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A Data Analytics Framework for Medical Prescription Pattern Dynamics

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Abstract

Research on prescription pattern dynamics aims to highlight the issues concerning the raising antibiotic resistance among the Italian country, using a subset of data regarding the Campania region.

After a clear understanding of the problem and the available information along with its quality and possible uses, a first analytical approach allows reconstruction of diagnosis and prescriptions global trending, from which is possible to extract patient journeys and underline changes.

A deeper insight on antibiotics verifies national studies on overprescription, giving additional information on general practitioners' behaviour, brands popularity and seasonality of prescriptions, obtained with time series analysis and clustering.

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Chapter 1

Introduction

1.1 Antibiotic resistance and misuse

Antimicrobial resistance is a rising global problem which threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.²⁵

Microorganisms exposed to antimicrobial drugs develop the ability to defeat substances designed to kill them, making infections persist in the body due to the unsuccessful action of agents.

This issue threatens public health causing higher healthcare costs to treat patients, and potentially compromising surgeries and chemotherapy results due to the ineffectiveness of antibiotics. No one can completely avoid the risk of resistant infections, but some people are at greater risk than others (for example, people with chronic illnesses).¹⁵

Antimicrobial resistance occurs naturally over time, usually through genetic changes. However, **the misuse and overuse of antimicrobials is accelerating this process**. In many places, antibiotics are overused and misused in people and animals, and often given without professional oversight.²⁵

Infections such as the common cold or sore throats are often countered with antibiotics, which have no effect against viruses and could as well put patients at the risk of suffering adverse reaction.¹⁷

Therefore, to minimise the development of resistance, contributing factors must be reduced, optimising the use of drugs. This work requires effective surveillance and follow-up of consumption, at a local and national level.

To be effective in the long run, work to optimise use of antibiotics must influence the prescribing practices of individual physicians. The goal is “rational use”, i.e. the correct patient receives the correct antibiotic at the correct dose and for the correct duration of treatment, in accordance with evidence-based guidelines. Over-prescribing should be avoided without resulting in under-prescribing.¹⁶

Such work should be carried out close to the prescriber, something which also requires high resolution prescription data, down at the level of **individual prescribers**.

1.2 Italian National Sanitary Service

The Italian National Sanitary Service (SSN) consists the complex of functions, activities and healthcare services offered by the State. It is based on subsidiarity, a general principle of the European Union law, stating that a central authority should have a subsidiary function, performing only those tasks which cannot be performed at a more local level.¹⁸

SSN is articulated in different responsibility levels divided among the State, Regions, institutions and organisations, along with private structures and the Health Ministry, which coordinates the national sanitary plan.

Citizens benefit of healthcare services paying a related ticket,¹⁹ which represents the established way to contribute to expenses. It is used for:

- Specialist examinations;
- First-aid help in non-emergency situations;
- Thermal care.

Sanitary assistance on the territory is free, in fact general practitioners' visits are exempted from payment of tickets (while additional services such as certificates may require a fee). A general practitioner (GP) is a way for the citizen to access SSN in terms of global care and health education.

GPs manage types of illness that present in an undifferentiated way at an early stage of development, which may require urgent intervention. Their duties are not confined to specific organs of the body, and they have particular skills in treating people with multiple health issues.¹⁰

According to WONCA (World Organization of Family Doctors), they are responsible of supplying integrated and continuative care. Some fundamental skills and activities¹⁰ to pursue this goal are:

- Communication with patients;
- Management of the practice;
- Clinical tasks;
- Problem solving;
- Holistic modelling.

In Italy, GPs have a crucial role in preventing diseases, understanding the symptoms, introducing patients to therapeutical approaches and monitoring the development or regression of illnesses.²³ Primary aid is guaranteed through diagnoses, prescription, therapy and basic levels of assistance.

Visits take place at the medical office, according to methodologies established by the doctor, generically on appointment or at the patient's domicile. After a visit, a common task of the general practitioner in agreement with SSN is prescribing drugs or further medical checks through a prescription.

Prescriptions are healthcare documents that govern the plan of care for an individual patient,²⁴ consisting in written authorization to purchase a specific medicine from a pharmacy.

Drugs are dispensed according to the national guidelines,²¹ with the following regimes:

- OTC (Over The Counter), not subject to medical prescription;
- RR (Repeatable Prescription), to be sold after presenting a prescription;
- RNR (Non-Repeatable Prescription), to be sold after presenting a prescription which has to be renewed each time;
- RL (Limitative Prescription), used in hospitals and clinics;
- RMR (Ministerial Tracing Prescription), for narcotics and psychotropic substances.

1.2.1 Drugs and prescriptions

The Italian Pharmacy Agency (AIFA) is the public institution for regulatory activity of drugs in Italy. Its main duty consists in all the activities related to the regulatory process of drugs, registering and authorising them to commercialization with a negotiated price.

Before a drug can be sold in pharmacies among the Italian territory, it must have received the authorisation by AIFA: each medicine is subject to checks regarding chemical, pharmaceutical, biological, toxicological, and clinical aspects and researches, to see if it satisfies security and efficacy standards.²⁹

After passing all the quality controls, a product is assigned an unique AIC code for it to be identified with its specific details.

AIFA guarantees uniformity and equity of the pharmaceutical system, coordinating national and local authorities such as Regions. Procedures are based on safeness, innovation and accessible healthcare: pharmaceutical costs are regulated in a context of financial compatibility with industry competitiveness, while pursuing goals of economic balance and population' safeguard.

From the year 2000 every form of participation to sanitary expenses from citizens has been abolished,¹⁹ yet most Regions have introduced special drugs classes with a fixed quota for each medical prescription or package, to remedy the profit deficit.

Currently existing categories according to reimbursement are:²⁰

- A, entirely at the expense of SSN, comprehending essential medicines and the ones for chronic diseases;
- H, at the expense of SSN only in a hospital environment;
- C, fully paid by citizens according to the brand price.

Complete lists for classes A and H are publicly available, while each single drug or active principle can be individually looked up on the official AIFA database. Prescriptions can fall into any category, while OTCs follow a C regime.

Generic drugs have reduced costs, and to have a brand product the citizen must explicitly ask for it and pay the additional price.¹⁹

1.2.2 Antibiotic resistance in Italy

Italy is the European nation with the highest antibiotic resistance mortality (10.000 deaths every year), in terms of infection caused by resistant bacteria.³¹

1.3 Healthcare data

1.4 Data classification

Healthcare data needs to be classified according to national or international standards, in a way that information cannot be misinterpreted and fields can be mapped to wider categories.

1.4.1 ICD

ICD (International Classification of Diseases) is the foundation for global identification of health trends and statistics, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes,²⁵ maintained by the World Health Organization (WHO).

ICD defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive, hierarchical fashion that allows for:

- Easy storage, retrieval and analysis of health information for evidenced-based decision-making;
- Sharing and comparing health information between hospitals, regions, settings and countries;
- Data comparisons in the same location across different time periods.²⁵

The ICD is revised periodically and is currently in its 10th version, while in Italy the latter has only been adopted to classify death causes.²⁶ Until a complete upgrade, the diagnostic system is standardised using ICD-9.

ICD-9

ICD-9, officialized in 1978, is the 9th version of the International Classification of Diseases, ordering diseases and traumas in groups according to defined criteria, allowing a common language to code information related to morbidity and mortality for comparisons and statistics.²⁶

ICD9-CM is an adaption to ICD-9 used in Italy to assign diagnostic and procedure identifiers, providing additional morbidity detail. Diagnoses are extended with codes for surgical, diagnostic and therapeutical procedures.

It is composed by a group of three digits followed by up to two optional ones adding further details, separated with a dot:

1. The first number (001-999) represents the macro-category based on the type of the disease or the injury they describe;
2. The second group provides more specific information about the type, location, and severity of the disease or injury.

There are also two sets of alphanumeric codes in ICD-9-CM. E-codes describe external causes of injury, while V-codes describe factors that influence health status and/or describe interactions with health services.²⁷

Example: 414.12, falling in diseases of the circulatory system (390-459), specifically into ischaemic heart disease (410-414).

- 414: other forms of chronic ischaemic heart disease;
- 1: aneurysm and dissection of heart;
- 2: dissection of coronary artery.

1.4.2 ATC

The Anatomical Therapeutic Chemical Classification System (ATC) is a drug coding system adopted worldwide, controlled by World Health Organisation.

Medicines are divided into different groups according to the organ or system on which they act, their therapeutic intent or nature, and the drug's chemical characteristics. Different brands share the same code if they have the same active principle and indications.

One single drug can have multiple codes, since ATC also comprehends instructions regarding administration or use, and a code can represent more than one active ingredient.

The ATC classification is composed by seven alphanumeric symbols split into five adjacent hierarchical sets, defined levels and having the following structure:³⁰

1. One letter indicating the anatomical/pharmacological main group among 14;
2. Two digits indicating the therapeutic subgroup;
3. One letter indicating the pharmacological subgroup;
4. One letter indicating the chemical subgroup;
5. Two digits indicating the chemical substance.

The ATC system also includes many defined daily doses (DDDs). This is a measurement of the assumed average maintenance dose per day for a drug used for its main indication in adults.

