Supplementary Material

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Supplementary Text S1. Observed to Expected ratio calculation.

Given a set of patients $\mathcal{P} = \{p_1, \dots, p_N\}$ and a set of medications $\mathcal{D} = \{d_1, \dots, d_M\}$, each patient $p_i \in \mathcal{P}$ is prescribed with a subset of medications $D_i \subseteq \mathcal{D}$. Therefore, our data is of the form $\{p_i, D_i\}_{i=1}^{N}$.

Definition (Prevalence). The prevalence of a drug $d_m \in \mathcal{D}$ is defined as

$$P(d_m) = \frac{1}{N}\sum_{i=1}^{N} \mathbb{1}_{D_i}(d_m),$$

where $\mathbb{1}$ is the *indicator function* $\mathbb{1}_A(x) = \begin{cases} 1 \text{ if } x \in A \\ 0 \text{ if } x \notin A \end{cases}$, indicating whether drug d_m is in the medications D_i of patient p_i.

The prevalence of a set of drugs $\mathcal{X} \subseteq \mathcal{D}$ taken together is then

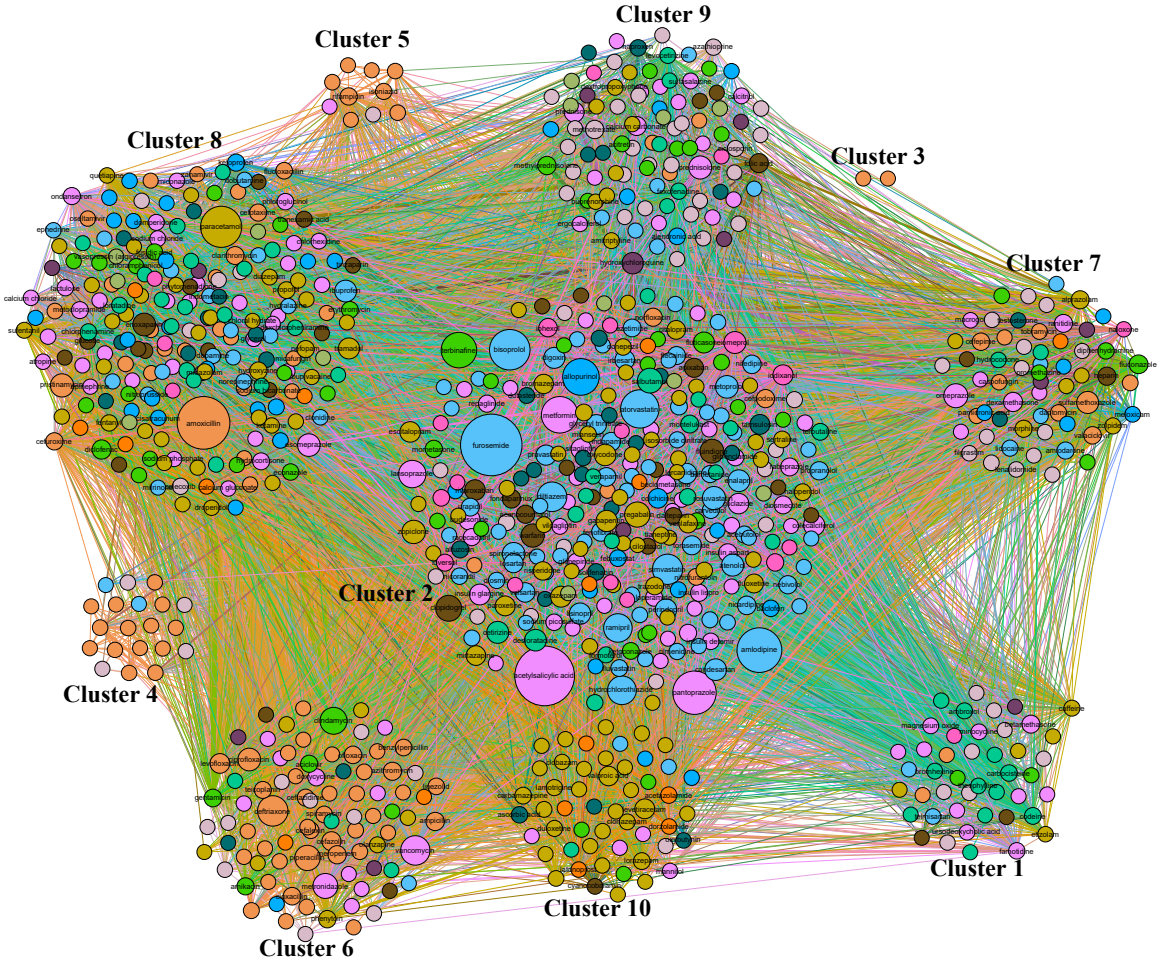
$$P(\mathcal{X}) = \frac{1}{N}\sum_{i=1}^{N} \prod_{d_m \in \mathcal{X}} \mathbb{1}_{D_i}(d_m)$$

Definition (O/E ratio). The Observed to Expected ratio (O/E ratio) of a set of drugs $\mathcal{X} \subseteq \mathcal{D}$ is defined as the prevalence of the drugs in $\mathcal{X}$ taken together divided by the product of the prevalence of the individual drugs in $\mathcal{X}$.

$$\text{O/E ratio } (\mathcal{X}) = \frac{P(\mathcal{X})}{\prod_{d_m \in \mathcal{X}} P(d_m)} = \frac{\sum_{i=1}^{N} \prod_{d_m \in \mathcal{X}} \mathbb{1}_{D_i}(d_m)}{\prod_{d_m \in \mathcal{X}} \sum_{i=1}^{N} \mathbb{1}_{D_i}(d_m)}$$

Example (O/E ratio).

