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STRATEGIES TO ASSESS AND PROMOTE APPROPRIATE DRUG PRESCRIBING AND USE AMONG ADULT OUTPATIENTS IN CAMPANIA AND LOMBARDY REGIONS

Tutor and PhD programme Coordinator:

Professor **Alberico L. Catapano**

Co-tutor:

Dr. **Elena Tragni**

Candidate:

Federica Galimberti

R11573

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''All men make mistakes, but a good man yields when he knows his course is wrong, and repairs the evil. The only crime is pride.''

-Sophocles, Antigone-

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ABSTRACT

Pharmacological intervention is an essential step in health promotion. However, the process of setting a diagnosis and choosing appropriate drug treatment is complex and lots of drugs are often prescribed and used in inappropriate ways, especially in elderly patients. The direct consequence is an increase of adverse drug events, hospitalization and mortality rates, along with healthcare resource wastage, and additional healthcare costs.

Therefore, the main objectives of the present thesis were to: (1) deeply investigate the prescribing practice among general practitioners (GPs) in two Italian regions, (2) evaluate the appropriate drug use by their patients, (3) develop and administer tailored educational and/or informative intervention addressed to GPs and their patients, in order to promote appropriate drug prescribing and use.

The present thesis was based on baseline data from the EDU.RE.DRUG project (funded by the Italian Medicines Agency), including all GPs and their adult patients (≥40 years) from eight local health units (LHUs) in Campania and Lombardy (respectively, 4.8 million and 4.7 million of adult subjects included, of which 1.6 million and 1.7 million were 65 years or older). We defined a set of explicit indicators for potential inappropriate prescription (polypharmacy, drug consumption, potential drug-drug interactions, therapeutic duplication , drug to be avoided in the elderly according to the ERD-list [EDU.RE.DRUG-list], anticholinergic and sedative load in the elderly) and drug use (adherence to chronic therapies) and we adapted them to the Italian drug formulary. Using administrative health-care databases from the involved LHUs, we retrospectively assessed the annual prevalence rates of the selected indicators during the period 2014-2016.

Despite some remarkable geographical differences and time trend variability, overall we observed high rates of polypharmacy and drug consumption, and a high prevalence of inappropriate drug prescription in primary care setting in Italy. In particular, among older people (≥65 years)

about 40-50% and 10-20% received 5-9 drugs and at least 10 drugs, respectively; around 25-35% in Lombardy and 50-65% in Campania were prescribed at least one inappropriate drug included in the ERD-list; nearly 5-9% had a high anticholinergic load; and less than 2% showed a high sedative load. Furthermore, 10-25% of adult patients were exposed to at least one potential drug-drug interaction, and 3-7% to at least one therapeutic duplicate. In addition, a suboptimal level of adherence to chronic therapies was observed: for all the long-term therapies analysed, the mean adherence level was far lower than 80%, which is the threshold above which the medication has a reasonable likelihood of achieving the most clinical benefit.

These results highlight a widespread need for intervention to improve the quality of prescribing and drug use. In this regard, the strategies we implemented will contribute to define the optimal way to address this critical issue.

RIASSUNTO

L'intervento farmacologico è un elemento essenziale nella promozione della salute. Tuttavia, il processo che prevede la formulazione di una diagnosi e la scelta di un trattamento appropriato è complesso e, spesso, molti farmaci vengono prescritti e/o assunti in modo inappropriato, specialmente nei pazienti anziani. La conseguenza più frequente è un incremento degli eventi avversi da farmaco, del tasso di ospedalizzazione e della mortalità, in parallelo a un utilizzo non razionale delle risorse assistenziali e una spesa sanitaria onerosa.

Gli obiettivi primari della presente tesi sono stati: (1) indagare la pratica prescrittiva tra i medici di medicina generale (MMG) di due regioni italiane, (2) valutare l'uso appropriato del farmaco da parte dei loro pazienti, (3) sviluppare e implementare un intervento educativo e/o informativo su misura rivolto ai MMG e ai loro pazienti, al fine di promuovere l'appropriatezza prescrittiva e l'uso adeguato del farmaco.

Nella presente tesi è stata descritta l'analisi al basale del progetto EDU.RE.DRUG (finanziato dall'Agenzia Italiana del Farmaco), che ha incluso tutti i MMG e i loro pazienti adulti (≥40 anni) di otto ASL/ATS in Campania e Lombardia (rispettivamente, 4.8 milioni e 4.7 milioni di soggetti adulti inclusi, di cui 1.6 milioni e 1.7 milioni avevano un'età ≥65 anni).

Sono stati individuati una serie di indicatori espliciti di prescrizione (politerapia, consumo di alcune classi di farmaci, potenziali interazioni farmaco-farmaco, duplicati terapeutici, farmaci da evitare negli anziani secondo la lista ERD [lista EDU.RE.DRUG], carico anticolinergico e carico sedativo negli anziani) e d'uso del farmaco (aderenza alle terapie croniche) potenzialmente inappropriati, che sono stati, quando necessario, adattati al formulario farmaceutico italiano. Sono stati determinati in modo retrospettivo i tassi di prevalenza annui degli indicatori selezionati, utilizzando i database amministrativi sanitari delle ASL/ATS coinvolte, relativi agli anni 2014-2016.

Nonostante alcune differenze a livello geografico e nei trend temporali, nel

complesso sono stati osservati alti tassi di politerapia e consumo dei farmaci e un'elevata prevalenza di prescrizione inappropriata nel *setting* della medicina generale italiana. In dettaglio, dei soggetti anziani (over 65 anni) circa il 40-50% e il 10-20% ha ricevuto 5-9 farmaci e almeno 10 farmaci, rispettivamente; circa il 25-35% in Lombardia e il 50-65% in Campania aveva almeno una prescrizione inappropriata dei farmaci inclusi nella lista ERD; circa il 5-9% presentava un elevato carico anticolinergico; e meno del 2% mostrava un elevato carico sedativo. Inoltre, il 10-25% dei pazienti adulti era esposto ad almeno una potenziale interazione farmaco-farmaco, mentre il 3-7% ad almeno un duplicato terapeutico. Infine, è stato osservato un livello non ottimale di aderenza alle terapie croniche: per tutti i trattamenti a lungo termine analizzati, il livello medio di aderenza era di gran lunga inferiore all'80%, soglia sopra la quale il farmaco ha una ragionevole probabilità di raggiungere il massimo beneficio clinico.

Questi risultati evidenziano una diffusa e profonda necessità di intervento per migliorare la qualità della prescrizione e dell'utilizzo dei farmaci. In questo contesto, le strategie implementate nell'ambito della presente tesi contribuiranno a definire il metodo più efficace per affrontare in maniera ottimale questa grave problematica.

Chapter 1

APPROPRIATENESS OF PRESCRIBING

Health assessment and medical care quality improvement are important issues in several countries. Political managers, health professionals and customers continuously require information on health care, in order to describe current levels of quality care, to identify critical areas, and to design and plan appropriate interventions. Since the general practitioner-patient interaction leads in most cases to a drug prescription, the prescribing quality in general practice is a crucial issue, having a significant impact on the well-being of patients and representing a substantial part of healthcare expenditure.

1.1 CONCEPTUALIZATION OF APPROPRIATENESS

Several and sophisticated definitions of appropriateness have been suggested for health care in general, but none provides a solidly unequivocal conceptualisation *[Buetow et al, 1997]*.

Harvey *[Harvey, 1991]* defined appropriate care as "that strategy of action which maximises the potential health benefits valued by informed individuals or populations after considering the likely outcomes, their probabilities and their costs, for each of the separate components of the strategy, and that health care professionals are willing to provide". He considered the appropriate care as an evaluation of available choices about alternative uses of resources. By contrast, the Health Services Utilization Study (HSUS) of the RAND Corporation and University of California defined appropriateness by making a more explicit comparison of the health benefits and costs, and support for this conceptualisation can be inferred from Donabedian's pivotal definition of quality of care *[Donabedian, 1980]*.

In the HSUS study, health care is supposed to be appropriate "when for an average group of patients presenting to an average U.S. physician, the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, excluding considerations of monetary cost" *[Kahn et al, 1988].* Briefly, if the risks

outweigh the benefits, the procedure is stated to be inappropriate. Although it was one of the most widely used definition, it was criticized because of the lack of explicitly respect of the patient's choice and because it did not take in account the healthcare resources available. In response to such deficiencies, five years later, a Working Group for the National Health Service (NHS) Executive defined appropriate health care as the selection of "the intervention that is most likely to produce the outcomes desired by the individual patient" and specified certain criteria that must be met for an intervention to be appropriate *[Working Group for the Director of Research and Development of the NHS Management Executive, 1993]*. Again, it was pointed out a lack of mentions of cost-effectiveness concern.

The chance to define appropriateness is facilitated, with reference to prescribing, by comparing this construct with that of rationality. Is (ir)rational prescribing necessarily the same as (in)appropriate prescribing? These terms are at the same time related but different, and an understanding of these differences will help to define appropriateness in prescribing.

1.1.1 Rationality and Appropriateness in Prescribing

The World Health Organization (WHO) defined the rational use of medicines as a situation where "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" *[WHO, 1985]*. Rational prescribing refers to a process, and it emphasises how prescribing decisions are to be made. Accordingly, prescribing is rational when prescribers logically process the information available to them, whereas erroneous reasoning defines irrational prescribing.

Although (in)appropriate prescribing and its dimensions are true or proximal outcomes of the process of (ir)rational prescribing, it is not always

the case. Thus, for example, prescribing may be rational yet inappropriate when correct reasoning leads to a poor outcome because of informational deficits or major differences in the perceptions or cognitive styles of the doctor and patient. Conversely, prescribing may also be irrational yet fortuitously appropriate. In addition, (in)appropriate prescribing may be influenced by factors that transcend logic, including feelings, values and intuition, and prior outcomes.

In operational terms, the rationality of prescribing tends to be viewed solely from a medical perspective, making it inherently more limited than prescribing appropriateness. The latter construct extends the address on "rational drug use" and summarises the complex rationales that underlie prescribing *[Nichter et al, 1994]*. What is deemed rational from a medical perspective may be considered irrational by the patient, and vice versa *[Brahma et al, 2012].* It is therefore essential that both medical and consumer/patient perspectives are considered in order to gain a full understanding of the appropriate use of medicines. Accordingly, appropriateness can be defined as the outcome of a process of decision-making that maximises net individual health gains within society's available resources *[Buetow et al, 1997]*. This definition implies that appropriateness depends on equity in resource allocation as defined by care that meets the needs of individual patients within population-centred constraints. And, also, it suggests that net individual health gains depend on achieving a balance between maximising patient welfare and distributing resources according to needs. To prescribe appropriately, therefore, is a science and an art; the challenge is to get the right balance between pharmacological rationality, the need of individual patients, and an economic issue.

As previously discussed, appropriate prescribing can be achieved through a continuous process of shared decision making with the patient, which consists of six steps *[WHO, 1994]*. Ideally the process of appropriate prescribing is a continuous cycle (**Figure 1.1**):

1) Definition of the patient's problem

A patient usually presents a complaint or a problem. Making the correct

diagnosis is important to start the appropriate treatment.

2) Specification of the therapeutic goal(s)

Before choosing a treatment, the therapeutic aims must be specified. For example, when a patient has been diagnosed with colon cancer and an operation would be the best treatment, but the patient will probably suffer greatly from the operation, the physician and patient may decide against the operation and choose for symptomatic treatment instead, in order to maintain functionality of the patient as long as possible.

3) Suitability of the selected intervention(s)

The next step is to investigate whether and which non-pharmacological interventions are appropriate, and if a pharmacological intervention is necessary. If that is the case, a physician needs to make an evidence-based selection of a medication, for example based on treatment guidelines. However, guidelines offer medication advice appropriate for the general population. Therefore, the physician subsequently needs to check if this medication advice is suitable for the individual patient. Suitability can be determined based on patient and drug factors. Patient factors include physiological status (e.g., pregnancy, kidney failure) and susceptibility to adverse effects, as well as on-going drug therapy, as there may be potential for drug–drug interactions. Drug factors that could influence selection include evidence of safety and efficacy (a review of the drug indication and convenience of the dosage form), as well as pharmacokinetic and pharmacodynamic properties. For instance, a medicine with a once-daily dosing regimen may be preferred over one with multiple dosing for reasons of compliance *[Ofori-Asenso et al, 2016]*.

4) Writing of prescriptions and updating the medication list

It is important to document all changes to the medication regimen and adjust the patient's medication list, to make it readily available for the patient and other involved health care providers.

5) Informing the patient

Patients need information, instructions, and warnings to provide them with knowledge to accept and follow the treatment and to acquire the skills to take the medication appropriately. For most patients, in fact, transitioning

into the role of someone who has to take medicines is often a difficult process, and the presentation of a diagnosis by medical personnel only as a basis to take medicine may not be a sufficient motivator *[Britten et al, 2000]*. For this reason, this stage is very crucial and essential: effective communication with patients is a skill that any prescriber should aspire to achieve, as this is the instrument through which medical information is communicated, as well as addressing patient's needs, expectations, and even emotions *[Ha et al, 2010]*.

6) Monitoring (stopping) the treatment

Monitoring the treatment outcome enables the physician to determine whether the initiated treatment really was appropriate, or whether additional action is required. If the problem has been solved, the treatment can be stopped. If not, re-examination of all the steps is needed. Monitoring can be performed passively, by explaining the patient what to do if the treatment is not effective, inconvenient, or if side effects occur. Monitoring can also be performed actively by making an appointment with the patient to determine whether the treatment has been appropriate.

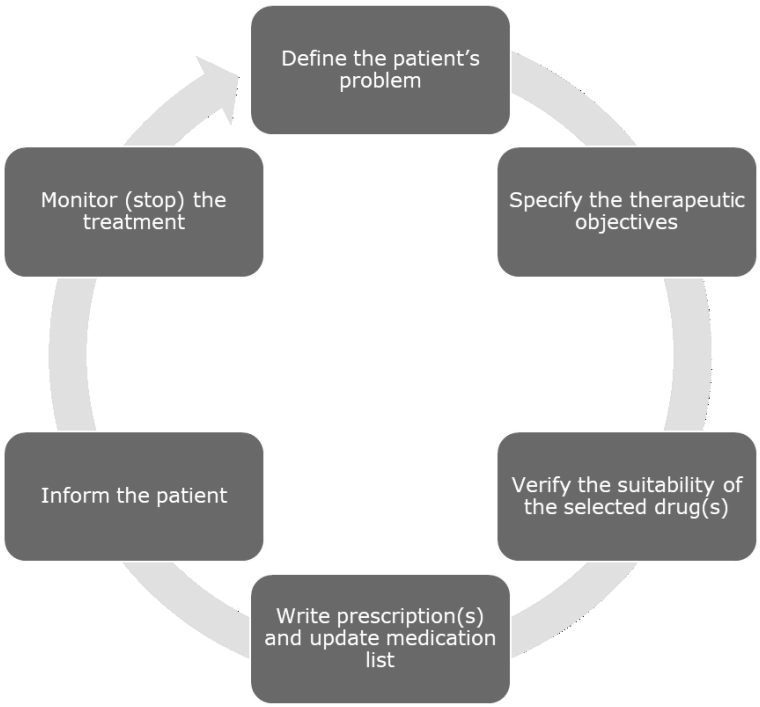


Figure1.1 – Appropriate prescribing process

In summary, there are four aims that a good prescriber should try to achieve, both on first prescribing a drug and on subsequently monitoring it *[Barber, 1995]*:

- MAXIMIZING EFFECTIVENESS

There is little doubt that maximizing effectiveness should be an aim of good prescribing. During a therapy we try to re-establish, modify or improve certain physiological functions and we can verify if it works by testing and measuring the relative parameters. The aim is to achieve the standard values as quickly and completely as possible.

- MINIMIZING RISKS

It is not possible to achieve an absolute level of safety, but it is considered as an "acceptable level of risk" to a culture, a context, or an individual. Thus, the aim would be to reduce the frequency and severity of the adverse drug reaction, taking into consideration all unexpected reactions, even the minor side effects.

- MINIMIZING COSTS

The economic assessment of drug treatment has undergone sudden, rapid growth to the extent that it has produced the neologism "pharmacoeconomics". Health expenditure has a strong impact on the economy of several countries; hence, the main aim is the reduction of costs: it can be achieved quickly by identifying and reducing money and resources wastage and, more slowly, by paying more attention during the prescription of a therapy. In fact, a correct prescription often leads to more rapid healing, while an inappropriate prescription can lead to the prolongation and worsening of the disease; the lower incidence of adverse effects, moreover, would avoid having to take further drugs, favouring adherence to therapy by the patient. Costs should be taken from the perspective of the NHS. This is funded by public money, and reducing costs frees money for more health care -both facts providing ethic justification for including cost minimization.

Assessing the benefits of drug treatment in financial terms is more difficult and questionable, best avoided by most prescribers until methodological issues are better refined.

- RESPECTING PATIENT CHOICES

There are many ethical and practical reasons why the patient's choices, particularly informed choices, should be taken into consideration during prescribing. It is important to listen to the patients and to inform him/her about everything related to therapy: he/she is the one who practically has to take the drugs and to follow the dosing and timing schedule or the clinician's instructions. The doctor must also understand, based on any objections raised by the patient, whether it is necessary and possible to prescribe alternative and more suitable therapies, such as a cheaper drug. Being listened to and involved in the choice of therapy makes the patient more satisfied and predisposed to treatment, leading to the establishment of a trust relationship between patient and doctor, which is often lacking and is, instead, fundamental. Obviously, it does not mean that it is always possible to make the patient's needs coincide with the therapy he/she will be prescribed.

Box 1.1 – Definition of good prescribing *[Duerden et al, 2011]*

"…Whereas consensus may be gained within medicine on how to balance effectiveness, risk, and cost of drug treatment for a condition, including the patient makes judgement on the quality of prescribing difficult to conduct at a distance. In contrast, drug and therapeutics committees, pharmacists, medical advisers, and commissioning agencies are increasingly making judgements on the acceptability of prescribing. These approaches need not be mutually exclusive. The model of good prescribing proposed can be integrated with the proscriptive, protocol driven approach currently gaining favour – for example, by setting a standard that 80 per cent of prescribing meets the protocol. The level at which the standard is set must come from debate among prescribers, patients, and commissioning agencies."

1.1.2 Types of Inappropriate Prescribing

The failure to prescribe appropriate drug therapy is named 'inappropriate prescribing'. In some cases, inappropriate prescribing simply results in the absence of any clinical effect. In other, more serious cases, the consequences may include aggravation of the illness, additional diagnostic testing, increased hospitalizations and mortality, especially in older people, or in co-morbid individuals who may have compromised physiologic functions *[Hamilton et al, 2009]*.

Other possible adverse outcomes related to inappropriate prescribing are the decreased quality of life, adding discomfort to the patient, and the deterioration of clinician-patient relationship. Furthermore, the inappropriate use of medicines can lead to increasing costs for the patient and health care system and to wastage of scarce health resources, which can further reduce the availability of other vital medicines or increase treatment cost *[Ofori-Asenso et al, 2016]*.

For its association with all these negative outcomes inappropriate prescribing has become a global healthcare concern.

There are different types of inappropriate prescribing. The most common are the following:

- PRESCRIPTION *CASCADE*

It refers to the process in which an adverse drug reaction (ADR) is not recognized as such, but is interpreted as manifestation of a new pathology. Consequently, for the treatment of this new clinical manifestation, new unnecessary therapies are prescribed, which expose the patient to the risk of develop other ADRs. This phenomenon can be easily prevented by knowing and promptly identifying the side effects of drugs.

- DRUG INTERACTIONS

Drug interaction is the phenomenon that occurs when a drug (drug-drug interaction, DDI), a food (drug-food interaction) or a pathological condition (drug-pathology interaction) interacts with a drug taken by the patient, with consequent alteration of the profile risk/benefit.

- UNDER-PRESCRIBING

It indicates the instance where the drugs required are not prescribed, or an insufficient treatment duration or dosage is issued. Under-prescribing can contribute to significant morbidity and mortality, although it remains an area of medicine use that has attracted less attention.

- OVER-PRESCRIBING

It refers to instances where a drug that is not indicated is prescribed, or if indicated, the duration of treatment is too long, or the quantity of medicine given to patients exceeds the amount required for the current course of therapy.

- DUPLICATE OR MULTIPLE PRESCRIBING

It refers to the simultaneous prescription of two molecules of the same therapeutic class to treat a certain pathology or different pathologies, causing a substantial increase in iatrogenic risk.

- INCORRECT PRESCRIBING

This category refers to drugs for which risks, under conditions specific, exceed the potential benefits and their use would be avoided. It occurs when a medicine is given for the wrong diagnosis, the prescription is prepared improperly, or adjustments are not made to incorporate the patient's co-existing medical, genetic, or environmental conditions.

- EXTRAVAGANT PRESCRIBING

It occurs when the GP prescribes the most expensive drug, when a less expensive one of comparable safety and efficacy and suitable for the patient and his pathology exists. This prescription is driven by no therapeutic rationale and does not provide any additional therapeutic advantage compared to cheaper drugs. Similarly, extravagant prescribing is said to have occurred when a patented product in a class is prescribed when low costs generics are available in the same class, which could have been used without compromising care.

1.2 EVALUATION OF MEDICATION PRESCRIPTIONS

Drug prescribing is one of the most important processes in health care and an essential step in health promotion. However, the process of setting a diagnosis and choosing appropriate drug treatment is complex. It is a medical act characterized not only by clinical, but also administrative and ethical aspects. It involves not only the choice, but also the decision of optimal dosing and scheduling, informing and educating the patient, and doing the follow-up of the effectiveness of the medications. Bell and colleagues *[Bell et al, 2004]* proposed a framework, consisting of five main domains, for the evaluation of medication prescriptions (**Figure 1.2**).

1) The first main domain is the act of prescribing by clinicians. As previously described, clinicians need to assess and fill in the needs for a medication therapy, and the patient's preferences. The combined data input of medication data, patient data and possible drug formulary restrictions yield the output (a prescription). The prescriber may lack adequate training, or there may be inadequate continuing education, resulting in the reliance on out-dated prescribing practices which may have been learnt while under training. Potential threats for errors during electronic prescribing are mistakes during the selection of patients (wrong patient), clinical problems (wrong diagnosis, or not reporting a diagnosis), or medication selection (wrong dosages).

2) The second domain is the transmission of the prescription. In primary care, patients usually perform this domain themselves, although telephoning or secure emailing of prescriptions by clinicians to pharmacists are possible. Potential threats include transcribing errors.

3) The dispense activity can be done by clinicians (when medications are available on hand), or by pharmacists. In clinical practice, the separation of prescribing and dispensing activities is considered to be a safety mechanism to ensure an additional independent assessment of the proposed therapy before patient begins treatment *[Chou et al, 2003]*. Therapeutic knowledge by the dispenser is essential to cross-check any loopholes in the prescription made and make appropriate

recommendations/interventions to the prescriber, if necessary *[Ofori-Asenso et al, 2016]*. Pharmacists more and more employ electronic systems to store and to access the same information as in the prescribing phase. Potential threats include errors in the drug choice, meaning dispensing other medications.

4) The administration of the medication involves the patient, and sometimes a wide range of other allied health personnel (e.g. nurses in the home or hospital setting). Potential beneficial aspects include the generation of medication administration aids, reminders for renewals, or the consultation of educational material. Potential threats mainly refer to adherence.

5) Finally, the monitoring involves the patient and a clinician, but can also involve other allied health personnel. Feedback during this step could yield changes in the prescriptions of a patient. Potential beneficial aspects include the generation of alerts when a renewal of a medication was not done, the automated generation of questionnaires to detect adverse effects, or corollary orders (e.g. monitoring tests). Potential threats include the negligence to report adverse effects by the patient or health care professionals or non-adherence to medications.

Electronic systems can aid medication prescribers and dispensers during the whole process. Potential beneficial aspects of electronic systems include safety alerts (based on known allergies, interactions, laboratory tests), formulary alerts (e.g. to improve medication adherence), or the automatic possibility of dosage calculations.

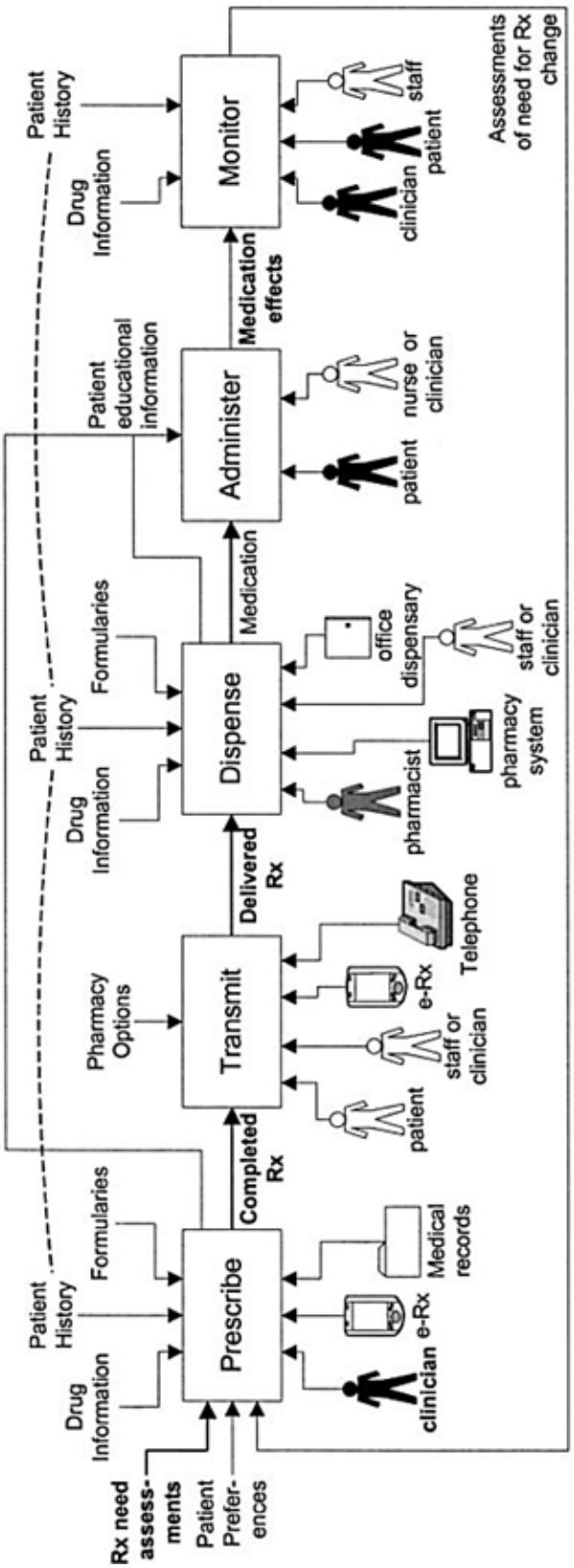


Figure1.2 – The functional model of medication management proposed by Bell and colleagues

1.2.1 Measurement of Appropriateness of Prescribing

In the last decades there has been an increased focus on the measurement of the appropriateness of prescribing, which means finding reliable indicators, systematically developed, that allow to identify the appropriate, effective, safe, and cost-effective use of medicines, based on continuously updated and valid knowledge, in a health protection perspective. According to the Organisation for Economic Co-operation and Development (OECD), an indicator is "a quantitative or qualitative factor or variable that provides a simple and reliable means to measure achievement, to reflect changes connected to an intervention, or to help assess the performance of a development actor." *[DAC Working Party on Aid Evaluation, 2002].* A prescribing indicator is therefore a measurable element of prescribing performance in clinical practice, for which there is evidence or consensus that it can be used to assess quality, and hence change in the quality, of care provided *[Lawrence et al, 1997].* In these terms, indicators provide a quantitative basis for clinicians, planners, and organizations aiming to achieve improvement in health care and the processes by which patient care is provided *[Mainz, 2003]*.

Indicators measurement and monitoring serve many purposes, but the objectives of their evaluation are essentially two. Firstly, to raise the standard of care and achieve the best practice in terms of health outcomes. Data from the WHO show that more than 50% of all drugs are prescribed or dispensed inappropriately, while 50% of patients do not use them in a correct way *[WHO 2012]*. This alters the balance between risk and benefit, leading to ineffective and useless therapy but also increasing the risk of occurrence of unnecessary and avoidable side effects. Secondly, to rationalize the healthcare pharmaceutical expenditure. According to the WHO, the economic burden of futile services (those that do not provide benefit to patients) represents between 20 and 40% of all health expenditure *[WHO 2010]*. In such a condition in which resources are limited, the economic budget must be placed in first line among the criteria of choice between alternative solutions, also at health level. A correct use

of resources would lead to an expenditure control that, in turn, may allow reinvesting resources in areas of highest need.

