system of a large tertiary referral and teaching hospital, the University Hospitals (UZ) Leuven in Belgium, and to describe the clinical epidemiology of AAL and the characteristics of the reported reactions and registration methods.

Methods

UZ Leuven is a 1 764-bed tertiary referral and teaching hospital for secondary, tertiary and quaternary care in all different specialties and for all age groups; only the psychiatry department (Universitair Psychiatrisch Centrum UPC KU Leuven) was not taken into account in this study.

Alleged allergic reactions can be registered in the EPR system using a dedicated allergy registration module (ARM), by selecting the suspected drug or drug class from a drop-down list set up according to the Anatomical Therapeutic Chemical (ATC) classification (see supplementary Figures E1-E3). Moreover, the onset date and symptoms of the reaction can be specified, along with the source of information and probability of the allergy.

All patients that consulted and/or were hospitalized in UZ Leuven between February 1st, 2010 (entry of the current ARM) and December 31, 2018, and who have been registered as having an AB allergy (ATC code J01 in the ARM), were selected for further analysis. Inpatients were defined as all patients with at least one overnight stay in our hospital, outpatients consulted our hospital at least once.

The following characteristics were evaluated: patients' age and sex distribution, reporting date of the allergic reaction, drug, clinical function as well as department of the reporter, onset date and symptoms of the reaction, source of information, and probability of the label accuracy as indicated by the reporter. The involved AB were analyzed according to their AB (sub)classes.

Descriptive statistics of categorical data were reported using percentages of respectively the total number of outpatients, inpatients and all patients that visited or were hospitalized in UZ Leuven within the study period; continuous outcomes were reported using means ($\pm$ standard deviation). Differences between out- and inpatients were evaluated using chi-square tests for proportions and independent-sample t-tests for means, with a *p*-value less than 0.05 considered statistically significant.

AAL prevalences were calculated as the number of patients with (at least one) label for a certain drug or drug class divided by respectively the total number of outpatients, inpatients and all patients that visited or were hospitalized in UZ Leuven within the study period.

The study was approved by the Ethics Committee Research UZ/KU Leuven (S62975, approved 18 October 2019). Data analysis was performed using Microsoft Excel power query editor tool and SPSS statistical software (IBM SPSS Statistics 20, Chicago, IL).

Results

Study population

In total, 1 009 598 unique patients, of whom 459 820 (46%) men and 549 778 (54%) women, visited the hospital or were hospitalized during the 107-month study period.

Of those, 28 147 (3%) were registered as having at least one AB allergy, of whom 8 948 (32%) men and 19 199 (68%) women, with a mean age of 52 (± 22) versus 53 (± 19) years old when the (first) label was registered, respectively. Their characteristics are shown in **Table 1**. The proportion of women within those with an AAL (68%) was significantly higher when compared to the proportion of women in the general population that consulted our hospital (54%, $p < 0.001$). Only 1 569 of the patients (6%) were younger than 18 years old when the (first) label was registered, while 8 171 (29%) were older than 65 at the time of labeling. As also illustrated in **Figure 1**, 2 491 (9%) patients had more than one AAL (explaining the discrepancy between the amount of patients (28 147) and labels/reactions (31 276)), of whom 1 430 (5%) to different AB classes. Their mean age was 55 (± 19) and 56 (± 17), respectively, which is significantly higher compared to the patients with only one AAL and patients with labels for one AB class (both 52 (± 20) years; $p < 0.001$ for comparison with both, respectively). Women were more frequently involved, namely, in 73% of those with more than one AAL and 75% of those with labels for more than one AB class ($p < 0.001$ for comparison with the proportion of women with only one AAL as well as with labels for one AB class, respectively).

Looking at the 736 469 outpatients, 9 562 (1%) carried an AAL, of whom 2 722 (28%) men and 6 840 (72%) women ($p < 0.001$ for comparison with the ratio men/women in the general population). Out of the 273 129 inpatients, 18 585 (7%) carried an AAL, that is 6 226 (34%) men and 12 359 (66%) women ($p < 0.001$).

Comparison of the characteristics of out- and inpatients with an AAL showed a significantly higher amount of women in the outpatient population ($p < 0.001$). Moreover, outpatients were generally younger, with a significantly higher amount of children and adolescents (minus 18) and a lower amount of seniors (65 plus) involved ($p < 0.001$ for both). Inpatients more frequently had more than one AAL ($p < 0.001$), also to more than one AB class ($p < 0.001$) (see **Figure 1**).

Given the discrepancy of AAL prevalence between out- and inpatients, possibly due to a lower likelihood of registration for outpatients, a subanalysis on patients with at least one pre-operative anesthesia consultation was performed. These patients all underwent routine questioning and registration on medication allergy. Here, the prevalence amounted to 5% (10 001 out of 191 613 patients).

Antibiotics

In **Table 2** the prevalences of the involved AB can be found, in respectively out-, in-, and all patients (more details on the individual labels can be found in the Online Repository, **Table E1**).

Mostly BL were involved, in 26 370 out of 31 276 labels (84%). In total, 25 062 patients (2%) had at least one BL allergy label, being 1% for out- and 6% for inpatients, respectively.

The highest prevalence was reported for penicillin allergy labels (2%). This was mostly labelled as 'penicillin allergy', without further specification of the culprit drug ($n = 21\,564$, 82% of the labels) (**Table E1**). For the AAL with specification, amoxicillin (with or without betalactamase inhibitor (BLI)) was mostly indicated as the culprit ($n = 1\,191$, 63% of specified BL AAL).

Cephalosporin AAL had a prevalence of 0.1%. Carbapenems and monobactams were only rarely reported ($<0.01\%$).

In addition, 1 572 patients carried a general label 'BL allergic', of which 1 465 'BL antibiotics with exclusion of carbapenems and monobactams' (the rationale for this label is provided in the Online Repository), thus penicillins and cephalosporines, and 115 others. The prevalence of 'BL allergic' label was significantly higher in the in- versus the outpatient population (6% versus 1%, $p < 0.001$), whereas more out- than inpatients had a specific BL (8% versus 7%, $p = 0.1$) or BL subclass (15% versus 10%; $p < 0.001$) indicated as the cause of their alleged allergy (see Online Repository, **Table E2**).

Second, quinolone AB accounted for 1 929 labels (7%), amounting to a prevalence of 0.2% among the total population, with a significantly higher prevalence in the inpatient population (0.5% versus 0.07% in outpatients; $p < 0.001$). For only 46 labels, the specific quinolone was not specified, the amount of specification being not significantly different in out- versus inpatients (98% for both; $p = 0.8$).

Sulfonamides were involved in 3% of the labels ($n = 1\,043$), the prevalence being significantly higher in inpatients (0.3% versus 0.04%; $p < 0.001$). Most frequently, co-trimoxazol, a combination of sulfamethoxazole and trimethoprim, was involved, with a prevalence of 0.07% (0.03% in out- and 0.18% in inpatients, $p < 0.001$). However, the culprit drug was more frequently specified in the outpatient population (80% versus 74%, respectively; $p = 0.046$).

Macrolides also accounted for 3% ($n = 853$) of the labels, mostly neomacrolides such as clarithromycin ($n = 316$), with an overall prevalence of less than 0.1%, and predominance for inpatients (0.2%). Also the prevalence of nitrofurantoin derivatives was only above 0.1% in inpatients, particularly nitrofurantoin ($n = 243$, 0.12%).

Other drugs of interest, however, occurring with prevalences lower than 0.1% in both out- and inpatients, were tetracyclines in 228 patients (0.02%), mostly doxycycline (n= 100); glycopeptides such as vancomycin (n= 165) in 166 patients (0.02%); and aminoglycosides, of whom tobramycin (n= 20), in 72 patients (0.01%).