Drug 1	Drug 2	Observed Prevalence	Prevalence Drug 1	Prevalence Drug 2	Expected Prevalence	O/E ratio
paracetamol	amoxicillin	4.11%	15.0%	21.6%	15.0% · 21.6% = 3.2%	$\frac{4.11\%}{3.2\%} = 1.28$



Supplementary Figure S1 Network overview of 2649 ICSRs that reported ≥2 drugs after applying the Louvain algorithm for cluster detection. In total ten different clusters were identified. Nodes represent medications, the size of the nodes are proportional to the prevalence of the drug, the links indicate that the two connected drugs were taken concomitantly, the width of the link is proportional to the number of times the pair of drugs was reported. Only labels of nodes with a degree higher than 75 are shown.

Supplementary Table S1. Demographic characteristics of individual case safety reports with AGEP, stratified by age.

	<65 (n=1379)		≥65 (n=1043)		Unknown (n=227)		
	N	%	N	%	N	%	p-value
Sex							
Male	602	(43.8)	354	(34.2)	64	(35.6)	<0.001
Region of Report							<0.001
Europe	727	(52.7)	712	(68.3)	146	(64.3)	
Asia	435	(31.5)	161	(15.4)	23	(10.1)	
Africa	21	(1.5)	2	(0.2)	3	(1.3)	
North America	164	(11.9)	158	(15.1)	52	(22.9)	
Oceania	25	(1.8)	8	(0.8)	2	(0.9)	
South America	7	(0.5)	2	(0.2)	1	(0.4)	
Reporter Type							0.006
Physician	862	(81.5)	729	(86.2)	148	(80.4)	
Other Health Professional	167	(15.8)	103	(12.2)	26	(14.1)	
Non Health Professional	29	(2.7)	14	(1.7)	10	(5.4)	
Seriousness (Yes)	1058	(89.1)	920	(94.7)	201	(94.8)	<0.001
Death	11	(0.8)	43	(4.1)	12	(5.3)	<0.001
Number of reported Drugs							
Mean (SD)	3.68	(2.65)	4.86	(3.66)	4.53	(3.80)	<0.001
Median (IQR)	3.00	[2.00,4.00]	3.00	[2.00,6.00]	3.00	[2.00,6.00]	<0.001

Abbreviations: SD, Standard Deviation; IQR, interquartile range.

P-values correspond to comparison between younger (aged <65 years) and older (≥65 years) ICSRs

Supplementary Table S2. Summary of the top 20 drugs based on the reported drug for each of the clusters identified with the Louvain algorithm in the network analysis (N=2649).
Cardiovascular drugs highlighted in grey.

Cluster 1 (N_{drugs}=44)				**Cluster 2** (N_{drugs}=283)				**Cluster 3** (N_{drugs}=2)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
betamethasone	280	45	1.70%	furosemide	688	197	7.44%	cefprozil	2	1	0.04%
codeine	248	26	0.98%	acetylsalicylic acid	692	189	7.13%	famciclovir	2	1	0.04%
carbocisteine	196	23	0.87%	amlodipine	534	126	4.76%				
famotidine	212	22	0.83%	pantoprazole	538	121	4.57%				
ambroxol	180	17	0.64%	bisoprolol	466	108	4.08%				
caffeine	154	16	0.60%	atorvastatin	498	99	3.74%				
magnesium oxide	188	14	0.53%	metformin	464	92	3.47%				
bromhexine	114	12	0.45%	allopurinol	450	92	3.47%				
minocycline	78	11	0.42%	terbinafine	294	87	3.28%				
telmisartan	104	9	0.34%	simvastatin	406	65	2.45%				
theophylline	112	9	0.34%	diltiazem	306	62	2.34%				
ursodeoxycholic acid	88	8	0.30%	hydrochlorothiazide	354	59	2.23%				
fluorouracil	74	8	0.30%	ramipril	324	58	2.19%				
etizolam	118	7	0.26%	lansoprazole	328	53	2.00%				
pemetrexed	56	6	0.23%	clopidogrel	330	47	1.77%				
oxaliplatin	34	6	0.23%	pregabalin	358	44	1.66%				
tipepidine	38	5	0.19%	salbutamol	338	42	1.59%				
olopatadine	48	4	0.15%	fluindione	208	38	1.43%				
tulobuterol	46	4	0.15%	zopiclone	326	36	1.36%				
cetuximab	16	3	0.11%	warfarin	248	35	1.32%				

Supplementary Table S2. (continued) Summary of the top 20 drugs based on the reported drug for each of the clusters identified with the Louvain algorithm in the network analysis (N=2649).
Cardiovascular drugs highlighted in grey.

Cluster 4 (N_{drugs}=18)				**Cluster 5** (N_{drugs}=10)				**Cluster 6** (N_{drugs}=85)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
ritonavir	72	10	0.38%	rifampicin	206	34	1.28%	ceftriaxone	472	234	8.83%
darunavir	68	9	0.34%	isoniazid	92	19	0.72%	vancomycin	392	219	8.27%
emtricitabine	32	7	0.26%	pyrazinamide	24	10	0.38%	clindamycin	468	181	6.83%
lamivudine	30	6	0.23%	moxifloxacin	70	9	0.34%	piperacillin	428	157	5.93%
cisplatin	50	6	0.23%	ethambutol	48	8	0.30%	metronidazole	448	150	5.66%
etoposide	58	4	0.15%	streptomycin	14	1	0.04%	ciprofloxacin	358	116	4.38%
bleomycin	18	4	0.15%	cycloserine	14	1	0.04%	levofloxacin	300	72	2.72%
peginterferon alfa-2a	6	4	0.15%	protionamide	4	1	0.04%	cefazolin	282	60	2.27%
nevirapine	6	3	0.11%	ethionamide	14	1	0.04%	ampicillin	170	53	2.00%
efavirenz	18	3	0.11%	tegafur	8	1	0.04%	meropenem	260	49	1.85%
atazanavir	16	2	0.08%					azithromycin	208	48	1.81%
didanosine	18	2	0.08%					gentamicin	264	42	1.59%
stavudine	12	2	0.08%					cloxacillin	162	40	1.51%
nelfinavir	8	1	0.04%					ofloxacin	216	40	1.51%
abacavir	6	1	0.04%					phenytoin	124	35	1.32%
raltegravir	12	1	0.04%					amikacin	180	34	1.28%
nadolol	6	1	0.04%					aciclovir	184	33	1.25%
zofenopril	20	1	0.04%					doxycycline	98	30	1.13%
								ceftazidime	118	29	1.09%
								teicoplanin	140	29	1.09%

Supplementary Table S2. (continued) Summary of the top 20 drugs based on the reported drug for each of the clusters identified with the Louvain algorithm in the network analysis (N=2649). Cardiovascular drugs highlighted in grey.