1.2.2 Characteristics and Classification of Indicators of Appropriate Drug Prescription

An ideal indicator would have the following key characteristics: (i) valid and reliable; (ii) highly or optimally specific and sensitive, i.e. it detects few false positives and false negatives; (iii) based on agreed definitions, and described exhaustively and exclusively; (iv) able to discriminates well; (v) be related to clearly identifiable events for the user (e.g. if meant for clinical providers, it is relevant to clinical practice); (vi) suitable for comparisons; and (vii) evidence-based *[Mainz, 2003]*. Each indicator should be defined in detail, with explicit data specifications in order to be specific and sensitive (**Table 1.1**).

Table 1.1- Attributes of indicators

Attribute	Description
Valid	-Meeting the indicator is considered a better quality (content/face validity) -Measure is a good translation of actual clinical situation or problem (concurrent or construct validity)
Reliable	Data should be complete, accurate, consistent and reproducible
Credible/ Communicable	Indicator must be considered acceptable by both assessors and those being assessed and therefore be developed with the help of prescribers. Outcome must be understandable and relevant for clinical practice
Objective	Data should be independent as possible
Available	Data required should be collected for routine clinical or organizational reasons or be available quickly with minimum of extra effort and cost
Contextual	Indicator should be context free or important context effects (i.e. population size, distribution of age and sex, case-mix) should be adjusted for
Comparable	Indicator should refer to a golden standard, or to other data in similar circumstances
Repeatable	Indicators should be sensitive to improvements over time
Remediable	Intervention is possible when improvements are needed
Interpretation	Indicator should be used appropriately in its presentation and interpretation
Suitable	Indicator should be useful for more than one organization

There are different types of prescribing quality indicators, which reflect the three areas of the medical care quality, namely structure, process and outcomes *[Donabedian, 1988]*:

- **Structural indicators** that assess the quality of organizational factors in health care. Structural indicators are aspects of the health system, organization of care and available resources. They describe the type and amount of resources used by a health system or organization to deliver programs and services, and they relate to the presence or number of staffs, clients, money, beds, supplies, and buildings. In the area of prescribing, it may be access to necessary drugs, availability of industry-independent drug information, an updated formulary or prescribing guidelines.
- **Process indicators** that measure the quality of processes in health care. Process indicators assess what the provider did for the patient and how well it was done. Processes are a series of inter-related activities undertaken to achieve objectives. They cover the actual performance, the decisions and actions of the clinicians, for example prescribing the appropriate treatment or choosing a drug according to recommendations. Notably, prescribing quality indicators are most often process-oriented.
- **Outcome indicators** that measure results achieved in health care (**Box 1.2**). An ideal outcome indicator would capture the effect of care processes on the health and well-being of patients and populations. In the area of prescribing, they are related to the benefit or harm to the patient, equivalent to what is measured in clinical trials, but assessed as consequences of prescribing in a non-experimental setting. Thus, outcome indicators cover all types of drug effects: risk of death or hospitalisation, measures of disease severity or activity, functional impairment, and impact on patients' well-being and quality of life. Outcome may be influenced by both structures and processes (e.g. a patient may die if there are no physicians with appropriate skills available (structure) or if the patient was prescribed an inappropriate drug (process)). Outcome

indicators are important, as improvement in patient health (outcome) is the aim of drug prescribing *[Campbell et al, 2016]*.

Box 1.2 – Definition of outcomes in health care *[Mainz, 2003]*

Outcomes can be articulated as 'The Five Ds':

1) **death**: a bad outcome if untimely

2) **disease**: symptoms, physical signs, and laboratory abnormalities

3) **discomfort**: symptoms such as pain, nausea, or dyspnea

4) **disability**: impaired ability connected to usual activities at home, work, or in recreation

5) **dissatisfaction**: emotional reactions to disease and its care, such as sadness and anger

The taxonomy grid proposed to categorize prescribing quality indicators subdivided them not only on structure, process and outcome indicators axis, but also on a second drug-, disease-, and patient- axis *[Hoven et al, 2005]*. Examples of indicators for each category is reported in **Table 1.2**. The latter classification is based on the amount of clinical information they incorporate (**Figure 1.3**):

- **Drug-oriented indicators** include information solely on drugs. are based on drug prescribing/dispensing data alone and can be used irrespective of the indication for which the drug is prescribed. Access to patient-level data enables construction of more clinically relevant drug-oriented indicators linking different drugs to one another or over time *[Campbell et al, 2016]*.
- **Disease-oriented indicators** include information on drugs linked to diagnosis, where prescribing quality is seen as a part of the treatment quality. They may indicate either to what extent patients are being treated with the recommended drugs for a certain condition or to what extent drugs are avoided in patients with conditions for which they should not be used.

- **Patient-oriented indicators** include information on individual clinical characteristics of the patient, e.g. severity of the disease. For such an indicator, very detailed information at the individual patient level is necessary. It may involve access to clinical data from patient records, maybe even individual patient assessments, using interview and clinical examination *[Hanlon et al, 1992; Pont et al, 2004]*.

Table 1.2 – Examples of process and outcome prescribing quality indicators

Indicator	Drug oriented	Disease oriented	Patient oriented
PROCESS	Co-prescribing gastro protective drugs and NSAID's in elderly patients Off label drug use in children Avoidance of drugs with strong anticholinergic properties in elderly patient	Ratio prescribing lipid-lowering drugs for primary/secondary prevention in hypercholesterolemia	Algorithm for benzodiazepine prescribing in individual patient in nursing home
OUTCOME	Drug induced hospitalization	% of patient with hypertension under control % diabetics with complications	Morbidity/mortality in relation to adherence to guidelines, taking into account clinical characteristic of the patient Readmission to hospital

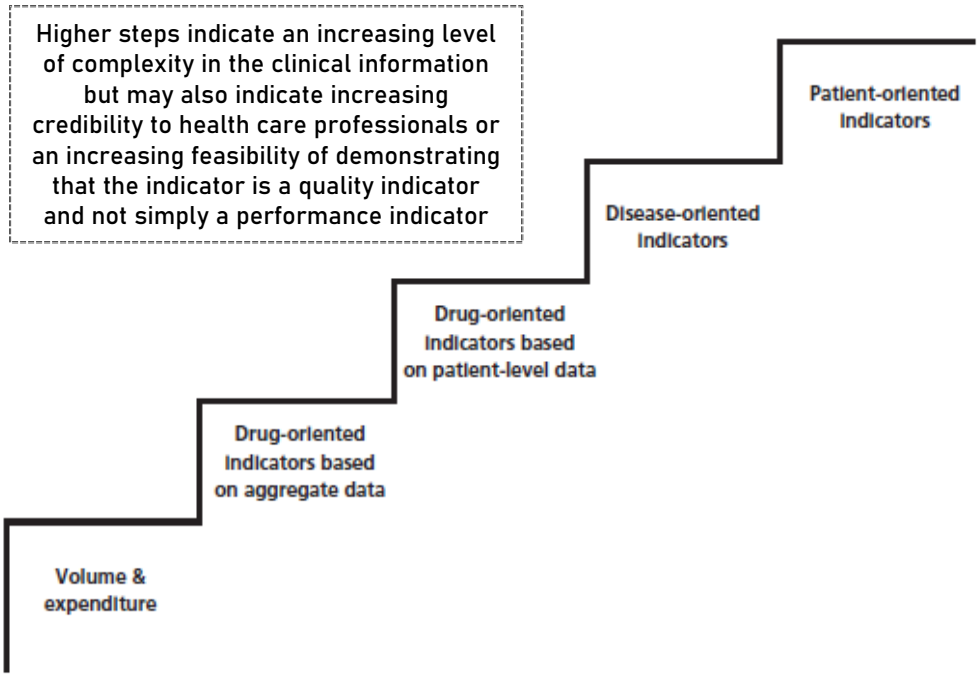


Figure 1.3 – Representation of theoretical model to describe different types of quality assessment and quality indicators of drug prescribing *[adapted from Campbell et al, 2016]*

1.2.3 Selection of Indicators of Appropriate Drug Prescription

The selection of indicators should be done on a clinical basis, as the indicators are functional to the improvement of the clinical outcome, and on an economic basis, as the indicators are functional to the reduction of patient management cost, apart from the price of the drug.

In fact, a prescribing behaviour conforming to the therapeutic recommendations decreases the likelihood of using other services, such as diagnostic tests, treatment of side effects, hospital admissions; in addiction, it obviously increases the probability of achieving a favourable therapeutic outcome. The indicators play a central role in improvement programs of healthcare performances and are commonly used for monitoring of interventions aimed at improving diagnostic-therapeutic prescribing behaviour among prescribers.

The indicators of appropriateness that can be used as essential tools in the process of driving pharmaceutical expenditure and clinical outcomes

include:

- **Prescribing indicators**, which describe the prescribing variability of the clinicians in different clinical or pathological conditions in terms of prevalence of patients.
- **Consumption indicators**, which describe the variability in the use of medicines in terms of volume or cost. The variability of prescribing is usually expressed in terms of volumes (Defined Daily Dose per 1,000 inhabitants/die) or expenditure (*per capita* expenditure) and shows the deviation of the units being evaluated from the average of the evaluation context: the regions in the national context, the Local Health Units (LHU) in the regional context, individual Medical Specialists or General Practitioners (GP) in the local context.
- **Adherence indicators**, which describe the adherence of prescribing behaviour to predefined standards. They include indicators of both adherence to drug use (e.g. the continued use of drugs in chronic treatment) and adherence to the therapeutic indications (e.g. prescription of drugs with a specific indication for the type of patient considered).

  Adherence indicators are characterized by a change of perspective in the measurement and assessment of the appropriateness of prescribing with respect to the more traditional consumption indicators. Instead of a method that identifies as inappropriate the use of drugs that induces an excess (or lack) of consumption compared to an average reference, without providing an explanation of such variability, they are based on a method that classifies as inappropriate the use of drugs under recommendations different from those for which its effectiveness has been tested or will be reimbursed. In order to explain the prescribing variability, the indicators of adherence are a necessary tool in the interpretation of the results described through consumption indicators. However, it must be kept in mind that if, on one hand, the unexplained prescribing variability (in excess or in defect compared to the average reference) indicates potential appropriateness problems, on

the other greater homogeneity with respect to the average level does not mean a high prescribing appropriateness.

1.2.4 Prescribing Indicators

Medication appropriateness can be measured by evaluating the content or quality of a prescribing decision (i.e. a process measure) or its outcome (i.e. an outcome measure) *[O'Connor et al, 2012]*. Different tools to assess appropriate prescribing have been developed and published (**Figure 1.4**); they can be grouped roughly into implicit and explicit tools, and tools showing a combination of both approaches *[Kaufmann et al, 2014]*.

1.2.5 Implicit tools

Implicit tools rely on expert professional judgement, relating to the appropriateness or inappropriateness of a specific treatment option, based on all the available clinical evidence. One of their advantages is focusing on the patient and decisions with regard to prescribing appropriateness at an individual level. However, implicit criteria often are time-consuming to apply and, as they depend on clinicians' knowledge and attitudes, can be subject to differences in opinions and therefore generally exhibit a poor level of inter-rater reliability. Implicit criteria are also often difficult to apply to administrative databases and national registers, as they are less easily standardized.

An example of implicit criteria is MAI (Medication Appropriateness Index), developed in USA *[Hanlon et al, 1992]*, which is based on the evaluation of 10 questions (concerning indications, efficacy, patient's condition, possibility of using the drug in the individual patient, drug-drug and drug-disease interactions, unnecessary therapeutic duplicates, duration of therapy, cost) aimed at assisting the clinician in assessing the quality of the patient's pharmacological prescriptions.

Figure 1.4 - Categories of measures of appropriateness of prescribing and their main characteristics

Another example is the AOU (Assessment Of Underutilization of Medication) tool *[Jeffry et al, 1999]* which is based on an instrument reported by Lipton and colleagues *[Lipton et al, 1992]*. It requires the clinician to have a detailed list of the medical conditions and current drugs used by the patient in order to determine prescription omissions based on existing evidence in the medical literature.

1.2.6 Explicit tools

Explicit tools are criterion-based indicators and are often developed from literature reviews, evidence-based guidelines, expert opinions, and consensus techniques. Explicit criteria are generally drug- or disease-oriented (rather than patient-oriented) and usually include lists of drugs or drug classes, dosages, drug–drug combinations and drug–disease combinations that are known to cause harmful effects and should be avoided. The advantage of explicit criteria is that they can be applied to prescriptions even in the absence of clinical interpretation and judgment. Therefore, these criteria are quick and easy to apply and generally exhibit a good level of inter-rater reliability. However, they usually do not take into account the presence of comorbidities, nor do they consider previously unsuccessful therapeutic approaches or patient preferences *[O'Connor et al, 2012]*. Furthermore, they need regular updates and country-specific adaptation, failing to address international comparisons of prescribing patterns.

There is no ideal approach to assessing appropriateness of prescribing, and both types have advantages and disadvantages which should be taken into consideration when developing or choosing a suitable screening tool. However, due to the time-consuming nature, poor inter-rater reliability and limited application to administrative databases of implicit criteria, the majority of studies that have examined potentially inappropriate prescribing (PIP) to date have used explicit criteria, even though implicit

criteria are considered more sensitive *[Taxis et al, 2016]*. The term "potentially" is used because a drug prescription doesn't necessarily mean that the patient will take the medication (even if it is often the case), or that the use of the drug will cause a negative health outcome.

1.2.6.1 BEERS CRITERIA

Beers and collaborators first published a list of potentially inappropriate medications (PIMs) in 1991, developed by the Delphi method for nursing home residents *[Beers et al, 1991]* and then expanded to other geriatric settings in 1997 *[Beers et al, 1997]* and 2003 *[Fick et al, 2003].* Since 2011, the American Geriatric Society (AGS) has been the steward of the criteria and has produced updates on a 3-year cycle that began in 2012 *[AGS Beers Criteria Update Expert Panel, 2012]*. The following update have occurred in 2015 *[AGS Beers Criteria Update Expert Panel, 2015]* and at the beginning of 2019. The 2019 Beers criteria *[AGS Beers Criteria Update Expert Panel, 2019]* consist of a list of medications or medication classes that must be avoided as they are deemed potentially inappropriate in all older individuals, a list of medications that are considered potentially inappropriate in older individuals who have one of the specified health problems, and a list of medications/medication classes that should be used with caution in all older individuals. For each criterion, the quality of the evidence is graded and the clinical significance (severity) is rated. Since the 2015 update, these criteria also include a list of drug-drug interactions with a high risk of harmful outcome in older people as well as a list of drugs to be avoided/adjusted in individuals with kidney impairment *[Taxis et al, 2016]*. The AGS Beers Criteria continue to be useful and necessary as a clinical tool, as an educational tool at the bedside, and as a public health tool to improve medication safety in older adults. The AGS Beers Criteria can increase awareness of polypharmacy and aid decision making when choosing drugs to avoid in older adults. The main limitation to the Beers criteria is their limited transferability to markets other than United States, where they were developed *[Fialovác et al, 2005].*

1.2.6.2 STOPP/START CRITERIA

The Irish tool was first developed using the Delphi consensus method in 2008 *[Gallagher et al, 2008]*, and an update was published in 2014 *[O'Mahony et al, 2015]*. It consists of two complementary parts: a list of 34 evidence-based prescribing indicators for commonly encountered diseases in older people – the Screening Tool to Alert Doctors to Right Treatment (START; with 'right' meaning appropriate, indicated) – and a list of 80 clinically significant criteria for potentially inappropriate prescribing – the Screening Tool of Older Persons' Prescriptions (STOPP). The criteria are organized according to the physiological systems to which each relate, thereby enhancing their usability. In addition, each criterion is accompanied by a brief explanation, outlining the reason why each PIM is considered potentially inappropriate or why a particular condition is under-prescribed. The STOPP/START criteria have been validated and shown a higher sensitivity at detecting PIP in different settings. However, the number of criteria involved and the length of the lists make the manual application time-consuming.

1.2.6.3 EU(7)-PIM LIST

The EU(7)-PIM list *[Renom-Guiteras et al, 2015]* was the first attempt to unify other lists of explicit criteria on potentially inappropriate medications. The general basis of the EU(7)-PIM list derives from the earlier developed German PRISCUS list *[Holt et al, 2010],* but has now integrated criteria from the Laroche list (France) *[Laroche et al, 2007]*, McLeod's list (Canada) *[McLeod et al, 1997]* and Beers criteria (United States) *[Beers et al, 1997; Fick et al, 2003]*. It is developed with participation of experts from seven European countries (Estonia, Finland, France, Germany, the Netherlands, Spain, Sweden), that allows identification and comparison of PIM prescribing patterns for older people across European countries. The EU(7)-PIM lists 282 drugs (including seven medication classes), of which some are accompanied with dosage information. An additional strength of this method is the proposed dosage adjustment for each medication, as well as the option of an alternative medication or therapy.

1.2.6.4 ANTICHOLINERGIC LOAD

Another approach to the evaluation of medication use in older adults is to determine a patient's anticholinergic load. Drugs with anticholinergic properties are frequently used in older people despite their high potential risk of central and peripheral side effects. These effects can include constipation, heat intolerance, dry eyes, dry mouth, tachycardia, urinary retention, forgetfulness, agitation, paranoia, and delirium, among others. A number of different scales/methodologies have been developed to assist in the calculation of an individual's anticholinergic load, including the Anticholinergic Cognitive Burden (ACB) *[Boustani et al, 2008]*. The ACB scale was generated through a combination of laboratory data, literature review, and expert opinion. This scale has been shown to be associated with an increased risk in mortality and worsening cognitive function in multiple populations, including 13,000 older adults in the United Kingdom *[Fox et al, 2011]*. The ACB scale was updated in 2012 *[Campbell et al, 2013]* and include drugs that are rated in an ordinal fashion from 0 to 3, with 0 signifying no known anticholinergic activity and 3 signifying marked activity (**Box 1.3**).

Box 1.3 – Criteria for drug categorization in the ACB scale

1) **ACB score of 1**: evidence from in vitro data that the medication has antagonist activity at muscarinic receptors

2) **ACB score of 2**: evidence from literature, prescriber's information, or expert opinion of clinical anti-cholinergic effect

3) **ACB score of 3**: evidence from literature, prescriber's information, or expert opinion of the medication causing delirium

1.2.6.5 SEDATIVE LOAD

Besides anticholinergic drugs, also medication with sedative properties can worsen cognitive impairment and physical functioning, increase the risk of falls and negatively impact activities of daily living, hospitalization and mortality. Despite that, sedatives are more frequent among older people

than among the general population. Cumulative exposure to and use of multiple drugs with sedative properties can be assessed using the Sedative Load (SL) Model *[Linjakumpu et al, 2003]*. The SL Model classified drugs into 4 groups based on their sedative potential. Group 1 included only psychotropics (primary sedatives, 40 drugs). Group 2 included many drugs for somatic disorders (drugs with sedation as a prominent side effect or preparations with a sedating component, 80 drugs). Psychotropics were included in almost all pharmaceutical classes in group 2. Group 3 included the major medicinal categories, and only drugs for somatic disorders (drugs with sedation as a potential adverse effect, 220 drugs). Group 4 included all the other medicines (drugs with no known sedation).

1.2.6.6 POTENTIAL DDIs

Another indicator of potentially inappropriate prescription is the concurrent use of interactive drugs as prescribed by one or more different prescribers. Drug–drug interactions (DDIs) are defined as "two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered" *[Gagne et al, 2008].* Although combination therapies are generally used to achieve better therapeutic results, DDIs can lead to life-threatening adverse reactions or therapeutic failure by changing the therapeutic efficacy of drugs *[Gören Z et al, 2017]*. Not all adverse events can be avoided, but DDIs may be among the most preventable and manageable because of their potential predictability. Recently, several web-based tools have been developed in the attempt to identify potential DDIs and to prevent medication errors associated with them, such as Intercheck, Micromedex, MediRisk and Lexi-Interact software programs. Note that, when the interactions present in the prescription are theoretically evaluated through databases and not by their actual occurrence as a negative clinical outcome, they are considered "potential" *[Rodrigues et al, 2017].* All drug interactions are classified according to two parameters (**Figure 1.5**):

- **clinical relevance** that takes into account potential clinical outcomes, and the type, quality and relevance of supporting clinical

data *[Tragni et al, 2013]*;

- **pharmacological documentation** that refers to how deeply the interaction has been studied and investigated, and reported in literature

CLINICAL RELEVANCE	PHARMACOLOGICAL DOCUMENTATION
Contraindicated (the drugs are contraindicated for concurrent use)	**Excellent** (controlled studies have clearly established the existence of the interaction)
Major (the interaction may be life - threatening and/or require medical intervention to minimize or prevent serious adverse effects)	**Good** (documentation strongly suggests the interaction exists, but well - controlled studies are lacking)
Moderate (the interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy)	**Fair** (available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or, documentation is good for a pharmacologically similar drug)
Minor (the interaction would have limited clinical effects; manifestations may include an increase in the frequency or severity of the side effects but generally would not require a Major alteration in therapy)	**Unknown**
Unknown	

Figure 1.5 - Classification of severity of DDIs based on Micromedex software.

1.2.6.7 THERAPEUTIC DUPLICATION

In addition to DDIs, also therapeutic duplication (TD) can increase the risk of adverse drug reactions, without additional therapeutic benefits for the patient, and reduce individual safety and excess healthcare costs.

TD is the practice of prescribing two or more drugs from the same therapeutic category simultaneously, such that the combined daily dose puts the patient at increased risk of adverse drug reactions without additional therapeutic benefits. The risk of TD increases as patients receive more drugs from multiple health care institutions or from different prescribers. The elderly, for instance, are at increased risk of TD as they use many medications *[Kim et al, 2015].*

1.3 STRATEGIES TO TACKLE INAPPROPRIATE PRESCRIBING

As pharmacotherapeutic developments have taken place and use of medicines have increased, there has consequently been a growing recognition of the significant burden associated with the harm caused by drugs to individual patients and their cost to society *[Søndergaard J et al, 2016]*.

One important approach is to identify potentially inappropriate prescribing and correct and optimize it where necessary, with the expectation that this will avoid serious harm *[Avery AJ et al, 2018].* A wide range of interventions can be implemented to change patients' and prescribers' behaviour to improve drug prescribing. Interventions can occur at the individual clinician/health professional level (micro-level), at group or team level (meso-level) or at an organization/policy/regulatory level (macro-level) *[Søndergaard J et al, 2016]*.

These strategies can be grouped broadly as targeted or system-oriented approaches *[Ofori-Asenso et al, 2016]*. In details, targeted approaches comprise educational/professional and managerial/organizational interventions, while system-oriented strategies include regulatory and economic/financial interventions *[Hogerzeil, 1995]*.

- **Educational/professional strategies** are often aimed at persuading or informing, and this usually involves the use of printed materials, seminars, bulletins and face-to-face interventions. Continuing medical education (CME) was the most common educational intervention and utilized various methods, including interactive teaching complemented by a decision algorithm, mailed educational material combined with individualized feedback, and face-to-face visits to physicians *[Kaur et al, 2009]*.
- **Managerial/organizational interventions** are mainly aimed at guiding practice and supporting decision-making. They refer to various restrictions on prescribing, e.g. restrictive lists, a maximum number of drugs per prescription, budgetary or cost restrictions, endorsement by higher qualified consultants, patient co-payment

strategies, price measures, structured prescription forms or a maximum duration for inpatient prescriptions (automatic stop-orders).

- **Regulatory measures** utilize laws and regulations to influence prescribers' practices through restrictions and requirements. Examples include procedures to critically evaluate drugs and product information (e.g. datasheet, patient information leaflet) before market approval is granted, scheduling drugs for different sales levels (over the counter, pharmacy only, prescription only) and specifying for each drug a minimum level of prescriber or health facility (for example, no injectable antibiotics at health centres).
- **Economic/financial strategies** are aimed at promoting positive financial incentives while at the same time eliminating perverse incentives for prescribers *[Gurbani, 2011]*. Economic interventions that may be employed include the implementation of significant changes in service providers' reimbursement schemes or disallowing prescribers to sell medicines themselves, which can remove the financial motivation for over-prescribing *[Hogerzeil, 1995]*.

1.3.1 Educational/professional interventions

Educational interventions are designed and implemented to influence prescribing clinicians in order to encourage a modification of their practice performance using clinical information strategies. It is important to keep in mind that there is not a single strategy to suit all circumstances and that there is not a precise guidance on which combinations of strategies are more effective when a multiple-component intervention is implemented. With respect to influencing prescribing patterns, several systematic reviews that have examined interventions targeting individual professionals showed academic detailing, audit and feedback, use of local opinion leaders and reminders (for drug dosing) to be generally effective *[Grimshaw et al, 2001; Ostini et al, 2004; Ross et al, 2009; Brennan et al,*

2013; Davey et al, 2017].

1.3.1.1 PRINTED EDUCATIONAL MATERIAL

Passive distribution of printed educational material is widely used to influence prescribing patterns. However, there is evidence of only a marginal beneficial impact on professional practice when it is used as a standalone intervention and compared to no intervention. The effectiveness of printed educational materials compared to other interventions, or of printed educational materials as part of a multifaceted intervention, is still uncertain *[Giguère et al, 2012].*

1.3.1.2 AUDIT AND FEEDBACK

Audit and feedback continue to be widely used as a strategy to improve professional practice. In an audit and feedback process, an individual's professional practice or performance is measured and then compared to professional standards (e.g. clinical guidelines) or targets or with other practices. Feedback can be given in a written, electronic or verbal format, and may include recommendations on clinical action.

Audit and feedback can be effective in improving professional practice to a small or moderate degree, even more when feedback is intense and when baseline adherence to recommended practice is low. A Cochrane systematic review including 140 trials of audit and feedback showed a 4.3% increase in healthcare professionals' compliance with desired practice *[Ivers et al, 2012]*. Feedback was most effective when delivered by a supervisor or respected colleague, and presented frequently, and if featuring both specific goals and action plans, aiming to decrease a targeted behaviour, targeting lower baseline performance, and being delivered to non-physicians *[Ivers et al, 2014]*.

1.3.1.3 ACADEMIC DETAILING

Also referred to as 'educational outreach' and 'educational visiting', academic detailing (a trained educator visits a prescriber or group of prescribers in their practice setting to deliver key messages) has been

found to be effective in influencing prescribing and changing behaviour *[Bloom, 2005].* Results from a Cochrane systematic review involving 69 studies and more than 15,000 health professionals reported an increase (+5.6%) in compliance with desired practice *[O'Brien et al, 2007]*.
Despite these findings, educational outreach is an expensive strategy and thus may not be cost effective in all circumstances. One of the key features of successful academic detailing is a sound understanding of the clinical content of the programme to be implemented.

1.3.1.4 REMINDERS, ALERTS AND COMPUTERIZED DECISION SUPPORT SYSTEMS

Reminders are potentially effective and are likely to result in moderate improvements in process of health care. Reminder systems have been used for many years. Manual paper reminders (involving no computers) range from simple notes attached to the front of every chart to more sophisticated reminders given under specific conditions for specific types of patient. Computer-generated reminders using physicians' patient record systems are generally delivered to health professionals when they are making decisions regarding treatment. In this regard, a meta-analysis of 16 randomized controlled trials showed that computer-based reminders improved preventive care performance by 77% when compared to control condition *[Shea et al, 1996].* Furthermore*,* different systematic reviews showed that reminders to health care professionals could be effective in promoting change in practice across a variety of clinical settings and areas, including test ordering, vaccination, drug selection, dosing, prescribing and general disease management *[Buntinx et al, 1996; Balas et al, 2000; Kawamoto et al, 2005]*

Chapter 2

THE ITALIAN SCENARIO

2.1 THE ITALIAN NATIONAL HEALTH SYSTEM

The Italian National Healthcare System (NHS) was founded in 1978, based on the principles of universal coverage, social financing through the use of general taxation and non-discriminatory access to the health care services *[Ministero della salute website]*. It is designed on the Beveridge model, providing uniform and comprehensive care, free of charge, to the entire population *[Folino-Gallo et al, 2009]*. The Italian NHS is organised into three levels: national (the Central Government), regional (Regions' Governments), and local (Local Health Units, LHU) level, and it is regionally based (**Figure 2.1**).