Reactions

A mean of 3 475 (± 823) reactions are registered in the EPR annually, the total number increasing almost each year, ranging from 2 419 to 4 680. However, the annual amount of outpatient visits as well as hospitalizations grew simultaneously (see Online Repository, **Table E3**). Only for outpatients, the annual increase in labeling outreached the growth in yearly visits.

Table 3 summarizes the characteristics of the reactions. In 26 796 out of 31 276 (86%), the onset date of the reaction was not specified, however, in those indicated, 27% occurred more than 10 years ago (n= 1 200). Looking only at the 4480 patients (14%) of whom the onset date was known, the average age at which the first reaction occurred was 45(± 24) years. In 663 (15%) the reaction occurred at a young age (minus 18), whereas in 999 (22%) of the reactions, it took place in patients aged above 65.

27 660 were self-reported (88%), while only 800 were confirmed (3%); 460 by an allergy test, 74 by (accidental) rechallenge, and/or 282 because an anaphylactic shock or angioedema was observed by the clinician. The latter were all indicated as 'certain', together with 30 other reactions, for unspecified reasons. Most reactions, however, were indicated as 'likely' (n=19 064) or marked 'unclear'(n= 11 382).

The reactions were mostly described as 'rash' (16 731, 54%), urticaria (4 032, 13%) and angioedema (3 780, 12%). Life-threatening anaphylactic shock or severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), were reported in 1 520 (5%) and 73 (0.2%), amounting to a prevalence of 0.15% and 0.007% among the total population, respectively. Anaphylactic shock was most often reported for penicillins (n= 990), cephalosporines (n= 178) and quinolones (n= 137); SJS for penicillins (n= 28) and (sulfonamides with) trimethoprim (n= 17) (see Online Repository, **Table E4**).

Comparison between out- and inpatients showed that the onset date was more frequently defined in inpatients (16% versus 11%). Considering symptoms, inpatients more frequently reported rash, angioedema or asthma (54%, 13% and 2.9% compared to 52%, 11% and 2.5%, respectively), while outpatients more frequently reported anaphylactic shock (6% versus 4%). Slightly more inpatients had no details of their reaction symptoms reported (5% versus 4%). Amongst the other reactions,

nausea, gastrointestinal complaints and edema were most frequently reported (2%, 0.6% and 0.5%, respectively), but also other side effects such as tendinitis, hepatitis and (vulvovaginal) candidiasis were occasionally indicated (0.5%, 0.3% and 0.2%). Outpatient reactions were slightly more frequently self-reported (89% versus 88%), while those of inpatients were more reported by UZ physicians (2% versus 4%). For outpatients the reactions were more frequently objectified (3% versus 2%), more by allergy test (2% versus 1%), while inpatients more frequently had an (accidental) rechallenge (0.3% versus 0.1%) reported. The reactions of outpatients more frequently were indicated as 'certain' (2% versus 1%), but conversely, also more of their reactions were marked 'unclear' (43% versus 33%).

Most reactions were reported by residents (11 753, 37%), supervisors (11 398, 36%) or nurses (6 275, 20%). They were reported particularly at the departments of anesthesiology (6 598, 21%), general internal medicine (1 803, 6%), and cardiology (745, 2%), except for the outpatient department where the third most reports came from the allergy unit.

Discussion

With an overall prevalence of 3% of the patients that consulted our hospital, being 1% of outpatients and 7% of those hospitalized, AAL are reported less in our center when compared to literature. The largest US study in 411 543 patients, reported a prevalence of 15% for AAL in the outpatient population of San Diego county (3), while large studies in hospitalized patients reported prevalences around 11% (5,16). Smaller studies in selected inpatient populations in Australia reported prevalences between 14 and 23% (19–22); and in Canadian studies prevalences between 10 and 14% were noted (23,24). To our knowledge, no previous European study addressed the prevalence of AAL in hospital EPRs; most previous reports were based on prospective questionnaire studies (10,25–27), and/or the studies primarily focused on penicillin (7–9,14,28)(see **Table 4**, for an overview of the literature).

The prevalence of penicillin allergy labels in EPRs in US literature ranges from 9 to 13% (3,4,29), while European studies report prevalences of 0.6% in primary care in The Netherlands (7), 0.9% of adult hospitalizations in Portugal (14), and 5% in the hospitalized patients in Denmark and the Netherlands (8,9). Although the Portuguese population consisted of 11 482 091 patients (14), selection was based on International Classification of Disease (ICD9) codes only, which possibly generated an underestimated prevalence. In a recent prospective study performed in Antwerp, Belgium, prevalence of self-reported penicillin allergy was 12%. However, it considered a population visiting the outpatients' allergy departments presumably inducing referral bias (28).

The lower prevalence in our study compared with studies outside Europe may be attributed to various differences: prescription guidelines, resistance profiles, genetic polymorphisms (30), diagnosis and management of drug hypersensitivity reactions (31), and/or reporting and documentation of AAL.

Study design and population selection also influence prevalence rates; e.g. higher prevalences were reported in patients with hematologic malignancies in the US (32), cancer patients in Australia (19), and in Canadian patients interviewed during the preoperative anesthesiology evaluation (24). In our study, no exclusion criteria were defined, hence allowing evaluation of AAL in a broad scale patient population. On the other hand, lower prevalences may also reflect underreporting in our population, or overreporting in the others, rather than real differences in the occurrence of reactions attributed to allergy.

Significantly more women were involved, as observed in other studies (3,4,6). Several authors demonstrated that female patients more frequently use AB compared with males (3,33). Also in Belgium, more AB were delivered to women during the study period, 476 187 023 versus 344 439 078 defined daily doses (DDD) to men, at least taking into account all outpatient pharmacies (34).

One may also suggest that female patients are more likely to report allergies spontaneously, or are more prone to recall the history of allergies. However, these differences might also reflect a truly higher amount of reactions attributed to allergy in women.

Particularly, penicillins were involved, mostly labeled as 'penicillin allergy', without further specification of the culprit drug. The latter might occur because the culprit is unknown, not asked for, or the importance of a careful documentation is not fully acknowledged. Amoxicillin (with or without BLI) was the most specified culprit. Also in Europe, penicillins are the first-choice AB to treat the majority of bacterial infections, and among them amoxicillin constitutes the most consumed one (35). Based on Pharmanet data (34), 374 403 457 DDD of amoxicillin (with or without BLI) were delivered to outpatients within the study period in Belgium, which constitutes 46% of the total DDD of AB. According to the Belgian Hospitals surveillance of antimicrobial consumption (BEH-SAC), 'combinations of penicillins with beta-lactamase inhibitors' was also the most used subclass used in-hospital (37.3% of the median antibiotic consumption in Belgian hospitals in 2017)(36).

Case reports also document hypersensitivity reactions to the BLI clavulanate (37,38), and one non-immunological hypersensitivity reaction to tazobactam was previously reported (39,40). However, the latter is not tested separately in our center.

Overall prevalence of cephalosporin labels was 0.1% in our population, compared to 1.3%-1.7% in US studies (3,4). In our hospital, cefazolin is the AB of choice for surgical prophylaxis, which was, with a total of 103 allergy reports (0.4%), the second most reported cephalosporin (after cefuroxime, with 123 reports).

Only a minor amount of labels concerned carbapenems and monobactams (n= 141). Liang et al reported prevalences of 0.0007% for carbapenems, and 0.001% for monobactams (29), compared with 0.002% and 0.0004% in our population respectively.

Interestingly, quinolones were the second most involved ABs (7% of the labels, prevalence 0.2%), followed by sulfonamides and macrolides (both 3% of the labels, prevalence 0.1%), whereas in US studies, BL are followed by sulfonamides and macrolides (prevalences of 5-7% and 1-3%, respectively)(3,4). A smaller study in The Netherlands reported a top 3 of BL followed by tetracyclines and sulfonamides (65%, 12% and 11% of the labels, respectively)(10), most likely reflecting differences in local use of AB. 85 836 467 DDD of quinolones were delivered to outpatients within the study period in Belgium, constituting 10% of the total DDD of AB, which makes it the 4th most consumed drug class in ambulatory setting (following 53% BL, 13% macrolides, and 11% nitrofurans derivatives). According to the Belgian Hospitals surveillance of antimicrobial consumption (BEH-SAC), providing information on in-hospital use, quinolones were the second most consumed drug class in this setting (accounting for 10.5 %) after combinations of penicillins with betalactamase inhibitors.