Alterations in ATC classification can be made when the main use of a product has clearly changed, and when new groups are required to accommodate new substances or to achieve better specificity in the groupings. Changes are twice annually submitted to the WHO official database.

Example: C03BA12.

- C: cardiovascular system;
- 03: diuretics;
- B: low-ceiling diuretics, excluding thiazides;
- A: sulfonamides, plain;
- 12: Clorexolone.

1.4.3 AIC

AIC represents authorisation to admission to commerce of a medicine, and is a 9-digit code conceded by AIFA after a careful check of safeness and efficacy. It is a sort of “identity card” of the drug, since it contains the essential characteristics defining it.²⁸ Different brands are identified by different AIC.

AIC establishes:

- The drug name;
- Its composition (active principle);
- Description of the fabrication method;
- Therapeutical instructions, contraindications and adverse reactions;
- Dosage and way of administration;
- Conservation measures;
- Characteristics of the product and its packaging;
- Brochure;
- Risks evaluation for the environment.

Every possible modification of those characteristics involves a further request for authorization to AIFA. Official databases such as Fedefarma contain information related to every product, along with its eventual expire of authorisation.

1.5 Healthcare analytics

Healthcare analytics is a field of growing importance which allows a deep understanding of results collected in the healthcare area.

Extracting insights can be a complex challenge: health big data gives a huge *volume* and *variety* of information, therefore accessing the resources in a quick way is necessary.

Other issues to deal with are *veracity*, *validity* and *viability*, fundamental characteristics to ensure reliable and relevant analytics. Checking for integrity and quality can be difficult to verify without domain knowledge.¹

One of the various applications of this field is the change of patterns in the historical data: this research specifically focuses on **prescription pattern changes** on chronic patients, highlighting the development of some common medicines through time.

The considered healthcare data is a dump of a database created and handled by Millennium Srl,² a leader company in IT services for medicine. This has been obtained through an extraction procedure on the original DB, assigning unique names to each table and column.

There are five main necessary fields for analysis:⁴

1. **Spatial data**, in different granularity levels;
2. **Personal data** of patients;
3. **Temporal data**, in a range from 2000 to 2018, for time-series analysis;
4. **Pharmacotherapeutic data**, classifiable according to different identification codes;
5. **Diagnostic data**, for cross-validation of diagnoses.

The two main risks encountered while doing analysis are information loss and inappropriate prescribing, that compromise the quality of statistics. Data may be incomplete, biased or filled with noise: another goal of analytics is to contrast incompleteness and incorrectness, obtaining coherent and clear results.

Chapter 2

Goals definition

2.1 Methodologies

This research is specifically focussed on the doctor-patient relationship: person-centred care concerning diagnoses and prescriptions, analysing their changes according to habits, physiological aspects, time and geographical area of both interested parts.

There are several external factors influencing market trends of medicines, for instance the advent of generic drugs, having the same active principle and bioequivalence with brand medicines, but lower prices thanks to their dissociation from pharmaceutical companies.

The concept of generic drug has been introduced in Italy in 1995, to be legally formalised in 1996,³ yet it has initially been perceived by general practitioners and pharmacists as a mere instrument to save money at the expense of quality.⁹

Only in the past 10 years, advertisement efforts have been made to make the population aware of the strict quality checks and the reliability of generic drugs, starting a slow switching process. If sales of a brand product decrease, then, it might have been replaced with its equivalent.

This is only an instance of event which cannot be predicted using the raw data: information about market withdrawals, advertisement or economic availability need to be cross-checked with analytical results.

Considering a wide time span is essential to have an overall idea of data quality, information loss and potentiality of available resources. All those factors contribute to progressive rescaling of the dataset:

1. Detailed analytics must be done according to restricted areas (pathologies, products);
2. Different time spans can be compared, going deeper into the general view;
3. Incorrect or unclear information has to be removed, causing retention of total records whose amount gets narrower while cleaning is in progress (funnel).

The dataset is modelled in a relational schema, which allows organization of records in structures (tables) to maintain integrity and compatibility between different kind of fields.

This allows flexibility using dynamic views and query optimisation based on set theory. For a better fruition of the workload, table names have been changed to standard English keywords.

2.2 Considerations

Since health big data can provide a high variety of information, it is required to have some clear *objectives* in mind to keep on track and avoid losing focus.

The research is centred on the **changes of prescription patterns of antibiotics**: this is a wide goal, and more information is needed to achieve results. It's necessary to narrow the field down, only concentrating on some classes of medicines, and define subgroups of GPs and patients in a restricted amount of time.

To obtain constraints the more objective as possible, some further analysis can be useful. For instance, focussing on chronic patients is a relatively fast way to reduce the huge amount of rows to elaborate, but causes the loss of most information.

The first step to take, having a deep understanding of the data, is recognising the extent and impact of the **progressive information loss**, to define the final amount of clear records. Trying to fix mistakes is a risk, since the outcome could be incorrect, so deleting is the most practical option.

Removing unclear and futile data may not be enough to have consistent results: 18 years of data is a wide range, and *splitting the dataset* or deciding to only consider a smaller scope can be beneficial for the analysis quality.

Some constraints can be imposed on general practitioners as well: since the results have to be coherent and accurate, it's best practice to only consider **active GPs** with a **constant number of patients** (to be defined).

This would partially remedy the fact that doctors may have different approaches to the same disease.

The creation of cohorts (chronic patients) among the statistical population is an example of **cluster sampling**.

After the initial parsing, there will be a rough draft of the final result which then will be subject of the following steps:

1. Further analysis on data correctness (record linkage);
2. Elaboration of the statistics and time series clustering.

Another relevant instance for analysis is the **subset** of diseases to consider: choices have to be made according to *external studies*, *marketing researches* and further *discoveries on the provided data*. Focussing on the **most common ones** is a guideline to start.

Having an idea of which illnesses and prescription have unstable patterns might give a better vision, and can be done through statistics on the whole database.

Some examples of analytics are:

- Most common diseases through the years;
- Most common *chronic* diseases through the years;
- Changes of the number of prescriptions for diseases in the same area;
- Changes of prescriptions based on the patient phenotype or market trends.

An obstacle to perceiving the meaning of results is the restricted domain knowledge: to compensate, confronting some experts in the field is required. The team comprehends computer scientists, statisticians, biologists and healthcare workers.

2.3 Practical goals

Having a better vision of the medical domain and the rising issues in the Italian system, before approaching analytical procedures it is necessary to underline practical objectives and expected outcomes.

The first essential statistic to extract is about progressive information loss: this makes possible to estimate how much data can give reliable and complete results, compared to the total. It is defined *progressive* since the more iterations of cleaning are being made, the more data is going to be lost.

Parsing remaining data is essential to have a correct functioning of database interrogations. Fields need to be checked for correctness using lookup tables, record linkage or regular expression matching; text has to be cast to numbers to apply mathematical operations, and dates can be divided into months and years.

Performances require a high level of optimisation due to the huge workload of information, obtained through targeted expressions, strict constraints and better memory management of records.

A global overview of the data allows to detect anomalies or trends of specific areas to focus on: potential analysis pertains dividing patients according to distinctive characteristics (sex, age group) to observe variations of diagnoses and prescriptions.

After collecting the first batch of results and checking them using external knowledge, information with unusual patterns is outlined, and further examination is made on a subset of features.

Final outcomes are then subject of more advanced techniques, which include:

- Time series analysis;
- Clustering of trajectories;
- Graph algorithms.

2.4 Tools

Modern technologies make possible to process big data with reduced costs: there are plenty of data stores, development and integration tools for each research purpose.

Since the project requires a relational structure along with statistical computing and machine learning, analysing and elaborating the health data is made through:

- **PostgreSQL**,¹¹ an open source object-relational database management system known for its robustness and reliability:
 - The development platform to interface with the web server containing the dataset is **PgAdmin 4**;
 - Indexes and Common Table Expressions are useful to avoid huge computational times.
- **Neo4j**,¹² a native graph database which gives data a different representation, processing entities as nodes while highlighting their connections:
 - Queries are expressed using **Cypher**;
 - The additional plugin Graph Algorithms returns implemented, parallel version of common network problems.
- **R**,¹³ a free software environment for statistics and graphics computing, offering a wide range of techniques and formulae:
 - *ggplot2* is a package to create and visualise plots;
 - Clustering is performed using embedded functions.

Reports and slide-shares have been created and accessed using the **Google Suite**.

Due to the amount of sensitive data, detailed results are going to be omitted: the final conclusions will be a product of aggregation and schematisation.

Chapter 3

Data description

3.1 Dataset description

3.2 Overview of the database

The database used for analytics contains data on medical histories of patients between **January 2000** and **October 2018**. This leads to some observations:

1. The year 2018 is present only up to June, so it cannot be used while making time series within years (there is going to be a drop of values due to incompleteness which may lead to wrong conclusions);
2. A timespan of 20 years is too wide to make consistent analytics;
3. Early dated records might contain outdated or incomplete information.

Global inferences have been made with the entire dataset, while the need of detailed recent reports leads to the decision of using a limited range of years for prescription pattern changes and patient journey.