Cluster 7 (N_{drugs}=61)				**Cluster 8** (N_{drugs}=212)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
omeprazole	614	137	5.17%	amoxicillin	786	573	21.63%
sulfamethoxazole	422	106	4.00%	paracetamol	916	397	14.99%
dexamethasone	366	61	2.30%	pristinamycin	370	124	4.68%
fluconazole	308	58	2.19%	enoxaparin	484	118	4.45%
ranitidine	330	47	1.77%	esomeprazole	566	116	4.38%
heparin	412	47	1.77%	ibuprofen	324	102	3.85%
alprazolam	398	46	1.74%	tramadol	380	93	3.51%
cefepime	164	39	1.47%	diclofenac	296	64	2.42%
valaciclovir	176	38	1.43%	clarithromycin	228	45	1.70%
amiodarone	244	32	1.21%	hydroxyzine	256	36	1.36%
morphine	282	31	1.17%	cefuroxime	250	34	1.28%
diphenhydramine	234	22	0.83%	nefopam	252	34	1.28%
daptomycin	148	21	0.79%	ketoprofen	180	33	1.25%
lidocaine	226	20	0.76%	ondansetron	312	32	1.21%
zolpidem	248	18	0.68%	cefotaxime	216	32	1.21%
phenoxymethylpenicillin	38	12	0.45%	metoclopramide	260	31	1.17%
mupirocin	22	12	0.45%	hydrocortisone	334	30	1.13%
tobramycin	188	11	0.42%	propofol	242	28	1.06%
meloxicam	100	11	0.42%	flucloxacillin	182	26	0.98%
lenalidomide	128	10	0.38%	erythromycin	136	25	0.94%

Supplementary Table S2. (continued) Summary of the top 20 drugs based on the reported drug for each of the clusters identified with the Louvain algorithm in the network analysis (N=2649). Cardiovascular drugs highlighted in grey.

Cluster 9 (N_{drugs}=97)				**Cluster 10** (N_{drugs}=51)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
prednisolone	432	120	4.53%	levetiracetam	270	71	2.68%
hydroxychloroquine	286	98	3.70%	valproic acid	254	67	2.53%
prednisone	356	76	2.87%	lorazepam	262	28	1.06%
calcium carbonate	472	62	2.34%	carbamazepine	136	26	0.98%
folic acid	404	61	2.30%	ascorbic acid	232	24	0.91%
methylprednisolone	264	51	1.93%	acetazolamide	164	22	0.83%
methotrexate	222	50	1.89%	lamotrigine	166	19	0.72%
alendronic acid	186	25	0.94%	duloxetine	144	16	0.60%
azathioprine	80	23	0.87%	clonazepam	120	13	0.49%
naproxen	120	23	0.87%	bupropion	58	13	0.49%
ciclosporin	128	17	0.64%	cyanocobalamin	138	11	0.42%
fexofenadine	156	17	0.64%	aripiprazole	64	11	0.42%
levocetirizine	140	15	0.57%	oxybutynin	100	7	0.26%
acitretin	114	14	0.53%	phenobarbital	36	7	0.26%
amitriptyline	134	14	0.53%	dorzolamide	84	7	0.26%
sulfasalazine	84	12	0.45%	latanoprost	96	7	0.26%
calcitriol	118	12	0.45%	clobazam	76	6	0.23%
infliximab	46	12	0.45%	mannitol	110	5	0.19%
dextropropoxyphene	94	12	0.45%	glucosamine	34	5	0.19%
adalimumab	52	9	0.34%	tropatepine	68	5	0.19%

Supplementary Table S3. Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among male ICSRs (N=1020).

Cluster 1 (N_{drugs}=193)				**Cluster 2** (N_{drugs}=26)				**Cluster 3** (N_{drugs}=104)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
acetylsalicylic acid	422	79	7.75%	carbocisteine	96	12	1.18%	amoxicillin	482	213	20.88%
furosemide	366	68	6.67%	ambroxol	102	9	0.88%	paracetamol	568	167	16.37%
amlodipine	288	47	4.61%	pemetrexed	52	5	0.49%	ibuprofen	184	49	4.80%
bisoprolol	302	46	4.51%	caffeine	48	5	0.49%	diclofenac	140	29	2.84%
allopurinol	282	44	4.31%	theophylline	74	5	0.49%	tramadol	144	27	2.65%
prednisolone	244	41	4.02%	cefotiam	14	3	0.29%	ampicillin	80	23	2.25%
atorvastatin	272	41	4.02%	etizolam	70	3	0.29%	cloxacillin	82	21	2.06%
pristinamycin	174	40	3.92%	bromhexine	48	3	0.29%	betamethasone	102	17	1.67%
pantoprazole	266	38	3.73%	tipepidine	24	3	0.29%	benzylpenicillin	40	16	1.57%
metformin	208	30	2.94%	cefmetazole	12	2	0.20%	chlorphenamine	112	14	1.37%
cefazolin	100	25	2.45%	telmisartan	46	2	0.20%	cetirizine	108	10	0.98%
ramipril	172	25	2.45%	fenspiride	10	2	0.20%	desloratadine	112	10	0.98%
terbinafine	106	24	2.35%	palonosetron	34	1	0.10%	domperidone	70	9	0.88%
levofloxacin	160	23	2.25%	potassium citrate	34	1	0.10%	celecoxib	38	8	0.78%
simvastatin	224	23	2.25%	cefozopran	4	1	0.10%	cefixime	18	7	0.69%
diltiazem	130	22	2.16%	sitafloxacin	8	1	0.10%	fusidic acid	50	7	0.69%
folic acid	170	19	1.86%	gefitinib	34	1	0.10%	naproxen	36	7	0.69%
lansoprazole	146	18	1.76%	ticlopidine	6	1	0.10%	ketoprofen	32	7	0.69%
rosuvastatin	112	16	1.57%	beraprost	10	1	0.10%	mefenamic acid	26	7	0.69%
iomeprol	82	15	1.47%	carbazochrome	34	1	0.10%	phloroglucinol	56	6	0.59%

Supplementary Table S3. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among male ICSRs (N=1020).