High in-hospital consumption of quinolones was mainly explained by the use of ciprofloxacin and moxifloxacin (63.7% and 21.1% of the median quinolone consumption in Belgian hospitals in 2017 respectively)(36).

According to our data, multiple drug allergy syndrome (MDAS), defined as drug hypersensitivity reactions to 2 or more drug classes (41), occurred in 5% of the patients with alleged AB allergy, or 4% of out- versus 6% of inpatients. Other studies addressing its prevalence in EPRs reported prevalences ranging from 2.1% to 4.9% of patients with alleged drug allergy (4,42,43). In accordance with those studies, significantly more woman had multiple AAL, and patients with MDAS were found to be significantly older than those with only one AAL, although this could also be attributed to co-morbidities that were not included in our analyses. However, these results are based on clinical history taking alone, whereas Landry et al. reported a prevalence of only 0.5% on the basis of positive allergy test results, indicating that true multiple drug hypersensitivity, defined as proven hypersensitivity to two or more distinct drugs after drug allergy evaluation, is a very rare condition (44).

Differences in prevalence might also be attributed to differences in clinicians' expertise and interpretation. In the current study, the majority of the reactions (75%) were reported by physicians (residents, supervisors, and/or external physicians), in both the out- and inpatient population (61% and 82%, respectively). However, in the outpatient population 34% was documented by nurses, compared to 13% in inpatients, which could explain differences in the documentation.

Still, the descriptions of the reactions frequently lacked specificity, e.g. the onset date was not specified in 86% of the reactions, and specific symptoms lacked in 4%. The alleged culprit was only indicated in 20%, more frequently in inpatients (21% compared to 19%) and for non-BL AB (90% compared to 7%). This could be due to insufficient knowledge on the culprit and/or because physicians are also offered a wider label upon filing for a specific AB (such as 'penicillins' or 'betalactams except monobactams and carbapenems' in case of amoxicillin), thereby already taking into account possible cross-reactivity.

Undetailed description of reaction symptoms may reflect patients not providing or knowing more information, but also, physicians not asking for it. It was hypothesized that inpatients more frequently undergo more detailed history taking, however statistical comparison demonstrated more details in outpatient reports.

When looking exclusively into the data of patients that have undergone a pre-operative anesthesia evaluation that specifically questions drug allergy and reports this via the allergy module, the prevalence of AAL increased from 3% to 5%. This might result from relative overrepresentation of

inpatients (prevalence of 7%) in this population. Next, there may be underreporting in outpatients (prevalence of 1%), due to absence of active questioning on allergies or perceived unnecessary to use the allergy module for registration. Evaluation of AAL using ICD-codes for AB allergy was not performed since we observed this would underestimate the prevalence of AAL (data not shown).

Our results indicate the need for an improved allergy registration tool. First, a rash, used 16 731 times to describe the symptoms, is a general term for a temporary skin eruption, including maculae, papules, plaques, urticaria/hives, vesicles, etc. The exact morphology of skin lesions, ideally supplemented by the distribution and evolution over time of the lesions, would be helpful to classify the reaction (45). Second, timing is essential for the differentiation between immediate reactions, occurring within hours after administration of the drug, and non-immediate or delayed-type reactions, that occur only after a delay of hours until days, especially because the diagnosis and management differs for both (46).

Currently, only limited distinction between the reaction types is made in our registration module. Third, 20% of symptoms was classified as 'other', often specifying non-immunologic reactions, such as gastro-intestinal complaints and (vulvovaginal) candidiasis. These patients are at low risk of having experienced a genuine allergic reaction to AB. Other low-risk histories, at least for penicillin allergy, include patients reporting only a family history of a penicillin allergy, or remote (>10 years) unknown reactions; moderate-risk histories include urticaria or other pruritic rashes and reactions with features of IgE-mediated reactions; and high-risk histories include patients with anaphylaxis, recurrent reactions, or hypersensitivities to multiple BL (47). Therefore, sufficiently detailed documentation can most likely already facilitate labeling and delabeling strategies.

Study limitations include the retrospective nature hampering cause-effect identification and absence of invasive objectivation of the allergy labels. The assets of this study, however, are the very large sample size with broad inclusion of all patients rather than selected (at risk) patients, and the long study period, in the largest Belgian hospital.

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Figure legend

Figure 1. Multiple antibiotic (classes) allergy labels per patient (logarithmic scale)

Tables

Table 1. Characteristics of the (out-/in-) patients with at least one AAL

	Outpatients	Inpatients	Total	<i>p</i> -value of comparison between out- and inpatients
Total n with at least one AAL	9 562	18 585	28 147	
N women (%)	6840 (72)	12 359 (66)	19 199 (68)	p<0.001
Mean age ($\pm$ SD)	48 ($\pm$ 19)	54 ($\pm$ 20)	52 ($\pm$ 20)	p<0.001
N aged <18 at (first) labeling (%)	644 (7)	925 (5)	1 569 (6)	p<0.001
N aged $\geq$ 65 at (first) labeling (%)	1 896 (20)	6 275 (34)	8 171 (29)	p<0.001
N with more than 1 AAL label (%)	734 (8)	1 757 (9)	2 491 (9)	p<0.001
N with AAL for more than 1 AB class (%)	401 (4)	1 029 (6)	1 430 (5)	p<0.001
Average n of labels per person ($\pm$ SD)	1.09 ($\pm$ 0.38)	1.11 ($\pm$ 0.41)	1.10 ($\pm$ 0.40)	p<0.001

Table 2. Numbers of (out-/in-) patients with an AALⁱ, and the respective prevalences (%), presented per AB classⁱⁱ. For more details on the separate culprits, see Online Repository Table E1.