It's important to note that the research work has been done on only a part of the original Millewin database, consisting in **4 tables**. There is information available on **general practitioners, patients, diagnoses** and **prescriptions**: each macro-category is included in a separated table, so it's necessary to identify the relationship between fields.

The 5 tables with their sizes are:

- *pazienti*, 1.015.618 tuples;
Basic information about patients, identified by an encrypted UID;
- *nos_002*, 1.015.618 tuples;
Extension of *pazienti* with the same key, containing more detailed information and linkage with GPs;
- *cart_pazpbl*, 15.460.199 tuples;
Information about diagnoses and relative description;

- *cart_therap*, 118.716.403 tuples;
Information about therapies and prescribed medicines;
- *cart_accert*, 151.478.456 tuples;
Information about medical checks and examinations.

It's easy to see that the number of rows is varying: there are a much more prescriptions than diagnosis, and 150 millions of medical examinations.

Each diagnosis, prescription and examination is uniquely distinguished by the triplet patient-GP-date, which maps to *codice-userid-time_last* in the database.

There are many other date fields, but *time_last* (last update of the record) is the only one of type *timestamp*, making each one different from the others (it's unlikely to have a diagnosis or prescription for the same patient, by the same doctor and at the same exact moment).

Analysis is performed using dates in the *YYYY-MM-DD* format, since there's no need of unique data: there are lots of different prescription for the same patient made on the same day.

3.3 Description of the tables

Below is reported a brief description of the 5 tables, along with the main fields used for analytics, statistics and meaning.

3.3.1 *pazienti*

The table *pazienti* includes information about patients. To maintain privacy, there are no real names: everything is **encrypted** as a 22-character string containing letters, numbers and special symbols.

Other relevant fields are:

- *data_open*, date of beginning of the doctor-patient relationship;
- *nascita*, date of birth;
- *decesso*, eventual date of death;
- *comune_di_nascita*, name (and code) of the birth municipality;
- *Sesso*, birth sex;
- *pa_convenzione*, type of convention with the Italian insurance system.

The principal features of the table are:

3.3.2 *nos_002*

The table *nos_002* contains the same information as *pazienti*, with additional fields which are essential to link and analyse data:

- *pa_medi*, **encrypted** UID of the general practitioner of the patient;
- *pa_cap*, zip-code of the patient (for geographical analysis);
- *pa_pro*, province of the patient;
- *pa_drevoca*, eventual date of termination of the doctor-patient relationship (a patient changing GP).

All the IDs of the GPs, along with all other data on GPs, are stored in an external table *users* (the research has been made considering a subset of the original DB). The latter will be used to identify active doctors, but doesn't contain any other useful information.

3.3.3 *cart_pazpbl*

The table *cart_pazpbl* comprehends the diagnoses associated to patients and relative GPs. Each diagnosis is defined by its **ICD-9** code, an international identifier for diseases maintained by the World Health Organization.

Fields summary:

- *codice*, patient ID;
- *userid*, corresponding to *pa_medi* in *nos_002* (general practitioner ID);
- *data_open*, date of insertion of the diagnosis in the database;
- *time_last*, timestamp of last edit of the tuple;
- *nome_pbl*, a textual description of the diagnosis;
- *cp_code*, code of the diagnosis according to the ICD-9 standards.

3.3.4 *cart_terap*

The table *cart_terap* contains the prescribed medicines for each patient. There is no linkage between diagnosis and prescriptions in the database, so additional work is required to detect correlation.

Each prescription is defined by an **ATC code**, from the Anatomical Therapeutical Chemical classification system maintained by the World Health Organization. Furthermore, there are **active principle code** and **authorisation for commerce code**.

Fields summary:

- *codice*, patient ID;
- *userid*, corresponding to *pa_medi* in *nos_002* (general practitioner ID);
- *data_open*, date of insertion of the prescription in the database;

- *time_last*, timestamp of last edit of the tuple;
- *co_codifa*, AIC code (authorisation for commerce);
- *co_des*, textual description of the medicine;
- *te_npezzi*, number of boxes;
- *te_attivo*, active principle code;
- *co_atc*, ATC code;
- *euro*, price.

3.3.5 *cart_accert*

The table *cart_accert* includes all the medical checks and examination for each patient. The first goals of the research only included diagnoses and prescriptions, hence why the comprehension of this table isn't as deep as the others.

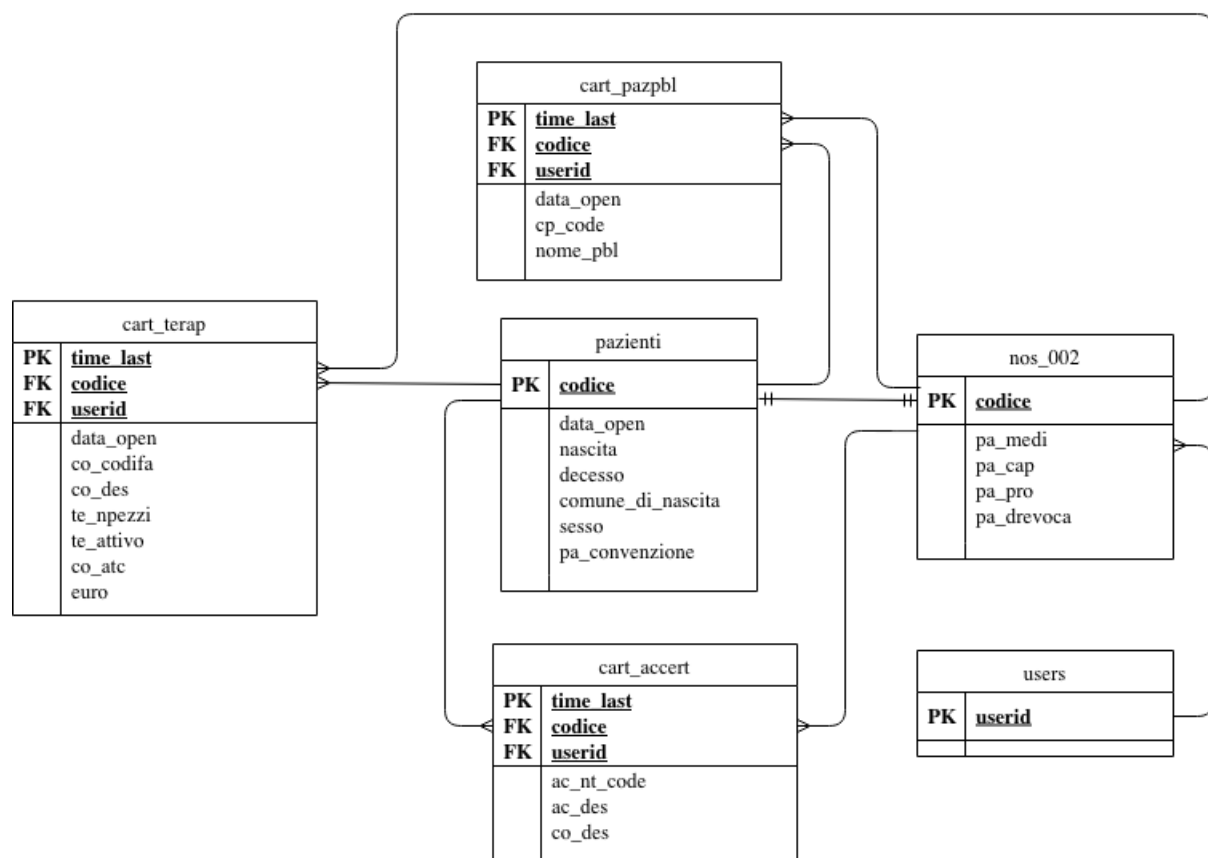
Each examination is defined by an **ICD-9-CM** code, an extension of the ICD-9 database with standard procedures.

Fields summary:

- *codice*, patient ID;
- *userid*, corresponding to *pa_medi* in *nos_002* (general practitioner ID);
- *data_open*, date of insertion of the examination in the database;
- *time_last*, timestamp of last edit of the tuple;
- *ac_nt_code*, ICD-9-CM code;
- *ac_des*, textual description;
- *cod_ese*, exemption code for the examination.

3.4 ER model

After identifying the main fields, it's useful to build and include an **ER model**⁵ to have a better understanding of the tables and their relationship.



Chapter 4

Information loss

The first analysis aims to give a **qualitative assessment** of the whole database, giving an overall idea on how impactful is the progressive information loss.

After understanding the correctness and completeness of records, some fields will be eventually excluded from the analysis, while others that cannot be removed will have a major impact on the results.

Having missing fields, particularly in the process of joining tables, can take to a cumulative augmentation of the information loss: empty data such as the patient date of birth or gender will cause the deletion of the entire patient, in case analytics is centred on pathologies by age or gender.

Joining is in fact an operation which requires all fields of reference to be present, combining entries of the selected tables.⁷

4.1 General overview

Before starting running queries, there are some factors to consider and issues which sometimes cannot be addressed just with database interrogations:

1. The geographic information is sometimes imprecise and hard to comprehend;
2. Some diagnoses descriptions don't match with the corresponding ICD-9 code;
3. A lot of missing data is originated when a general practitioner doesn't prescribe anything but makes other operations (medical certificates, examinations and such);
4. Prescriptions in hospitals are missing;
5. Some medicines don't need prescriptions, so there is no entry in the DB;
6. General practitioners might prescribe a medicine to a different patient than the one who actually needs it (relatives, friends, ...);
7. There is inappropriate prescribing, misuse or over-use of medicines;
8. A patient can change doctor, so the approach to the same disease may vary.