Cluster 4 (N_{drugs}=2)				**Cluster 5** (N_{drugs}=111)				**Cluster 6** (N_{drugs}=11)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
flomoxef	2	1	0.10%	vancomycin	268	87	8.53%	rifampicin	160	17	1.67%
cefcapene	2	1	0.10%	omeprazole	376	59	5.78%	methotrexate	74	17	1.67%
				clindamycin	212	58	5.69%	isoniazid	34	9	0.88%
				enoxaparin	276	45	4.41%	infliximab	14	7	0.69%
				esomeprazole	308	35	3.43%	pyrazinamide	8	4	0.39%
				dexamethasone	244	32	3.14%	ethambutol	6	2	0.20%
				ranitidine	240	25	2.45%	ustekinumab	6	2	0.20%
				fluconazole	210	23	2.25%	dalbavancin	2	1	0.10%
				gentamicin	210	22	2.16%	apremilast	4	1	0.10%
				meropenem	222	21	2.06%	permethrin	4	1	0.10%
				ondansetron	226	18	1.76%	acitretin	6	1	0.10%
				cefotaxime	140	17	1.67%				
				cefepime	126	17	1.67%				
				heparin	232	17	1.67%				
				amikacin	96	17	1.67%				
				doxycycline	26	16	1.57%				
				flucloxacillin	140	16	1.57%				
				cefuroxime	148	15	1.47%				
				amiodarone	134	15	1.47%				
				hydrocortisone	238	14	1.37%				

Supplementary Table S3. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among male ICSRs (N=1020).

Cluster 7 (N_{drugs}=2)				**Cluster 8** (N_{drugs}=82)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
cefprozil	2	1	0.10%	methylprednisolone	168	24	2.35%
famciclovir	2	1	0.10%	prednisone	100	22	2.16%
				tamsulosin	216	19	1.86%
				hydroxychloroquine	98	17	1.67%
				calcium carbonate	192	14	1.37%
				azathioprine	36	11	1.08%
				glucose	80	9	0.88%
				famotidine	118	8	0.78%
				ritonavir	64	8	0.78%
				hydroxyzine	58	8	0.78%
				itraconazole	38	7	0.69%
				darunavir	58	7	0.69%
				magnesium oxide	90	6	0.59%
				emtricitabine	26	6	0.59%
				cisplatin	50	6	0.59%
				nifedipine	58	6	0.59%
				dutasteride	80	5	0.49%
				mirtazapine	66	5	0.49%
				trimebutine	34	4	0.39%
				fluorouracil	42	4	0.39%

Supplementary Table S3. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among male ICSRs (N=1020).

Cluster 9 (N_{drugs}=74)				**Cluster 10** (N_{drugs}=3)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
ceftriaxone	292	83	8.14%	ivermectin	4	1	0.10%
piperacillin	312	70	6.86%	benzyl benzoate	4	1	0.10%
sulfamethoxazole	264	57	5.59%	darbepoetin alfa	4	1	0.10%
metronidazole	284	56	5.49%				
ciprofloxacin	224	48	4.71%				
azithromycin	100	23	2.25%				
phenytoin	70	21	2.06%				
valaciclovir	78	17	1.67%				
aciclovir	106	17	1.67%				
ofloxacin	102	16	1.57%				
levetiracetam	154	16	1.57%				
valproic acid	136	15	1.47%				
carbamazepine	64	13	1.27%				
mupirocin	22	11	1.08%				
spiramycin	56	10	0.98%				
phenoxymethylpenicillin	32	9	0.88%				
tazobactam	42	8	0.78%				
lamotrigine	118	8	0.78%				
lorazepam	42	7	0.69%				
temozolomide	12	6	0.59%				

Supplementary Table S4. Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among female ICSRs (N=1571).

Cluster 1 (N_{drugs}=157)				**Cluster 2** (N_{drugs}=86)				**Cluster 3** (N_{drugs}=10)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
amoxicillin	628	354	22.53%	ceftriaxone	336	142	9.04%	rifampicin	72	17	1.08%
furosemide	580	127	8.08%	vancomycin	284	118	7.51%	isoniazid	70	10	0.64%
pantoprazole	458	81	5.16%	clindamycin	358	113	7.19%	moxifloxacin	58	8	0.51%
bisoprolol	316	62	3.95%	metronidazole	294	92	5.86%	pyrazinamide	22	6	0.38%
allopurinol	284	46	2.93%	piperacillin	250	83	5.28%	ethambutol	48	6	0.38%
clarithromycin	126	35	2.23%	ciprofloxacin	194	64	4.07%	streptomycin	14	1	0.06%
salbutamol	308	33	2.10%	sulfamethoxazole	246	46	2.93%	cycloserine	14	1	0.06%
betamethasone	220	28	1.78%	levofloxacin	202	46	2.93%	protionamide	4	1	0.06%
fluindione	176	27	1.72%	fluconazole	198	32	2.04%	ethionamide	14	1	0.06%
azithromycin	142	25	1.59%	ampicillin	120	30	1.91%	tegafur	8	1	0.06%
spironolactone	220	24	1.53%	meropenem	122	27	1.72%				
warfarin	166	21	1.34%	ranitidine	202	21	1.34%				
candesartan	180	21	1.34%	valaciclovir	128	21	1.34%				
cetirizine	208	19	1.21%	cefepime	110	20	1.27%				
fluticasone	216	18	1.15%	gentamicin	106	20	1.27%				
oxazepam	228	18	1.15%	cloxacillin	98	19	1.21%				
digoxin	124	17	1.08%	teicoplanin	66	17	1.08%				
bromazepam	208	17	1.08%	amikacin	124	17	1.08%				
budesonide	182	16	1.02%	amiodarone	168	16	1.02%				
irbesartan	166	16	1.02%	aciclovir	102	16	1.02%				

Supplementary Table S4.(continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among female ICSRs (N=1571).