Antibiotic allergy label	Outpatients (% of total, n = 736 469)	Inpatients (% of total, n= 273 129)	Total (% of total, n= 1 009 598)
Betalactams (BL)(any label)	8647 (1.17)	16 415 (6.01)	25 062 (2.48)
Penicillins	7 966 (1.08)	14 858 (5.44)	22 824 (2.26)
Penicillins general label (unspecified)	7 367 (1.00)	13 910 (5.09)	21 277 (2.11)
βlactamase-sensitive penicillins	75 (0.01)	74 (0.03)	149 (0.01)
βlactamase-resistant penicillins	15 (<0.01)	56(0.02)	71 (0.01)
Aminopenicillins	468 (0.06)	740 (0.27)	1 208 (0.12)
Carboxypenicillins	3 (<0.01)	4 (<0.01)	7 (<0.01)
Ureidopenicillins	9 (<0.01)	60 (0.02)	69 (0.01)
Extended spectrum penicillins	50 (0.01)	74 (0.03)	124 (0.01)
Combination of penicillins	38 (0.01)	51 (0.02)	89 (0.01)
Cephalosporins	400 (0.05)	957 (0.35)	1 357 (0.13)
Cephalosporins general label (unspecified)	272 (0.04)	693 (0.25)	965 (0.10)
Cephalosporins 1 ^e generation	64 (0.01)	113 (0.04)	177 (0.02)
Cephalosporins 2 ^e generation	64 (0.01)	118 (0.04)	182 (0.02)
Cephalosporins 3 ^e generation	6 (<0.01)	51 (0.02)	57 (0.01)
Cephalosporins 4 ^e generation	3 (<0.01)	3 (<0.01)	6 (<0.01)
Carbapenems	0	23 (0.01)	23 (<0.01)
Monobactams	1 (<0.01)	3 (<0.01)	4 (<0.01)
Combination BL labels (unspecified)	467 (0.006)	105 (0.40)	1572 (0.16)
BL antibiotics excl. carbapenem, monobactam	452 (0.06)	1 013 (0.37)	1 465 (0.15)
Other BL antibiotics: carbapenem, monobactam	16 (<0.01)	97 (0.04)	114 (0.01)
Other cephalosporines and carbapenems	0	1 (<0.01)	1 (<0.01)
Quinolones	535 (0.07)	1 301 (0.48)	1 836 (0.18)
Sulfonamides/Trimethoprim	307 (0.04)	701 (0.26)	1 008 (0.10)
Macrolides	299 (0.04)	522 (0.19)	821 (0.08)
Macrolides general label (unspecified)	65 (0.01)	130 (0.05)	195 (0.02)
Neomacrolides	168 (0.02)	265 (0.10)	433 (0.04)
Other macrolides	73 (0.01)	141 (0.05)	214 (0.02)
Nitrofurans derivatives	103 (0.01)	275 (0.10)	378 (0.04)
Tetracyclines	54 (0.01)	174 (0.06)	228 (0.02)
Glycopeptides	11 (<0.01)	155 (0.06)	166 (0.02)
Lincosamides	22 (<0.01)	96 (0.04)	118 (0.01)
Aminoglycosides	16 (<0.01)	55 (0.02)	71 (0.01)
Imidazole derivatives	6 (<0.01)	32 (0.01)	38 (<0.01)
Amphenicols	3 (<0.01)	14 (0.01)	17 (<0.01)
Polypeptides	0 (<0.01)	6 (<0.01)	6 (<0.01)
Other antibiotics	9 (<0.01)	46 (0.02)	55 (0.01)
At least one antibiotic allergy label	9 562 (1.30)	18 585 (6.80)	28 147 (2.79)

ⁱ Specific AAL were clustered according to their subgroup. AAL that were unspecified are indicated.

ⁱⁱ As it is possible to have more than one label within the same drug class, the total number of patients per class may be less than the sum of the parts.

Table 3. Information about the AAL

Label information	Outpatient labels n (% of total, 10 480)		Inpatient labels n (% of total, 20 796)		Total labels n (% of total, 31 276)		p-value for comparison out- and inpatient labels
Onset date							
< 1 week ago	85	(0.81)	374	(1.80)	459	(1.47)	<0.001
1 week - 1 month ago	50	(0.48)	265	(1.27)	315	(1.01)	<0.001
1 month - 1 year ago	162	(1.55)	765	(3.68)	927	(2.96)	<0.001
1 year - 5 years ago	190	(1.81)	651	(3.13)	841	(2.69)	<0.001
5 - 10 years ago	67	(0.64)	287	(1.38)	354	(1.13)	<0.001
10 -20 years ago	327	(3.12)	539	(2.59)	866	(2.77)	0.007
> 20 years ago	249	(2.38)	468	(2.25)	717	(2.29)	0.48
Not specified	9 350	(89.2)	17 447	(83.9)	26 797	(85.7)	<0.001
Symptoms (<i>multiple answers possible</i>)							
Rash	5 450	(52.0)	11 281	(54.3)	16 731	(53.5)	<0.001
Urticaria	1 305	(12.5)	2 727	(13.1)	4 032	(12.9)	0.10
Angioedema	1 168	(11.2)	2 612	(12.6)	3 780	(12.1)	<0.001
Itching	553	(5.28)	1 435	(6.90)	1 988	(6.36)	<0.001
Anaphylactic shock	629	(6.00)	891	(4.28)	1 520	(4.86)	<0.001
Asthma	263	(2.51)	611	(2.94)	874	(2.79)	0.03
Stevens-Johnson syndrome	18	(0.17)	55	(0.26)	73	(0.23)	0.11
Other (free text) ⁱⁱ	2 301	(22.0)	4 472	(21.5)	6 773	(21.7)	0.36
<i>No details known/provided</i>	431	(4.11)	963	(4.63)	1 394	(4.45)	0.04
<i>Nausea, vomiting</i>	167	(1.59)	320	(1.54)	487	(1.56)	0.72
<i>Reaction in childhood</i>	122	(1.16)	175	(0.84)	297	(0.95)	0.005
<i>Gastrointestinal upset, diarrhea</i>	75	(0.71)	113	(0.54)	188	(0.60)	0.06
<i>Swelling, edema</i>	60	(0.57)	99	(0.47)	159	(0.51)	0.26
<i>Tendinitis</i>	14	(0.13)	121	(0.58)	155	(0.50)	<0.001
<i>Itching</i>	54	(0.52)	101	(0.49)	155	(0.50)	0.73
<i>Rash, toxicodermia</i>	41	(0.40)	103	(0.50)	144	(0.46)	0.20
<i>Malaise, vertigo</i>	31	(0.30)	66	(0.32)	97	(0.31)	0.75
<i>Hepatitis</i>	18	(0.17)	81	(0.39)	99	(0.32)	0.001
<i>Candida</i>	50	(0.47)	47	(0.22)	97	(0.31)	<0.001
<i>Fever, shivering</i>	31	(0.29)	59	(0.28)	90	(0.29)	0.85
<i>Syncope, loss of consciousness</i>	22	(0.21)	51	(0.25)	73	(0.23)	0.54
<i>Dyspnea</i>	24	(0.23)	37	(0.18)	61	(0.20)	0.33
<i>Oral aphthosis</i>	15	(0.14)	40	(0.19)	55	(0.18)	0.33
<i>Intolerance</i>	12	(0.11)	39	(0.19)	51	(0.16)	0.13
<i>Heart palpitations</i>	21	(0.20)	27	(0.13)	48	(0.15)	0.13
<i>Family history</i>	16	(0.15)	25	(0.12)	41	(0.13)	0.45
Information source (<i>multiple answers possible</i>)							
Self-reported	9 376	(89.5)	18 284	(87.9)	27 660	(88.4)	<0.001
External physician	1 066	(10.2)	2 187	(10.6)	3 253	(10.4)	0.34
UZ Leuven physician	192	(1.83)	842	(4.05)	1 034	(3.30)	<0.001

Objectivation (<i>multiple answers possible</i>)						
Allergy test	203	(1.94)	257	(1.24)	460	(1.47)
Rechallenge	14	(0.13)	60	(0.29)	74	(0.24)
Observed	84	(0.80)	198	(0.95)	282	(0.90)
Not objectified (none of the above)	10 183	(97.2)	20 293	(97.6)	30 476	(97.4)
Probability						
Unclear	4 457	(42.5)	6 925	(33.3)	11 382	(36.4)
Likely	5 711	(54.5)	13 353	(64.2)	19 064	(61.0)
Certain	312	(2.98)	518	(2.49)	830	(2.65)
Reporter						
Clinical function (top 5)						
<i>Resident</i>	2 987	(28.5)	8 766	(42.2)	11 753	(37.6)
<i>Supervisor</i>	3 319	(31.7)	8 079	(38.9)	11 398	(36.4)
<i>Nurse</i>	3 591	(34.3)	2 684	(12.9)	6 275	(20.1)
<i>Last-year med student</i>	258	(2.46)	655	(3.15)	913	(2.91)
<i>External physician</i>	87	(0.83)	227	(1.09)	314	(1.00)
<i>Others</i>	238	(2.27)	384	(1.85)	622	(1.99)
Department (top 5)						
<i>Anesthesiology</i>	1 523	(14.5)	5 431	(26.2)	6 954	(22.2)
<i>General internal medicine</i>	743	(7.12)	1 060	(5.10)	1 803	(5.76)
<i>Cardiology</i>	116	(1.11)	629	(3.02)	745	(2.38)
<i>Maternity</i>	25	(0.24)	505	(2.43)	530	(1.69)
<i>Allergology</i>	227	(2.17)	203	(0.98)	430	(1.37)
<i>Others</i>	859	(8.20)	4 564	(22.0)	5 423	(17.3)
<i>Unknown</i>	6 987	(66.7)	8 404	(40.4)	15 391	(49.2)