Furthermore, there have been noticed some common patterns of incorrect data:

- Some dates don't fall in the given range (e.g. 1999, 2034, ...), a date is considered wrong if it's before 01-01-2000 or after 10-01-2018;
- A lot of fields are empty or null.

Overall, the loss on single data isn't a relevant issue since the total amount of rows allows safe removal, yet the cumulative augmentation (funnel analysis) gives a progressive deletion of information.

4.2 Information loss on records

4.2.1 *pazienti* and *nos_002* (1 million of tuples)

Summary

Both tables contain similar data related to patients, with a 1 : 1 correspondence between primary keys, so joining them is an elementary operation and there is no information loss.

- Patients with null or empty sex: $2.752 \rightarrow 0,27\%$;
- Patients with sex different from M and F: $54 \rightarrow 0.005\%$;
- Patients with beginning of the patient-doctor relationship outside the accepted range: $226.858 \rightarrow 22,33\%$;
- Patients with null province: $99.981 \rightarrow 9,84\%$.

pazienti_ok

An auxiliary view *pazienti_ok* has been created to highlight the information loss augmentation on patients and be compared to the original tables.

The view is derived by the union of *pazienti* and *nos_002*, with the following conditions:

1. Join on equal patient code (*codice*);
2. Not null date of birth;
3. Dates between 2000 and 2018;
4. Existing and not null sex;
5. Existing and not null province.

The total rows respecting all those constraints are 713.352, so approximately 300.000 tuples (patients) have been lost.

This means that during analysis there will be at least $\frac{1}{3}$ of the data which will be removed due to incompleteness and inaccuracy: not considering patients will imply deleting their diagnoses and prescriptions as well.

4.2.2 *cart_pazpbl* (15 millions of tuples)

ICD-9

An ICD-9 code is correct if it's in the official ICD-9 database.⁶ General practitioners may use different formats and notations, so before removing codes each one has been subject to some parsing.

An ICD-9 code is considered wrong if there is no match in the official DB after none of those transformations:

1. Removal of the dot;
2. Addition of 0 at the beginning;
3. Addition of 0 at the end;
4. Removal of the last 0.

There are 76 incorrect ICD-9 codes, a very small amount considering the total records.

Summary

- Incorrect ICD-9 codes: $76 \rightarrow 0,0005\%$;
- Null or empty ICD-9 codes: $2.103.169 \rightarrow 13.02\%$;
- Null or empty descriptions: $656.067 \rightarrow 4,24\%$;
- Dates out of range: $807.985 \rightarrow 5,23\%$.

4.2.3 *cart_terap* (118 millions of tuples)

ATC code

The ATC code, unlike ICD-9, has only one possible format (a numeric string of 6 digits), and no parsing is needed. All the codes have been checked with the ontologies in a well-known biology portal,⁸ and an ATC is considered incorrect if there is no match.

There are 1.750.292 non-existent codes, which are caused by:

1. Alteration of the codes within the years without updating the database;
2. Single prescriptions indexed using the superclass code;
3. Codes only recognised by local pharmacies.

The latter is the most common reason: there are up to 90.000 occurrences of a single unofficial code. Those numbers, despite being high, aren't really relevant considering the total amount of 118 millions of records.

Summary

- Incorrect ATC codes: $1.750.292 \rightarrow 0, 1, 47\%$;
- Null or empty ATC codes: $1.577.749 \rightarrow 1, 33\%$;
- Null or empty AC codes: $1.310.719 \rightarrow 1, 1\%$;
- Null or empty descriptions: $101.248.410 \rightarrow 85, 28\%$;
- Dates out of range: $3.472.119 \rightarrow 2, 92\%$.

Clearly, the prescription description is not a field which can be used for reliable analytics since empty values prevail.

The field *te_npezzi* (number of boxes) might be useful to check for appropriate prescribing, but since the field is a string it requires casting and parsing to integer, and it's more important to focus on chronic patients analysis.

4.2.4 *cart_accert* (151 millions of tuples)

Summary

- Null or empty examination codes: $208.939 \rightarrow 0, 14\%$;
- Null or empty descriptions: $9.377 \rightarrow 0, 006\%$;
- Dates out of range: $4.451.626 \rightarrow 2, 94\%$.

The official ICD-9-CM database is available for future checks on correctness of the codes.

Chapter 5

Global analytics

Chapter 6

Patient journey

After the preliminary analysis and deciding the main focus area, there are enough information to begin reconstructing the **patient journey**. The goal of this process is to highlight changes in *prescription patterns for chronic diseases*, starting from the medical history of patients.

An objective definition of patient journey can be created using the following guidelines:

1. Patients with **complete medical history** for a fixed amount of years;
2. Records with patient, prescribing GP, diagnosis and prescription on the **same date**;
3. Only **first-time** diagnoses and prescriptions considered.

The imposed criteria is very strict: taking diagnoses and prescriptions on the same day means removing *all prescriptions* following the first diagnosis. In other words, all the instances of patients coming back to their GP to renew a prescription for a chronic disease have been deleted.

This can be useful to extract a cohort of patients beginning their treatment, and analyse the variations of first-time prescriptions. It's important to notice that not all doctors may have patients with a new chronic illness.

6.1 Imposed criteria

Aside from the completeness and correctness of the data, there are more restrictions to maintain the consistency:

- The prescribing general practitioner mustn't change in the time range;
- The patient mustn't be deceased;
- There must be a sanitary convention;
- The general practitioner must be active.

All those constraints can be checked using the related fields in the database: *pa_drevoca* for interruption of the relationship, *decesso* for death and *pa_convenzione* for the sanitary convention.

The table *users* contains all the IDs of active general practitioners, so joining it with other tables is enough to remove all the rows with an inactive GP. Data is up to date, but since the patient journey will include 2018 (the focus is on the most recent information) there is no need to check for active GPs in the previous years.

The biggest risk is again the **loss of information**: the impact of data cleansing is heavy, and the obtained results might not give an insightful prospective.

6.2 Initial data cleaning

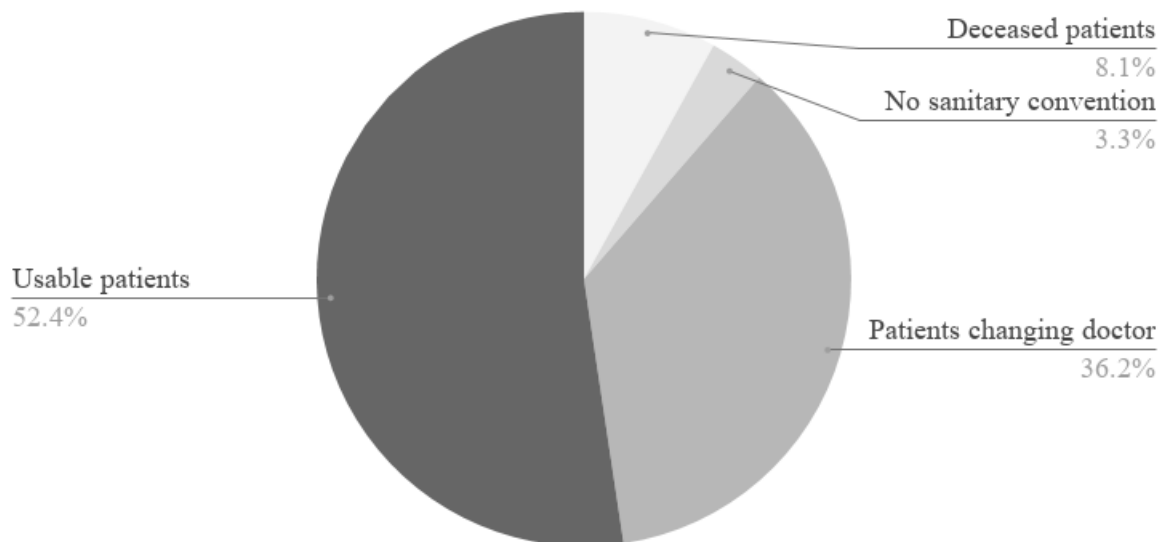
An initial data cleaning has been made on the whole database to have a first understanding of the potential information loss.

In this case, having such a big amount of tuples is useful: it's possible to remove a considerable percentage of them without losing generality and still having numerous samples.

Information on the general loss is already available thanks to the specific analysis on each single field, so the shown data cleaning will only consider patients and GPs.

The active general practitioners are **432**: this result has been retrieved counting the different IDs in *users* (438) and removing the ones that weren't present in *nos_002* (6).

The following *pie chart* illustrates the data loss on patients according to the criteria defined in the previous section.



About half of patients is going to be lost, due to not respecting the consistency criteria. Starting from a million of records, concrete results are still obtainable.

6.3 First approach

The first approach consists in testing with an **arbitrary range constraint**: all dates must fall in the span between 2010 and 2018.