Regions, in fact, enjoy significant autonomy in determining the macro structure of their health systems and have power to legislate within the framework established by the Central Government. At local level, geographically based LHUs are managed by a general manager appointed by the governor of the Region, and deliver public health care, community health services and primary care directly, and secondary and specialist care directly or through public hospitals or accredited private providers *[Cicchetti et al, 2016].*

The NHS provides all citizens and legal foreign residents with economic coverage of drugs with documented clinical efficacy and used for treating serious and chronic diseases *[Onder et al, 2014]*. The amount of public money to be spent on health care is annually established by the Central Government and assigned to the regions in order to provide the ''essential levels of care'' (LEA), which must be assured homogenously to citizens throughout the country. Each region allocates the funds to its LHUs mainly on an age-adjusted capitation basis. Assigned funds are used by LHUs for the direct provision of both in-patient and out-patient care, for GPs remuneration, and for the costs reimbursement of healthcare services afforded by independent and university hospitals and/or accredited private providers *[Folino-Gallo et al, 2009]*.

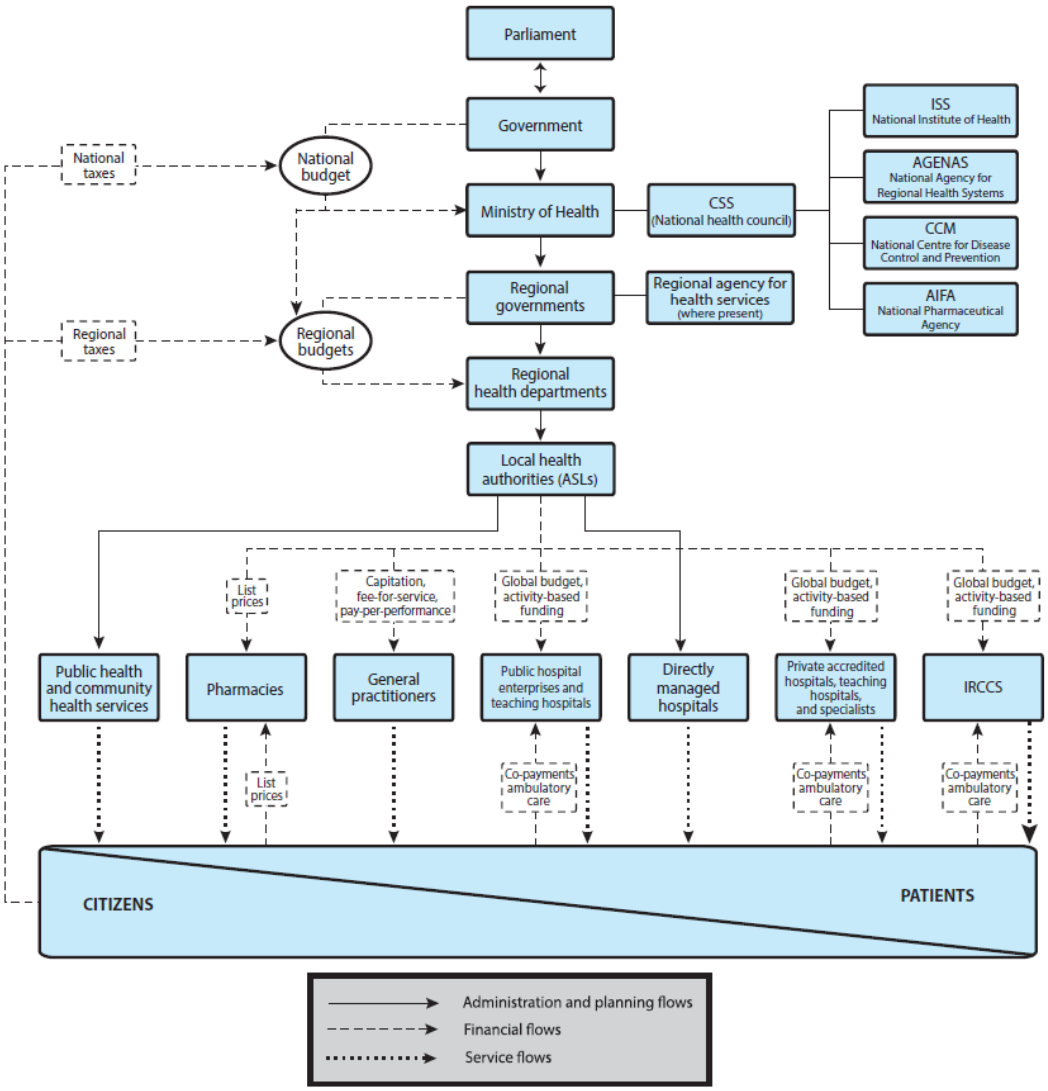


Figure 2.1 – Detailed overview of the Italian health care system
[Ferré F et al, 2014]

It is clear that the Italian health system is highly decentralized, with most organizational powers governed by regions and rather limited powers at national level. Although the state has full control over the definition of the benefit package (LEA), there is evidence that the actual provision and quality of these services varies greatly across regions, as shown by the significant flows of patients moving from the south-central regions to central-northern ones in order to obtain care. The decentralization of the health system has allowed the stronger northern and central regions to design their own models and to fully exploit higher degrees of autonomy

obtained over the last 20 years. Interestingly, these regions have followed rather different pathways, without contradicting the basic principles of the NHS, and thus they have designed rather different regional NHS models. This diversification suggests that there may be different ways to shape a universal tax-funded national health system and that important variants may be generated by different environmental factors, even within a single nation. The most salient issue with the Italian decentralization process is that it benefitted much less (if not even harmed) the southern regions of the country. This gap between the southern and the northern parts of the country is mainly attributable to the lower quality of the political, managerial and professional capacities available in the southern regions *[Ferré F et al, 2014]*.

2.1.1 The Italian Pharmaceutical System

The Italian NHS is responsible for providing pharmaceutical care and accounts for the majority of total pharmaceutical spending. The main national authority responsible for the pharmaceutical regulations in Italy is the Italian Medicines Agency (*Agenzia Italiana del Farmaco* or AIFA), which was established on July 2004 and replaced the Department of Drugs at the Ministry of Health in the responsibility of medicines for human use: marketing authorisation, pricing and reimbursement, governance of pharmaceutical expenditure, pharmacovigilance, and information to health professionals and patients. The Ministry of Health and the Ministry of Economics have a function of control on AIFA activities and cooperation for the elaboration of pharmaceutical policies, regulation and control of pharmaceutical expenditure.

One of AIFA's main missions is indeed to promote and guarantee a safe and appropriate use of medicines, thus contributing to enhance the standards of public health care.

2.1.1.1 THE PHARMACEUTICAL REIMBURSEMENT SYSTEM

The Italian pharmaceutical reimbursement system covers all relevant diseases and the whole country providing universal pharmaceutical coverage to the whole population, including legal residents. The general conditions of the reimbursement system are established on a national level. The current reimbursement classification categorises medicines into two reimbursement classes, according to a combination of criteria in terms of effectiveness and cost:

- Class A comprises essential medicines and medicines for serious and chronic diseases (i.e. antihypertensive drugs, antibiotics, hypoglycaemics agents, antibiotics, antidepressants, antiaggregants, anticoagulants, anti-Parkinson drugs, etc.). Medications of this class are partially (involve a modest co-payment that varies across Regions) or fully reimbursed by NHS and are available only through a medical prescription. The class also includes the subgroup H, consisting of medicines requiring specialist supervision and eligible for reimbursement only when used for in-patient care (hospital use only).
- Class C includes pharmaceutical products that are not reimbursed by the NHS and can be acquired with or without prescription. They usually are medicines for disease of slight importance and for minor ailments (i.e. benzodiazepines, antispasmodics, topical treatments, etc.).

AIFA applies a price regulation only to reimbursed pharmaceuticals. By contrast, for non-reimbursed medicines price is freely determined (with some limitations) by manufacturers and monitored by the Agency and the Ministry of Health.

2.1.2 The Primary Care

The health care system consists of the structures and human resources assigned to primary care, both medical and diagnostic services, and other

services such as assistance provided in residential or semi-residential facilities. The primary care is provided by self-employed and independent physicians, general practitioners, and paediatricians, under contract and paid a capitation fee based on the number of people on their list. This form of care, capillary widespread on the territory, rotates around the figure of the general practitioner (GP), who represents the benchmark for the citizen's general care and the main actor in drug management for the benefit of patients.

In 2016, the GP number was about 44 000 in Italy, with a mean value of 7.3 GPs per 10 000 inhabitants. At regional level, the number ranged from 6.7 GPs per 10 000 inhabitants in the North-West and North-East to 8.0 GPs per 10 000 inhabitants in the Islands *[ISTAT data, 2016]*.

As first-level care providers, GPs are directly involved in the appropriate selection and efficient use of the majority of drugs. Furthermore, taking the overall health care of the patients who rely on them, they are also required to manage the drug therapies prescribed by hospital or ambulatory specialists. In support of the GP, the pharmacist plays a very important role, since he is an expert on the drug and its related problems and often represents a guide for the patient, helping him through communication and listening.

Over the last 15 years, there have been attempts to reorganize the primary care providing, with the objective of moving from the traditional model of GPs and other health professionals working in single practices to an integrated care model that connects different health care professionals and bridges the gap between front-line staff and patients *[Ferré F et al, 2014]*. Again, different institutional and managerial capacities may result in very heterogeneous solutions across regions.

2.2 DEMOGRAPHIC AND EPIDEMIOLOGIC DATA OF ITALIAN POPULATION

The knowledge of the demographic structure of the population by age and gender represents the starting point for understanding the main health needs of a country, needs that differ depending on people's life stages.

2.2.1 Demographic projections

It is estimated a slight decrease in the resident Italian population in a few years: from 60.6 million at January 1st, 2017 (index date) to 60.5 million in 2025. It is also estimated that in Italy the resident population will decrease to 59 million in 2045 and 54.1 million in 2065 (**Figure 2.2**). Compared to 2017 (60.6 million), the decline would be equal to 1.6 million residents in 2045 and 6.5 million in 2065. Taking into account the variability associated with demographic events, the estimate of population at 2065 fluctuates from a minimum of 46.4 million to a maximum of 62. The probability of increasing the population between 2017 and 2065 is 9% *[ISTAT Annual Report, 2018].*

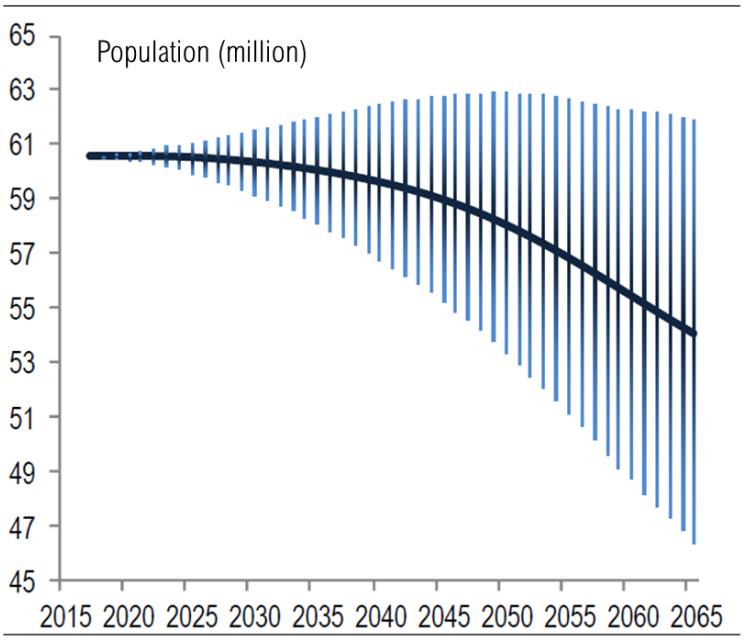


Figure 2.2 – Projection of resident population in Italy (median value and 90% confidence intervals)

In this instance also, there are differences between North and South of Italy. In details, the southern regions would lose population for the whole projection period, while the centre-northern area would see a progressive decline of the population only from 2045 onward, after a positive demographic balance in the first thirty years. The empirical probability that the population of the Centre-North will be larger in 2065 than today is about 30% while in the South it is nearly zero. A shift in the weight of the population from the South to the Centre-North of the country is expected in the coming years. In 2065 the Centre-North would hold 71% of Italian residents against the current 66%; on the contrary, the South would reach 29% against the current 34%. In almost all demographic and health indicators, there are marked regional differences for both men and women, reflecting the economic and social imbalance between the north and south of the country.

Demographic projections also provide a picture of how the age structure of the population may change in the future (**Figure 2.3**). These variations are determined by several factors, including birth and death rates, migration and aging.

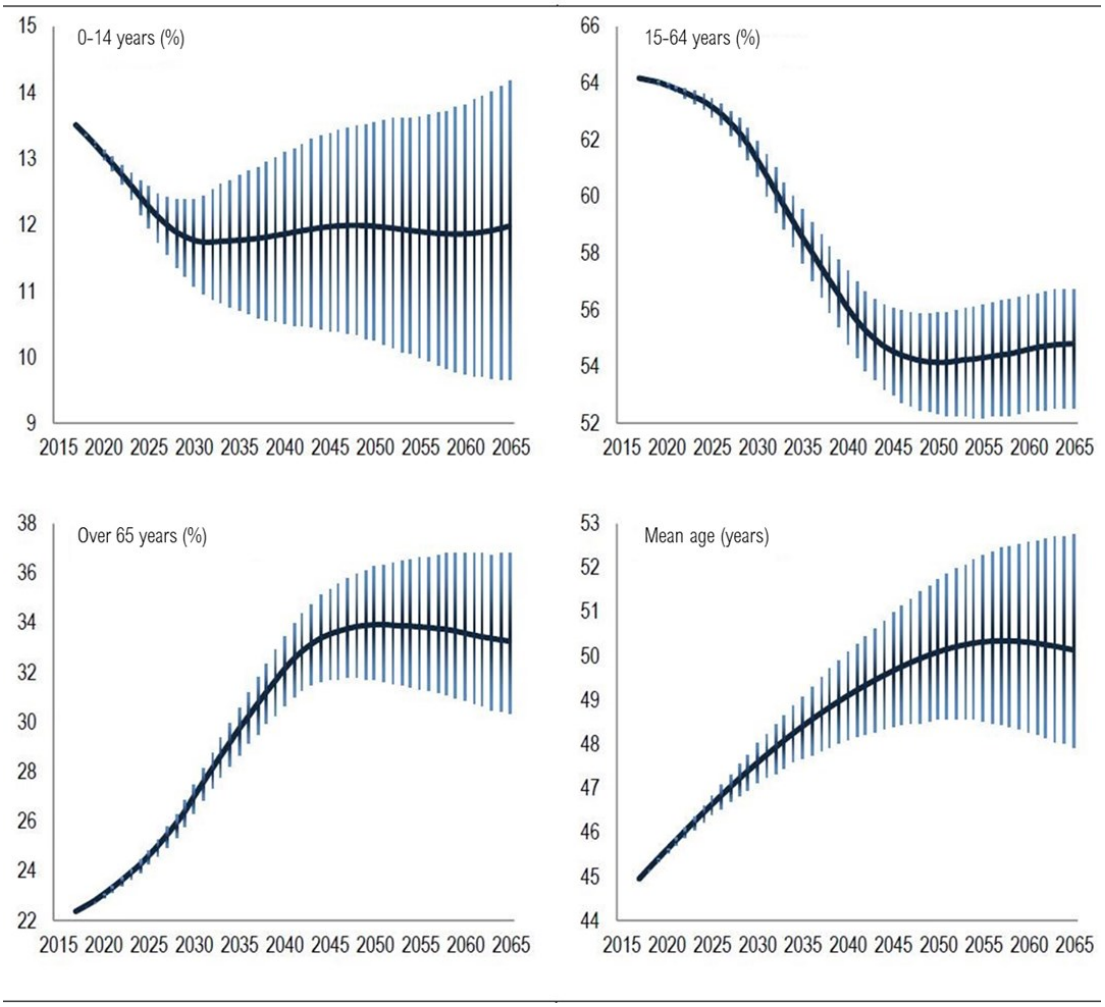


Figure 2.3 – Projections for age classes (median value and 90% confidence intervals) and mean age (90% confidence intervals) of resident population in Italy

Based on projections, the population aged 15-64 years would reach its minimum percentage level in 2050 (54.1%) and then get weight up to 54.8% by 2065 in the median scenario, with uncertainty margins between 52.5 and 56.7%. The elderly population (people aged at least 65), in turn, would reach its maximum around 2051 (33.9%) and then start a decline phase of such as to fall back to 33.3% by 2065. The portion of young people (up to 14 years of age) would tend to stabilize around a median value of 12% in the long term, actually hiding a great range of likelihoods ranging from a minimum of 9.7% to a maximum of 14.2% in 2065.

2.2.2 Aging and health status

Italy is one of the most long-lived countries in the world: life expectancy is nearly 81 years for males and 85,6 years for females. Even with respect to life expectancy at 65 years, in Italy men and women live longer than the European average (19.4 years vs 18.2 years and 22.9 years vs 21.6 years, respectively). In the presence of a falling birth rate, the demographic imbalance increases: with almost 170 elderly (over 65 years) for every 100 young people (between 0 and 14 years), Italy is the second oldest country in the world after the Japan (**Table 2.1**) *[ISTAT data, 2018].*

Table 2.1 – Percent of older population in Italy from 2008 to 2018

Variable	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
0-14 years (%)	14.1	14.1	14.1	14.1	14.0	14.0	13.9	13.8	13.7	13.5	13.4
15-65 years (%)	65.7	65.6	65.5	65.4	65.2	64.8	64.7	64.5	64.3	64.2	64.1
15-39 years (%)	31.5	31.0	30.5	29.9	29.6	29.0	28.6	28.1	27.7	27.3	27.0
40-64 years (%)	34.2	34.6	35.0	35.5	35.6	35.8	36.1	36.3	36.6	36.9	37.1
Over 65 years (%)	**20.2**	**20.3**	**20.4**	**20.5**	**20.8**	**21.2**	**21.4**	**21.7**	**22.0**	**22.3**	**22.6**
65-84 years (%)	17.8	17.8	17.8	17.8	17.9	18.2	18.3	18.6	18.8	18.9	19.1
Over 85 years (%)	2.4	2.5	2.6	2.7	2.9	3.0	3.1	3.2	3.3	3.4	3.5
Mean age (years)	43.1	43.2	43.4	43.6	43.8	44.0	44.2	44.4	44.7	44.9	45.2
Population (millions)	58.7	59.0	59.2	59.4	59.4	59.7	60.8	60.8	60.7	60.6	60.5

However, among elderly aged 75 years and over, health conditions in Italy appear to be worse than in other European countries. As regards chronic diseases, in comparison with the European Union, Italian people report better health conditions among younger elderly people (aged 65-74 years) with lower rates for almost all chronic diseases. On the contrary, elderly people aged 75 years and over have worse health conditions. In Italy, about half of the elderly is affected by at least one severe chronic disease or has more than three chronic diseases. Among the elderly aged 80 years and over, the estimates are even higher, 59.0% and 64.0% respectively.

There are not only differences in disease prevalence related to age, but also related to sex and geography. Women report severe chronic pathologies less frequently than men, but more often comorbidity and physical and sensory functional limitations. In Southern Italy, comorbidity is estimated to be higher (56.4%) than in Northern Italy (42.7%), also taking into account the age distribution. Also, the percentage of elderly with at least one severe chronic disease is higher in the South (49.4% vs 39.4%), as is the percentage of elderly with severe mobility limitations (27.7% vs 17.0%) or severe sensorial limitations (16.5% vs 12.8%) or severe difficulties in personal care activities. In general, the most common chronic diseases are: hypertension (17.8%), arthrosis/arthritis (16.1%), allergic diseases (10.7%), osteoporosis (7,9%), chronic bronchitis and bronchial asthma (5.9 percent), diabetes (5.7%). With the exception of allergic diseases, all other chronic diseases increase with age *[ISTAT Report, 2017]*.

2.2.3 Patient complexity

Although the constant increase in life expectancy has led to reaching old age in conditions of discrete well-being and independence, it has determined the exponential growth of a new category of patients, characterized by a particular vulnerability due to the presence of different chronic diseases at the same time (multimorbidity), fragility, and physic and cognitive disability.

This patient presents a complexity that poses new challenges to the "traditional" medicine focused on the treatment of individual diseases. In particular, the pharmacological treatment of chronic diseases, based on the systematic application of the guidelines is currently criticized and for many reasons it is often considered inappropriate in the complex patient. Thus, from a health care model based on the identification, elimination or control of the etiologic agent, in a few decades a "chronic disease setting" started to take precedence. In this scenario, it is clear that the

pharmacological treatment in the elderly represents a remarkable issue. Polypathology, non-periodic revision of therapy (i.e. lack of medication review and reconciliation), excess of self-medications, and prescribing errors contribute to determine the use of a high number of drugs and the risk of possible drug-drug interactions as well as adverse drug reactions. Almost 8% of medical visits in older patients end up with a potentially inappropriate prescription *[WHO, 2002]*. Findings from an Italian study showed even higher percentage: 18% of elderly outpatients aged 65 years and over had one or more occurrences of potentially inappropriate medication prescribing *[Maio et al, 2006]*.
The appropriate use of drugs is therefore one of the major challenges of clinical geriatrics. The scientific literature has been devoting considerable attention to identifying explicit criteria to evaluate the appropriateness of drug therapy in the elderly, starting from data on pharmaceutical consumption.

2.2.3.1 POLYTHERAPY AND COMORBIDITY IN THE ELDERLY

Data on the drug utilization from six Italian regions (Lombardy, Veneto, Lazio, Tuscany, Campania and Puglia), which represent more than 55% of the whole Italian population, shows that drug consumption and pharmaceutical expenditure are highly concentrated in some age classes of the population *[OsMed Report 2017]*.
Overall, in 2017 there was a prevalence of drug use of 66.1%, with a significant difference between men (61.8%) and women (70.2%). The prevalence of drug use increased from about 50% in children and up-to-54-years adults, to over 95% in the elderly population (over 74 years) (**Figure 2.4**). Simultaneously, there has been an increase of average drug consumption, estimated as defined daily dose (DDD) per 1000 inhabitants per day: from about 400 doses for adults between 40 and 50 years to 3000 for elderly over 74 years. Individually, a subject between the ages of 65 and 74 consumes an average of 2.6 doses of drug every day, while it rises to 3.5 for over 74 years (**Figure 2.5**).
The combination of increasing prevalence of drug use and growing average

pharmaceutical consumption results in an increment in expenditure for drugs reimbursed by the NHS in older people. In details, subjects over 64 years of age show a per capita expenditure up to three times higher than the national average; furthermore, for every individual over 64 years, pharmaceutical expenditure is about 6 times higher compared to the average expenditure incurred for an individual belonging to lower age classes.

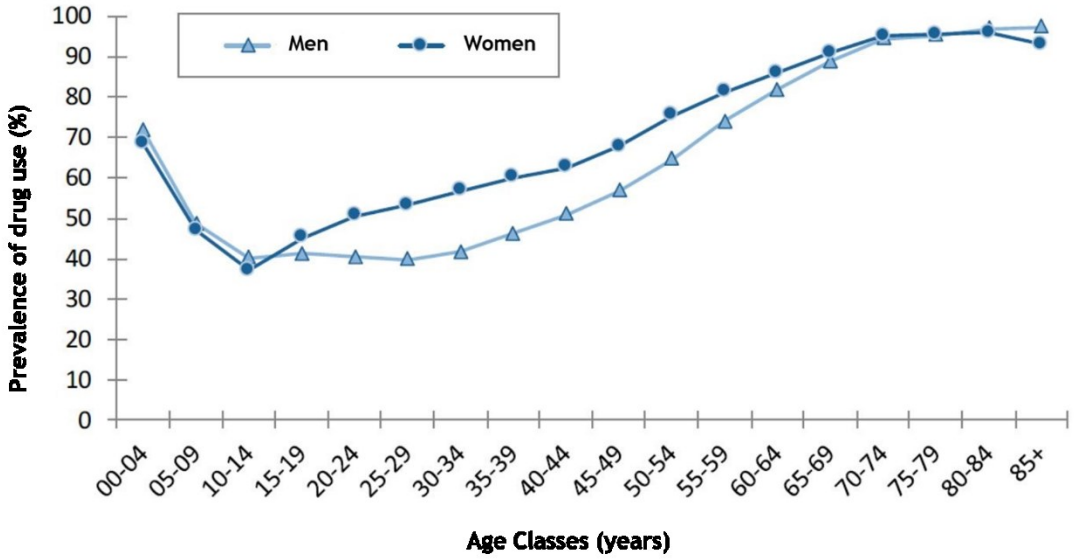


Figure 2.4 – Trend in drug use by sex and age classes in Italy in 2017

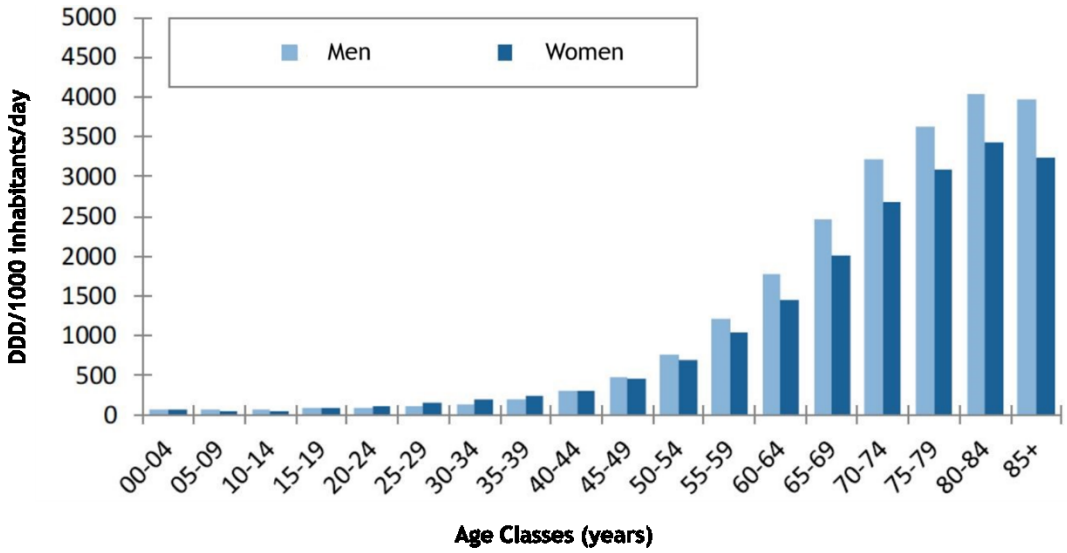


Figure 2.5 – Trend in drug consumption by sex and age classes in Italy in 2017

In both sexes and in all age classes under study, an average of 9.7 different drugs per user is recorded, with a difference between classes, ranging from the lowest average value of 7.7 medications in the 65-69 age class to the highest value of 11.8 in subjects aged 85 or over (**Table 2.2**). In particular, in both sexes, an increase in the number of drugs taken was observed with the progression of the decades of age: in men, from the average value of 7.6 drugs in the 65-69 age class to 12.1 in subjects aged 85 years or older; a similar trend was also found in women with 7.8 different pharmaceuticals taken in the 65-69 age class and 11.6 different active substances in women aged 85 years or older. The distribution of users by number of different drugs showed that over 64% of elderly users were prescribed at least 5 substances during the year 2017 and that 21.6% of subjects over 65 years took at least 10 medications, thus suggesting a frequent use of polypharmacy in the elderly. The most prescribed therapeutic categories in the geriatric population were the drugs for cardiovascular system, antimicrobial drugs for systemic use, and drugs for gastrointestinal system and metabolism.