ⁱⁱ Non-exhaustive, only the most frequent texts are listed here

Table 4. Overview of the literature on AAL

Study	Region	Study population	Datasource	AAL prevalence	Subspecifications on AAL prevalence
Macy et al, 2009 ³	US, California	411 543 outpatients	EPR	15.3%	Penicillins 9% Sulfonamides 5.4% Cephalosporins 1.3% Macrolides 1.3% Tetracyclines 0.9% Quinolones 0.6%
Charneski et al, 2011 ⁵	US, Maryland	11 872 adult inpatients, who received at least one AB	EPR	11.2%	NA
Khasawneh et al, 2013 ⁴⁸	US, Texas	2 589 inpatients in internal medicine service	Medical record review	NA	Penicillin 14.9%
Macy et al, 2014 ¹⁶	US, California	51 582 inpatients	EPR	NA	Penicillin 11.2%
Moskow et al, 2016 ⁴⁹	US, Florida	319 051 primary care patients	EPR	NA	Betalactam 9.1%
Zhou et al, 2016 ⁴	US, Boston	1 766 328 out- and inpatients	EPR	NA	Penicillin 12.8% Sulfonamides 7.4% Macrolides 2.6% Cephalosporins 1.7% Fluoroquinolones 1.3% Tetracyclines 1.2% Lincosamides 0.4%
Huang et al, 2018 ³²	US, Pennsylvania	4 671 inpatients with hematologic malignancy requiring AB	EPR	NA	Nonmonobactam betalactams 35.1% of AAL Penicillin 16.5% of AAL Cephalosporins 7.1% of AAL
Liang et al, 2020 ²⁹	US, California	6 144 442 out- and inpatients (population based)	EPR of all outpatient, inpatient and pharmacy data of Southern California	NA	Penicillin 9.2% Clindamycin 0.4% Carbapenem 0.007% Monobactam 0.001%
Trubiano et al, 2015 ¹⁹	Australia	198 inpatients with cancer, and at least one infective episode and AB prescription	Medical and pharmacy record review	23%	Betalactams 65% of AAL Sulfonamides 11% of AAL Glucopetides 6% of AAL Fluoroquinolones 5% of AAL Macrolides 5% of AAL Tetracyclines.2% of AAL
Trubiano et al, 2016 ²²	Australia	21 031 inpatients receiving AB	National Antimicrobial Prescribing Survey (NAPS) database for Australian hospitals (a voluntary standardized electronic auditing tool)	18%	Betalactams 13.3% Penicillins 8.9% Cephalosporins 2.3% Sulfonamides 2.1%

					Aminopenicillins 1.4% Macrolides 1.3% Tetracyclines 0.8% Antistaphylococcal penicillins 0.7% Fluoroquinolones 0.6% Glycopeptides 0.5%
Knezevic et al, 2016 ²¹	Australia	687 inpatients	NAPS voluntary annual audit 2013 and 2014 (medical chart review by ward pharmacists)	18%	Betalactam 83% of AAL Penicillins 13% (71% of AAL)
Torda et al, 2017 ²⁰	Australia	3 855 adult inpatients	EPR	14.35%	Subsequent allergy history taking and medical record data review in 352 patients: Penicillin 64.8% of AAL Cephalosporins 9.6% of AAL Macrolides 8.5% of AAL Sulfonamides/trimethoprim 7.5% of AAL
Hung et al, 1994 ²⁴	Canada	1 818 inpatients	Preoperative anaesthetic assessment	14% [calculated as 50% of all drug allergy labels: 28.1%]	Penicillins 58.1% of AAL Sulfonamides 25.3% of AAL Trimethoprim 5.3% of AAL Erythromycins 3.1% of AAL Tetracyclines 3.1% of AAL Cephalosporins 2.2% of AAL
Picard et al, 2013 ²³	Canada	1 738 inpatients	Medical record review	NA	Penicillin 9.9%
Gomes et al, 2004 ²⁷	EU, Portugal	2 307 adults of the general population of Porto	Questionnaires	NA	Penicillins or other betalactams 4.5%: Penicillin G or V 76.2% of betalactam allergy labels Amoxicillin with clavulanic acid 14.3% of betalactam allergy labels
Borch et al, 2006 ⁹	EU, Denmark	3 642 inpatients	Medical record review + questionnaires	NA	Penicillin 5%
Lange et al, 2008 ²⁵	EU, Germany	1 447 children visiting the hospital	Questionnaires	NA	4.2% had a history suspicious for a potential allergic mechanism; the suspected drugs were AB in 85%: 32.7% aminopenicillins, 29.5% penicillins, 11.5% cephaclo, 8.2% macrolides and 18% others.
Branellec et al, 2008 ²⁶	EU, France	1 057 primary care patients	Questionnaires	NA	Penicillin 9.4%
Salden et al, 2015 ¹¹	EU, The Netherlands	8 288 primary care patients	EPR, by means of ICPC-2 codes (International classification for primary care 2) + pharmacy labels	NA	Betalactams 2%
Van Dijk et al, 2016 ⁸	EU, The Netherlands	17 959 inpatients	EPR, based on systematically performed pharmacotherapeutic interviews	NA	Penicillin 5.6%
Sousa-Pinto et al, 2018 ¹⁴	EU, Portugal	11 482 091 inpatients	EPR	NA	Penicillin 0.9%
Su et al, 2017 ⁷	EU, The Netherlands	194 440 primary care patients	EPR (Utrecht General Practitioner Network Database)	NA	Penicillin 0.6%
Lin et al, 2019 ¹⁰	EU, The Netherlands	492 inpatients with a AAL	Medication verification interviews	NA	Penicillin 65% of AAL

					Tetracyclines 12.2% of AAL Cephalosporins 12.1% Sulfonamides 11.4% of AAL Quinolones 10.8 of AAL Nitrofurans derivatives 10.8% of AAL Carbapenems 9.3% of AAL Macrolides 7.7% of AAL Lincosamides 4.9% of AAL
Van Gasse 2020 ²⁸	EU, Belgium	1498 outpatients visiting the allergology or pediatric department	Interviews	NA	Penicillin 12%

AAL, antibiotic allergy label; AB, antibiotics; EPR, electronic patients records; NA, not available

Probleemlijst item registratie - TEST LABEL 1 (86339736, 700101V827, 50j)

☒ Anaesthetica, algemeen, barbituraten	Thiopental	Allergie definitie
☒ Anaesthetica, algemeen, opioïde	Fentanyl	Allergie definitie
☒ Anaesthetica, algemeen, overige	Ketalar	Allergie definitie
☒ Anaesthetica, lokaal	Procaine hcl	Allergie definitie
☒ Antibiotica, betalactam (excl. carbapenem, monobactam)	Amoxicilline eg	Allergie definitie

☐ Anaphylactic shock	☐ Rash
☐ Angioedema	☐ Itching
☐ Steven Johnson/Lyell	
☐ Asthma	
☐ Urticaria	
☐ Others	

Source of information:	Objectified by:
☐ Self-reported	☐ Allergy test
☐ External physician	☐ Rechallenge
☐ MvNexus physician	☐ Anaph. shock or angioedema observed

Probability:		
☐ Unclear	☐ Probable	☐ Certain

Probleemlijst item registratie - TEST LABEL 1 (86339736, 700101V827, 50j)

Antibiotica, betalactam (excl. carbapenem, monobactam)