The analysis has pure research purposes, to understand the impact of a cut of the dataset in terms of information loss. All the previously introduced criteria must be considered as well, so there must be a continuous doctor-patient relationship between active GPs and non-deceased patients with sanitary conventions.

The outcome is a patient journey table containing data from 2000 to 2018, with a total amount of **144.618** tuples: this means that there are roughly 150k of first-time diagnosis and prescriptions to patients.

6.3.1 Results breakdown

Seeing that the starting tables had number of rows in the order of millions, some deeper analysis is necessary to figure out the causes of this huge loss.

The 144.618 complete tuples are composed by:

- 27.733 patients;
- 422 general practitioners;
- 1.381 unique diagnoses;
- 904 unique prescriptions.

Further causes for those low values can be found counting how many dates would not fall in the considered range. The percentage of records with date earlier than 2010 in each table is:

- Patients: 75%;
- Diagnosis: 54,6%;
- Prescriptions: 44,7%.

There is an enormous loss on patients: the possible reason might be that most patients started treatment earlier than 2010, plus diagnosis and relative prescription are in different dates.

8 years is a too wide range to obtain a consistent patient journey, and such information loss isn't negligible: the conclusion of the first approach is that introducing time boundaries is something which needs an accurate control, to avoid missing out most of the data.

6.4 Second approach

Since just removing according to the date is an abrupt approach, it's necessary to tune parameters and introduce more detailed constraint, to have a bigger amount of information.

The focus is on the number of prescriptions: given a small range of years, only patients with at least one new prescription are going to be considered. All the previous criteria must be respected, so there must be a continuous doctor-patient relationship between active GPs and non-deceased patients with sanitary conventions.

This methodology allows cluster sampling without having to remove half of the dates: criteria based on the number of prescriptions creates another patient cohort which can be used to accurately select rows from the other tables.

The proposed time range is 2016-2018: pharmaceutical companies generally use the last two years of sales, so picking the last three years gives additional information without compromising the consistency of data.

The outcome is a patient journey consisting of 1.465.005 tuples: almost 10 times the previous result. This leads to two important statements:

1. The time range is appropriate, since the number is large enough to make analysis without loss of generality;
2. The new imposed criterion gives more consistent data and the possibility to build time series.

More cleaning is required to link diagnoses and prescriptions, since there is not a 1:1 correspondence: multiple diagnosis and prescriptions may be associated to the same date. This can be done using a lookup table.

6.4.1 Results breakdown

The 1.665.005 complete tuples are composed by:

- 230.381 patients;
- 422 general practitioners;
- 1.381 unique diagnoses;
- 904 unique prescriptions.

Only 7% of the total prescription has been taken in consideration, yet a million and half is still a satisfying amount.

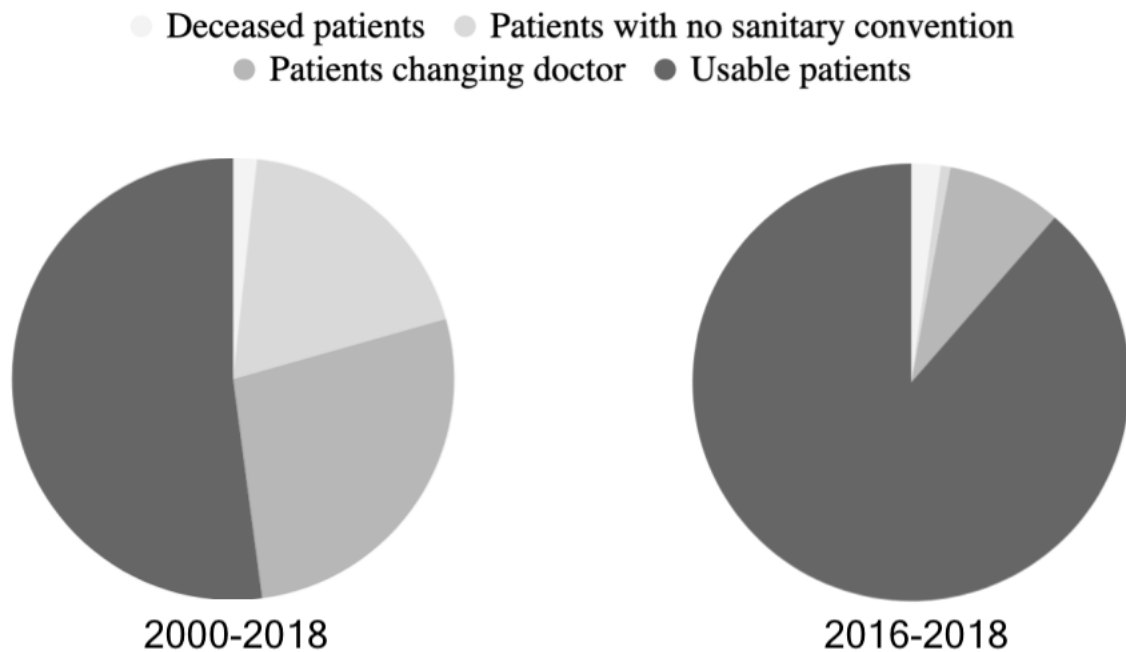
6.5 Results comparison

Comparing the two patient journey outcomes through graphs is a good way to visualize changes and improvements.

6.5.1 Changes in data composition

6.5.2 Improvement on patients information loss

A pie chart for data loss on patients in the range 2016-2018 has been made to compare with the previous one.



It's easy to see that the number of usable patients has noticeably increased: using a smaller time span reduces the chances of death and change of GP.

6.5.3 Funnel graph of patients

A funnel graph is useful to see how imposing every restriction made the patients number decrease: starting from a million, in the end there only is about $\frac{1}{4}$ of it.

Chapter 7

Antibiotic trends analytics

Having obtained a general analytical view on couples of first-time diagnoses and prescriptions, and cross-checking those results with global trends, the research focusses on antibiotic prescriptions to identify changes of patterns.

Defined time frames in limited temporal windows are selected to make a detailed trajectory analysis related to prescriptive appropriateness compared to antibiotic resistance, without going into details of pathologies.

Such analytics are useful for research, highlighting rising health issues alongside the AIFA reports, and to support pharmaceutical companies using the potentiality of healthcare data. Having information about AICs allows to give a new insight not only on ethical matters, but also on the global market trends.

7.1 Identifying antibiotics

Antibiotics, also known as antibacterials, are medications produced by microorganisms that destroy or slow down the growth of bacteria. They include a range of powerful drugs and are used to treat diseases caused by bacteria.

A doctor can prescribe a broad-spectrum antibiotic to treat a wide range of infections. A narrow-spectrum antibiotic is only effective against a few types of bacteria. In some cases, a healthcare professional may prescribe to prevent rather than treat an infection, as might be the case before surgery.

ATC codes related to antibiotics divided by class are:

- A01AB, A02BD, A07A;
- D01, D06, D07C, D09AA, D10AF;
- G01;
- J, the whole class;
- R02AB;
- S01A, S02A, S03A (removing hormones).

7.2 Subset extraction

The first criteria to impose, considering analytics is going to be made on antibiotic prescriptions, is the actual presence of such. This can be reworded by removing all data related to patients who never had a prescription of an ATC code among the ones previously listed.

There are 794 267 patient with at least one antibiotic prescription in the whole time range (2000-2018), whose total prescriptions consist in 114 044 470 tuples. This implies the remaining 200 000~ patients only have 4m~ prescriptions, which is probably justified by a healthier physical state.

Since antibiotics patterns are subject to major changes during years, a big amount of data can be dispersive: pharmaceutical companies make analysis only considering 2-3 years, yet for research purposes an intermediate range is the most informative. A good time span is 10 years, considering most recent ones: since 2018 has to be excluded due to incompleteness, 2008-2017 is the final choice.

Progressive data loss has to be considered, imposing additional constraints of completeness and accuracy. The latest version of the used dataset is a subset of the table prescriptions, with the following restrictions:

- AIC corresponding to an antibiotic;
- Prescription date between 2008-01-01 and 2017-12-31;
- Active general practitioners;
- Patients with usable information about sex, date of birth and location.

The obtained record set is composed by 8 386 057 tuples, each representing a single prescription.

7.3 Global statistics

Global statistics help to have a general overview of the data, aggregating values to identify most impactful changes and the broad behaviour.

7.3.1 Average prescriptions

The average number of prescriptions has been calculated only considering the number of patients with at least one antibiotic prescription from 2008 onwards (670 634).

Values are calculated using the R functions `mean` and `sd`, only considering the number of patients who received at least one prescription in the determined year.

Year	Average	Standard deviation
2008	2,72	2,73
2009	2,75	2,78
2010	2,72	2,76
2011	2,69	2,73
2012	2,68	2,76
2013	2,74	2,84
2014	2,79	2,88
2015	2,79	2,79
2016	2,77	2,91
2017	2,72	2,84

Values show the average tends to slowly increase, and although there are patients getting up to 30 antibiotic prescriptions each month, the standard deviation is low: the mode both for year and month is 1, so lower values weigh more.