Table 2.2 – Number of drugs prescribed in Italian older people in 2017

Age Classes (years)	Average number of medications		
	MEN	**WOMEN**	**TOTAL**
65-69	7.6	7.8	7.7
70-74	9.1	9.3	9.2
75-79	10.1	10.3	10.2
80-84	11.4	11.4	11.4
≥ 85	12.1	11.6	11.8
Total	**9.6**	**9.9**	**9.7**

Considering these data, together with the estimates on population aging, it is clear how important the prescribing appropriateness in the elderly is, as regard both to correct allocation of the NHS resources and to greater safety in drug use. Everybody who prescribes for older people needs to be aware of the important physiological changes that occur with aging that

affect drug pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (the effect a drug has on the body). The elderly patient appears to be a subject who, due to the presence of comorbidity and the physiological changes that different systems undergo with age, is treated on average with a high number of drugs. However, the simultaneous intake of more drugs predisposes older people to adverse outcomes arising from prescribing errors. Moreover, this type of patient often presents neurosensory, cognitive and motor limitations that make the diagnostic procedures -indispensable for a correct clinical diagnosis- even more difficult. Finally, the increased risk of adverse events with polytherapy is exacerbate by a lower compliance to the treatment. Indeed, latest data from the National Report on Medicines use in Italy *[OsMed Report 2018]* shows that, for treatment with chronic therapies (including statins, antihypertensives, antiosteoporotic, and antidepressant drugs), both medication adherence and persistence decrease with age.

Chapter 3

AIM OF THE PROJECT

Prescription of medicines is a fundamental component of the healthcare of people. However, the process of setting a diagnosis and choosing appropriate drug treatment is complex. Appropriateness of prescribing occurs when patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirement, for adequate length of time and at the lowest cost for them and their community *[WHO, 1985]*. The failure to prescribe appropriate drug therapy, which is called inappropriate prescribing, has become an important public-health issue worldwide because of its association with negative health outcomes, including adverse drug events (ADEs), increase of hospitalization and mortality, but also healthcare resource utilization and wastage. Therefore, inappropriate prescribing represents a clinical and economic burden to patients and society *[Gurwitz et al, 1990; Hanlon et al, 2001; Simonson et al, 2005].*

This issue is particularly relevant in older people, which are characterized by chronic conditions and multimorbidity, leading to an increased use of drugs or polypharmacy. These features of ageing, together with others of geriatric medicine, affect drug prescribing in this age group, making the selection of appropriate pharmacotherapy even more challenging and complex.

Notably, appropriate prescribing does not guarantee a proper drug use. Evidence suggests that non-compliance to physicians' prescriptions is very common *[Casula et al, 2012]*, partly because of the complexities of daily therapy regimen as well as other patient-related factors, or poor patient-physician communication.

Thus, it is necessary to implement strategies aiming at assessing and reducing the number of inappropriate medications and at optimizing appropriate drug use, including education and information for healthcare professionals and the public, from independent sources and with the support of well-trained staff.

In this context, the Epidemiology and Preventive Pharmacology Centre (SEFAP) of the Department of Pharmacological and Biomolecular Sciences (University of Milan) have designed and conducted a project

(EDU.RE.DRUG project) aiming to deeply investigate the prescribing practice among general practitioners (GPs) and the appropriate drug use by their patients in two Italian regions.

In details, the project consisted of three phases, with the objectives of:

- characterizing inappropriate prescription and drug use profiles and highlighting the most frequent events of inappropriateness (phase 1);
- implementing tailored interventions for GPs and their patients focused on this critical issue (phase 2);
- comparing the prescriptive behaviour of GPs pre- and post-interventions, in order to define whether an effective change in prescribing has occurred (phase 3).

The present thesis describes the first two phases of the EDU.RE.DRUG project, which is currently in progress.

Accordingly, the main objectives of the thesis project were:

(i) to develop indicators of inappropriate prescribing suitable to Italian context;

(ii) to retrospectively assess the rates of the selected indicators of inappropriate prescribing and drug use during the period 2014-2016, with a particular focus on older patients;

(iii) to compare two different geographical areas in Italy;

(iv) to develop and administer informative and/or educational interventions addressed to GPs and their patients, aimed at improving prescribing quality and promoting proper drug use.

The results obtained will represent the basis for assessing the effectiveness of implemented interventions for GPs and their patients in a real-life setting. Moreover, analysis of baseline data will be used to identify factors to be studied as predictors of inappropriate prescribing, and therapeutic areas most affected by inappropriate prescribing, in order to establish priorities for action, to focus efforts and optimize the scarce available resources.

Chapter 4

METHODS

4.1 DATA MANAGEMENT

The EDU.RE.DRUG project is a prospective, pragmatic, multicentre and open-label trial, which started in April 2017 (registration details on clinicaltrial.gov: NCT04030468; EudraCT number: 2017-002622-21).
The EDU.RE.DRUG project was supported by project grants from the Italian Medicines Agency (Bando 2012 per la Ricerca Indipendente) and funded in 2016 (funding code: FARM12KSBT). The study was then approved by the Ethics Committee of the University of Milan on 07 June 2017 (code 15/17).

4.1.1 Study population

For the EDU.RE.DRUG project, eight Local Healthcare Units (LHUs) were enrolled: four in Campania region, in the southern part of Italy, and four in Lombardy region, in the north of Italy (**Table 4.1** and **Figure 4.1**). Each LHU informed their own GPs through a letter about the participation to the EDU.RE.DRUG project, coordinated by the Epidemiology and Preventive Pharmacology Service (SEFAP) of the department of Pharmacological and Biomolecular Sciences at the University of Milan.

Table 4.1 – Local Healthcare Units involved in the EDU.RE.DRUG project. Data from DEMO-ISTAT website updated to 1 January 2017

Region	LHU	Municipalities	Population	Population over 40 yy
Lombardy	Bergamo	242	1,109,933	639,481
	Brianza (Lecco area*)	88	339,238	203,847
	Brianza (Monza Brianza area*)	55	868,859	517,916
	Val Padana (Mantova area*)	69	412,610	249,647
Campania	Avellino	118	432,506	244,287
	Caserta	104	924,166	483,167
	Napoli 1 Centro	31	979,381	542,098
	Napoli 2 Nord	32	1,052,947	522,778

*The term 'area' refers to a subdivision of the Local Health Units, instituted at the end of 2015 in Lombardy.

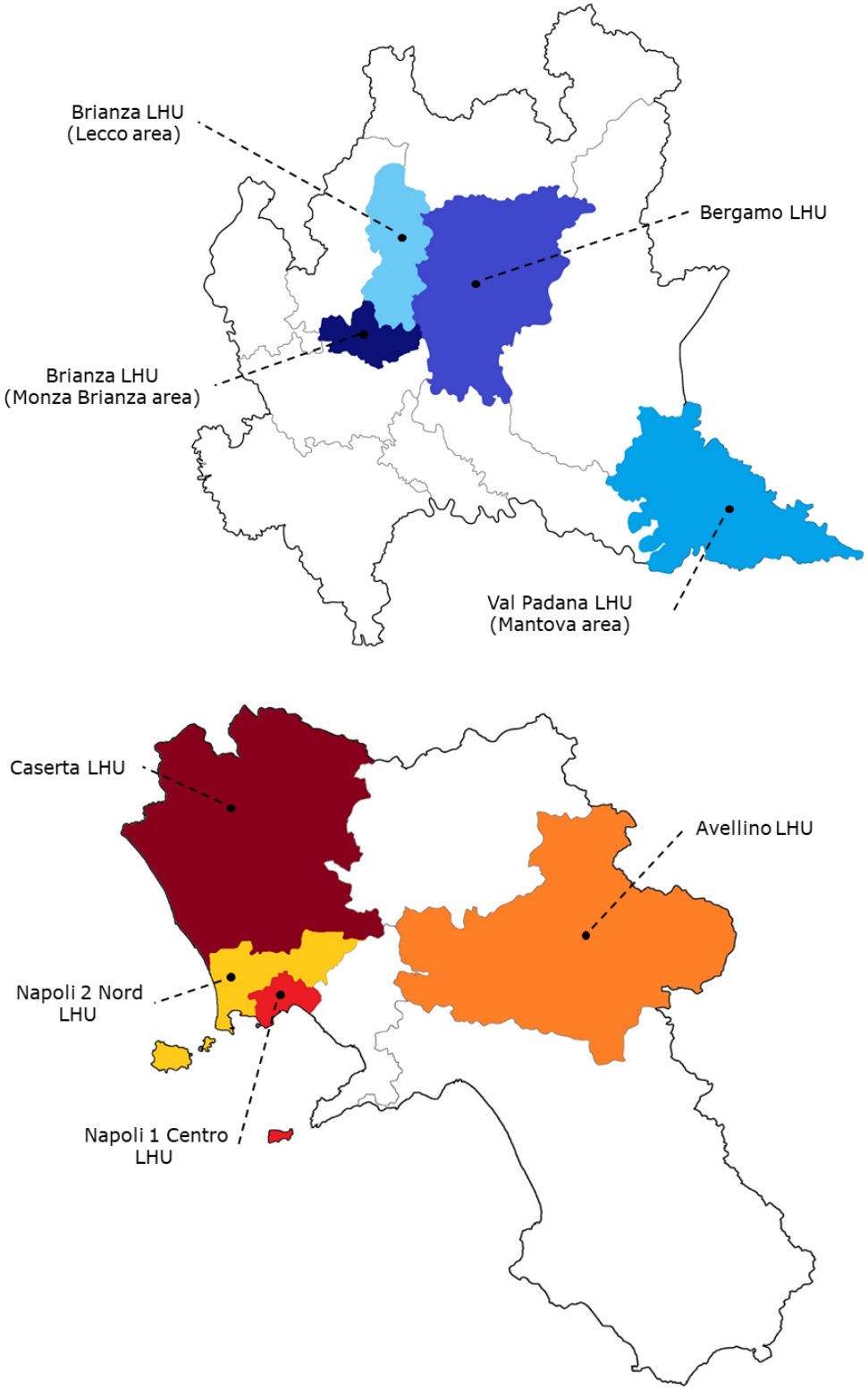


Figure 4.1 – Geographical maps showing LHUs involved in the EDU.RE.DRUG project

The EDU.RE.DRUG population was selected among all citizens (**Table 4.2**) assisted by those GPs from the enrolled LHUs who were active at the end of 2016 (physicians retired in 2016 were excluded from the study). Eligible subjects were all the patients referring to the selected GP cohorts, aged ≥40 years in 2016 and with at least one drug prescription in the same year.

Table 4.2 – Number of total assisted citizens in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	945,052	943,147	930,147
	Brianza (Lecco area)	299,098	299,298	349,104
	Brianza (Monza Brianza area)	758,365	759,795	893,112
	Val Padana (Mantova area)	414,745	413,793	414,304
Campania	Avellino	362,766	383,886	399,166
	Caserta	763,993	817,095	886,809
	Napoli 1	811,784	873,881	949,594
	Napoli 2	850,009	913,070	1,043,959

4.1.2 Data source

The study data were retrieved from administrative databases containing healthcare data of all beneficiaries of the NHS in the LHUs involved. In fact, since 1997, NHS has managed healthcare delivery through a system based on electronically linkable databases containing information on NHS-reimbursable health services *[Corrao et al, 2008]*. These databases, which are set up and constantly updated by regional or local health authorities, include:

- Demographic Databases: this is an inhabitant registry where the GP chosen by each subject is recorded. It stores information on residents who receive NHS assistance, including birth date, sex, district of residence, and GP code and information on GPs, such as birth date, sex, and number of patients.

- Pharmacy Databases: information based on dispensing records of prescribed drugs reimbursable by the NHS, including prescription date, dispensing date, the name of each drug dispensed, WHO Anatomical Therapeutic Classification (ATC) code (**Box 4.1**), marketing authorization code (AIC), dose(s), number of items per prescription, number of boxes, and cost for NHS.
- Hospital Databases: information on all hospitalizations at public or private hospitals of the LHUs, including admission date, primary and secondary diagnoses, that are expressed as codes of the International Classification of Diseases ICD-9 or ICD-10, and date of discharge. This kind of information was not used in the present thesis, but it will be examined in the third phase of the EDU.RE.DRUG project.

Box 4.1 – WHO Anatomical Therapeutic Classification (ATC) classification system

In the ATC classification system, the active substances are classified in a hierarchy with five different levels. The system has fourteen main anatomical/pharmacological groups or 1st levels. Each ATC main group is divided into 2nd levels which could be either pharmacological or therapeutic groups. The 3rd and 4th levels are chemical, pharmacological or therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups *[WHOCC website].*

Example:

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	Metformin (5th level, chemical substance)

Reimbursement data are deemed highly accurate for information on the utilization of reimbursed drugs dispensed to patients and capture drugs

prescribed by multiple prescribers; however, drugs documented in the database are limited to those that are reimbursed by NHS.
Individual-level pharmacy dispensing and reimbursement data also contain unique identifiers per patient (fiscal code), prescriber (ID code) and pharmacy dispensing the drug.
By translating the fiscal code of each patient and the ID code of each GP into unequivocal alphanumeric codes, the LHUs provided anonymized data, for which they locally stored the conversion tables, providing guarantees in respect of the privacy of every citizen (according to art. 110 on medical and biomedical and epidemiological research, Legislation Decree 101/2018). The presence of unique patient and prescriber identifiers allows to link pharmaceutical data to information on patients and GPs (e.g. age, sex, number of patients) stored in separate databases. These more extensive data on patients and prescribers are necessary to analyze drug utilization patterns and assessing the appropriateness of drug use and prescribing.

4.1.3 Data collection and preparation

For each LHUs involved, drug dispensing data regarding patients included in the study population were collected for a three-year period, between 01/01/2014 and 12/31/2016. In the **Box 4.2** the query for data extraction is reported in Italian language, as reported in the original agreement; the query was defined and shared with the LHUs' coordinators. Once the data were collected, they entered the "pre-processing" stage, at which raw data were cleaned up and organized for the following stage of data processing. During preparation, raw data were diligently checked for any errors. In details, the data management comprised missing values identification, duplicate records removal, errors detection and correction, unused or irrelevant information discarding. Additionally, for each drug prescription record, the number of days covered by prescribed therapy was estimated merging with a database specifically developed starting from the Tunnel

software by Farmadati. It includes the Defined Daily Dose (DDD) (**Box 4.3**) for every ATC code of single and in combination drugs available on the Italian market and reimbursed by Italian NHS; therefore, the number of days' supply was calculated as the active substance quantity dispensed divided by the DDD.

Box 4.2 – Query for extracting data for the EDU.RE.DRUG project

- Dall'anagrafe medici dicembre 2016 si selezionano i medici attivi. Si crea così la coorte dei medici che verrà anonimizzata nel campo codice regionale.

  Variabili estratte: codice medico anonimizzato, età, sesso, distretto di appartenenza, carico assistiti.

- Dall'anagrafe assistiti dicembre 2016, si crea la coorte dei pazienti attivi (con almeno una prescrizione) con data di nascita ≤ 31/12/1976 che hanno come medico uno di quelli della coorte precedentemente selezionata.

  Variabili estratte: codice anonimizzato paziente, sesso, data di nascita, codice medico anonimizzato.

- Dal Data Warehouse della regione, si estraggono le prescrizioni della coorte dei pazienti relative alla farmaceutica.

  Variabili estratte: codice anonimizzato paziente, data di prescrizione, data di spedizione (quella su cui si farà il filtro delle date 2014-2016), ATC, AIC, descrizione specialità, pezzi, codice medico prescrittore anonimizzato (sarà presente quello dei medici della coorte, di altri medici oppure nullo quando non valorizzato).

Box 4.3 – Defined Daily Dose (DDD) definition *[WHOCC website]*

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. Therapeutic doses for individual patients and patient groups will often differ from the DDD as they will be based on individual characteristics (such as age, weight, ethnic differences, type and severity of disease) and pharmacokinetic considerations. Only one DDD is assigned per ATC code and route of administration (e.g. oral formulation). The DDD is nearly always a compromise based on a review of available information including doses used in various countries when this information is available. The DDD is sometimes a "dose" that is rarely if ever prescribed, because it might be an average of two or more commonly used doses. Drug utilization data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use. DDDs provide a fixed unit of measurement independent of price, currencies, package size and strength enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups.

Furthermore, each pharmacy dataset was organized with the same structure and the same variables. Finally, pharmaceutical databases were matched with demographic data of each patient and relative GP through record linkage procedures. Data linkage used in this project was deterministic, as it combined different datasets by single and stable identifiers (ID code of each patient and GP), achieving exact matches and perfect linking (**Figure 4.2**).

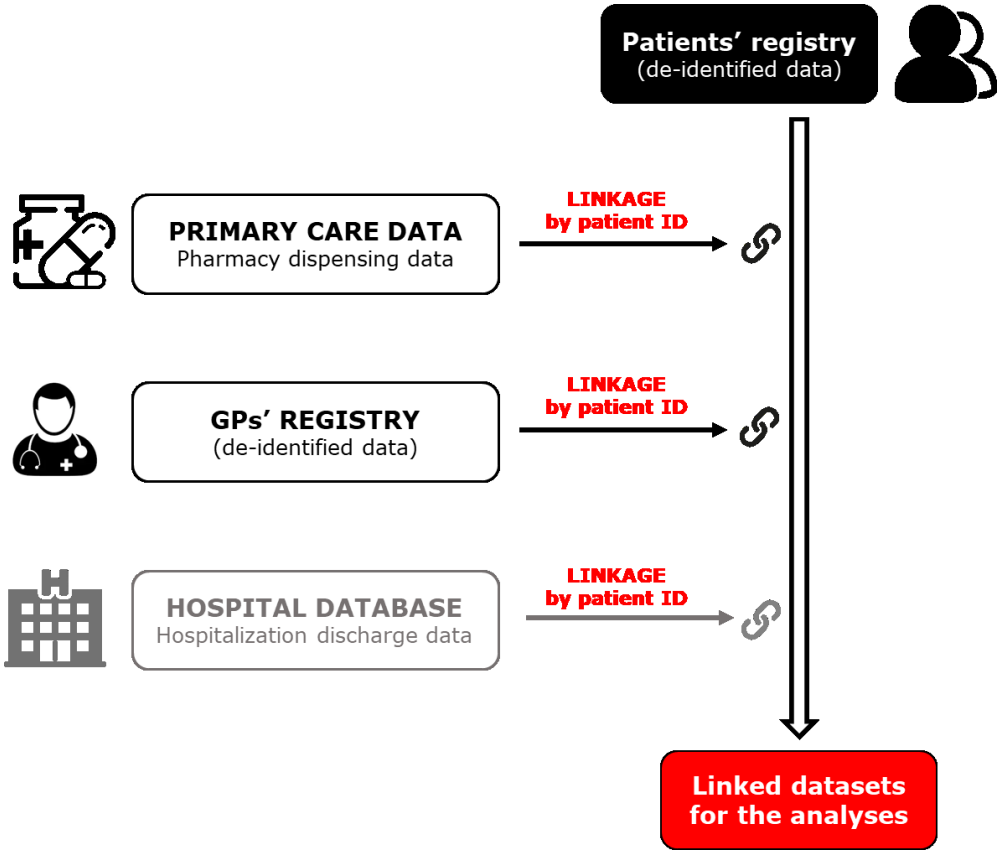


Figure 4.2 – Record linkage procedure

Importantly, record linkage facilitates more elaborate studies, which can generate knowledge about explanatory factors underlying observed drug use patterns, identify patient and prescriber characteristics that determine drug use and evaluate the benefits and adverse effects of drug use in clinical practice, as well as related economic consequences.

The number of records for each dataset, arranged and ready for the analyses, are reported in **Table 4.3**.

Table 4.3 – Number of prescriptions per year for the LHUs involved in the EDU.RE.DRUG project

Region	LHU	N. of prescriptions in 2014	N. of prescriptions in 2015	N. of prescriptions in 2016
Lombardy	Bergamo	7,151,126	6,973,259	7,023,774
	Brianza (Lecco area)	1,939,096	2,005,800	2,168,987
	Brianza (Monza Brianza area)	4,961,097	5,051,594	5,395,832
	Val Padana (Mantova area)	3,346,692	3,245,871	3,213,563
Campania	Avellino	4,262,365	4,541,996	4,528,166
	Caserta	9,487,371	9,699,224	10,030,833
	Napoli 1 Centro	9,287,737	10,554,317	11,697,540
	Napoli 2 Nord	7,985,602	9,969,854	10,791,272

All analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA) and SAS software (version 9.4; SAS Institute, Cary, NC, USA).

4.2 DATA ANALYSIS

4.2.1 Selection of Drug Consumption Indicators

For the evaluation of prescribing practice, prevalence of polytherapy was evaluated as percentage of patients with 1-4 drugs, 5-9 drugs, and ≥10 drugs during 1-year period, for each year considered (2014-2016). In details, the number of drugs in each quarter was calculated, and the highest number of drugs dispensed in a single quarter was used to define polytherapy over the 1-year period *[Onder et al, 2014]*.

Moreover, we selected some of the most commonly used drug classes (ACE-inhibitors [C09AA, C09B], angiotensin receptor blockers [C09CA, C09D], anti-asthmatics [R03], antibiotics [J01], proton pump inhibitors [A02BC, A02BD], selective serotonin reuptake inhibitors [N06AB],

serotonin-norepinephrine reuptake inhibitor [N06AX], and statins [C10AA]) to be described as percentage of patients on each treatment and as amount of DDD prescribed per 1000 inhabitants/die (DID).

4.2.2 Selection of Appropriateness Prescribing Indicators

An intensive searching and screening activity in literature was performed regarding indicators of appropriate prescribing in adult and older population which could be applied to the EDU.RE.DRUG population and evaluated using available data.
After reviewing the scientific literature on the topic, a set of indicators was identified, that had to:

- be explicit indicators, that require each prescription to be compared with a set of pre-defined standards, within the context of the individual patient;
- be applicable and valid regardless of the patient's clinical characteristics;
- refer only to drugs available on Italian market and reimbursed by Italian NHS (which are therefore traced into administrative databases).

Afterwards, the following indicators were identified:

- **Potential drug-drug interactions (pDDIs).** We analysed dispensing data to assess the annual prevalence of prescriptions of pDDI through *MediRisk software*, developed by Medilogy group, based on INXBASE by Medbase, a Finnish company formed by experts in pharmacotherapy, which produces medical decision support databases to safeguard effective and safe use of drugs. INXBASE is a drug-drug interaction database containing short, and concise evidence-based information concerning consequences of and recommendations for over 20.000 drug interactions *[Inxbase website]*. DDIs are classified according to clinical significance (A-D, from minor [A] to contraindicated or very serious drug-drug interaction [D]) and documentation level (0-4, where 0

corresponding to evidence from *in vitro* studies and 4 documentations from randomized clinical trial, systematic review, or meta-analysis).

In this project, two drugs included in the DDI database were considered potentially interacting if their coverage periods (calculated since dispensation date and based on DDDs) overlapped of at least 1 day. Only pDDIs with clinical significance C, excluded those with a level of documentation of 0, and D were considered for this analysis.

- **Therapeutic Duplicates (TD).** We assessed the annual prevalence of TD, that occurs when two or more drugs from the same chemical subgroup (same ATC code at the fourth level but different ATC code at the fifth level) are prescribed with at most 3 days between their dispensation dates.

  The prevalence of TD, as well as of pDDI, was calculated for each LHU as the proportion of patients over 40 years with any occurrence of TD (or pDDI) relative to the total number of citizens aged 40 years or over.

- **Inappropriate prescriptions in the elderly.** Only for the elderly population (aged ≥65 years), we defined the ERD-list (**E**DU.**R**E.**D**RUG list) developed based on the updated Beers criteria, the STOPP&START criteria and the EU(7)-PIM list. The three lists were merged and adapted to Italian NHS. We considered only the list of drugs that should generally be avoided in the elderly because drugs considered inappropriate in older people with specific medical conditions cannot be assessed using the LHU outpatient pharmacy data because the data do not include information regarding indications for use. Several drugs were excluded because they have never been marketed in Italy (such as desiccated thyroid) or they are no longer available (such as

barbiturates except phenobarbital). In addition, drugs not reimbursed by the 2016 Italian National Formulary were not included in the list, because they could not be assessed by the analysis of the LHU outpatient pharmacy data.
A total of 80 potentially inappropriate medications in subjects aged 65 years or older were included in the ERD-list (**Table 4.4**). We defined prescription of potentially inappropriate medication (PIM) as having a prescription claim for at least one of the drugs in the ERD-list and we estimated annual rates of prevalence of the overall PIM prescription rate in the elderly for each LHU.

- **Anticholinergic Cognitive Burden (ACB) Score**. The indicators of appropriate prescribing in elderly comprised also high score (≥3) of the Anticholinergic Cognitive Burden scale (see paragraph 1.2.6.4). Drugs available on the Italian market and reimbursed by Italian NHS, which are included in the list, are reported in **Table 4.5.** A total ACB score for each participant was calculated by adding the individual scores of different medications in a patient's regimen. Patients with ACB score equal or greater than 3 have increased risk of cognitive impairment compared with non-users of anticholinergics *[Boustani et al, 2008]*.

- **Sedative Load (SL) Score**. We also evaluated the Sedative Load in the elderly (see paragraph 1.2.6.5), applying the published lists *[Linjakumpu et al, 2003]*, again selecting only drugs available on the Italian market and reimbursed by Italian NHS (**Table 4.6**). For each patient, scores of all the medications received are summed to determine a total patient score (SL score). Patients with SL score equal or greater than 3 are recorded as inappropriate occurrence.

  The annual prevalence of ACB and SL occurrence was calculated in the elderly for each LHU.

Table 4.4 – The ERD-list

ATC code	Drug Name	Reason for PIM
A02BC01	Omeprazole (PPI>8 weeks)	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication
A02BC02	Pantoprazole (PPI>8 weeks)	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication
A02BC03	Lansoprazole (PPI>8 weeks)	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication
A02BC04	Rabeprazole (PPI>8 weeks)	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication
A02BC05	Esomeprazole (PPI>8 weeks)	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication
A10AB01	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10AB04	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10AB05	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10AB06	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10BB01	Glibenclamide	Risk of protracted hypoglycemia
A10BB07	Glipizide	Risk of protracted hypoglycemia

A10BB12	Glimepiride	Risk of protracted hypoglycemia
A10BD02	Glibenclamide	Risk of protracted hypoglycemia
A10BD05	Pioglitazone	Age-related risks include bladder cancer, fractures and heart failure. Use for more than one year has been associated with an increased risk of bladder cancer. May increase the incidence of fractures of the upper arms, hands and feet in female diabetics (compared to other oral antidiabetic agents). Can cause fluid retention in older adults, which may exacerbate or precipitate heart failure
A10BD06	Glimepiride/pioglitazone	Risk of protracted hypoglycemia/see pioglitazone
A10BD09	Pioglitazone	Age-related risks include bladder cancer, fractures and heart failure. Use for more than one year has been associated with an increased risk of bladder cancer. May increase the incidence of fractures of the upper arms, hands and feet in female diabetics (compared to other oral antidiabetic agents). Can cause fluid retention in older adults, which may exacerbate or precipitate heart failure
A10BF01	Acarbose	No proven efficacy
A10BG03	Pioglitazone	Age-related risks include bladder cancer, fractures and heart failure. Use for more than one year has been associated with an increased risk of bladder cancer. May increase the incidence of fractures of the upper arms, hands and feet in female diabetics (compared to other oral antidiabetic agents). Can cause fluid retention in older adults, which may exacerbate or precipitate heart failure
B01AA07	Acenocoumarol	Risk of bleeding, especially in people with difficult control of INR value
B01AC05	Ticlopidine	Risk of altered blood counts

B01AC56	Esomeprazole (PPI>8 weeks)	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication
C01AA08	Metildigoxin	Elevated glycoside sensitivity in older adults (women>men); risk of intoxication
C01BA03	Disopyramide	Potent negative inotrope; anticholinergic side effects; may induce heart failure; may cause sudden cardiac death. Data suggest that for most older adults' rate control yields better balance of benefits and harms than rhythm control
C01BC03	Propafenone	High risk of drug interactions. Data suggest that for most older adults' rate control yields better balance of benefits and harms than rhythm control
C01BC04	Flecainide	Higher rate of adverse effects, especially in older adults. Data suggest that for most older adults' rate control yields better balance of benefits and harms than rhythm control
C02AB01	Methyldopa	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)
C02AC05	Moxonidine	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)
C08CA05	Nifedipine	Increased risk of hypotension; myocardial infarction; increased mortality
G02CB03	Cabergoline	CNS side effects
G03AA09	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women

G03AA10	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03AB06	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03BA03	Testosterone	Potential for cardiac problems
G03CA01	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CA03	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CA04	Estriol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CA09	Promestriene	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CX01	Tibolone	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA01	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA11	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA14	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women

G03FA17	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB05	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB08	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB09	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB12	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
H01BA02	Desmopressin	High risk of hyponatremia
L02AB01	Megestrol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
M01AB01	Indometacin	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; risk of CNS disturbances
M01AB05	Diclofenac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AB15	Ketorolac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal
M01AB16	Aceclofenac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AC01	Piroxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal

M01AC05	Lornoxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AC06	Meloxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal
M01AE03	Ketoprofen	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal
M01AE09	Flurbiprofen	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AX01	Nabumetone	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
N02AD01	Pentazocine	Risk of delirium and agitation
N02AX02	Tramadol	More adverse effects in older adults; CNS side effects such as confusion, vertigo and nausea
N03AA02	Phenobarbital	Risk of sedation, paradoxical excitation High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages
N03AB02	Phenytoin	Narrow therapeutic window; increased risk of toxicity in older adults (e.g. CNS and hematologic toxicity)
N03AE01	Clonazepam	Risk of falls, paradoxical reactions
N03AX11	Topiramate	Risk of cognitive-related dysfunction (e.g., confusion, psychomotor slowing)
N04AA01	Trihexyphenidyl	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia
N04AA02	Biperiden	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia

N04AB02	Orphenadrine	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia
N04BC01	Bromocriptine	Risk of CNS side effects
N05AC01	Propericiazine	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia
N06AA02	Imipramine	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling
N06AA04	Clomipramine	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling
N06AA06	Trimipramine	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling
N06AA09	Amitriptyline	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling

N06AA10	Nortriptyline	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling
N06AB03	Fluoxetine	CNS side effects (nausea, insomnia, dizziness, confusion); hyponatremia
N06AB05	Paroxetine	Higher risk of all-cause mortality, higher risk of seizures, falls and fractures. Anticholinergic adverse effects
N06AB08	Fluvoxamine	Higher risk of all-cause mortality, self-harm, falls, fractures and hyponatraemia
N06BA04	Methylphenidat	May cause or worsen insomnia; concern due to CNS-altering effects; concern due to appetite-supressing effects
R06AD02	Promethazine	Anticholinergic side effects (e.g. confusion, sedation)

CNS: central nervous system; GI: gastrointestinal; INR: international normalized ratio; PPI: proton pump inhibitors.