Free text

As from: 14-05-2020

Zeer ernstige re

Selecteer een dag

vanaf vandaag 2020

jan feb mrt apr mei jun

jul aug sep okt nov dec

ma	di	wo	do	vr	za	zo
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

OK Annuleer

Informatiebron

Ge

Gedoc

Vastge

Zekerheid

Probleemlijst item registratie - TEST LABEL 1 (86339736, 700101V827, 50j)

Antibiotica, betalactam (excl. carbapenem, monobactam)

Free text

As from: 14-05-2020

Very severe reactions

Anafylactische shock

Datum: --

Angioedema

Steven Johnson/Lyell

Asthma

Urticaria

Severe reactions

Rash

Itching

TEST /// *01-01-1960 Eadnr: 60617351 Emdnr: 600101V081

60j

NL

KS

AS

OB

0

Patient info

1 A1 ABD 105 — voorbereid x274624 / x274624

Zoek naar een pagina

Favorieten

Patient info

Contacten

Overzicht

Telgsm/email/communicatietaal

Taal

Externe info

Externe info historiek

Foetus info

Aandachtspunten

Algemene info

Naam: TEST Voornaam: ///

Eadnr: 60617351 Emdnr: 600101V081 Geslacht: vrouw

Alergie (Problemen)

• vorig J. Alergie Antibiotica, penicillines - Waarschijnlijk

Registreer allergie

Open probleemlijst

Nieuw medicatievoorschrift

vochtditisch

Medicatie

☒ gestructureerd ☐ tpi ☐ magistraal

☐ Thuismed.

AMOXICILLINE SANDOZ TABL DISP 500MG € 0.2 500 mg /par /tijd 500 mg € 0.2

Effectieve dosis 500

Toedieningsweg PO

Uurschema +0

Dosis per gift 500 mg

vorm +00

TABL DISP 500MG 1.0 stuks 0

Opgelet!

Als één van deze geneesmiddelen (tijdelijk) niet strikt noodzakelijk is, of indien voor één van deze geneesmiddelen een alternatief kan voorgeschreven worden dat niet interageert, klik dan op 'annuleren' en pas het elektronisch voorschrift aan.

Om redenen van patiëntveiligheid dient u de start van deze medicatie met risico op allergie bij deze patiënt te motiveren door het formuleren van een expliciete afweging tussen indicatie en het risico op allergie verbonden aan de medicatie.

Allergie-interactie

Gecontroleerde periode: 25-08-2020 00:00 - 24-09-2020 23:59

Deze patiënt heeft in het verleden allergisch gereageerd op: **ANTIBIOTICA, BETALACTAM (EXCL. CARBAPENEM, MONOBACTAM)**

met een **Angio-oedeem**

Uitslag (Zeer ernstig)

Medicatie: AMOXICILLINE SANDOZ (TABL DISP 500MG)

Overname nodig

Online Repository

Allergy module at UZ Leuven - Description

Allergy module at UZ Leuven - Screenshots

Figure E1. Allergy registration module (the most important items were translated and added to the print screens (white text boxes) to improve readability): Step 1, selection of the suspected drug or drug class from a drop-down list, set up according to the Anatomical Therapeutic Chemical (ATC) classification; Step 2, specification of the reaction date, with registration date as default when no date has been selected; Step 3, symptoms of the reaction, with optional date and free text registration; Step 4, Source of information selection; Step 5, possibility to specify if the reaction has been objectified; Step 6, probability of the label according to the reporter, with the option to choose between 'unclear' and 'likely', or, in case the reaction has been objectified, automatically indicated as 'certain'

Figure E2. Pop-up of the allergy label in the electronic patient record of the patient

Figure E3. Pop-up of the allergy label in the e-prescription module

Tables

Table E1. Number of allergy labels for each antibiotic class, subclass and drug

Table E2. Number of labels with specification of the alleged culprit per antibiotic class

Table E3. Number of reports for out- and inpatients per reporting year

Table E4. Alleged culprits of severe reactions

Allergy module at UZ Leuven - Description

Alleged allergic reactions can be registered (and updated) in the EPR system by all healthcare providers employed at UZ Leuven, using a dedicated allergy registration module (see **Figure E1-E3**). Since 2016, the EPR system is also available to other UZ Leuven partner institutions in Flanders (Nexuzhealth), and to external physicians (Mynexuzhealthpro).

First, the suspected drug or drug class has to be chosen from a drop-down list, which was set up according to the Anatomical Therapeutic Chemical (ATC) classification. For BL, it is also possible to select a combination label such as 'BL antibiotics with exclusion of carbapenems and monobactams', for example, in case of a history or observation of a severe reaction to penicillin/cephalosporin when it was deemed best to prohibit all BL, except those with the lowest possibility for cross-reactivity, retaining a broad antimicrobial spectrum and in-hospital administration. Other combination labels include 'other BL antibiotics, being carbapenems, monobactams', and 'other cephalosporines and penems'. The combination label 'other cephalosporines and penems' is currently considered irrelevant and will be removed. It was initially generated to enable future labeling of penems (other than imipenem, meropenem) or cephalosporins not yet available within our database. Only one patient received this label.

Second, the onset date of the alleged allergy can be specified, however, when no date has been selected, the date of registration is chosen by default. Third, the symptoms of the reaction can be specified (not obligatory; it is possible to save incomplete registrations), the choices being very severe reactions (anaphylactic shock, angioedema, Stevens-Johnson syndrome (SJS) or Lyell syndrome, and/or asthma) or severe reactions (rash or itching without rash), or other reactions, with the option to add free text and to specify the date at which the symptoms occurred. In a fourth step the source of information needs to be indicated, which can be self-reported by the patient, documented by an external physician, or assessed by a physician of the UZ Leuven or a partner institution. In addition, the possibility is given to specify if the reaction has been confirmed by an allergy test, (accidental) rechallenge, or because an anaphylactic shock or angioedema was observed by the clinician. In those cases, the probability of the label will automatically become 'certain' in the last step of the module, whereas for the others, the reporter can choose between 'unclear' or 'likely'. A registered allergy will pop-up when the EPR is consulted, as well as when an e-prescription with the respective ATC code is composed. The combination labels provide an additional layer of safety; for example, in those with for instance a confirmed penicillin allergy the combination label 'BL antibiotics with exclusion of carbapenems and monobactams' can be used, so that prescription of other BL would result in a warning.

Aside from the allergy module, an adverse event module is in place to report non-allergic (severe) reactions, although a minority of these adverse events, such severe side effects, have been reported as allergies.

Tables

Table E1. Number of allergy labels for each antibiotic class (**bold**), subclass and drug (*italic*), for both men (m) and women (w)

	Outpatients			Inpatients			Total		
	<u>m</u>	<u>w</u>	<u>Total</u>	<u>m</u>	<u>w</u>	<u>Total</u>	<u>m</u>	<u>w</u>	<u>Total</u>
Penicillins	2318	5824	8143	5022	10160	15 182	7340	15984	23324
Penicillins general label (unspecified)	2112	5361	7473	4628	9461	14089	6740	14822	21562
βlactamase-sensitive penicillins	25	52	77	25	52	77	50	104	154
<i>Penicillin G (Benzylpenicillin)</i>	21	46	67	18	41	59	39	87	126
<i>Penicillin V (Phenoxymethylpenicillin)</i>	2	4	6	4	6	10	6	10	16
<i>Pheneticillin*</i>	0	0	0	0	1	1	0	0	1
<i>Penamecillin*</i>	0	1	1	0	0	0	0	1	1
<i>Clometocillin*</i>	0	0	0	0	1	1	0	0	1
<i>Unspecified</i>	2	1	3	3	3	6	5	4	9
βlactamase-resistant penicillins	6	9	15	27	29	56	33	38	71
<i>Flucloxacillin</i>	6	8	14	26	28	54	32	36	68
<i>Cloxacillin*</i>	0	1	1	0	0	0	0	1	1
<i>Oxacillin*</i>	0	0	0	1	0	1	1	0	1
<i>Unspecified</i>	0	0	0	1	0	1	1	0	1
Aminopenicillins	144	333	477	256	500	756	400	833	1233
<i>Amoxicillin</i>	104	235	339	143	303	446	247	538	785
<i>Amoxicillin + betalactamase-inhibitor</i>	35	85	120	106	180	286	141	265	406
<i>Ampicillin</i>	5	13	18	7	17	24	12	30	42
Carboxypenicillins	1	2	3	2	2	4	3	4	7
<i>Temocillin</i>	1	2	3	2	2	4	3	4	7
Ureidopenicillins	3	6	9	39	33	72	42	39	81
<i>Piperacillin (+ tazobactam)</i>	3	6	9	39	33	72	42	39	81
Extended spectrum penicillins	13	37	50	26	50	76	39	87	126
Combination of penicillins	14	24	38	19	33	52	33	57	90