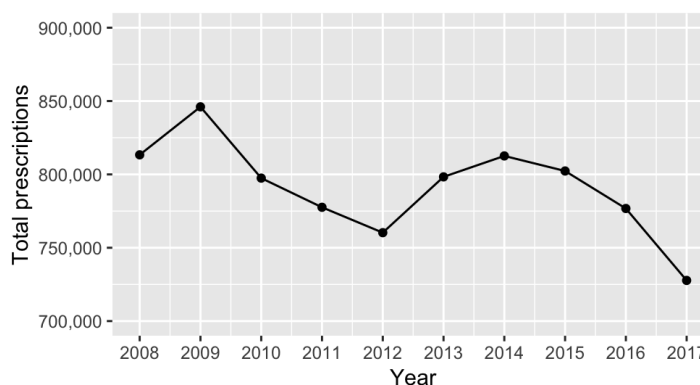
Statistics related to the number of patients with only one antibiotic prescription:

Interval	Average	Standard deviation
Year	118 301,4	2 831,65
Month	40 130,83	6 004,2

7.3.2 Yearly prescriptions

The number of yearly antibiotic prescriptions is:

Year	Antibiotics
2008	813 337
2009	846 067
2010	797 472
2011	777 582
2012	760 280
2013	798 320
2014	812 594
2015	802 323
2016	776 756
2017	727 723

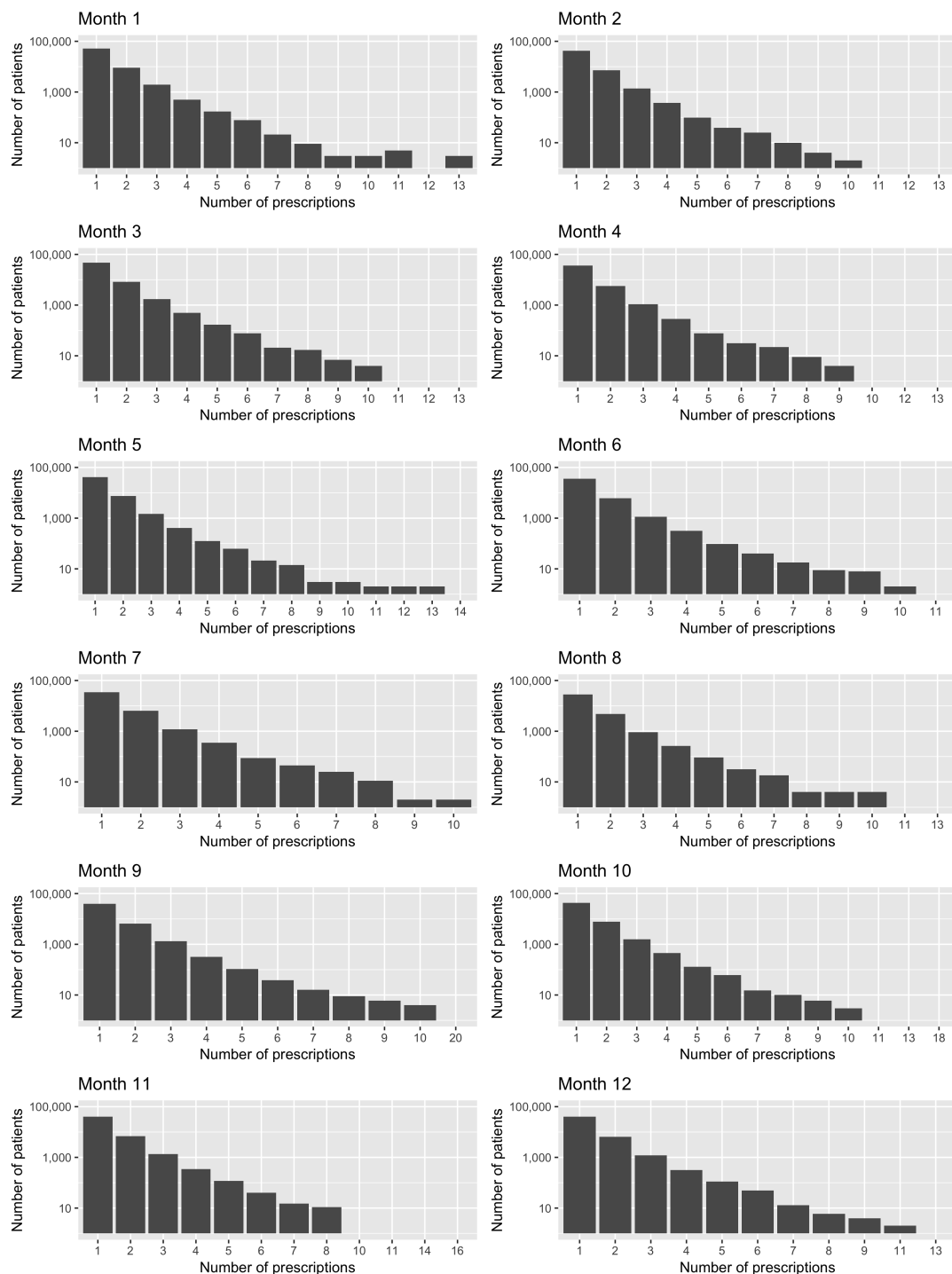


The 2012 fall might be caused by the substantial decrease of the approved antibiotics by AIFA,³³ but is noticeable that the number rises starting from 2013 due to antibiotic resistance.

7.3.3 Number of prescriptions trends

A barplot is the most informative way to visualise trending of number of prescriptions and highlight seasonality. For each month, the amount of patients having the number of prescriptions stated in the x-axis is plotted, using a logarithmic scale.

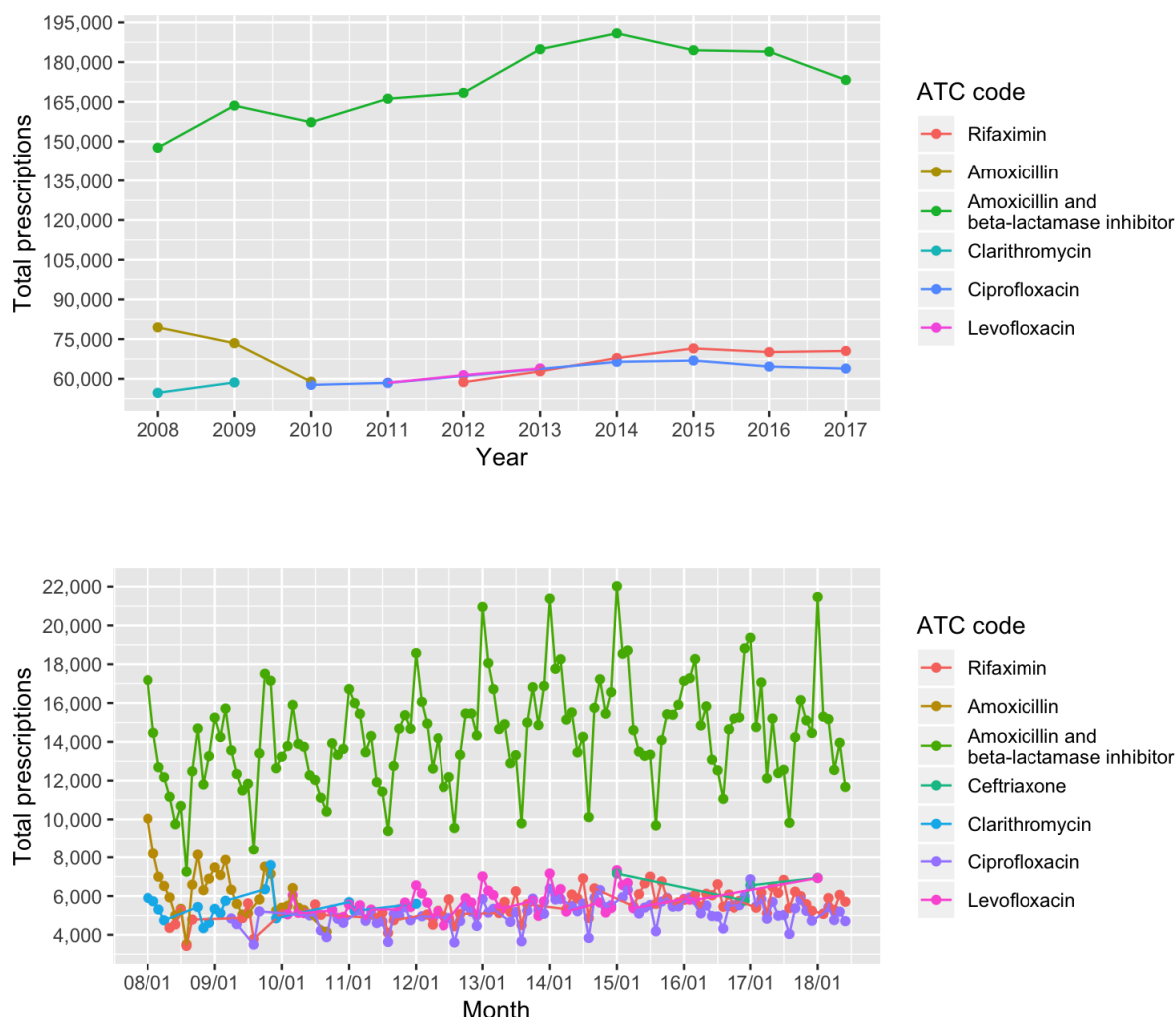
The scale has been adopted to standardise the quantity of patients having a smaller number of prescriptions (1-2), giving higher bars to larger values.