Table 4.5 - List of drugs for ACB score

ATC code	Drug Name	Score
A02BA01	Cimetidine	1
A02BA02	Ranitidine	1
A03AA07	Dicyclomine (Dicycloverine)	3
A03AX08	Alverine	1
A03BA01	Atropine	3
A03BA03	Hyoscyamine	3
A03BA04	Belladonna	2
A03CA02	Clidinium	1
A03CA34	Propantheline	3
A04AB02	Dimenhydrinate	3
A04AD01	Scopolamine	3
A07DA03	Loperamide	1
B01AA03	Warfarin	1
B01AC07	Dipyridamole	1
B01AC30	Dipyridamole	1
C01AA05	Digoxin	1
C01BA01	Quinidine	1
C01BA03	Disopyramide	1
C01DA14	Isosorbide	1
C02DB02	Hydralazine	1
C03BA04	Chlorthalidone	1
C03CA01	Furosemide	1
C03EB01	Furosemide/Triamterene	2
C03DB02	Triamterene	1
C07AB02	Metoprolol	1
C07AB03	Atenolol	1
C07CA02	Chlorthalidone	1
C07CB02	Chlorthalidone/Metoprolol	2
C07CB03	Chlorthalidone/Atenolol	2
C08CA05	Nifedipine	1
C09AA01	Captopril	1
C09BA01	Captopril	1
D07AB02	Hydrocortisone	1
G04BD02	Flavoxate	3
G04BD04	Oxybutynin	3
G04BD06	Propiverine	3
G04BD07	Tolterodine	3
G04BD08	Solifenacin	3
G04BD09	Trospium	3
G04BD10	Darifenacin	3

ATC code	Drug Name	Score
G04BD11	Fesoterodine	3
H02AB07	Prednisone	1
M03BA03	Methocarbamol	3
M03BC01	Orphenadrine	3
N04AB02	Orphenadrine	3
M03BX07	Colchicine	1
M04AC01	Colchicine	1
M03BX08	Cyclobenzaprine	2
N02AA01	Morphine	1
N02AB02	Meperidine	2
N02AB03	Fentanyl	1
N02AG01	Atropine/Morphine	3
N02AJ06	Codeine	1
N02BG06	Nefopam	2
N03AF01	Carbamazepine	2
N03AF02	Oxcarbazepine	2
N04AA01	Trihexyphenidyl	3
N04AC01	Benztropine	3
N04BB01	Amantadine	2
N05AA01	Chlorpromazine	3
N05AA02	Methotrimeprazine (Levomepromazine)	2
N05AB03	Perphenazine	3
N05AB06	Trifluoperazine	3
N05AC02	Thioridazine	3
N05AD01	Haloperidol	1
N05AE02	Molindone	2
N05AG02	Pimozide	2
N05AH01	Loxapine	2
N05AH02	Clozapine	3
N05AH03	Olanzapine	3
N05AH04	Quetiapine	3
N05AH05	Asenapine	1
N05AX08	Risperidone	1
N05AX12	Aripiprazole	1
N05AX13	Paliperidone	1
N05AX14	Iloperidone	1
N05BA01	Diazepam	1
N05BA05	Clorazepate	1
N05BA12	Alprazolam	1
N05BB01	Hydroxyzine	3
N06AA01	Desipramine	3
N06AA02	Imipramine	3

ATC code	Drug Name	Score
N06AA04	Clomipramine	3
N06AA06	Trimipramine	3
N06AA09	Amitriptyline	3
N06AA10	Nortriptyline	3
N06AA12	Doxepin	3
N06AA17	Amoxapine	3
N06AB05	Paroxetine	3
N06AB08	Fluvoxamine	1
N06AX05	Trazodone	1
N06AX12	Bupropion	1
N06AX16	Venlafaxine	1
R03DA04	Theophylline	1
R05DA04	Codeine	1
R05DA20	Codeine	1
R06AA02	Diphenhydramine	3
R06AA04	Clemastine	3
R06AA08	Carbinoxamine	3
R06AA09	Doxylamine	3
R06AB01	Brompheniramine	3
R06AB04	Chlorpheniramine	3
R06AD01	Alimemazine	1
R06AD02	Promethazine	3
R06AE05	Meclizine	3
R06AE07	Cetirizine	1
R06AE09	Levocetirizine	1
R06AX02	Cyproheptadine	2
R06AX13	Loratadine	1
R06AX27	Desloratadine	1

Table 4.6 - List of drugs for SL score

ATC code	Drug Name	Score
A03CA02	Chlordiazepoxide with klidin	1
A03CA05	Diazepam with glycopyrronium	1
A03CA07	Oxazepam with ambutonium	1
A03FA01	Metoclopramide	1
A04AD01	Scopolamine	1
G04BE30	Meprobamate with testosterone and yohimbine	1
M01AB51	Indometacin with ethylmorphine	1
M01AE51	Ibuprofen with codeine	1
N02AA01	Morphine	1
N02AA05	Oxycodone	1
N02AA55	Oxycodone	1
N02AB03	Fentanyl	1
N02AE01	Buprenorphine	1
N02AG01	Morphine	1
N02AJ17	Oxycodone	1
N02AJ06	Codeine	1
N02AX02	Tramadol	1
N02BA51	Metoclopramide with ASA	1
N02CC	Triptans	1
N03AB	Hydantoin derivatives	1
N03AF	Carbamazepine and derivatives	1
N03AG01	Valproic acid	1
N03AX12	Gabapentin biperiden	1
N05A	Traditional antipsycotics	2
N05AD	Butyrophenones	2
N05AF	Thioxanthenes	2
N05AH02	Clozapine	1
N05AH03	Olanzapine	1
N05AH04	Quetiapine	1
N05AL01	Sulpiride	2
N05AN01	Lithium	2
N05AX08	Risperidone	1
N05B	Anxiolytics	2
N05BA01	Diazepam with kinin, orphenadrine, baclofen, tizanidine	1
N05BB01	Hydroxyzine	2
N05BC51	Meprobamate with kinin, orphenadrine, baclofen, tizanidine	1
N05CX01	Meprobamate with kinin, orphenadrine, baclofen, tizanidine	1
N05C	Hypnotics and sedatives	2
N05CF01	Zopiclone	2
N05CF02	Zolpidem	2

ATC code	Drug Name	Score
N05CF03	Zaleplon	2
N05CM02	Clometiazole	2
N05CM09	Valerian	2
N05CX01	Meprobamate with ergot alcaloid	1
N06AA04	Clomipramine	2
N06AA06	Trimipramine	2
N06AA09	Amitriptyline	2
N06AA10	Nortriptyline	2
N06AA12	Doxepin	2
N06AB03	Fluoxetine	1
N06AB04	Citalopram	1
N06AB05	Paroxetine	1
N06AB06	Sertraline	1
N06AB08	Fluvoxamine	1
N06AX03	Mianserin	2
N06AX05	Trazodone	1
N06AX06	Nefazodone	1
N06AX11	Mirtazapine	1
N06AX16	Venlafaxine	1
N06AX17	Milnacipran	1
N06CA01	Amitriptyline + chlordiazepoxide	2
N06CA01	Amitriptyline + perphenazine	2
R03DA74	Theophylline	1
R03DA04	Theophylline, combinations	1
R05CB02	Bromhexine	1
R05DA01	Ethylmorphine	1
R05DA04	Codeine	1
R05DA20	Codeine	1
R06AE05	Meclozine	1
R06AE53	Cyclizine (with diazepam)	1
S01FA02	Scopolamine	1

4.2.3 Selection of Appropriate Drug Use Indicators

Among indicators of appropriate drug use, adherence to chronic treatments is one of the most utilized, because it is a primary determinant of the effectiveness of therapy.

Prescription and dispensing administrative data can be used to assess adherence to treatment, defined as the extent to which a patient's behavior (e.g. taking medications with respect to timing, dosage, and frequency) corresponds with agreed recommendations from a health-care provider.

In administrative claims data, adherence is most often assessed through measures such as the proportion of days covered (PDC) or medication possession ratio (MPR), which are the most common measures of medication adherence using refill records. Briefly, PDC is defined as the number of days covered by medication divided by the total number of days in follow-up, while MPR is the sum of the days' supply (daily doses) for all fills of a given drug during follow-up divided by the number of days of follow-up (**Box 4.4**) *[Steiner et al, 1997; Clancy, 2013]*.

For each prescription, the coverage is calculated as total amount of drug divided by the specific DDD.

Despite the fact that both MPR and PDC are sufficient at measuring medication adherence, the PDC ratio provides a more accurate representation of medication adherence because it eliminates the possibility of being unreasonably elevated. In fact, the MPR can be difficult to be interpreted since this index can assume values greater than one.

Basically, the difference between the two methods lies in the days count for overlapping prescriptions: the overlapping days are count once for PDC while are equal to the number of overlapping drug doses for MPR. Furthermore, PDC is recommended for assessing the medication adherence of patients on multiple therapies at the same time, and in addition, it is the preferred method for assessing adherence by the Pharmacy Quality Alliance (PQA) for use in Medicare Star Ratings and also by the US Centers for Medicare and Medicaid Services.

Box 4.4 – Adherence Measurements

Two measures of medication adherence are currently utilized in the widely available research assessing the adherence to prescriptions. The primary measures of medication adherence, PDC (proportion of days covered) and MPR (medication possession ratio), can easily be calculated with the extraction of retail pharmacy data.

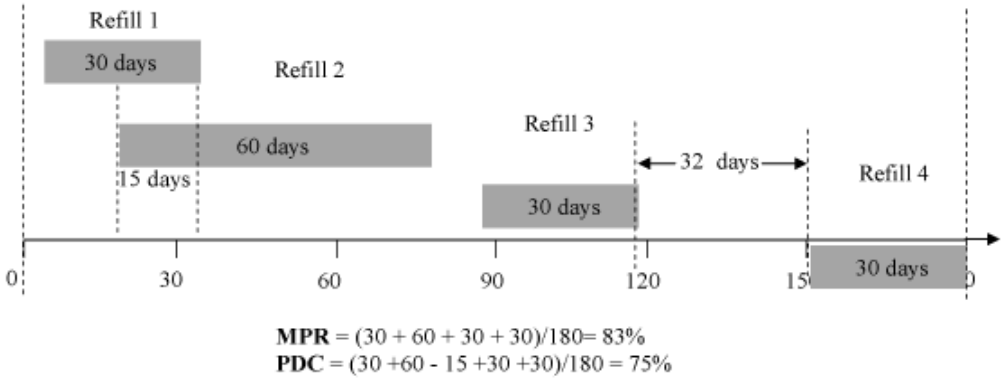
MPR is the sum of the days' supply for all fills of a given drug in a particular time period, divided by the number of days in the time period:

$$\text{MPR} = \left(\frac{\sum days' supply\ for\ all\ fills\ in\ period}{\sum days\ in\ period}\right) * 100\%$$

For the PDC the formula is similar to MPR, but instead of simply adding the days' supplied in a given period, the PDC considers the days that are "covered":

$$\text{PDC} = \left(\frac{\sum days\ in\ period\ "covered"}{\sum days\ in\ period}\right) * 100\%$$

An example of medication adherence calculation with MPR and PDC is depicted below.



On this basis, within the EDU.RE.DRUG project, adherence was measured through the PDC calculation.

For each year considered (2014, 2015, and 2016), we assessed medication adherence rate for the following chronic therapies [ATC]:

- antidiabetics [A10B]
- anti-hypertensive drugs [C02, C03, C07, C08, C09]
- lipid-lowering drugs [C10A]
- anti-osteoporosis drug [M05B]

PDC ranges from 0 to 1, with 1 corresponding to 100% medication adherence.

For each LHUs involved, adherence to the specific medication was assessed following two approaches:

- for each year, all patients with at least one prescription of the drug of interest during the year were selected and adherence was calculated as the number of days covered by medication divided by 365. This approach does not take into account the possibility that the beginning of the therapy for a patient may have occurred during the year of observation, nor include drug available from prescriptions dispensed at the end of the previous year. However, this approach provides a crude estimate for each year that allows to evaluate adherence trend over time and to make a comparison between LHUs.
- adherence was calculated by selecting all patients with a first prescription for the medication of interest between January 1, 2015 and December 31, 2015. Patients were required not to have prior prescription of that drug in the year before the index date (defined as the date of the first prescription fill in the period for the selected therapy), to select only incident users. Patients were also required to have 1 year of enrolment after the index date to allow complete adherence evaluation at 1-year of follow-up. Adherence was calculated as mentioned above for the first approach. Notably, we limited this second phase of analysis to incident users in an attempt to limit the influence of confounding factors, as the inclusion of prevalent users, more tolerant to the medication, may bias the result. This approach also allowed to select a sample of patients with comparable treatment timing and to avoid the heterogeneity due to the fact that prevalent users may be characterized by a progressive reduction of medication adherence over time.

4.3 THE INTERVENTION

The EDU.RE.DRUG project has a parallel-arm design.

According to LHUs, the GPs and their patients were assigned to one of the following four intervention arms (**Figure 4.3**):

- A: intervention on GPs and patients (LHUs of Napoli 2 Nord and Brianza-Lecco area);
- B: intervention on GPs (LHUs of Napoli 1 Centro and Bergamo);
- C: intervention on patients (LHUs of Avellino and Val Padana-Mantova area);
- D: control group (LHUs of Caserta and Brianza-Monza Brianza area).

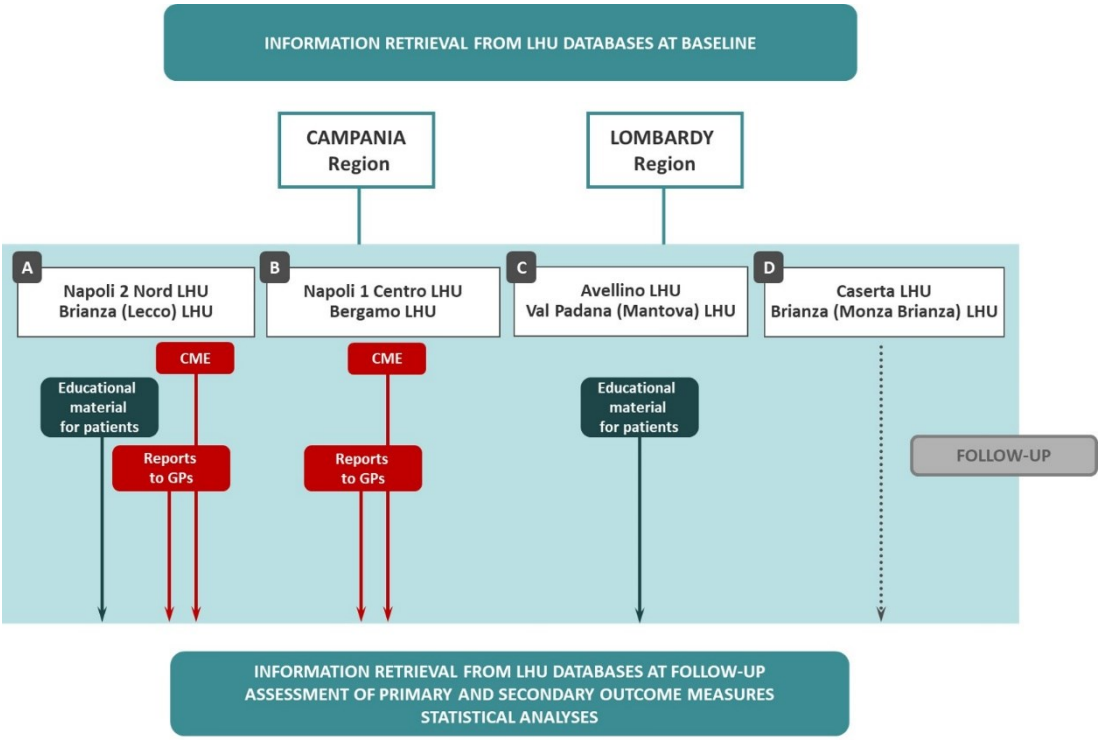


Figure 4.3 – Flow chart of the EDU.RE.DRUG project

The intervention designed for GPs consisted in:

- feedback reports regarding inappropriate prescription status for their patients in comparison to median levels of LHU. Specifically, the report contained the prevalence of each pre-defined indicator of drug consumption and of inappropriate prescribing, evaluated in

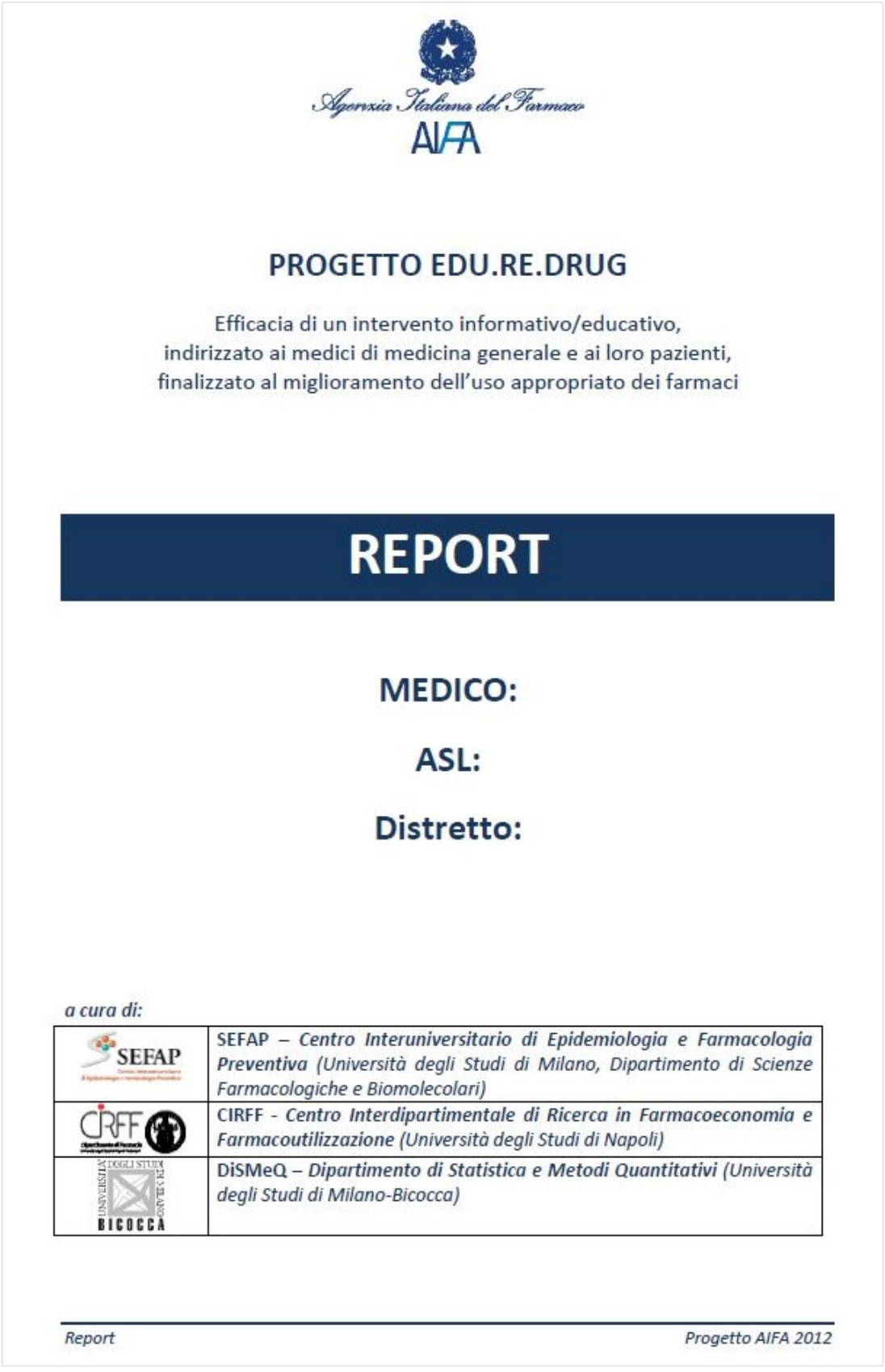
2016 (the report front page can be found in **Figure 4.4;** a full example can be found in the **Appendix I** section). Once arranged, the reports were transferred to the LHUs. After translating anonymous codes, the LHUs sent to each GP the relative report;

- free on-line Continuous Medical Education (CME) course about pharmacotherapy, evidence-based medicine, rational prescribing and indicators of appropriateness, polypathology management, doctor-patient concordance and communication skills, and healthcare continuity from hospital to territory. CME lessons were registered in Italian language and provided by specialists with clinical experience. A full list of the lessons is reported in the **Appendix II** section. The course, which is recognised by the Italian National Agency for Regional Healthcare Services (AGENAS), was worth 18 CME credits. It was structured into two modules (9 CME credits for each module) and uploaded on the FAD platform of the SiTeCS society, as CME provider; according to the protocol, it was available for GPs belonging to LHUs of Napoli 2 Nord, Napoli 1 Centro, Bergamo and Brianza-Lecco area, from November 15, 2017 and June 30, 2018 (**Figure 4.5**). In details, the first part was focused on the presentation of the project and on theoretical aspects concerning the inappropriate prescribing in general practice and the categories of the most vulnerable patients, such as the elderly or poly-treated patients, with the presentation of clinical cases of possible inappropriate prescriptions. The second one concerned the measurement of indicators of appropriateness of prescribing, the guided reading of reports, and recommendations for prescribing to the complex patient and for medication review.

Notably, participation to CME courses was not mandatory, as well as both the course and the reports received at baseline may not necessarily lead to changes in GPs' prescriptive behaviour.

The intervention administered to patients consisted in flyers and posters, focusing on correct drug use, including efficacy/safety of drugs, adherence to GP indications, self-medication. Posters (**Figure 4.6**) and leaflets (**Figure 4.7**) were distributed in GPs' ambulatories and community pharmacies, through Federfarma network, in the LHUs of Napoli 2 Nord, Avellino, Val Padana-Mantova area and Brianza-Lecco area, according to the protocol. The preparation of these materials involved professionals in the topic, in order to communicate educational messages in a language appropriate to the subjects' needs and level of understanding.

At the beginning of the study, the GPs belonging to the LHUs involved in the A and B intervention arms received a presentation letter from their own LHU, with the general description of the project and a formal invitation to sign up for the FAD platform and attend the proposed CME course. Similarly, local pharmacies and general practices in the LHUs involved in the A and C intervention arms received a presentation letter from their own LHU with the general description of the project, including a formal invitation to publicly exhibit and to promote educational material for citizens. Therefore, citizens have not directly received project information from the LHUs or the local coordinator operative units.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SEFAP	SEFAP – *Centro Interuniversitario di Epidemiologia e Farmacologia Preventiva (Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari)*
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Report *Progetto AIFA 2012*

Figure 4.4 – Front page of the feedback report sent to each GP

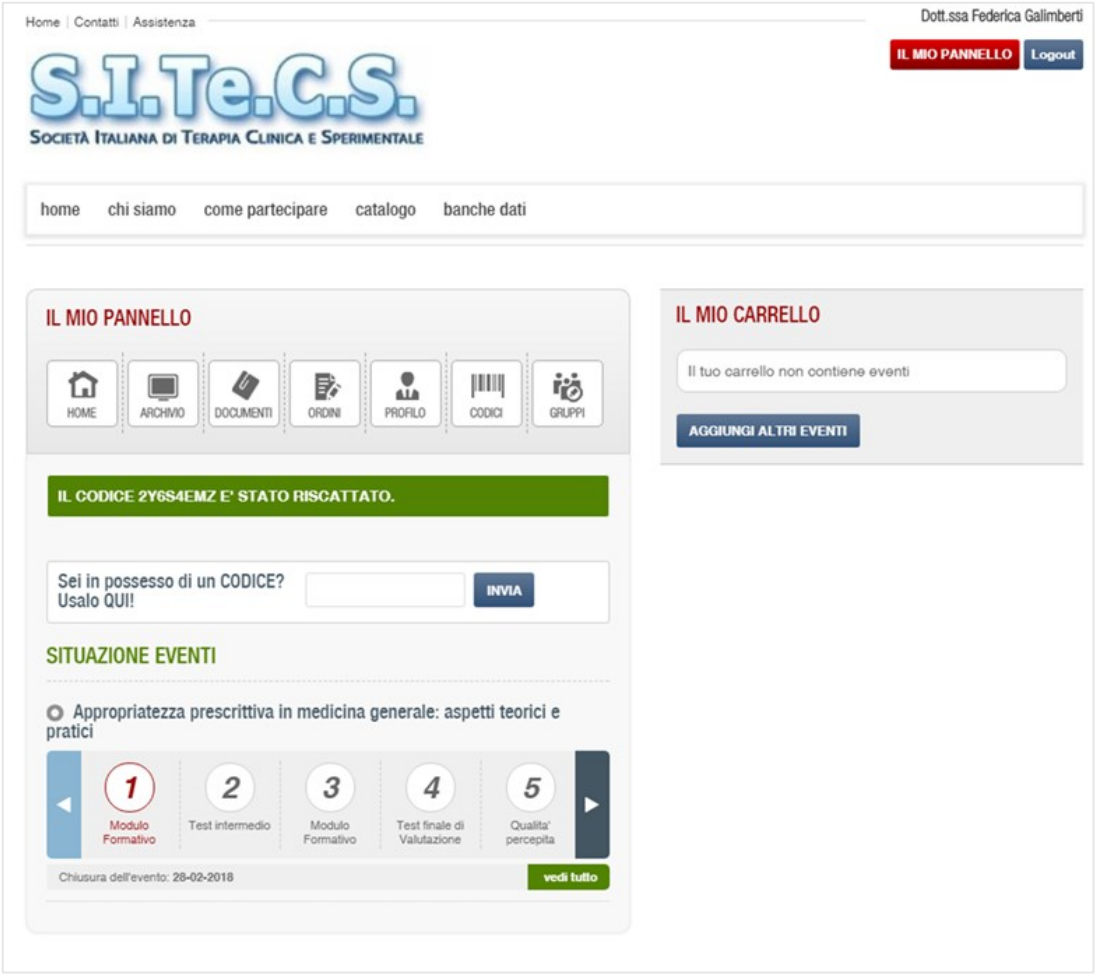


Figure 4.5 – On-line CME course for GPs

Figure 4.6 – Poster (50x70cm) for patients

Figure 4.7 – Front and back side of the flyer for patients

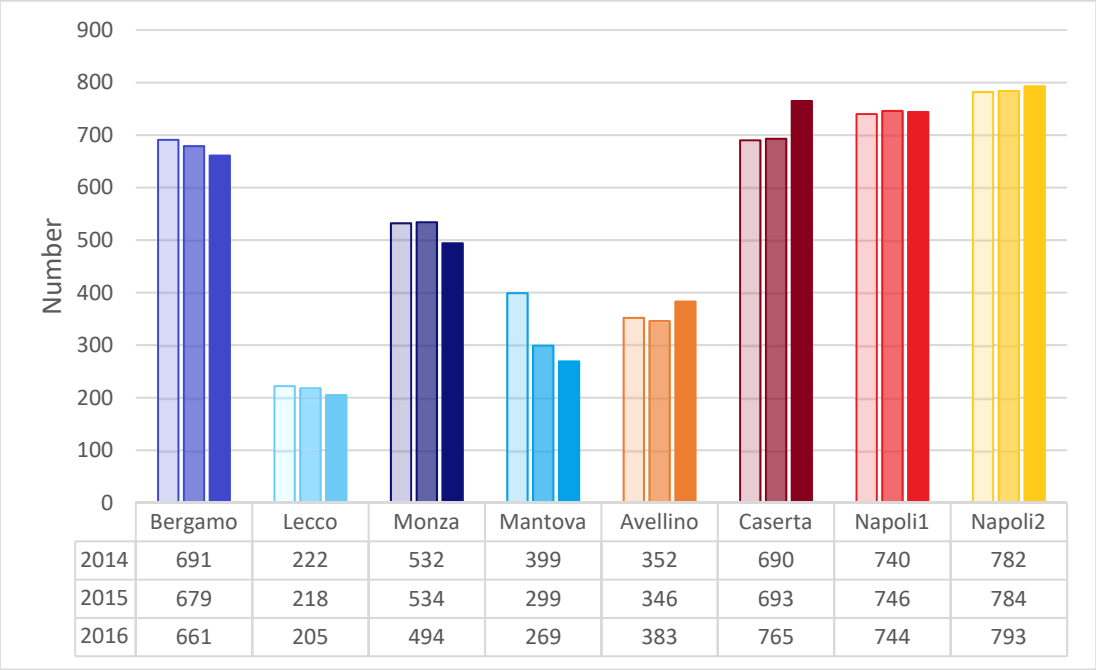
Chapter 5

RESULTS

5.1 DESCRIPTIVE ANALYSES

5.1.1 GPs' cohorts

The number of GPs included in the study is reported in **Figure 5.1**. It slightly increased in Avellino, Caserta, Napoli1 and Napoli2 LHUs, from 2014 to 2016, while there has been a small reduction in GP number for LHUs in Lombardy region (Bergamo LHU, Lecco, Monza Brianza and Mantova areas).