Cluster 4 (N_{drugs}=1)				**Cluster 5** (N_{drugs}=144)				**Cluster 6** (N_{drugs}=2)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
peginterferon alfa-2a	4	1	0.06%	acetylsalicylic acid	528	108	6.87%	anakinra	2	1	0.06%
				amlodipine	404	75	4.77%	canakinumab	2	1	0.06%
				omeprazole	436	72	4.58%				
				terbinafine	242	63	4.01%				
				metformin	384	62	3.95%				
				atorvastatin	390	56	3.56%				
				hydrochlorothiazide	300	46	2.93%				
				simvastatin	274	41	2.61%				
				folic acid	316	40	2.55%				
				diltiazem	244	40	2.55%				
				alprazolam	340	36	2.29%				
				ramipril	238	33	2.10%				
				clopidogrel	232	32	2.04%				
				pregabalin	288	31	1.97%				
				heparin	294	30	1.91%				
				zopiclone	270	29	1.85%				
				enalapril	144	23	1.46%				
				colecalciferol	248	21	1.34%				
				lorazepam	226	20	1.27%				
				metoprolol	216	18	1.15%				

Supplementary Table S4.(continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among female ICSRs (N=1571).

Cluster 7 (N_{drugs}=130)				**Cluster 8** (N_{drugs}=33)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
paracetamol	736	220	14.00%	levetiracetam	168	52	3.31%
pristinamycin	272	82	5.22%	valproic acid	154	48	3.06%
esomeprazole	416	80	5.09%	atenolol	176	21	1.34%
enoxaparin	376	72	4.58%	alendronic acid	156	19	1.21%
tramadol	314	62	3.95%	phenytoin	44	12	0.76%
ibuprofen	194	50	3.18%	fexofenadine	90	10	0.64%
diclofenac	216	34	2.16%	dextropropoxyphene	86	8	0.51%
cefazolin	238	31	1.97%	clonazepam	98	8	0.51%
nefopam	240	28	1.78%	thiamazole	34	6	0.38%
hydroxyzine	222	28	1.78%	pioglitazone	30	4	0.25%
ketoprofen	166	26	1.65%	clobazam	50	4	0.25%
metoclopramide	180	19	1.21%	lamivudine	24	3	0.19%
phloroglucinol	136	18	1.15%	vemurafenib	24	3	0.19%
oxycodone	198	18	1.15%	phenobarbital	24	3	0.19%
morphine	198	17	1.08%	ritonavir	20	2	0.13%
propofol	136	15	0.95%	darunavir	20	2	0.13%
iomeprol	96	15	0.95%	diflucortolone	14	2	0.13%
fenofibrate	126	14	0.89%	carbimazole	22	2	0.13%
iodixanol	92	14	0.89%	oxygen	18	2	0.13%
ondansetron	154	13	0.83%	nateglinide	8	1	0.06%

Supplementary Table S4.(continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among female ICSRs (N=1571).

Cluster 9 (N_{drugs}=92)				**Cluster 10** (N_{drugs}=86)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
hydroxychloroquine	248	81	5.16%	dexamethasone	238	28	1.78%
prednisolone	280	77	4.90%	ofloxacin	150	24	1.53%
prednisone	310	53	3.37%	desloratadine	234	19	1.21%
calcium carbonate	362	46	2.93%	acetazolamide	150	19	1.21%
lansoprazole	254	35	2.23%	rosuvastatin	198	18	1.15%
methotrexate	188	33	2.10%	cefuroxime	98	16	1.02%
methylprednisolone	136	27	1.72%	cefalexin	102	15	0.95%
hydrocortisone	150	15	0.95%	ascorbic acid	130	15	0.95%
acitretin	110	13	0.83%	fluoxetine	198	14	0.89%
ciclosporin	84	12	0.76%	duloxetine	124	14	0.89%
azathioprine	52	11	0.70%	gabapentin	150	13	0.83%
losartan	102	11	0.70%	valsartan	160	12	0.76%
calcitriol	116	10	0.64%	zolpidem	198	12	0.76%
flucloxacillin	58	10	0.64%	citalopram	138	12	0.76%
mefenamic acid	28	10	0.64%	propranolol	130	10	0.64%
tiaprofenic acid	34	9	0.57%	bupropion	44	10	0.64%
chlorphenamine	64	9	0.57%	lamotrigine	70	9	0.57%
domperidone	120	8	0.51%	tobramycin	164	8	0.51%
exemestane	42	8	0.51%	aripiprazole	44	8	0.51%
denosumab	74	8	0.51%	nitrofurantoin	102	7	0.45%

Supplementary Table S5. Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among ICSRs aged < 65 years old (N=1379).