In winter there are more patients having a larger number of prescriptions, while during the summer higher values tend to disappear and even patients with one prescription decrease.

7.4 ATC rankings

For each year and each month, the 3 most common antibiotics are extracted, according to their ATC code. Top 3 changes during the years, hence why there are more than 3 labels in the plots.



Most ATCs follow a similar pattern: the amount decreases in 2010-2012 to then have a small peak in 2016 and get lower again in 2017, similarly to the global amount of prescriptions.

The most noticeable unusual trend corresponds to amoxicillin and beta-lactose inhibitors (ATC J01CR02), which considerably detaches from the others. Amoxicillin is one of the most popular group of drugs, confirmed by global analytics on the database and USA trends.³⁴

It is evident that the monthly prescriptions follow a seasonal trend: the number of prescription rises during the winter and falls during the summer.

7.4.1 According to sex

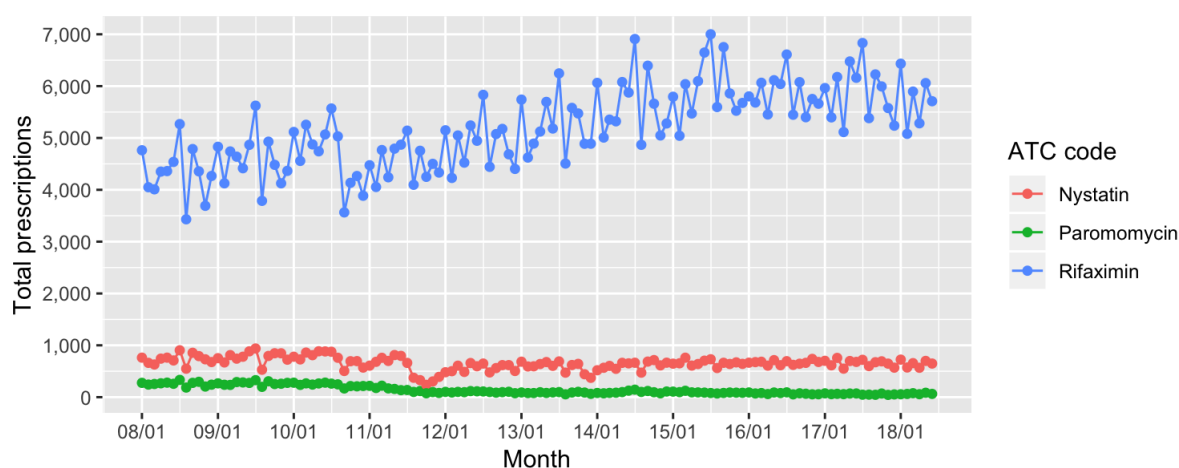
7.4.2 According to age

7.4.3 Comparison with ICD-9

Since ICD-9 have some unusual trends, comparing them with antibiotics might provide additional information. The interested area comprehends ICD-9 class A, diseases of the digestive tract whose diagnoses have doubled in the span of 10 years. Antibiotics to treat this subset are:

- Nystatin;
- Rifaximin;
- Paromomycin.

Cross-checking related codes with the antibiotics dataset, rifaximin is indeed one of the most prescribed drugs, while its numbers are still considerably inferior to amoxicillin (the most popular antibiotic). Seasonality is still present, yet less pronounced.

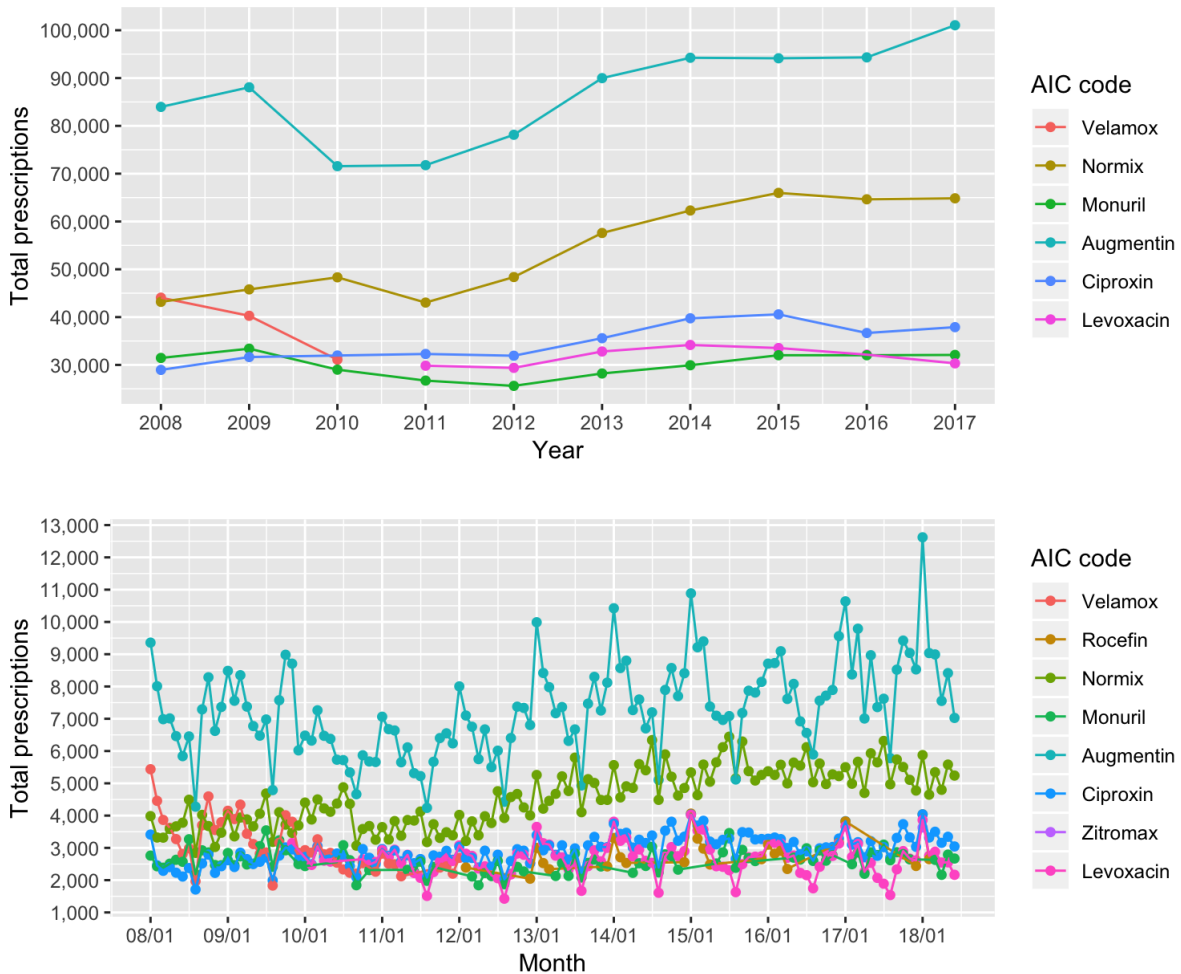


7.5 AIC rankings

Prescriptions with AICs don't have a public lookup table, yet drugs can be singularly searched on a public database by AIFA. Analytics have been made on the antibiotics subset of data, using the 5 most prescribed medicines for months and years.

Augmentin is the top ranked prescription, detaching from the others and with a progressive increase starting from 2010: values go up to 100 000 prescriptions in 2017, and January 2017 is the month with the maximum number.

Having a difference of 30 000 between 2010 and 2017 without a correspondent increase of diagnoses shows frequent episodes of antibiotic resistance and overprescribing.



The drug Velamox has an opposite behaviour compared to the others: while most medicines are increasing their number of prescriptions, while Velamox is subject to progressive decrease until disappearance from the most prescribed drugs.

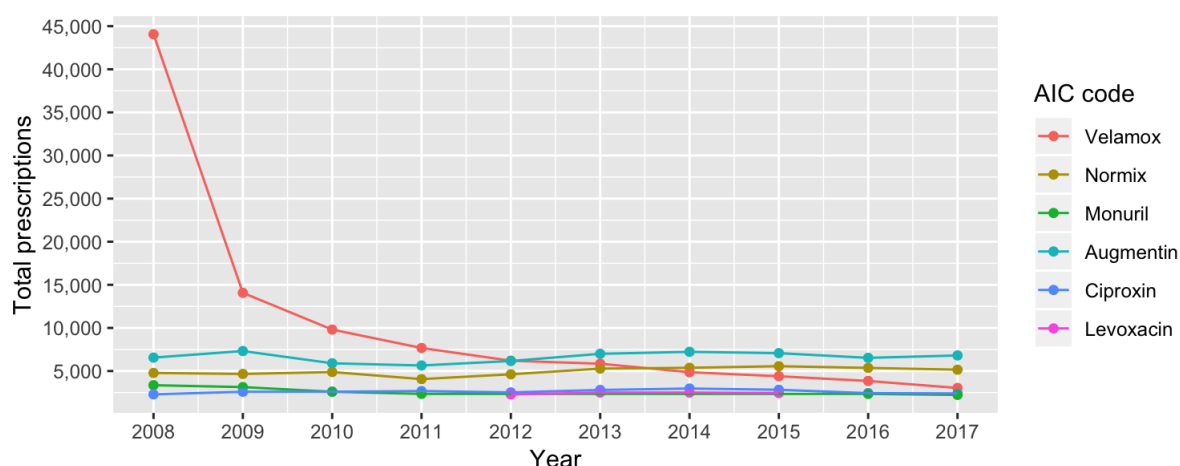
7.5.1 An insight on Velamox

Velamox, according to AIFA, is an amoxicillin-based drug used for respiratory tract, ear and genital infections. It is sold in different packages, whose the most popular is the 1g dispersible tablets with 12 tablets.