	Bergamo	Lecco	Monza	Mantova	Avellino	Caserta	Napoli1	Napoli2
2014	691	222	532	399	352	690	740	782
2015	679	218	534	299	346	693	746	784
2016	661	205	494	269	383	765	744	793

Figure 5.1 – Number of GPs for each LHU
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

The majority of physicians were males in all the LHUs, even if the portion of females increased in time (**Table 5.1**). In details, Monza Brianza and Bergamo were the LHUs with the highest percentage of women among GPs (over 30%); by contrast the lowest percentages, between 17.5 and 21.2%, were found in Napoli1 and Napoli2 LHUs.

Table 5.1 – Percentage of female GPs in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	31.4	32.1	40.9
	Lecco	27.9	28.0	28.8
	Monza Brianza	35.1	35.8	38.1
	Mantova	26.8	27.1	28.2
Campania	Avellino	23.0	24.0	25.6
	Caserta	22.3	22.7	25.5
	Napoli 1	20.9	21.2	21.0
	Napoli 2	17.5	17.9	18.2

The overall mean age ranged between 57 and 62 years. The GP age trend was growing in time for all the LHUs, except for Monza Brianza and Lecco areas; in the 3-year period analysed, Napoli1 LHU held the oldest GPs cohort, Bergamo LHU the youngest one (**Table 5.2**).

Table 5.2 – Mean age (SD) of GPs in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	56.7 (6.4)	57.2 (6.6)	57.7 (6.9)
	Lecco	58.4 (6.8)	59.1 (7.0)	58.3 (7.0)
	Monza Brianza	58.7 (6.0)	59.3 (6.3)	58.2 (6.5)
	Mantova	59.0 (5.9)	59.4 (6.0)	59.9 (6.2)
Campania	Avellino	59.1 (5.4)	60.1 (5.5)	60.8 (4.9)
	Caserta	59.2 (4.8)	59.8 (5.1)	60.2 (5.6)
	Napoli 1 Centro	58.9 (4.4)	60.7 (4.5)	61.7 (4.5)
	Napoli 2 Nord	58.0 (4.9)	59.0 (4.9)	60.0 (5.0)

Several differences in the median number of assisted individuals per GP were observed. In particular, GPs of LHUs of Bergamo, Lecco, and Monza-Brianza had a median value of about 1,500 registered citizens. The median number for Mantova area was around 1,400, while it ranged between 1,000 and 1,200 for LHUs in Campania (**Table 5.3**).

Several differences in the median number of patients per GP were also observed between LHUs (**Table 5.4** and **Table 5.5**). In each LHU, the median number of patients aged 40-64 years per GP (range 375-423 in

Lombardy and 344-409 in Campania) was higher than the median number of patients aged ≥65 years (range 275-335 in Lombardy and 179-284 in Campania).

Table 5.3 – Median number of citizens per GP in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	1,516	1,516	1,519
	Lecco	1,527	1,532	1,553
	Monza Brianza	1,552	1,557	1,588
	Mantova	1,365	1,366	1,458
Campania	Avellino	1,109	1,186	1,136
	Caserta	1,168	1,236	1,251
	Napoli 1	1,091	1,158	1,243
	Napoli 2	1,107	1,169	1,298

Table 5.4 – Median number of patients per GP aged 40-64 years in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	403	407	405
	Lecco	375	379	397
	Monza Brianza	399	408	423
	Mantova	378	386	394
Campania	Avellino	344	361	357
	Caserta	360	392	401
	Napoli 1	357	365	387
	Napoli 2	396	399	409

Table 5.5 – Median number of patients per GP aged ≥65 years in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	291	301	307
	Lecco	275	305	332
	Monza Brianza	282	303	335
	Mantova	319	318	329
Campania	Avellino	262	280	277
	Caserta	230	243	229
	Napoli 1	218	237	284
	Napoli 2	202	179	203

5.1.2 Assisted citizens' cohorts

The term "LHU population" is used to denote all citizens (of every age and sex) resident in the same LHU and covered by NHS. In other words, it includes all citizens registered with one of the GPs belonging to that LHU.
Number of assisted citizens aged 40-64 years increased over time for all the LHUs, except for Bergamo area, where a decrease from 400,716 to 398,836 was observed (**Table 5.6**). The proportion of this age class on the total population did not show a relevant variation over time, nor between Lombardy and Campania region (**Figure 5.3**).
On the other hand, the number of citizens aged ≥65 years rose in all the LHUs, with a marked increase in the Campania areas (**Table 5.7**). The proportion of this age class was higher for Lombardy LHUs than Campania LHUs, and showed a slight increase in time in Bergamo LHU and Mantova area (**Figure 5.4**).

Table 5.6 – Number of assisted citizens aged 40-64 years in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	400,716	402,602	398,836
	Lecco	121,336	121,935	128,998
	Monza Brianza	313,144	316,329	337,126
	Mantova	151,503	152,589	153,833
Campania	Avellino	133,147	140,425	145,909
	Caserta	272,304	290,617	314,205
	Napoli 1	294,243	315,321	341,684
	Napoli 2	302,833	324,218	359,897

Table 5.7 – Number of assisted citizens aged ≥65 years in 2014-2016

Region	LHU	2014	2015	2016
Lombardy	Bergamo	210,102	213,831	213,996
	Lecco	75,475	77,052	78,498
	Monza Brianza	186,162	189,702	189,806
	Mantova	95,193	95,901	96,865
Campania	Avellino	79,719	84,242	87,586
	Caserta	134,065	143,400	155,243
	Napoli 1	163,058	174,780	189,938
	Napoli 2	124,585	134,962	155,476

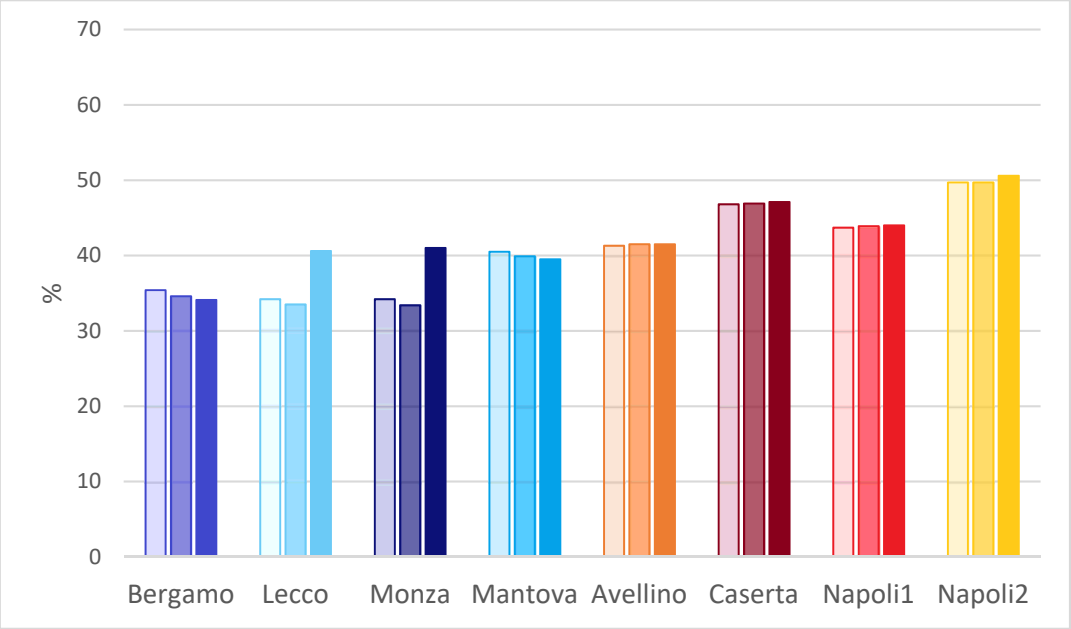


Figure 5.2 – Proportion of citizens aged <40 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

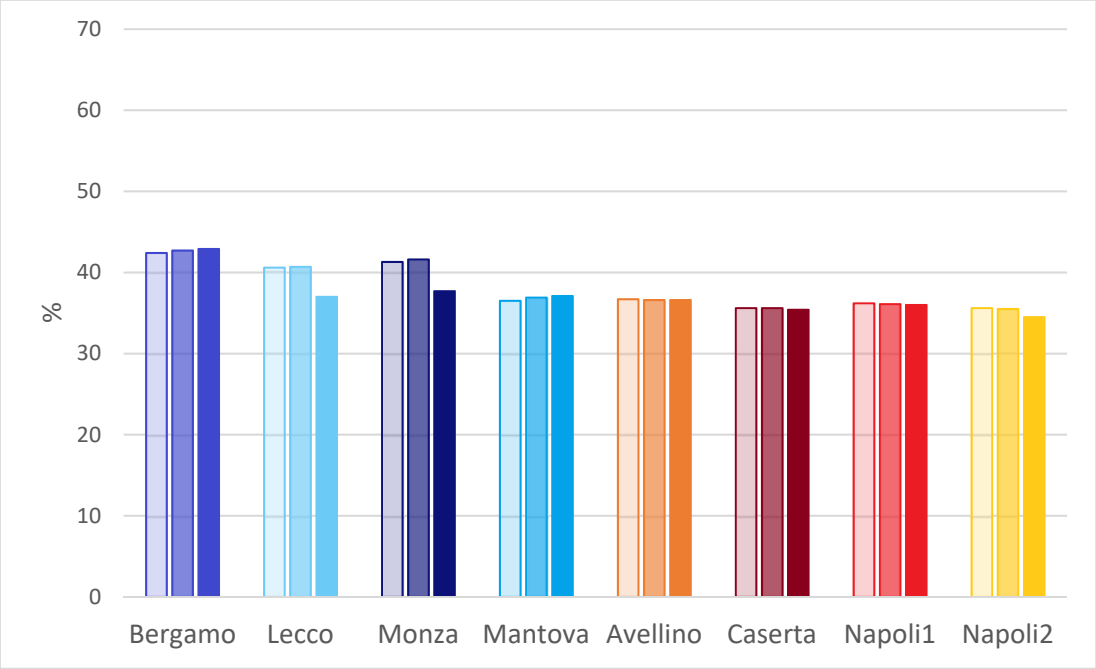


Figure 5.3 – Proportion of citizens aged 40-64 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

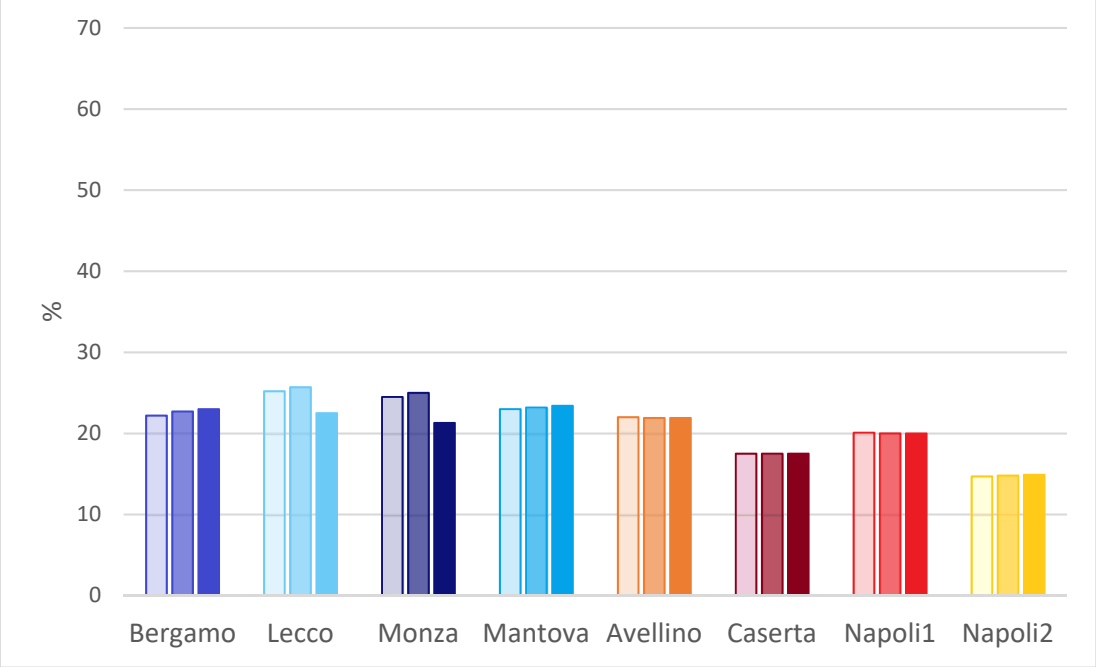


Figure 5.4 – Proportion of citizens aged ≥65 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

5.1.3 Patients' cohorts

The total number of adult patients included in the study, which corresponds to the number of patients aged 40-64 years with at least one prescription in the years considered, is reported in **Table 5.8**. For Bergamo and Mantova LHU there were a slightly decrease in number from 2015 to 2016, whereas an increase in patient number was found in all the other LHUs. The same time trend was observed for older patients (**Table 5.9**).

Table 5.8 – Number of patients aged 40-64 years included in the study

Region	LHU	2014	2015	2016
Lombardy	Bergamo	261,430	262,401	256,470
	Lecco	75,532	76,490	78,040
	Monza Brianza	195,283	199,257	199,963
	Mantova	101,352	101,699	99,278
Campania	Avellino	110,208	111,672	113,325
	Caserta	224,016	241,822	248,054
	Napoli 1	245,283	252,102	266,667
	Napoli 2	275,909	276,365	289,321

Table 5.9 - Number of patients over 65 years of age included in the study

Region	LHU	2014	2015	2016
Lombardy	Bergamo	193,483	196,806	196,633
	Lecco	57,831	61,874	66,577
	Monza Brianza	142,681	152,065	161,641
	Mantova	85,857	86,515	85,229
Campania	Avellino	83,246	87,079	90,754
	Caserta	146,285	153,084	160,737
	Napoli 1	156,793	169,940	200,768
	Napoli 2	152,447	134,970	154,256

The prevalence of patients on assisted citizens aged 40-64 years (**Figure 5.5**) showed a decrease from 2014 to 2016, though remaining always 10-percentage point higher for Campania LHUs. As expected, the prevalence of patients on assisted citizens aged ≥65 was very high in all LHUs.

Notably, these values were around 100% in the Campania areas (**Figure 5.6**).

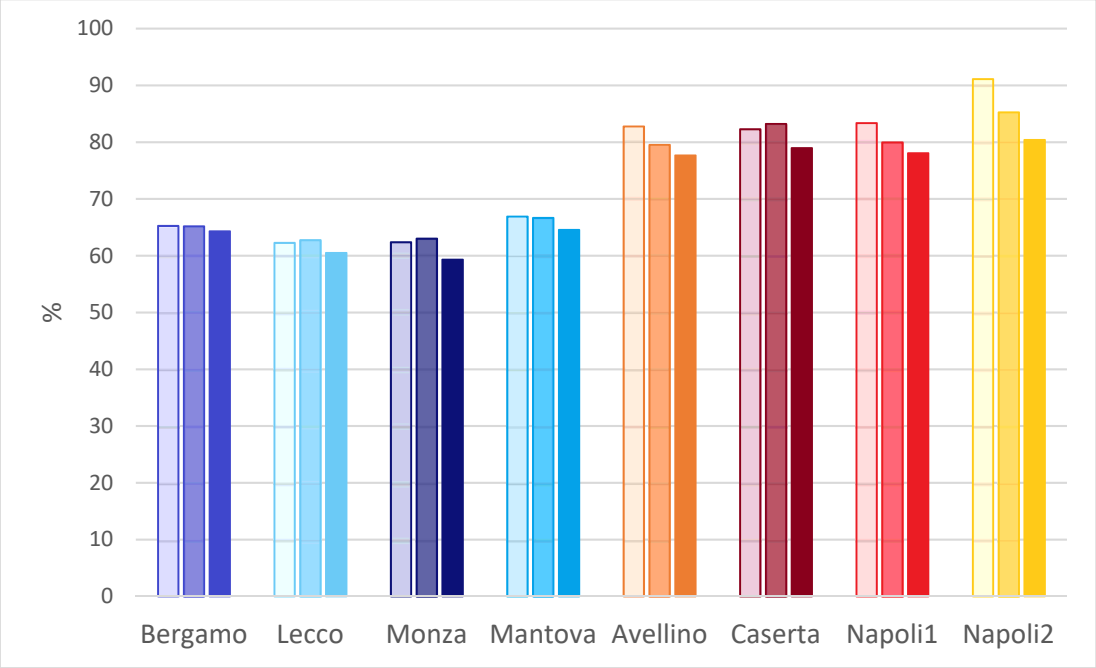


Figure 5.5 – Prevalence of patients on assisted citizens aged 40-64 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

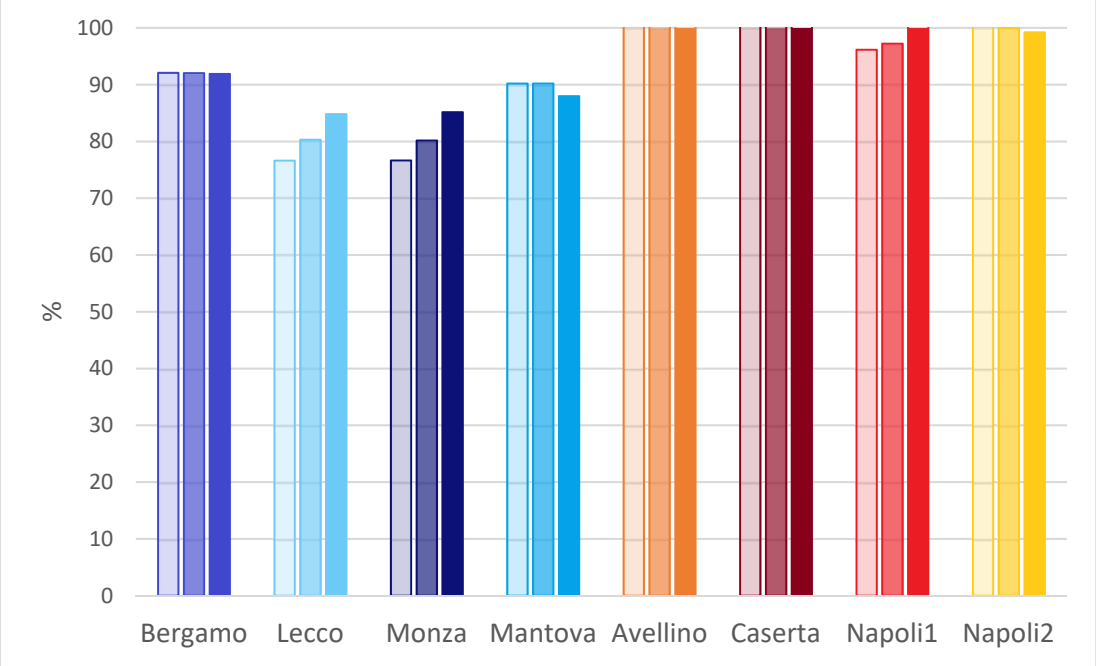


Figure 5.6 – Prevalence of patients on assisted citizens aged ≥65 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

The percentage of female patients was higher than men in all LHUs and was mostly unchanged during the study period, both for patients aged 40-64 and ≥65 years, and even higher in the latter age class than in the former one (**Table 5.10** and **Table 5.11**).

Table 5.10 – Proportion of females in patients of 40-64 years of age

Region	LHU	2014	2015	2016
Lombardy	Bergamo	53.1	53.1	53.2
	Lecco	53.8	53.6	53.4
	Monza Brianza	54.5	54.3	54.1
	Mantova	53.3	53.3	51.8
Campania	Avellino	53.1	53.3	53.1
	Caserta	54.0	54.0	53.7
	Napoli 1	55.8	55.1	55.4
	Napoli 2	54.1	54.1	53.9

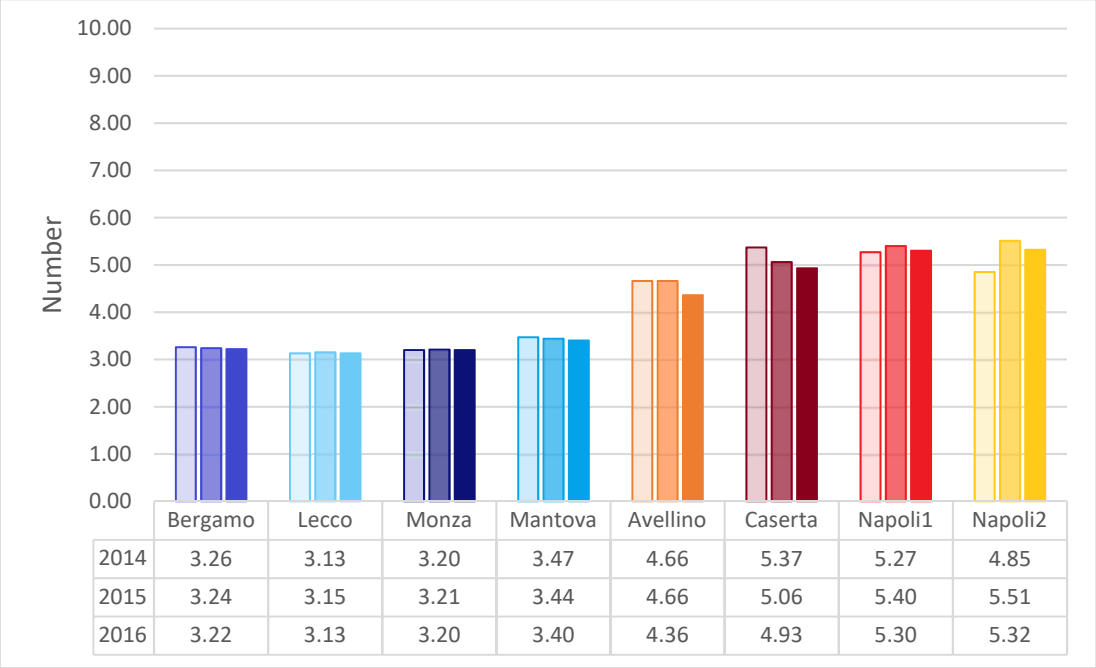
Table 5.11 – Proportion of females in patients over 65 years of age

Region	LHU	2014	2015	2016
Lombardy	Bergamo	56.3	56.1	56.4
	Lecco	57.3	56.8	56.5
	Monza Brianza	57.2	57.0	56.6
	Mantova	57.9	57.6	56.4
Campania	Avellino	56.7	56.6	56.4
	Caserta	57.0	56.8	56.5
	Napoli 1	59.4	58.7	58.3
	Napoli 2	55.6	55.7	55.3

5.2 DRUG CONSUPTION ANALYSES

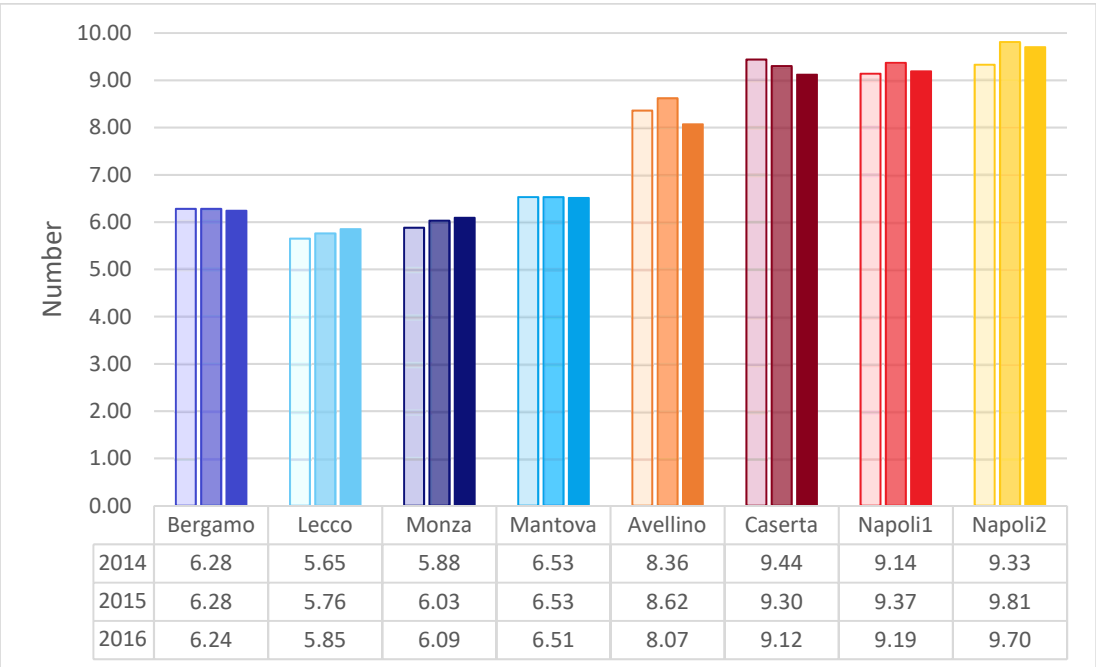
The mean number of drugs prescribed per patient was higher in patients aged ≥65 years, independently by the LHUs. Moreover, for both age classes, the average number of drugs prescribed per patient for Campania LHUs was higher than Lombardy areas: it was about 4-5 and 9 in Campania

compared to about 3 and 6 in Lombardy, respectively for patients aged 40-64 and ≥65 years (**Figure 5.7** and **Figure 5.8**).