Cephalosporins	120	303	423	312	679	991	432	982	1414
Cephalosporins general label (unspecified)	73	203	276	210	490	700	283	693	976
Cephalosporins 1 ^e generation	20	51	71	43	73	116	63	124	187
<i>Cefazoline</i>	7	24	31	28	44	72	35	68	103
<i>Cefadroxil</i>	1	11	12	6	18	24	7	29	36
<i>Cephradin*</i>	1	0	1	0	0	0	1	0	1
<i>Cefatrizine*</i>	1	2	3	2	4	6	3	6	9
<i>Cefalexine*</i>	2	1	3	1	0	1	3	1	4
<i>Unspecified</i>	8	13	21	6	7	13	14	20	34
Cephalosporins 2 ^e generation	18	46	64	39	81	120	57	127	184
<i>Cefuroxim</i>	11	26	37	26	60	86	37	86	123
<i>Cefaclor*</i>	6	16	22	9	15	24	15	31	46
<i>Cefoxitin*</i>	0	0	0	2	1	3	2	1	3
<i>Unspecified</i>	2	4	5	2	5	7	3	9	12
Cephalosporins 3 ^e generation	7	2	9	19	33	52	26	35	61
<i>Ceftazidim</i>	0	1	1	6	15	21	6	16	22
<i>Ceftriaxon</i>	4	0	4	7	10	17	11	10	21
<i>Cefotaxim</i>	2	1	3	4	3	7	6	4	10
<i>Cefodizime*</i>	1	0	1	0	0	0	1	0	1
<i>Unspecified</i>	0	0	0	2	5	7	2	5	7
Cephalosporins 4 ^e generation	2	1	3	1	2	3	3	3	6
<i>Cefepim</i>	2	1	3	1	2	3	3	3	6
Cephalosporins 5 ^e generation	0	0	0	0	0	0	0	0	0
<i>Ceftolozane</i>	0	0	0	0	0	0	0	0	0
<i>Ceftaroline</i>	0	0	0	0	0	0	0	0	0
Carbapenems	0	0	0	6	17	23	6	17	23
<i>Meropenem</i>	0	0	0	6	16	22	6	16	22
<i>Imipenem</i>	0	0	0	0	1	1	0	1	1
Monobactams	0	1	1	1	2	3	1	3	4

<i>Aztreonam</i>	0	1	1	1	2	3	1	3	4
Combination BL labels	148	331	479	403	723	1126	551	1054	1605
BL antibiotics excl. carbapenem, monobactam	146	317	463	365	662	1027	511	979	1490
Others BL antibiotics, carbapenem, monobactam	2	14	16	37	61	98	39	75	114
Other cephalosporines and penems	0	0	0	1	0	1	1	0	1
Quinolones	153	418	571	505	853	1358	658	1271	1929
<i>Levofloxacin</i>	18	53	71	150	211	361	168	264	432
<i>Moxifloxacin</i>	62	136	198	137	222	359	199	358	557
<i>Ciprofloxacin</i>	40	106	146	103	172	275	143	278	421
<i>Fluoroquinolones</i>	21	66	87	74	142	216	95	208	303
<i>Ofloxacin</i>	8	32	40	22	53	75	30	85	115
<i>Quinolones general label (unspecified)</i>	2	11	13	11	22	33	13	33	46
<i>Norfloxacin</i>	1	11	12	3	21	24	4	32	36
<i>Other quinolones</i>	1	3	4	5	10	15	6	13	19
Sulfonamides/Trimethoprim	87	236	323	233	487	720	320	723	1043
<i>Sulfamethoxazol + trimethoprim (Co-trimoxazole)</i>	63	178	241	169	326	495	232	504	736
<i>General label sulfonamides (+ trimethoprim) (unspecified)</i>	21	42	63	54	128	182	75	170	245
<i>Sulfanilamide*</i>	0	1	1	1	3	4	1	4	5
<i>Sulfadimidine (+ trimethoprim)*</i>	0	1	1	1	4	5	1	5	6
<i>Sulfisomidine*</i>	0	0	0	0	1	1	0	1	1
<i>Sulfadiazine + trimethoprim*</i>	0	0	0	1	0	1	1	0	1
<i>Sulfamoxol + trimetoprim (Co-trifamol)*</i>	0	1	1	0	0	0	0	1	1
<i>Sulfamethizol*</i>	0	0	0	1	0	1	1	0	1
<i>Trimethoprim</i>	3	13	16	6	25	31	9	38	47
Macrolides	73	238	311	126	416	542	199	654	853
Macrolides general label (unspecified)	17	50	67	33	97	130	50	147	197
Neomacrolides	40	131	171	63	208	271	103	339	442
<i>Clarithromycine</i>	25	96	121	41	154	195	66	250	316
<i>Azithromycine</i>	14	29	43	22	46	68	36	75	111

<i>Roxitromycine</i>	1	6	7	0	8	8	1	14	15
Other macrolides	16	57	73	30	111	141	46	168	214
<i>Erytromycine</i>	11	38	49	21	82	103	32	120	152
<i>Spiramycine</i>	2	8	10	5	7	12	7	15	22
<i>Telithromycine*</i>	2	7	9	3	10	13	5	17	22
<i>Other</i>	1	4	5	1	12	13	2	16	18
Nitrofuran derivatives	13	94	107	45	236	281	58	330	388
<i>General label nitrofurantoin derivatives (unspecified)</i>	2	10	12	8	33	41	10	43	53
<i>Nitrofurantoin</i>	7	24	72	65	147	171	31	212	243
<i>Nifurtimol*</i>	3	19	22	13	55	68	16	74	90
<i>Nitrofurantoin combinations</i>	1	0	1	0	1	1	1	1	2
Tetracyclines	16	39	55	48	129	177	64	168	232
<i>Doxycycline</i>	8	16	24	20	56	76	28	72	100
<i>Unspecified</i>	6	10	16	18	46	64	24	56	80
<i>Minocycline</i>	1	11	12	5	17	22	6	28	34
<i>Tetracycline</i>	1	0	1	2	10	12	1	12	13
<i>Lymecycline</i>	0	2	2	0	0	0	0	2	2
<i>Tigecycline</i>	0	0	0	1	0	1	1	0	1
<i>Oxytetracycline</i>	0	0	0	1	0	1	1	0	1
<i>Combinations of tetracyclines</i>	0	0	0	1	0	1	1	0	1
Glycopeptides	3	8	11	73	87	160	76	95	171
<i>Vancomycine</i>	3	7	10	71	84	155	74	91	165
<i>Teicoplanine</i>	0	1	1	0	1	1	0	2	2
<i>Unspecified</i>	0	0	0	2	2	4	0	4	4
Lincosamides	5	17	22	28	71	99	33	88	121
<i>Clindamycine</i>	3	15	18	27	66	93	30	81	111
<i>Lincomycine</i>	2	2	4	1	3	4	3	5	8
<i>General label lincosamides (unspecified)</i>	0	0	0	0	2	2	0	2	2
Aminoglycosides	3	13	16	20	38	58	23	51	74