Cluster 1 (N_{drugs}=61)				**Cluster 2** (N_{drugs}=93)				**Cluster 3** (N_{drugs}=57)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
vancomycin	236	104	7.54%	amoxicillin	508	288	20.88%	ranitidine	190	26	1.89%
ceftriaxone	266	103	7.47%	paracetamol	610	232	16.82%	clarithromycin	132	23	1.67%
clindamycin	324	94	6.82%	ibuprofen	226	80	5.80%	flucloxacillin	140	18	1.31%
metronidazole	290	73	5.29%	pristinamycin	208	66	4.79%	heparin	226	18	1.31%
piperacillin	182	57	4.13%	erythromycin	80	20	1.45%	rifampicin	122	16	1.16%
ciprofloxacin	200	47	3.41%	betamethasone	102	19	1.38%	hydrocortisone	186	15	1.09%
ampicillin	80	33	2.39%	mefenamic acid	34	15	1.09%	cefotaxime	124	15	1.09%
cefazolin	142	31	2.25%	chlorphenamine	54	15	1.09%	tranexamic acid	174	15	1.09%
meropenem	148	31	2.25%	fusidic acid	98	12	0.87%	isoniazid	46	12	0.87%
cloxacillin	118	27	1.96%	cefixime	22	10	0.73%	lactulose	142	11	0.80%
gentamicin	192	24	1.74%	tiaprofenic acid	40	10	0.73%	chlorhexidine	132	7	0.51%
doxycycline	46	23	1.67%	cetirizine	78	10	0.73%	minocycline	28	7	0.51%
benzylpenicillin	70	19	1.38%	naproxen	38	9	0.65%	pyrazinamide	22	7	0.51%
ceftazidime	78	19	1.38%	acetylcysteine	36	9	0.65%	ethambutol	20	6	0.44%
amikacin	92	19	1.38%	levocetirizine	68	9	0.65%	clotrimazole	34	5	0.36%
aciclovir	90	19	1.38%	cefpodoxime	42	8	0.58%	norepinephrine	108	5	0.36%
ofloxacin	72	13	0.94%	cefditoren	14	8	0.58%	moxifloxacin	32	4	0.29%
teicoplanin	46	11	0.80%	candesartan	66	8	0.58%	oseltamivir	86	4	0.29%
linezolid	66	11	0.80%	loratadine	30	8	0.58%	chloramphenicol	82	4	0.29%
cefoperazone	40	9	0.65%	piroxicam	26	7	0.51%	quetiapine	102	4	0.29%

Supplementary Table S5. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among ICSRs aged < 65 years old (N=1379).

Cluster 4 (N_{drugs}=2)				**Cluster 5** (N_{drugs}=10)				**Cluster 6** (N_{drugs}=33)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
cefprozil	2	1	0.07%	ritonavir	26	5	0.36%	allopurinol	162	34	2.47%
famciclovir	2	1	0.07%	emtricitabine	24	5	0.36%	caffeine	84	11	0.80%
				cisplatin	32	5	0.36%	carbocisteine	82	11	0.80%
				darunavir	20	4	0.29%	codeine	118	11	0.80%
				bleomycin	18	4	0.29%	bromhexine	78	8	0.58%
				etoposide	16	2	0.15%	colchicine	34	7	0.51%
				cetuximab	10	2	0.15%	ambroxol	76	7	0.51%
				peginterferon alfa-2a	6	2	0.15%	tipepidine	38	5	0.36%
				atazanavir	8	1	0.07%	bendamustine	12	3	0.22%
				capecitabine	6	1	0.07%	pemetrexed	42	3	0.22%
								rituximab	12	3	0.22%
								acebutolol	34	3	0.22%
								telmisartan	46	3	0.22%
								etizolam	56	3	0.22%
								tulobuterol	24	3	0.22%
								theophylline	52	3	0.22%
								clotiazepam	22	2	0.15%
								palonosetron	34	1	0.07%
								potassium citrate	34	1	0.07%
								cefozopran	4	1	0.07%

Supplementary Table S5. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among ICSRs aged < 65 years old (N=1379).

Cluster 7 (N_{drugs}=2)				**Cluster 8** (N_{drugs}=49)				**Cluster 9** (N_{drugs}=82)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
triptorelin	2	1	0.07%	sulfamethoxazole	162	47	3.41%	esomeprazole	328	51	3.70%
exemestane	2	1	0.07%	valaciclovir	122	21	1.52%	enoxaparin	248	46	3.34%
				fluconazole	120	20	1.45%	tramadol	256	44	3.19%
				levofloxacin	108	18	1.31%	diclofenac	198	43	3.12%
				cefepime	68	14	1.02%	dexamethasone	226	32	2.32%
				ciclosporin	104	13	0.94%	ondansetron	202	22	1.60%
				amiodarone	52	10	0.73%	propofol	208	22	1.60%
				mupirocin	16	10	0.73%	cefuroxime	144	21	1.52%
				fluindione	46	7	0.51%	ketoprofen	116	21	1.52%
				temozolomide	12	6	0.44%	hydroxyzine	154	21	1.52%
				lamivudine	20	5	0.36%	nefopam	162	20	1.45%
				mycophenolic acid	40	5	0.36%	metoclopramide	172	18	1.31%
				nystatin	36	4	0.29%	morphine	168	17	1.23%
				racecadotril	36	4	0.29%	phloroglucinol	92	13	0.94%
				ursodeoxycholic acid	20	3	0.22%	sufentanil	88	12	0.87%
				rifaximin	12	3	0.22%	lidocaine	126	11	0.80%
				diosmectite	26	3	0.22%	fentanyl	208	11	0.80%
				nevirapine	6	3	0.22%	midazolam	150	10	0.73%
				gemcitabine	16	3	0.22%	diphenhydramine	114	9	0.65%
				doxorubicin	24	3	0.22%	rivaroxaban	42	7	0.51%

Supplementary Table S5. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among ICSRs aged < 65 years old (N=1379).