	Bergamo	Lecco	Monza	Mantova	Avellino	Caserta	Napoli1	Napoli2
2014	3.26	3.13	3.20	3.47	4.66	5.37	5.27	4.85
2015	3.24	3.15	3.21	3.44	4.66	5.06	5.40	5.51
2016	3.22	3.13	3.20	3.40	4.36	4.93	5.30	5.32

Figure 5.7 – Average number of drugs prescribed per patient aged 40-64 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs



	Bergamo	Lecco	Monza	Mantova	Avellino	Caserta	Napoli1	Napoli2
2014	6.28	5.65	5.88	6.53	8.36	9.44	9.14	9.33
2015	6.28	5.76	6.03	6.53	8.62	9.30	9.37	9.81
2016	6.24	5.85	6.09	6.51	8.07	9.12	9.19	9.70

Figure 5.8 – Average number of drugs prescribed per patient aged ≥65 years
First, second, and third bar represent 2014, 2015, and 2016, respectively, for each LHUs

We estimated also the percentages of patients (over assisted citizens) prescribed polypharmacy (5-9 drugs) or hyperpolypharmacy (≥10 drugs). For the age class between 40 and 64 years (**Table 5.12**), about 8-9% of patients received 5-9 drugs in Lombardy; in Campania this percentage was two times higher (16-20%) along all the period. In addition, in Lombardy, less than 1% of patients belonging to this age class received at least 10 drugs, while the percentage ranged between 2 and 4.5% in Campania.
For the elderly (**Table 5.13**), there were great differences between the two regions: for Campania LHUs, about half of older patients received 5 to 9 drugs compared to one third in Lombardy LHUs. The prevalence of older patients with more than 10 drugs in Campania LHUs turned out to be considerably higher than Lombardy, ranging from 18 to 25% and from 5 to 9%, respectively.

Table 5.12 – Prevalence (%) of patients aged 40-64 years with polytherapy

	LHU	**2014**	**2015**	**2016**
5-9 drugs	Bergamo	8.20	8.13	7.95
	Lecco	7.33	7.46	7.15
	Monza Brianza	7.56	7.63	7.29
	Mantova	9.09	9.66	9.09
	Avellino	16.09	17.71	16.09
	Caserta	19.01	20.41	19.01
	Napoli 1	21.08	20.94	19.99
	Napoli 2	21.53	23.27	21.06
≥10 drugs	Bergamo	0.84	0.79	0.80
	Lecco	0.64	0.63	0.63
	Monza Brianza	0.45	0.74	0.70
	Mantova	1.02	0.95	0.96
	Avellino	2.99	2.88	2.39
	Caserta	4.27	3.88	3.52
	Napoli 1	4.17	4.25	4.25
	Napoli 2	3.60	4.53	4.06

Table 5.13 – Prevalence (%) of patients over 65 years of age with polytherapy

	LHU	2014	2015	2016
5-9 drugs	Bergamo	36.61	36.52	36.90
	Lecco	32.98	30.58	32.98
	Monza Brianza	33.93	31.34	33.93
	Mantova	38.44	38.57	37.60
	Avellino	48.12	47.69	47.01
	Caserta	50.46	49.09	47.10
	Napoli 1	43.91	44.92	46.53
	Napoli 2	52.39	46.50	45.35
≥10 drugs	Bergamo	8.90	8.83	8.68
	Lecco	4.91	5.58	6.23
	Monza Brianza	5.65	6.38	7.15
	Mantova	9.20	9.46	9.20
	Avellino	18.94	19.92	18.04
	Caserta	25.55	25.07	24.06
	Napoli 1	20.34	21.85	24.51
	Napoli 2	23.62	25.25	25.32

In addition, **Table 5.14** and **Table 5.15** show the percentages of patients in each age class prescribed by first level of ATC classification. For older people, the highest values were reported in C (Cardiovascular system) group in all LHUs, ranging from 77.6 to 85.3% in 2014, from 77.7 to 84.9% in 2015, and from 78.0 to 84.0% in 2016. The following group was the A (Alimentary tract and metabolism) which had some differences between LHUs in Lombardy and in Campania. In details, in Lombardy the percentages ranged between 61 and 69% over the 3-year period, while in Campania they rose up to 72-80%. About 50-52% of patients aged 40-64 years in Lombardy LHUs were prescribed anti-infectives medications (J group); in Campania the percentage was higher for all the years, ranging between 63.7 and 70.1% in 2014, between 67.3 and 71.0% in 2015, and between 65.6 and 69.3% in 2016. The second group for highest values was the A (Alimentary tract and metabolism) also for this age class, including about 40% of patients in Lombardy and approximately 50% of patients in Campania, followed by the C (Cardiovascular system) class.

Table 5.14 – Prevalence (%) of patients aged 40-64 years treated with drugs by ATC class at first level

ATC	LHU	2014	2015	2016
A-alimentary tract and metabolism	Bergamo	40.40	41.15	42.16
	Lecco	36.63	38.01	39.73
	Monza Brianza	36.47	37.03	38.52
	Mantova	40.25	40.66	41.10
	Avellino	46.13	46.11	42.62
	Caserta	50.99	49.85	50.28
	Napoli 1	54.30	56.17	56.16
	Napoli 2	51.08	54.94	54.14
B-blood and blood forming organs	Bergamo	14.35	14.22	14.52
	Lecco	14.52	14.83	14.94
	Monza Brianza	14.57	14.45	14.69
	Mantova	14.81	14.53	14.98
	Avellino	16.81	17.04	16.24
	Caserta	18.66	17.69	17.58
	Napoli 1	17.47	17.89	18.57
	Napoli 2	16.90	18.66	18.91
C-cardiovascular system	Bergamo	35.14	34.87	35.57
	Lecco	36.39	36.10	36.42
	Monza Brianza	36.41	36.13	36.85
	Mantova	40.47	39.74	40.23
	Avellino	46.13	46.36	46.68
	Caserta	47.38	44.65	44.68
	Napoli 1	44.57	44.28	44.11
	Napoli 2	44.94	44.54	44.69
D-dermatolo-gicals	Bergamo	1.74	1.60	1.52
	Lecco	1.51	1.39	1.29
	Monza Brianza	1.85	1.63	1.51
	Mantova	1.84	1.64	1.57
	Avellino	2.75	2.38	2.17
	Caserta	2.99	2.56	2.43
	Napoli 1	3.85	3.36	3.15
	Napoli 2	3.27	3.06	2.84

G-genito urinary system and sex hormones	Bergamo	6.94	6.70	6.36
	Lecco	6.92	6.69	6.51
	Monza Brianza	7.23	6.87	6.63
	Mantova	5.90	5.64	5.62
	Avellino	7.00	6.80	6.41
	Caserta	7.58	6.89	6.59
	Napoli 1	7.56	7.47	7.15
	Napoli 2	6.84	7.28	7.03
H-systemic hormonal preparations. excluding sex hormones	Bergamo	15.10	15.29	15.48
	Lecco	15.20	15.11	15.67
	Monza Brianza	13.92	13.95	14.31
	Mantova	16.33	16.44	17.16
	Avellino	23.25	23.20	22.26
	Caserta	26.89	26.13	25.32
	Napoli 1	24.24	25.08	24.65
	Napoli 2	25.51	29.66	28.42
J-general antiinfectives for systemic use	Bergamo	51.90	52.20	50.58
	Lecco	50.94	52.15	49.76
	Monza Brianza	51.50	52.79	50.40
	Mantova	51.29	52.06	50.25
	Avellino	68.11	68.28	66.49
	Caserta	70.07	69.50	68.00
	Napoli 1	66.23	67.33	65.60
	Napoli 2	63.69	71.04	69.28
L-antineoplastic and immunomodu-lating agents	Bergamo	2.17	2.12	2.11
	Lecco	2.02	2.04	2.13
	Monza Brianza	2.06	2.12	2.20
	Mantova	2.09	2.09	2.09
	Avellino	1.95	1.88	1.91
	Caserta	2.08	1.87	1.90
	Napoli 1	1.98	2.01	2.10
	Napoli 2	1.47	1.71	1.79
M-musculo-skeletal system	Bergamo	18.28	17.42	17.18
	Lecco	16.13	15.43	15.49
	Monza Brianza	18.08	17.58	17.64
	Mantova	20.54	20.10	19.44
	Avellino	35.80	33.80	30.37
	Caserta	40.93	37.95	36.18
	Napoli 1	46.34	45.90	43.93
	Napoli 2	44.99	48.24	45.43

N-nervous system	Bergamo	17.60	17.49	17.91
	Lecco	15.78	15.54	16.04
	Monza Brianza	14.79	14.88	15.43
	Mantova	16.80	16.70	17.39
	Avellino	15.95	15.44	15.33
	Caserta	18.39	16.95	16.99
	Napoli 1	16.04	16.09	16.46
	Napoli 2	14.98	15.79	16.06
P-antiparasitic products	Bergamo	1.50	1.52	1.60
	Lecco	1.53	1.52	1.52
	Monza Brianza	1.16	1.12	1.07
	Mantova	1.19	1.15	1.12
	Avellino	0.86	0.84	0.83
	Caserta	0.94	0.82	0.89
	Napoli 1	0.81	0.86	0.85
	Napoli 2	0.83	0.97	1.02
R-respiratory system	Bergamo	18.55	18.45	16.31
	Lecco	18.86	18.77	17.06
	Monza Brianza	20.74	21.03	19.03
	Mantova	20.88	20.87	18.64
	Avellino	22.10	22.13	20.73
	Caserta	27.10	26.67	25.93
	Napoli 1	29.45	30.52	29.64
	Napoli 2	27.42	31.61	30.04
S-sensory organs	Bergamo	1.38	1.35	1.40
	Lecco	1.57	1.55	1.60
	Monza Brianza	1.53	1.50	1.51
	Mantova	1.51	1.46	1.51
	Avellino	1.72	1.67	1.71
	Caserta	2.08	1.89	1.87
	Napoli 1	2.63	2.54	2.46
	Napoli 2	2.03	1.95	1.97
V-various	Bergamo	0.11	0.25	0.12
	Lecco	0.07	0.07	0.06
	Monza Brianza	0.08	0.10	0.10
	Mantova	0.08	0.19	0.07
	Avellino	0.13	0.15	0.13
	Caserta	0.12	0.12	0.13
	Napoli 1	0.14	0.15	0.16
	Napoli 2	0.07	0.12	0.15

Table 5.15 – Prevalence (%) of patients aged ≥65 years treated with drugs by ATC class at first level

ATC	LHU	2014	2015	2016
A-alimentary tract and metabolism	Bergamo	66.86	68.10	68.85
	Lecco	60.80	62.84	64.81
	Monza Brianza	62.26	64.00	65.55
	Mantova	67.12	68.24	69.07
	Avellino	73.93	74.97	72.21
	Caserta	76.68	77.68	77.67
	Napoli 1	78.13	79.95	79.04
	Napoli 2	73.97	80.36	80.30
B-blood and blood forming organs	Bergamo	37.84	38.05	38.27
	Lecco	35.59	36.49	37.32
	Monza Brianza	36.86	38.04	38.78
	Mantova	41.28	41.45	41.78
	Avellino	47.86	49.88	48.29
	Caserta	51.61	51.85	51.16
	Napoli 1	46.96	48.00	49.53
	Napoli 2	46.48	52.18	53.62
C-cardiovascular system	Bergamo	77.82	77.73	78.01
	Lecco	77.57	77.98	78.45
	Monza Brianza	77.72	78.23	78.82
	Mantova	83.24	83.09	83.12
	Avellino	83.81	84.10	82.82
	Caserta	85.26	84.62	83.58
	Napoli 1	83.78	83.99	81.76
	Napoli 2	81.20	84.94	83.99
D-dermatolo-gicals	Bergamo	1.77	1.62	1.56
	Lecco	1.60	1.49	1.29
	Monza Brianza	2.10	1.92	1.72
	Mantova	1.99	1.82	1.71
	Avellino	3.39	2.98	2.58
	Caserta	3.90	3.43	3.27
	Napoli 1	5.69	5.07	4.46
	Napoli 2	4.78	4.99	4.31

G-genito urinary system and sex hormones	Bergamo	12.71	12.85	12.94
	Lecco	12.59	12.70	13.17
	Monza Brianza	14.13	14.34	14.62
	Mantova	11.56	11.52	11.73
	Avellino	14.69	14.87	14.47
	Caserta	15.96	15.92	15.77
	Napoli 1	15.87	16.17	15.64
	Napoli 2	15.10	16.99	16.88
H-systemic hormonal preparations, excluding sex hormones	Bergamo	15.95	16.28	16.25
	Lecco	15.24	15.50	15.89
	Monza Brianza	15.21	15.64	15.62
	Mantova	18.64	18.75	18.98
	Avellino	25.81	26.75	25.96
	Caserta	28.37	28.34	27.76
	Napoli 1	26.85	27.94	27.77
	Napoli 2	25.93	31.42	30.97
J-general antiinfectives for systemic use	Bergamo	47.97	48.10	46.85
	Lecco	44.30	45.32	44.01
	Monza Brianza	46.30	47.66	45.87
	Mantova	44.76	44.78	44.25
	Avellino	67.32	68.51	66.87
	Caserta	70.91	70.36	69.67
	Napoli 1	68.10	69.65	67.29
	Napoli 2	62.92	73.46	72.28
L-antineoplastic and immunomodu-lating agents	Bergamo	3.64	3.61	3.59
	Lecco	3.14	3.24	3.38
	Monza Brianza	3.24	3.40	3.47
	Mantova	3.08	3.19	3.16
	Avellino	3.41	3.53	3.44
	Caserta	3.42	3.39	3.28
	Napoli 1	3.05	3.21	3.48
	Napoli 2	1.98	2.80	3.10
M-musculo-skeletal system	Bergamo	36.22	35.13	34.10
	Lecco	31.57	30.58	30.30
	Monza Brianza	32.75	31.99	31.68
	Mantova	34.17	33.49	32.70
	Avellino	55.05	54.08	49.72
	Caserta	57.71	55.55	53.33
	Napoli 1	56.99	56.57	52.50
	Napoli 2	53.39	60.65	57.56

N-nervous system	Bergamo	28.58	28.70	29.05
	Lecco	22.21	22.79	23.74
	Monza Brianza	21.85	22.72	23.76
	Mantova	26.05	25.86	26.33
	Avellino	26.65	26.75	26.35
	Caserta	30.27	29.68	29.64
	Napoli 1	26.42	26.87	28.54
	Napoli 2	25.47	27.67	29.35
P-antiparasitic products	Bergamo	1.23	1.26	1.26
	Lecco	0.95	0.94	0.98
	Monza Brianza	1.04	1.02	0.95
	Mantova	0.99	1.02	0.98
	Avellino	0.79	0.77	0.83
	Caserta	0.75	0.76	0.81
	Napoli 1	0.82	0.87	0.81
	Napoli 2	0.87	1.08	1.10
R-respiratory system	Bergamo	18.96	19.07	17.17
	Lecco	17.63	18.04	16.57
	Monza Brianza	19.81	20.67	19.09
	Mantova	21.99	22.11	20.23
	Avellino	27.33	27.82	26.46
	Caserta	33.21	33.23	32.73
	Napoli 1	33.92	35.40	34.49
	Napoli 2	31.17	37.35	36.53
S-sensory organs	Bergamo	5.26	5.29	5.45
	Lecco	5.54	5.60	5.74
	Monza Brianza	5.30	5.38	5.59
	Mantova	6.14	6.10	6.27
	Avellino	4.96	4.81	4.74
	Caserta	5.94	5.85	5.86
	Napoli 1	8.96	8.91	8.49
	Napoli 2	6.61	7.29	7.17
V-various	Bergamo	0.24	0.64	0.25
	Lecco	0.12	0.13	0.14
	Monza Brianza	0.20	0.29	0.33
	Mantova	0.13	0.37	0.14
	Avellino	0.38	0.42	0.38
	Caserta	0.52	0.55	0.53
	Napoli 1	0.42	0.49	0.62
	Napoli 2	0.39	0.49	0.59

In **Table 5.16** and **Table 5.17** the consumptions (expressed as DDD per 1,000 inhabitants die) of selected drug classes are reported. As expected, consumption of all considered drug classes was higher in patients aged ≥65 years compared to patients aged 40-64 years. Time trends were extremely heterogeneous not only among drug classes but also among LHUs. In particular, we observed an increased consumption of angiotensin receptor blockers (p-trend<0.05 for all LHUs except for Bergamo and Mantova), statins (all p-trends<0.05), selective serotonin reuptake inhibitors (p-trend<0.05 for all LHUs except for Bergamo and Mantova), and serotonin-norepinephrine reuptake inhibitors (p-trend<0.05 for all LHUs except for Mantova) for patients aged ≥65 years over time. The only decreasing trend that was consistent among LHUs was the consumption of angiotensin receptor blockers in patients aged 40-64 years, although the p-trends were significative only for Campania's LHUs. The consumption of antibiotics was about two times higher in Campania areas compared to Lombardy areas, independently by age classes.

Table 5.16 – Consumption (in terms of DDD per 1,000 inhabitants die) of some of the most commonly used drug classes in patients aged 40-64 years

ATC	LHU	2014	2015	2016	p-trend
Proton pump inhibitors	Bergamo	47.7	46.2	46.0	0.823
	Lecco	40.6	45.2	36.7	<0.001
	Monza Brianza	43.3	44.9	36.2	<0.001
	Mantova	51.9	52.1	51.8	0.901
	Avellino	74.5	74.1	55.8	<0.001
	Caserta	76.0	76.9	41.3	<0.001
	Napoli 1	79.4	87.1	83.9	<0.001
	Napoli 2	66.0	81.6	73.5	<0.001
ACE-inhibitors	Bergamo	89.9	88.8	92.3	0.585
	Lecco	119.6	120.6	116.3	0.222
	Monza Brianza	119.7	120.4	115.1	0.013
	Mantova	114.8	112.7	114.0	0.622
	Avellino	127.1	131.2	146.9	0.365
	Caserta	164.1	159.1	99.4	<0.001
	Napoli 1	137.5	142.0	144.6	<0.001
	Napoli 2	123.0	149.4	156.1	<0.001

Angiotensin receptor blockers	Bergamo	91.3	88.7	86.3	0.066
	Lecco	86.9	86.1	84.0	0.614
	Monza Brianza	81.5	82.3	79.5	0.145
	Mantova	117.4	111.5	111.9	0.577
	Avellino	165.6	155.7	150.7	<0.001
	Caserta	158.1	152.0	91.4	<0.001
	Napoli 1	132.9	139.4	131.7	<0.001
	Napoli 2	122.1	142.7	136.2	<0.001
Statins	Bergamo	51.9	50.8	53.2	0.100
	Lecco	43.8	44.5	42.8	0.018
	Monza Brianza	47.5	47.4	47.6	0.191
	Mantova	59.0	56.7	57.9	0.871
	Avellino	72.1	74.5	75.4	0.135
	Caserta	76.1	73.1	49.6	<0.001
	Napoli 1	60.1	64.1	63.5	<0.001
	Napoli 2	57.1	71.0	71.0	<0.001
Antibiotics	Bergamo	12.9	12.9	12.4	<0.001
	Lecco	11.6	11.7	10.9	0.029
	Monza Brianza	12.1	12.7	11.5	<0.001
	Mantova	11.6	11.9	10.9	0.002
	Avellino	24.0	23.3	21.2	<0.001
	Caserta	24.9	23.8	18.7	<0.001
	Napoli 1	22.3	22.3	21.1	<0.001
	Napoli 2	21.9	25.8	23.2	<0.001
Selective Serotonin Reuptake Inhibitors	Bergamo	25.7	26.0	26.0	0.108
	Lecco	24.1	25.0	24.7	0.182
	Monza Brianza	24.2	24.6	23.0	<0.001
	Mantova	28.7	29.4	29.6	0.227
	Avellino	25.4	25.7	25.2	0.004
	Caserta	30.7	30.2	19.4	<0.001
	Napoli 1	23.2	24.7	23.7	<0.001
	Napoli 2	20.9	25.0	24.0	<0.001
Serotonin-Norepinephrine Reuptake Inhibitor	Bergamo	7.9	8.1	8.3	0.191
	Lecco	7.2	7.6	7.2	0.575
	Monza Brianza	6.3	6.6	6.3	0.604
	Mantova	9.0	8.9	9.3	0.869
	Avellino	6.0	6.2	6.9	0.660
	Caserta	7.9	7.6	5.2	<0.001
	Napoli 1	5.0	5.2	5.2	<0.001
	Napoli 2	4.5	5.6	5.4	<0.001

Anti-asthmatics	Bergamo	23.3	22.7	22.7	0.360
	Lecco	20.5	19.9	20.7	0.903
	Monza Brianza	22.6	22.2	21.9	0.347
	Mantova	27.4	25.8	25.5	0.287
	Avellino	28.8	28.3	26.4	<0.001
	Caserta	32.9	31.90	26.0	<0.001
	Napoli 1	36.6	38.7	35.4	<0.001
	Napoli 2	30.9	35.8	33.1	<0.001

Table 5.17 – Consumption (in terms of DDD per 1,000 inhabitants die) of some of the most commonly used drug classes in patients aged ≥65 years

ATC	LHU	2014	2015	2016	p-trend
Proton pump inhibitors	Bergamo	192.8	198.6	201.9	0.156
	Lecco	117.2	134.8	131.2	<0.001
	Monza Brianza	142.5	161.1	153.3	<0.001
	Mantova	207.3	219.2	223.6	0.023
	Avellino	264.3	287.6	258.8	<0.001
	Caserta	281.5	291.8	157.9	<0.001
	Napoli 1	240.2	282.1	309.1	<0.001
	Napoli 2	236.0	281.6	326.3	<0.001
ACE-inhibitors	Bergamo	375.8	364.2	365.2	0.022
	Lecco	394.0	407.7	439.1	<0.001
	Monza Brianza	389.2	407.4	435.0	<0.001
	Mantova	399.5	395.1	398.3	0.659
	Avellino	383.2	401.4	429.9	0.002
	Caserta	504.1	491.9	299.7	<0.001
	Napoli 1	399.9	432.2	461.3	<0.001
	Napoli 2	393.4	446.7	525.9	<0.001
Angiotensin receptor blockers	Bergamo	345.5	345.3	351.6	0.336
	Lecco	303.2	316.5	348.8	<0.001
	Monza Brianza	282.8	293.6	325.6	<0.001
	Mantova	396.4	398.4	402.0	0.985
	Avellino	489.1	491.2	479.6	0.001
	Caserta	545.2	532.8	349.5	<0.001
	Napoli 1	429.5	475.3	477.7	<0.001
	Napoli 2	412.5	484.0	533.6	<0.001

Statins	Bergamo	216.9	222.6	234.0	<0.001
	Lecco	163.7	178.2	199.2	<0.001
	Monza Brianza	173.4	192.4	212.1	<0.001
	Mantova	244.6	254.2	266.9	0.020
	Avellino	228.4	248.5	253.1	0.001
	Caserta	270.0	280.5	196.8	<0.001
	Napoli 1	199.6	226.6	240.4	<0.001
	Napoli 2	204.7	255.1	297.5	<0.001
Antibiotics	Bergamo	19.4	19.4	18.7	0.026
	Lecco	13.3	14.2	15.5	<0.001
	Monza Brianza	14.6	16.0	16.7	<0.001
	Mantova	16.0	15.4	15.1	0.237
	Avellino	36.1	37.8	35.1	0.001
	Caserta	42.1	39.9	30.6	<0.001
	Napoli 1	31.8	34.6	37.1	<0.001
	Napoli 2	36.4	39.9	44.7	<0.001
Selective Serotonin Reuptake Inhibitors	Bergamo	55.4	55.8	58.5	0.211
	Lecco	33.9	38.0	44.2	<0.001
	Monza Brianza	36.8	40.3	44.7	<0.001
	Mantova	62.1	62.4	61.7	0.953
	Avellino	41.1	42.9	43.9	0.022
	Caserta	55.9	56.2	39.6	<0.001
	Napoli 1	39.7	46.3	49.2	<0.001
	Napoli 2	42.6	48.7	55.4	<0.001
Serotonin-Norepinephrine Reuptake Inhibitor	Bergamo	19.1	19.9	20.6	0.001
	Lecco	12.1	14.0	14.9	0.001
	Monza Brianza	11.5	12.5	14.1	<0.001
	Mantova	18.0	18.6	19.6	0.141
	Avellino	9.3	10.8	11.1	0.048
	Caserta	15.9	15.5	11.1	<0.001
	Napoli 1	8.4	9.5	11.5	<0.001
	Napoli 2	9.7	10.9	13.7	<0.001
Anti-asthmatics	Bergamo	72.0	69.4	66.2	<0.001
	Lecco	45.7	49.9	56.2	<0.001
	Monza Brianza	52.3	58.2	64.7	<0.001
	Mantova	79.8	75.7	70.8	0.004
	Avellino	108.1	114.5	105.2	<0.001
	Caserta	119.1	116.0	97.2.	<0.001
	Napoli 1	97.5	110.6	117.3	<0.001
	Napoli 2	104.6	109.8	127.9	<0.001

5.3 APPROPRIATE PRESCRIBING ANALYSES

Results from appropriate prescribing analyses are described as trend in annual prevalence rates of each indicator investigated. The annual prevalence of interested patients for each LHU is calculated as the median value between GPs with at least 100 older patients, in order to exclude GP at the beginning or at the end of their work activity period, who could overestimate the prevalence rates.

The prevalence rate of each indicator, as reported below, have been estimates at LHU level. In the **Appendix III** section, the GP distribution for every indicator in 2014, 2015 and 2016, separately by LHU, is reported.

5.3.1 Potential drug-drug interactions (pDDI)

Potential DDI occurred in 10-14% of adult patients in LHUs in Lombardy region; the prevalence in Campania is almost 10 percent points higher, reaching 20-24%. There is no defined time trend for this indicator: for Bergamo LHU, Lecco and Monza Brianza areas the prevalence has been consistent during time; for Avellino LHU, Caserta LHU and Mantova area it has remained stable in 2015 and then decreased by 2% in 2016; for Napoli 1 and Napoli 2 LHUs it has increased through the first year by 2 percent points and remained similar in the third year (**Figure 5.9**). However, overall, this indicator significantly changes over time for all the LHUs (p-trends <0.01).

The most frequent pDDI were 'hydrochlorothiazide-ibuprofen' and 'pantoprazole-levothyroxine' in Lombardy, and 'hydrochlorothiazide-diclofenac' in Campania for the three years (**Table 5.18**, **Table 5.19**, and **Table 5.20**).