The first hypothesis of such a drastic drop of a product is its switch with another one, changing prescriptive habits of doctors. If that was the case, graphs related to the specific subset of patients would have a correspondent rise of values belonging to another antibiotic.

Velamox in 2008, the year of maximum amount of prescriptions, has been given to approximately 32 000 patients. Extracting only the top 3 antibiotic prescriptions of those, in the last 10 years, along with Velamox, shows no substitution by another drug.

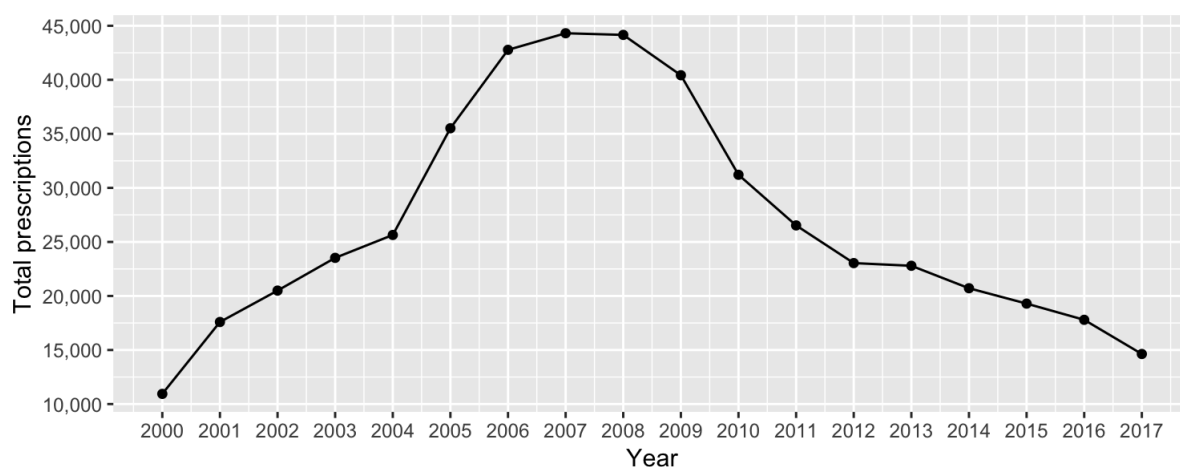
The fall starts in 2009, having a drop of 30 000 units, and gradually continues until 2017 with only 3 037 prescriptions:



ATC trends related to Velamox's AIC show usual patterns: since the same ATC is linked with more products, the curve is still leaning upwards, yet there is an offset equal to the decrease in Velamox.

Since analysis on a subset of patients gives little insight, a wider time range can give additional information on a complete picture of global trends.

Further knowledge is obtained counting the total number of Velamox prescriptions among all patients from 2000 to 2017:



Velamox has acquired popularity from 2005 to 2010, when antibiotic resistance still hadn't been recognised as a problem and before the advent of generic drugs, yet this does not provide an explanation for the decrease.

Additional analysis is made on the subset of 32 000 patients:

- 1 500 are dead;
- 8 000 have changed GP;
- 18 000 are females;
- 14 000 are males;
- 16 000 are born before 1960.

General practitioners assigned to the subset of patients have generally decreased their prescriptions quota, roughly halving it comparing 2008 to 2017.

AIFA has also revoked authorisation for most instances of Velamox packages, only leaving three out of ten. The company which produces the drug, Mediolanum Farmacy, has been acquired by Neopharmed Gentili in 2018.

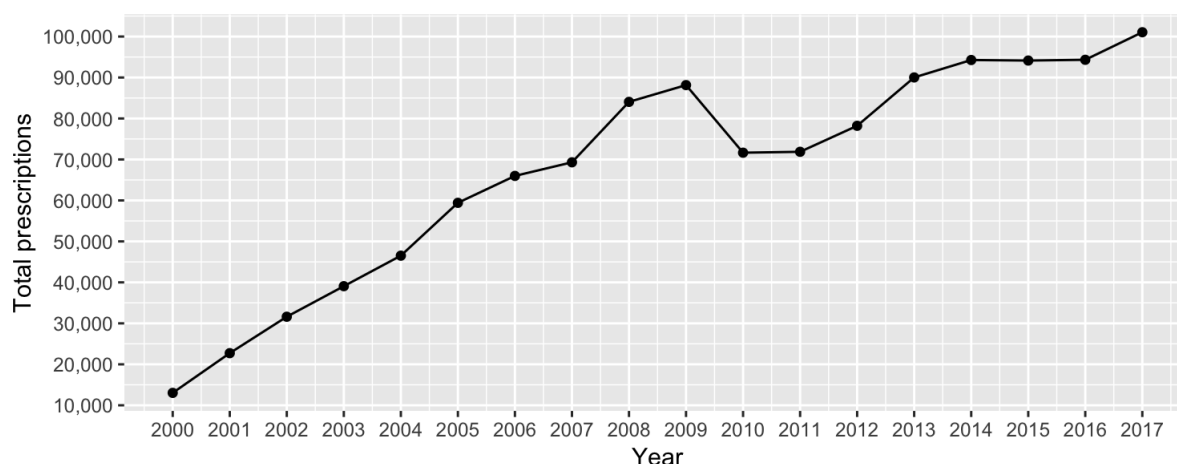
Summarising, changes in Velamox prescriptions are partially caused by:

- Doctors gradually abandoning it after authorisation revoking;
- Patients dying or switching doctor;
- Substitutions with other drugs, none of whose is prescribed enough to have a significant trend, such as generics;
- Different advertisement campaigns after the company acquisition.

7.5.2 An insight on Augmentin

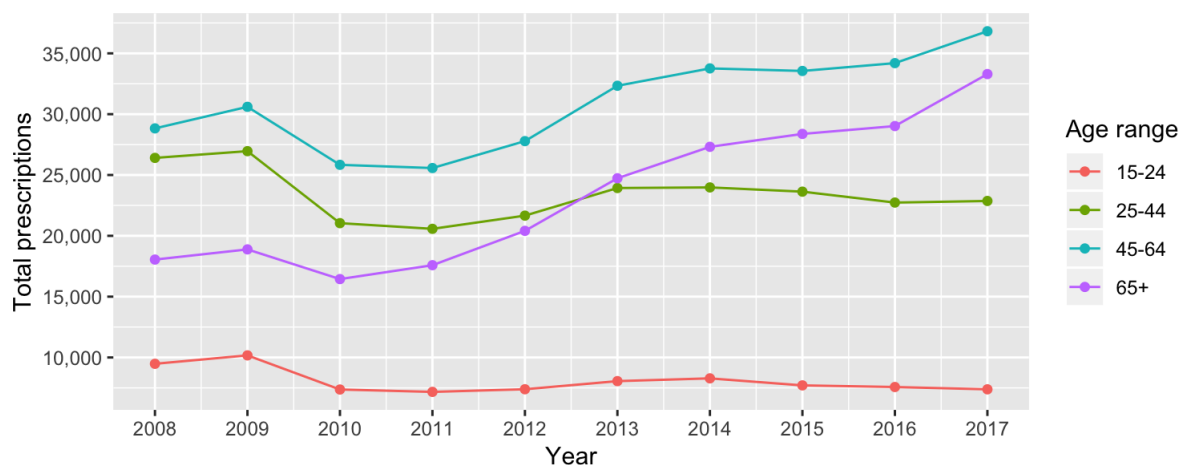
After analysing a drug with an unusual decrease, the focus can shift to the opposite side, considering the one with a noticeable increase.

Augmentin is the most prescribed antibiotic, with an almost constant positive trend:



2010 and 2011 have lower values, possibly explained by the Italian economic crisis or the diffusion of generic drugs. Starting from 2013 numbers continue to rise, reaching their highest peak in 2017.

Most Augmentin consumers are adults in the range of 45-64 years of age, following global trends previously obtained.



Prescription coupling

An excessive usage of antibiotics causes death of microorganisms in the human body which provide to maintaining immune cells and killing certain oral infections.³⁵

To equilibrate the intestinal flora, lactic ferments are often taken along with antibiotics, so that new “good” bacteria can restore the probiotic action.

7.5.3 According to sex

7.5.4 According to age

7.5.5 According to geographical area

7.6 ATC and AIC correlation

Chapter 8

k-means approach for cluster analysis

Chapter 9

Graph analysis

Chapter 10

Assessments of results and future directions

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