Cluster 10 (N_{drugs}=117)				**Cluster 11** (N_{drugs}=46)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
omeprazole	368	55	3.99%	levetiracetam	176	22	1.60%
acetylsalicylic acid	280	50	3.63%	valproic acid	130	21	1.52%
furosemide	262	47	3.41%	phenytoin	50	18	1.31%
metformin	258	43	3.12%	carbamazepine	68	17	1.23%
amlodipine	196	31	2.25%	lorazepam	132	14	1.02%
atorvastatin	242	27	1.96%	ascorbic acid	66	13	0.94%
diltiazem	152	25	1.81%	lamotrigine	114	13	0.94%
bisoprolol	152	24	1.74%	iomeprol	58	11	0.80%
simvastatin	176	24	1.74%	bupropion	50	10	0.73%
hydrochlorothiazide	150	18	1.31%	duloxetine	80	10	0.73%
perindopril	150	15	1.09%	iodixanol	40	10	0.73%
ramipril	86	13	0.94%	famotidine	82	9	0.65%
clopidogrel	136	12	0.87%	aripiprazole	40	8	0.58%
enalapril	76	12	0.87%	clonazepam	40	6	0.44%
zopiclone	144	12	0.87%	phenobarbital	32	5	0.36%
itraconazole	32	10	0.73%	cyanocobalamin	38	4	0.29%
salbutamol	102	10	0.73%	dapsone	20	4	0.29%
spironolactone	72	9	0.65%	glucosamine	22	4	0.29%
fluticasone	116	9	0.65%	lithium	34	4	0.29%
olanzapine	60	9	0.65%	clobazam	60	4	0.29%

Supplementary Table S5. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis among ICSRs aged < 65 years old (N=1379).

Cluster 12 (N_{drugs}=47)				**Cluster 13** (N_{drugs}=101)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
cefalexin	104	15	1.09%	prednisolone	260	78	5.66%
desloratadine	170	13	0.94%	hydroxychloroquine	170	62	4.50%
gabapentin	140	12	0.87%	pantoprazole	268	48	3.48%
fluoxetine	116	11	0.80%	prednisone	216	48	3.48%
rosuvastatin	110	10	0.73%	terbinafine	152	47	3.41%
propranolol	88	9	0.65%	methylprednisolone	160	34	2.47%
iohexol	60	8	0.58%	methotrexate	140	32	2.32%
metoprolol	86	7	0.51%	calcium carbonate	196	23	1.67%
ketoconazole	82	7	0.51%	folic acid	176	23	1.67%
ethinylestradiol	26	7	0.51%	azathioprine	72	19	1.38%
citalopram	108	6	0.44%	azithromycin	60	17	1.23%
risperidone	54	5	0.36%	alprazolam	168	15	1.09%
zolpidem	102	5	0.36%	atenolol	116	14	1.02%
sertraline	70	5	0.36%	pregabalin	138	14	1.02%
valsartan	62	4	0.29%	celecoxib	90	12	0.87%
mometasone	56	4	0.29%	lansoprazole	78	11	0.80%
bromazepam	62	4	0.29%	domperidone	114	11	0.80%
magnesium oxide	40	3	0.22%	alendronic acid	84	10	0.73%
cefaclor	6	3	0.22%	oxycodone	104	10	0.73%
tobramycin	92	3	0.22%	fexofenadine	64	10	0.73%

Supplementary Table S6. Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis for **≥ 65 years old** (N=1043).

Cluster 1 (N_{drugs}=120)				**Cluster 2** (N_{drugs}=152)				**Cluster 3** (N_{drugs}=68)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
amoxicillin	536	229	21.96%	acetylsalicylic acid	554	120	11.51%	valproic acid	136	41	3.93%
furosemide	590	130	12.46%	amlodipine	416	79	7.57%	levetiracetam	126	41	3.93%
bisoprolol	416	79	7.57%	atorvastatin	378	61	5.85%	lansoprazole	222	30	2.88%
esomeprazole	392	58	5.56%	metformin	320	45	4.31%	betamethasone	208	22	2.11%
allopurinol	360	54	5.18%	terbinafine	186	34	3.26%	diclofenac	138	19	1.82%
pristinamycin	234	48	4.60%	clopidogrel	264	33	3.16%	tamsulosin	194	16	1.53%
ramipril	292	41	3.93%	hydrochlorothiazide	218	33	3.16%	methylprednisolone	132	15	1.44%
fluindione	182	30	2.88%	diltiazem	220	33	3.16%	hydrocortisone	146	12	1.15%
warfarin	232	28	2.68%	metoprolol	200	23	2.21%	famotidine	130	12	1.15%
candesartan	186	21	2.01%	pregabalin	260	23	2.21%	magnesium oxide	158	11	1.05%
spironolactone	202	20	1.92%	cefazolin	174	22	2.11%	carbocisteine	128	11	1.05%
clarithromycin	116	19	1.82%	glyceryl trinitrate	238	22	2.11%	ascorbic acid	126	9	0.86%
oxazepam	208	19	1.82%	rosuvastatin	168	20	1.92%	nifedipine	72	8	0.77%
zopiclone	194	19	1.82%	fluticasone	196	17	1.63%	fentanyl	92	8	0.77%
pravastatin	150	17	1.63%	gliclazide	154	16	1.53%	carbamazepine	80	8	0.77%
digoxin	156	16	1.53%	sitagliptin	188	16	1.53%	phenytoin	38	7	0.67%
torasemide	180	16	1.53%	lisinopril	116	16	1.53%	donepezil	82	7	0.67%
insulin glargine	184	15	1.44%	valsartan	154	16	1.53%	propranolol	70	5	0.48%
cetirizine	200	15	1.44%	atenolol	114	15	1.44%	finasteride	50	5	0.48%
verapamil	112	14	1.34%	escitalopram	132	14	1.34%	ursodeoxycholic acid	48	4	0.38%

Supplementary Table S6. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis for **≥ 65 years old** (N=1043).