<i>Tobramycin</i>	1	3	4	4	12	16	5	15	20
<i>Streptomycin</i>	0	1	1	4	7	11	4	8	12
<i>Gentamicin</i>	1	2	3	5	4	9	6	6	12
<i>Neomycin</i>	0	2	2	2	5	7	2	7	9
<i>Amikacin</i>	0	0	0	5	2	7	5	2	7
<i>Netilmicin*</i>	0	1	1	0	0	0	0	1	1
<i>Other aminoglycosides</i>	1	4	5	0	7	7	1	11	12
<i>Aminoglycosides general label (unspecified)</i>	0	0	0	0	1	1	0	1	1
Amphenicols	1	2	3	7	7	14	8	9	17
<i>Thiamfenicol</i>	1	1	2	4	5	9	5	6	11
<i>Chlooramfenicol</i>	0	0	0	3	2	5	3	2	5
<i>Unspecified</i>	0	1	1	0	0	0	0	1	1
Polypeptides	0	0	0	2	4	6	2	4	6
<i>Colistin</i>	0	0	0	2	2	4	2	2	4
<i>Polymyxine B</i>	0	0	0	0	1	1	0	1	1
<i>Bacitracine</i>	0	0	0	0	1	1	0	1	1
Imidazole derivatives	1	5	6	7	26	33	8	31	39
<i>Imidazoles general label (unspecified)</i>	0	1	1	0	0	0	0	1	1
<i>Metronidazole</i>	1	3	4	0	5	5	1	8	9
<i>Ornidazole</i>	0	1	1	7	20	27	7	21	28
<i>Tinidazole</i>	0	0	0	0	1	1	0	1	1
Other antibiotics	1	9	10	7	16	23	8	25	33
<i>Fosfomycin</i>	0	7	7	1	9	10	1	16	17
<i>Linezolid</i>	1	0	1	5	3	8	6	3	9
<i>Fusidic acid</i>	0	1	1	0	1	1	0	2	2
<i>Others</i>	0	1	1	1	3	4	1	4	5
Total	2942	7538	10480	6845	13951	20796	9787	21489	31276

* = not marketed in Belgium (anymore)

Table E2. Number of labels with specification of the alleged culprit, per antibiotic class, for respectively out- and inpatients, along with p-values for comparison between both groups if total >100 (significant differences and highest amounts displayed in **bold**)

	Outpatients (% of total in the AB class)	Inpatients (% of total in the AB class)	Total (% of total in the AB class)	p-value for comparison out- and inpatients
Betalactam (BL)	700 (8)	1 247 (7)	1 947 (7)	0.1
Penicillins	578 (7)	958 (6)	1536 (7)	0.02
Cephalosporins	121 (29)	264 (27)	385 (27)	0.4
Carbapenems and monobactams	1 (100)	26 (100)	27 (100)	
Quinolones	558 (98)	1 325 (98)	1 883 (98)	0.8
Sulfonamides/trimethoprim	260 (80)	538 (74)	798 (97)	0.05
Macrolides	239 (77)	399 (74)	638 (75)	0.3
Nitrofurans derivatives	95 (89)	240 (85)	335 (86)	0.4
Tetracyclines	39 (71)	112 (63)	151 (65)	0.3
Glycopeptides	11 (100)	156 (97)	167 (98)	
Lincosamides	22 (100)	97 (98)	119 (98)	
Aminoglycosides	11 (69)	50 (86)	61 (82)	
Amphenicols	2 (67)	14 (100)	16 (94)	
Polypeptides	0	6 (100)	6 (100)	
Imidazole derivatives	5 (83)	33 (100)	38 (97)	
Others	8 (80)	19 (82)	27 (82)	
Total	2 012 (19)	4 386 (21)	6 398 (20)	

Table E3. Number of reports for out- and inpatients per reporting year

Year	N outpatient labels	% of unique outpatients (n unique outpatients)	% of outpatient visits (n outpatient visits)	N inpatient labels	% of unique inpatients (n unique inpatients)	% of hospitalisations (n hospitalisations)
2010	263	0.09 (285 362)	0.03 (1 049 471)	2 156	5.79 (37 242)	4.08 (52 819)
2011	556	0.18 (307 458)	0.05 (1 150 818)	2 407	6.10 (39 477)	4.23 (56 867)
2012	579	0.19 (305 267)	0.05 (1 164 761)	2 239	5.60 (39 978)	3.90 (57 347)
2013	748	0.24 (312 809)	0.06 (1 182 955)	2 173	5.40 (39 956)	3.81 (57 081)
2014	984	0.35 (281 352)	0.08 (1 209 905)	2 278	5.70 (39 502)	4.02 (56 656)
2015	1 166	0.43 (272 022)	0.09 (1 232 735)	2 222	5.63 (39 502)	3.94 (56 368)
2016	1 694	0.61 (275 945)	0.14 (1 251 659)	2 569	6.38 (40 235)	4.47 (57 419)
2017	2 198	0.78 (281 113)	0.16 (1 255 137)	2 482	6.06 (40 979)	4.24 (58 606)
2018	2 292	0.81 (282 386)	0.18 (1 269 871)	2 270	5.57 (40 734)	3.90 (58 253)
Total	10 480	1.42 (736 469)	0.10 (10 767 312)	20 796	7.61 (273 129)	4.07 (511 416)

Table E4. Alleged culprits of severe reactions

Anaphylactic shock	1 520		
Penicillins, unspecified	936	Josamycin	1
Betalactams, unspecified	107	Telithromycin	1
Cephalosporins, unspecified	106	Netilmicin	1
Moxifloxacin	53	Teicoplanin	1
Fluorochinolones, unspecified	45	Fenoxymethylpenicillin	1
Amoxicillin (+betalactamase-inhibitor)	40	Sulfadiazine + trimethoprim (co-trimazine)	1
Cephazolin	34	Ampicillin	1
Cefuroxime	19	Cefodizime	1
Sulfamethoxazol + trimethoprim (co-trimoxazol)	18	Cefepime	1
Vancomycin	16	Flucloxacillin	1
Nitrofurantoin	14	Tazobactam	1
Macrolides, unspecified	12	Temocillin	1
Ciprofloxacin	11	Tobramycin	1
Levofloxacin	11		
Quinolones, unspecified	9	Stevens-Johnson syndrome	73
Clarithromycin	8	Penicillins, unspecified	24
Sulfonamide + trimethoprim	7	Sulfamethoxazol + trimethoprim (co-trimoxazole)	11
Ofloxacin	6	Cephalosporins, unspecified	6
Ceftriaxone	5	Betalactams, unspecified	6
Nifurtinol	4	Amoxicillin (+beta-lactamase-inhibitor)	3
Piperacilline (+ beta-lactamase-inhibitor)	4	Fluoroquinolones	2
Nitrofur derivatives, unspecified	3	Sulfonamide + trimethoprim	2
Aminoglycosides, unspecified	3	Levofloxacin	2
Minocycline	3	Clarithromycin	1
Benzylpenicilline	3	Moxifloxacin	1
Erythromycin	3	Vancomycin	1
Cefaclor	3	Meropenem	1
Doxycycline	2	Trimethoprim	1
Cefadroxil	2	Macrolides, unspecified	1
Norfloxacin	2	Sulfadimidine + trimethoprim	1
Ceftazidime	2	Doxycycline	1
Cefotaxime	2	Ciprofloxacin	1
Combinations of penicillines, incl. BLI	3	Clindamycin	1
Azithromycin	1	Minocycline	1
Sulfamethoxazol	1	Benzylpenicilline	1
Gentamicin	1	Gentamicin	1
Tetracyclines, unspecified	1	Ceftriaxone	1
Streptomycines, unspecified	1		
Cefalexin	1		
Cefatrizine	1		
Cefradine	1		
Tetracycline	1		
Spiramycin	1		
Trimethoprim	1		