Cluster 4 (N_{drugs}=2)				**Cluster 5** (N_{drugs}=37)				**Cluster 6** (N_{drugs}=51)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
emtricitabine	6	1	0.10%	paracetamol	584	129	12.37%	hydroxychloroquine	150	29	2.78%
efavirenz	6	1	0.10%	omeprazole	410	71	6.81%	folic acid	278	29	2.78%
				pantoprazole	416	65	6.23%	prednisone	192	25	2.40%
				enoxaparin	338	58	5.56%	colecalciferol	232	19	1.82%
				fluconazole	188	30	2.88%	methotrexate	94	14	1.34%
				alprazolam	296	26	2.49%	apixaban	172	14	1.34%
				heparin	236	25	2.40%	aciclovir	108	13	1.25%
				dexamethasone	172	23	2.21%	lorazepam	154	13	1.25%
				cefepime	130	22	2.11%	mirtazapine	102	10	0.96%
				amiodarone	198	20	1.92%	venlafaxine	114	10	0.96%
				meropenem	180	17	1.63%	isoniazid	58	7	0.67%
				ranitidine	174	16	1.53%	telmisartan	62	5	0.48%
				morphine	156	13	1.25%	denosumab	48	5	0.48%
				zolpidem	176	12	1.15%	cefdinir	24	4	0.38%
				lidocaine	118	9	0.86%	ritonavir	48	4	0.38%
				daptomycin	96	8	0.77%	darunavir	48	4	0.38%
				diphenhydramine	70	8	0.77%	sotalol	50	4	0.38%
				metoclopramide	66	7	0.67%	levocetirizine	54	4	0.38%
				promethazine	92	7	0.67%	bilastine	60	4	0.38%
				meloxicam	62	7	0.67%	triamcinolone	24	3	0.29%

Supplementary Table S6. (continued) Summary of the top 20 drugs of each cluster found with the Louvain algorithm in the network analysis for **≥ 65 years old** (N=1043).

Cluster 7 (N_{drugs}=3)				**Cluster 8** (N_{drugs}=86)				**Cluster 9** (N_{drugs}=88)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
ivermectin	4	1	0.10%	simvastatin	318	39	3.74%	ceftriaxone	324	109	10.45%
benzyl benzoate	4	1	0.10%	prednisolone	260	36	3.45%	vancomycin	266	97	9.30%
darbepoetin alfa	4	1	0.10%	calcium carbonate	300	33	3.16%	piperacillin	304	79	7.57%
				salbutamol	256	28	2.68%	clindamycin	232	69	6.62%
				budesonide	230	22	2.11%	ciprofloxacin	204	63	6.04%
				lercanidipine	152	16	1.53%	metronidazole	252	61	5.85%
				enalapril	128	16	1.53%	levofloxacin	242	50	4.79%
				ibuprofen	136	15	1.44%	sulfamethoxazole	264	44	4.22%
				alendronic acid	136	14	1.34%	tramadol	218	39	3.74%
				hydroxyzine	122	13	1.25%	azithromycin	144	27	2.59%
				codeine	150	13	1.25%	ofloxacin	142	25	2.40%
				iodixanol	98	12	1.15%	ampicillin	102	17	1.63%
				iomeprol	90	12	1.15%	teicoplanin	108	16	1.53%
				nicardipine	118	10	0.96%	rifampicin	70	16	1.53%
				ketoprofen	86	10	0.96%	spiramycin	64	14	1.34%
				gabapentin	62	10	0.96%	gentamicin	124	14	1.34%
				montelukast	116	9	0.86%	cloxacillin	80	13	1.25%
				citalopram	76	8	0.77%	cefotaxime	78	10	0.96%
				flucloxacillin	52	7	0.67%	linezolid	54	10	0.96%
				cyanocobalamin	114	7	0.67%	amikacin	86	10	0.96%

Supplementary Table S7. Summary of the top 20 drugs of each cluster found by using the leading eigenvector clustering to the network analysis (N=2649).

Cluster 1 (N_{drugs}=412)				**Cluster 2** (N_{drugs}=2)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
paracetamol	916	397	14.99%	cefprozil	2	1	0.04%
ceftriaxone	472	234	8.83%	famciclovir	2	1	0.04%
vancomycin	392	219	8.27%				
clindamycin	468	181	6.83%				
piperacillin	428	157	5.93%				
metronidazole	448	150	5.66%				
omeprazole	614	137	5.17%				
enoxaparin	484	118	4.45%				
esomeprazole	566	116	4.38%				
ciprofloxacin	358	116	4.38%				
sulfamethoxazole	422	106	4.00%				
ibuprofen	324	102	3.85%				
tramadol	380	93	3.51%				
levofloxacin	300	72	2.72%				
levetiracetam	270	71	2.68%				
valproic acid	254	67	2.53%				
diclofenac	296	64	2.42%				
dexamethasone	366	61	2.30%				
cefazolin	282	60	2.27%				
fluconazole	308	58	2.19%				

Supplementary Table S7. (continued) Summary of the top 20 drugs of each cluster found by using the leading eigenvector clustering to the network analysis (N=2649).

Cluster 3 (N_{drugs}=273)				**Cluster 4** (N_{drugs}=181)			
Drug	Degree	Count	Prevalence	Drug	Degree	Count	Prevalence
amoxicillin	786	573	21.63%	prednisolone	432	120	4.53%
furosemide	688	197	7.44%	hydroxychloroquine	286	98	3.70%
acetylsalicylic acid	692	189	7.13%	prednisone	356	76	2.87%
amlodipine	534	126	4.76%	calcium carbonate	472	62	2.34%
pristinamycin	370	124	4.68%	folic acid	404	61	2.30%
pantoprazole	538	121	4.57%	methotrexate	222	50	1.89%
bisoprolol	466	108	4.08%	alprazolam	398	46	1.74%
atorvastatin	498	99	3.74%	pregabalin	358	44	1.66%
metformin	464	92	3.47%	metoprolol	278	33	1.25%
allopurinol	450	92	3.47%	iomeprol	146	30	1.13%
terbinafine	294	87	3.28%	oxycodone	294	28	1.06%
simvastatin	406	65	2.45%	lorazepam	262	28	1.06%
diltiazem	306	62	2.34%	colecalciferol	302	27	1.02%
hydrochlorothiazide	354	59	2.23%	gabapentin	222	27	1.02%
ramipril	324	58	2.19%	budesonide	276	26	0.98%
lansoprazole	328	53	2.00%	alendronic acid	186	25	0.94%
clopidogrel	330	47	1.77%	ascorbic acid	232	24	0.91%
betamethasone	280	45	1.70%	azathioprine	80	23	0.87%
salbutamol	338	42	1.59%	naproxen	120	23	0.87%
fluindione	208	38	1.43%	glyceryl trinitrate	238	22	0.83%