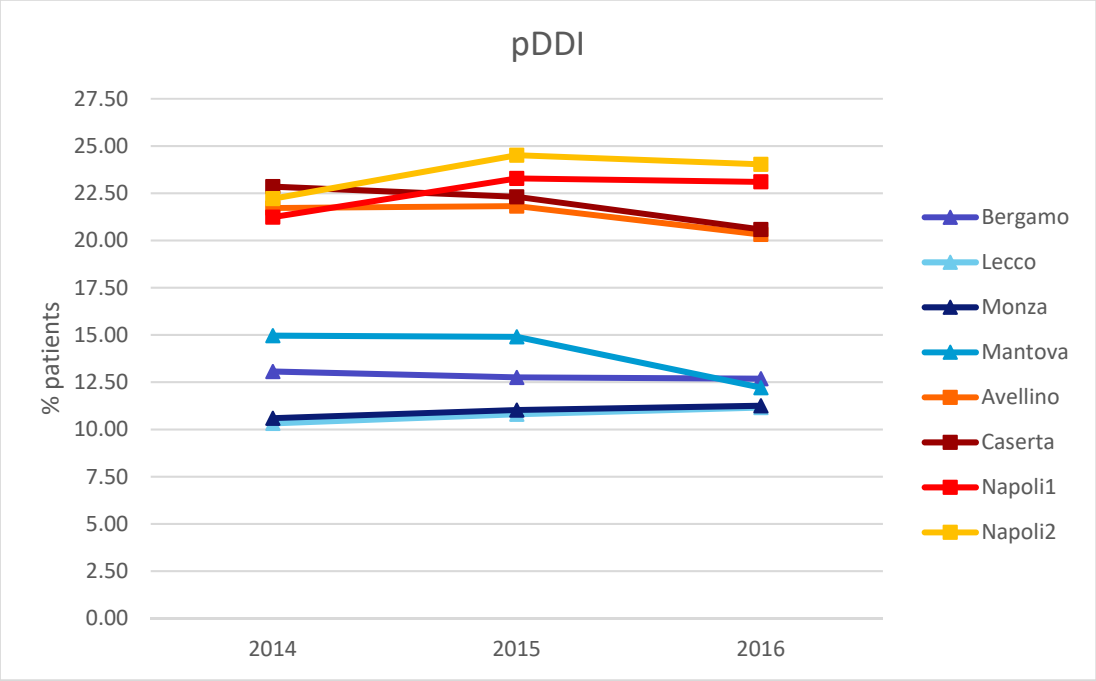


Figure 5.9 – Annual prevalence rates of pDDI in the population aged ≥40 years

Table 5.18 – Most frequently occurred pDDI, in 2014

	LHU	1°	2°	3°
Lombardy	Bergamo	Hydrochlorothiazide-Ibuprofen (3.35%)	Hydrochlorothiazide-Diclofenac (2.12%)	Ibuprofen-Acetylsalicylic acid, low dose (2.02%)
	Lecco	Hydrochlorothiazide-Ibuprofen (2.97%)	Hydrochlorothiazide-Diclofenac (2.54%)	Pantoprazole-Levothyroxine (1.99%)
	Monza Brianza	Pantoprazole-Levothyroxine (2.99%)	Hydrochlorothiazide-Diclofenac (2.71%)	Hydrochlorothiazide-Ibuprofen (2.12%)
	Mantova	Pantoprazole-Levothyroxine (2.19%)	Hydrochlorothiazide-Ibuprofen (2.16%)	Hydrochlorothiazide-Diclofenac (2.03%)
Campania	Avellino	Hydrochlorothiazide-Diclofenac (4.65%)	Hydrochlorothiazide-Ibuprofen (2.57%)	Allopurinol-Amoxicillin (1.90%)
	Caserta	Hydrochlorothiazide-Diclofenac (4.06%)	Pantoprazole-Levothyroxine (2.25%)	Ketoprofen-Betamethasone (1.86%)
	Napoli 1	Hydrochlorothiazide-Diclofenac (4.64%)	Omeprazole-Levothyroxine (2.69%)	Ketoprofen-Betamethasone (2.21%)
	Napoli 2	Hydrochlorothiazide-Diclofenac (4.42%)	Omeprazole-Levothyroxine (2.61%)	Ketoprofen-Betamethasone (2.59%)

Table 5.19 – Most frequently occurred pDDI, in 2015

	LHU	1°	2°	3°
Lombardy	Bergamo	Hydrochlorothiazide-Ibuprofen (3.12%)	Ibuprofen-Acetylsalicylic acid, low dose (2.02%)	Hydrochlorothiazide-Diclofenac (2.00%)
	Lecco	Hydrochlorothiazide-Ibuprofen (2.69%)	Hydrochlorothiazide-Diclofenac (2.37%)	Pantoprazole-Levothyroxine (2.35%)
	Monza Brianza	Pantoprazole-Levothyroxine (3.40%)	Hydrochlorothiazide-Diclofenac (2.54%)	Hydrochlorothiazide-Ibuprofen (1.92%)
	Mantova	Pantoprazole-Levothyroxine (2.52%)	Hydrochlorothiazide-Ibuprofen (1.91%)	Hydrochlorothiazide-Diclofenac (1.89%)
Campania	Avellino	Hydrochlorothiazide-Diclofenac (4.18%)	Hydrochlorothiazide-Ibuprofen (2.32%)	Pantoprazole-Levothyroxine (1.98%)
	Caserta	Hydrochlorothiazide-Diclofenac (3.85%)	Pantoprazole-Levothyroxine (2.52%)	Ketoprofen-Betamethasone (1.91%)
	Napoli 1	Hydrochlorothiazide-Diclofenac (4.15%)	Omeprazole-Levothyroxine (2.41%)	Ketoprofen-Betamethasone (2.27%)
	Napoli 2	Hydrochlorothiazide-Diclofenac (4.11%)	Ketoprofen-Betamethasone (2.93%)	Betamethasone-Diclofenac (2.43%)

Table 5.20 – Most frequently occurred pDDI, in 2016

	LHU	1°	2°	3°
Lombardy	Bergamo	Hydrochlorothiazide-Ibuprofen (2.83%)	Calcium-Levothyroxine (2.00%)	Hydrochlorothiazide-Diclofenac (1.98%)
	Lecco	Pantoprazole-Levothyroxine (2.68%)	Hydrochlorothiazide-Ibuprofen (2.55%)	Hydrochlorothiazide-Diclofenac (2.23%)
	Monza Brianza	Pantoprazole-Levothyroxine (3.64%)	Hydrochlorothiazide-Diclofenac (2.59%)	Hydrochlorothiazide-Ibuprofen (1.85%)
	Mantova	Pantoprazole-Levothyroxine (2.80%)	Hydrochlorothiazide-Ibuprofen (1.83%)	Hydrochlorothiazide-Diclofenac (1.79%)
Campania	Avellino	Hydrochlorothiazide-Diclofenac (4.18%)	Hydrochlorothiazide-Ibuprofen (2.41%)	Allopurinol-Amoxicillin (2.06%)
	Caserta	Hydrochlorothiazide-Diclofenac (3.87%)	Pantoprazole-Levothyroxine (2.71%)	Ketoprofen-Betamethasone (1.86%)
	Napoli 1	Hydrochlorothiazide-Diclofenac (4.12%)	Omeprazole-Levothyroxine (2.38%)	Pantoprazole-Levothyroxine (2.23%)
	Napoli 2	Hydrochlorothiazide-Diclofenac (4.23%)	Ketoprofen-Betamethasone (2.44%)	Omeprazole-Levothyroxine (2.26%)

5.3.2 Therapeutic Duplicates (TD)

Therapeutic duplicates interested a range between 2.26 and 3.26% of adult patients for Lombardy LHUs, while for Campania LHUs TD rates were two times higher, from 4.67 to 6.73%, during the entire period analysed.
In addition, in Lombardy, the annual prevalence rates did not change during time (with only a slight decrease for Bergamo and Mantova, p-trends <0.05), while a more dynamic situation was seen in Campania (p-trends <0.05, except for Caserta), as shown in **Figure 5.10**.

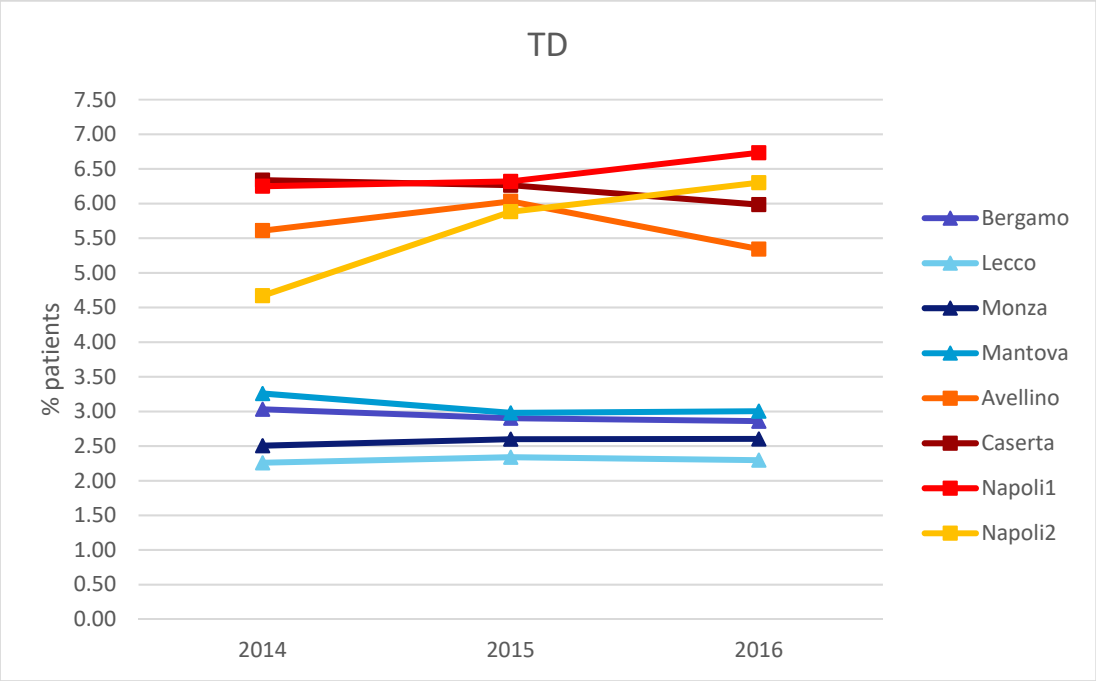


Figure 5.10 – Annual prevalence rates of TD in the population aged ≥40 years

The class of drugs that was the most frequently involved with TD was the 'platelet aggregation inhibitors excl. heparin' class (ATC code: B01AC), in all the LHUs over time (**Table 5.21**, **Table 5.22**, and **Table 5.23**).

Table 5.21 – Most frequently prescribed drug classes affected by TD, in 2014

	LHU	1°	2°	3°
Lombardy	Bergamo	Platelet aggregation inhibitors excl. Heparin (24.20%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (10.91%)	Calcium (5.33%)
	Lecco	Platelet aggregation inhibitors excl. Heparin (23.42%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (8.09%)	Calcium (5.29%)
	Monza Brianza	Platelet aggregation inhibitors excl. Heparin (22.09%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (12.55%)	Calcium (5.44%)
	Mantova	Platelet aggregation inhibitors excl. Heparin (23.56%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (9.54%)	Calcium (6.25%)
Campania	Avellino	Platelet aggregation inhibitors excl. Heparin (26.20%)	Proton Pump Inhibitors (6.17%)	Acetic acid derivatives and related substances (5.10%)
	Caserta	Platelet aggregation inhibitors excl. Heparin (23.61%)	Combinations of penicillins, incl. beta-lactamase inhibitors (5.78%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (5.34%)
	Napoli 1	Platelet aggregation inhibitors excl. Heparin (23.65%)	Proton Pump Inhibitors (6.83%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (6.31%)
	Napoli 2	Platelet aggregation inhibitors excl. Heparin (12.60%)	Proton Pump Inhibitors (6.88%)	Glucocorticoids (6.40%)

Table 5.22 – Most frequently prescribed drug classes affected by TD, in 2015

	LHU	1°	2°	3°
Lombardy	Bergamo	Platelet aggregation inhibitors excl. Heparin (24.93%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (10.72%)	Calcium (5.54%)
	Lecco	Platelet aggregation inhibitors excl. Heparin (24.98%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (8.87%)	Calcium (5.34%)
	Monza Brianza	Platelet aggregation inhibitors excl. Heparin (22.45%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (11.18%)	Calcium (5.40%)
	Mantova	Platelet aggregation inhibitors excl. Heparin (24.82%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (8.25%)	Calcium (6.56%)
Campania	Avellino	Platelet aggregation inhibitors excl. Heparin (28.14%)	Proton Pump Inhibitors (4.84%)	Angiotensin ii receptor blockers (ARBs) and diuretics (4.60%)
	Caserta	Platelet aggregation inhibitors excl. Heparin (26.49%)	Combinations of penicillins, incl. beta-lactamase inhibitors (5.45%)	Glucocorticoids (4.84%)
	Napoli 1	Platelet aggregation inhibitors excl. Heparin (24.52%)	Proton Pump Inhibitors (6.10%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (5.92%)
	Napoli 2	Platelet aggregation inhibitors excl. Heparin (27.27%)	Glucocorticoids (5.47%)	Proton Pump Inhibitors (5.05%)

Table 5.23 – Most frequently prescribed drug classes affected by TD, in 2016

	LHU	1°	2°	3°
Lombardy	Bergamo	Platelet aggregation inhibitors excl. Heparin (25.64%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (9.14%)	Vitamin D and analogues (5.90%)
	Lecco	Platelet aggregation inhibitors excl. Heparin (25.84%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (7.21%)	Calcium (5.49%)
	Monza Brianza	Platelet aggregation inhibitors excl. Heparin (22.84%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (10.20%)	Calcium (5.85%)
	Mantova	Platelet aggregation inhibitors excl. Heparin (26.33%)	Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics (7.44%)	Calcium (6.05%)
Campania	Avellino	Platelet aggregation inhibitors excl. Heparin (32.20%)	Glucocorticoids (4.82%)	Acetic acid derivatives and related substances (3.82%)
	Caserta	Platelet aggregation inhibitors excl. Heparin (29.50%)	Glucocorticoids (4.64%)	Combinations of penicillins, incl. beta-lactamase inhibitors (4.57%)
	Napoli 1	Platelet aggregation inhibitors excl. Heparin (26.70%)	Proton Pump Inhibitors (6.09%)	Glucocorticoids (4.89%)
	Napoli 2	Platelet aggregation inhibitors excl. Heparin (30.10%)	Glucocorticoids (5.56%)	Proton Pump Inhibitors (4.59%)

5.3.3 Inappropriate prescriptions in the elderly: the ERD-list

At least one drug/drug class included in the ERD-list has been found in about 25-27% of older patients in Lecco and Monza Brianza areas and in 32-35% in Bergamo LHU and Mantova area. Also in this case, Campania LHUs achieved higher values for prevalence rates: in 2016, 49% of Avellino elderly received at least one inappropriate drug belonging to ERD-list, 50% in Caserta, 56% in Napoli 1 and 65% in Napoli 2.

The time trend in prevalence was slight increasing in Napoli2 (p-trend <0.001), while decreased in Bergamo, Mantova, Avellino, and Caserta LHUs (all p-trends <0.001). No time trend was observed for Lecco (p-trend=0.79) (**Figure 5.11**).

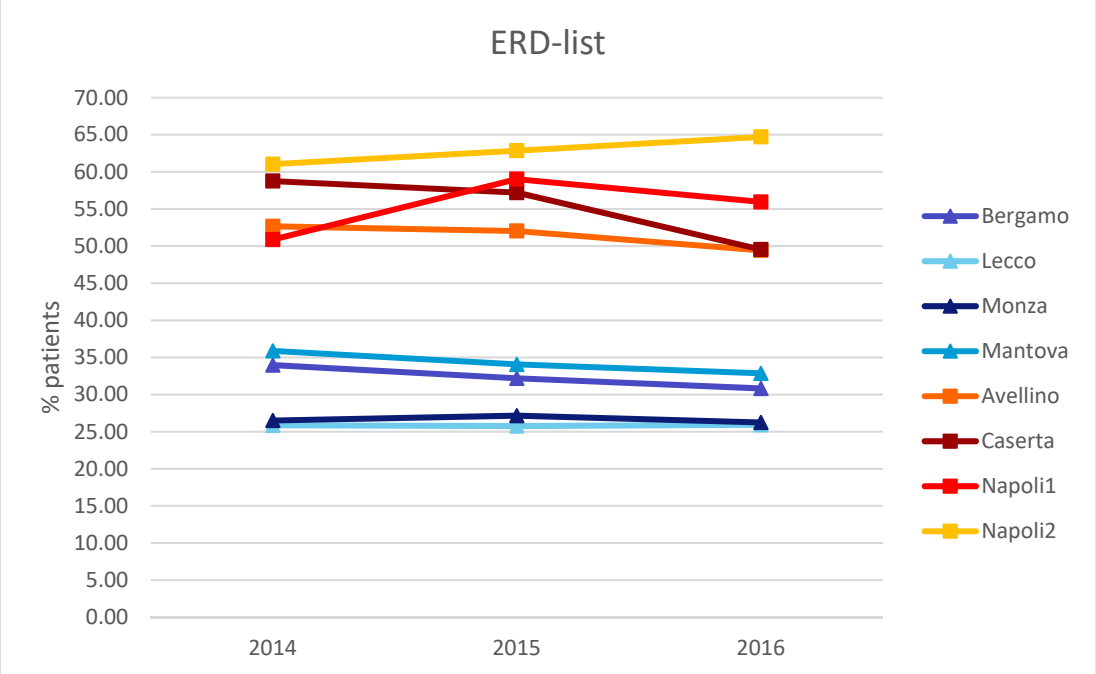


Figure 5.11 – Annual prevalence rates of ERD indicator in the population aged ≥65 years

Proton pump inhibitors represented the most frequently occurred ERD-list criterion in Lombardy for the entire period considered. In Campania, two NSAIDs, ketoprofen and diclofenac, were the most frequently prescribed

medications included in the ERD-list in 2014 and 2016, while PPIs and ketoprofen in 2015 (**Table 5.24**, **Table 5.25**, and **Table 5.26**).

Table 5.24 – Most frequently prescribed drug in the ERD-list in 2014

	LHU	1°	2°	3°
Lombardy	Bergamo	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Lecco	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Monza Brianza	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Mantova	Proton Pump Inhibitors	Ticlopidine	Diclofenac
Campania	Avellino	Diclofenac	Proton Pump Inhibitors	Ketoprofen
	Caserta	Ketoprofen	Diclofenac	Proton Pump Inhibitors
	Napoli 1	Ketoprofen	Diclofenac	Proton Pump Inhibitors
	Napoli 2	Ketoprofen	Diclofenac	Proton Pump Inhibitors

Table 5.25 – Most frequently prescribed drug in the ERD-list in 2015

	LHU	1°	2°	3°
Lombardy	Bergamo	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Lecco	Proton Pump Inhibitors	Diclofenac	Nifedipine
	Monza Brianza	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Mantova	Proton Pump Inhibitors	Ticlopidine	Diclofenac
Campania	Avellino	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Caserta	Ketoprofen	Proton Pump Inhibitors	Diclofenac
	Napoli 1	Proton Pump Inhibitors	Ketoprofen	Diclofenac
	Napoli 2	Proton Pump Inhibitors	Ketoprofen	Diclofenac

Table 5.26 – Most frequently prescribed drug in the ERD-list in 2016

	LHU	1°	2°	3°
Lombardy	Bergamo	Proton Pump Inhibitors	Diclofenac	Paroxetine
	Lecco	Proton Pump Inhibitors	Diclofenac	Nifedipine
	Monza Brianza	Proton Pump Inhibitors	Diclofenac	Ketoprofen
	Mantova	Proton Pump Inhibitors	Ticlopidine	Diclofenac
Campania	Avellino	Diclofenac	Proton Pump Inhibitors	Ketoprofen
	Caserta	Ketoprofen	Diclofenac	Ticlopidine
	Napoli 1	Ketoprofen	Diclofenac	Proton Pump Inhibitors
	Napoli 2	Ketoprofen	Diclofenac	Proton Pump Inhibitors

5.3.4 Anticholinergic Cognitive Burden (ACB) Score

The annual prevalence rates of ACB score ≥3 in the elderly ranged between 4.50 and 9.50% in all LHUs (**Figure 5.12**). Monza Brianza and Lecco areas showed the lowest percentages, even if they augmented over time (from 4.63 to 5.86% for Monza Brianza, p-trend <0.001; from 5.17 to 6.25% for Lecco, p-trend <0.001). Similarly, Napoli 1 and Napoli 2 LHUs had an increase during time, starting from 6.52% and 7.64% and reaching 8.11% and 9.27%, respectively (all p-trends <0.001). The growth registered by Avellino was smaller, from 7.28% in 2014 to 7.84% in 2016, although significant. Conversely, Mantova area and Bergamo LHU displayed a small reduction of ACB rates in time, from 6.98 to 6.67% and from 8.67 to 8.53%, respectively (p-trends <0.05). Finally, Caserta LHU had a more remarkable decrease over time, from 8.53 to 7.09% (p-trend <0.001).

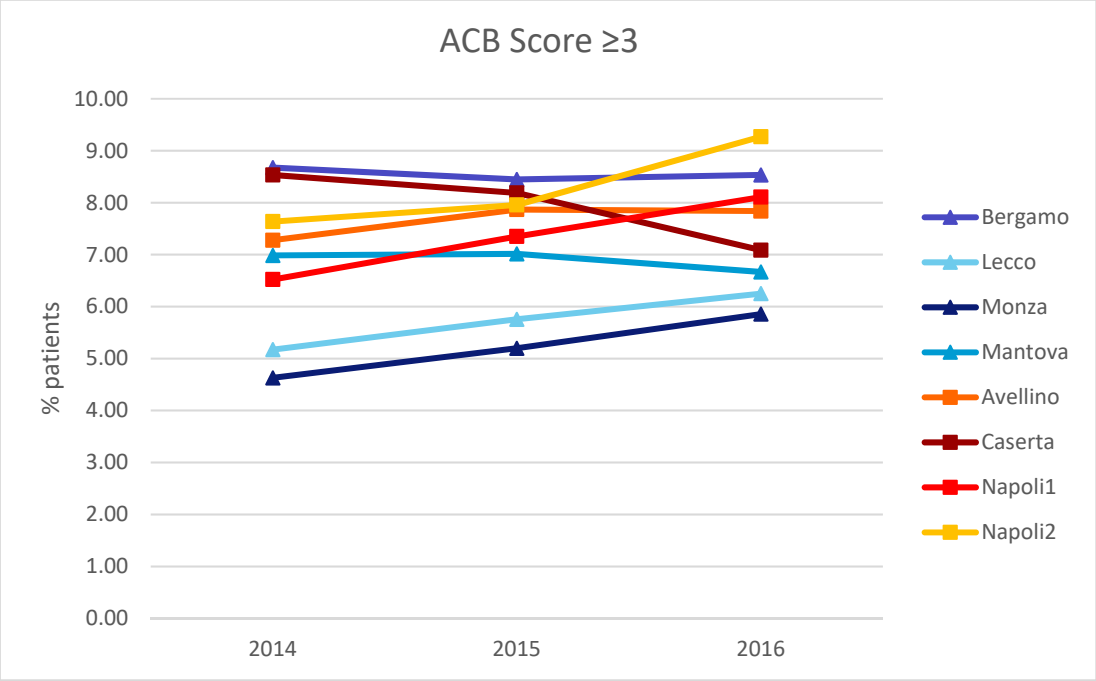


Figure 5.12 – Annual prevalence rates of ACB score in the population aged ≥65 years

The most commonly prescribed drug involved in the ACB Score was paroxetine, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, for Bergamo and Napoli 1 LHUs and for Lecco and Monza Brianza areas. In Mantova area and in Avellino, Caserta and Napoli 2 LHUs, instead, the diuretic furosemide was the first in terms of prescription frequency (**Table 5.27**, **Table 5.28**, and **Table 5.29**).

Table 5.27 – Most frequently prescribed drug with ACB score ≥3, in 2014

	LHU	1°	2°	3°
Lombardy	Bergamo	Paroxetine	Furosemide	Quetiapine
	Lecco	Paroxetine	Furosemide	Warfarin
	Monza Brianza	Paroxetine	Furosemide	Warfarin
	Mantova	Furosemide	Paroxetine	Warfarin
Campania	Avellino	Furosemide	Paroxetine	Warfarin
	Caserta	Furosemide	Paroxetine	Digoxin
	Napoli 1	Paroxetine	Furosemide	Warfarin
	Napoli 2	Furosemide	Paroxetine	Digoxin

Table 5.28 – Most frequently prescribed drug in the with ACB score ≥3, in 2015

	LHU	1°	2°	3°
Lombardy	Bergamo	Paroxetine	Furosemide	Quetiapine
	Lecco	Paroxetine	Furosemide	Warfarin
	Monza Brianza	Paroxetine	Furosemide	Quetiapine
	Mantova	Furosemide	Paroxetine	Warfarin
Campania	Avellino	Furosemide	Paroxetine	Quetiapine
	Caserta	Furosemide	Paroxetine	Quetiapine
	Napoli 1	Paroxetine	Furosemide	Ranitidine
	Napoli 2	Furosemide	Paroxetine	Ranitidine

Table 5.29 – Most frequently prescribed drug with ACB score ≥3, in 2016

	LHU	1°	2°	3°
Lombardy	Bergamo	Paroxetine	Furosemide	Quetiapine
	Lecco	Paroxetine	Furosemide	Warfarin
	Monza Brianza	Paroxetine	Furosemide	Quetiapine
	Mantova	Furosemide	Paroxetine	Warfarin
Campania	Avellino	Furosemide	Paroxetine	Quetiapine
	Caserta	Paroxetine	Furosemide	Quetiapine
	Napoli 1	Paroxetine	Furosemide	Quetiapine
	Napoli 2	Furosemide	Paroxetine	Quetiapine

5.3.5 Sedative Load (SL) Score

A SL Score ≥3 occurred in a small percentage of older patients. All the annual prevalence rates ranged between 0.75 and 1.50%, apart from Bergamo LHU, that showed percentages of 1.78, 1.89 and 1.93 in 2014, 2015 and 2016, respectively. For Napoli 1, and Napoli 2 LHUs, and for Monza Brianza areas, the SL rates' trend significantly increased over time (p-trends <0.001). On the contrary, for Caserta and Avellino LHU, it increased from 2014 to 2015 and then decreased in 2016, with p-trends <0.05 (**Figure 5.13**).

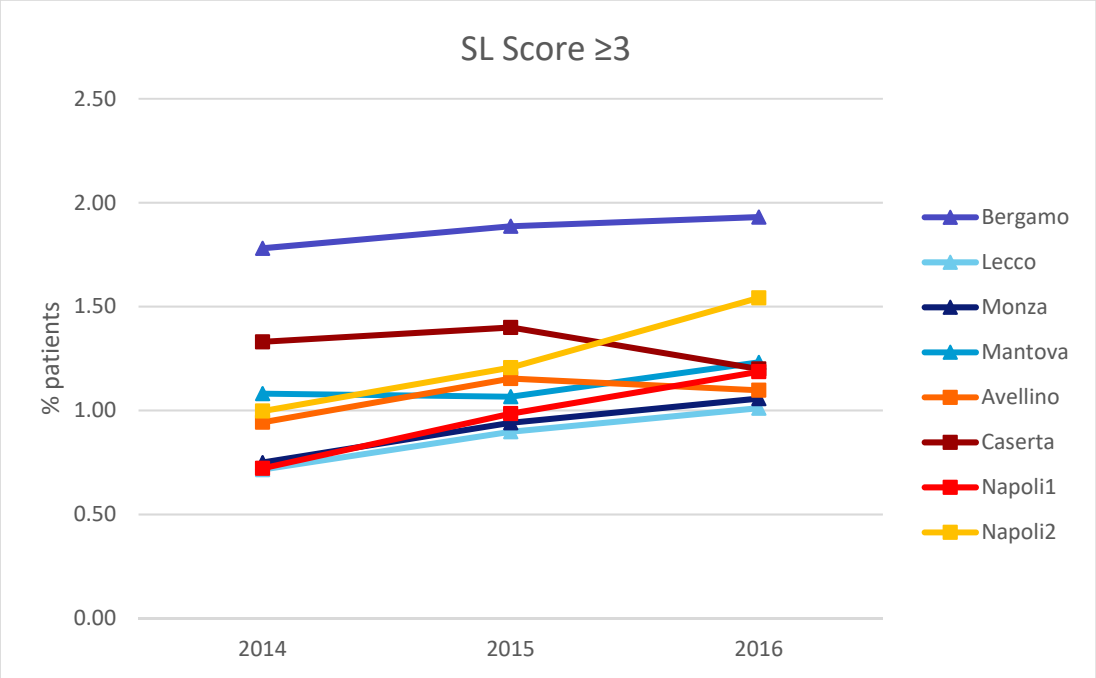


Figure 5.13 – Annual prevalence rates of SL score in the population aged ≥65 years

All the drugs reported in **Table 5.30**, **Table 5.31**, and **Table 5.32** belonged to the ATC code group "N" (Nervous system) and includes antidepressants, antiepileptics, psycholeptics, psychoanaleptics, etc. Among them, the most frequently prescribed drugs present in the SL list were traditional antipsychotics (ATC code: N05A).

Table 5.30 – Most frequently prescribed drug or drug classes with SL score ≥3, in 2014

	LHU	1°	2°	3°
Lombardy	Bergamo	Traditional antipsychotics	Trazodone	Amitriptyline
	Lecco	Traditional antipsychotics	Sertraline	Trazodone
	Monza Brianza	Traditional antipsychotics	Sertraline	Trazodone
	Mantova	Traditional antipsychotics	Trazodone	Sertraline
Campania	Avellino	Traditional antipsychotics	Trazodone	Valproic acid
	Caserta	Traditional antipsychotics	Valproic acid	Trazodone
	Napoli 1	Traditional antipsychotics	Paroxetine	Trazodone
	Napoli 2	Traditional antipsychotics	Trazodone	Sertraline

Table 5.31 – Most frequently prescribed drug or drug classes with SL score ≥3, in 2015

	LHU	1°	2°	3°
Lombardy	Bergamo	Traditional antipsychotics	Trazodone	Sertraline
	Lecco	Traditional antipsychotics	Trazodone	Sertraline
	Monza Brianza	Traditional antipsychotics	Sertraline	Trazodone
	Mantova	Traditional antipsychotics	Trazodone	Citalopram
Campania	Avellino	Traditional antipsychotics	Trazodone	Paroxetine
	Caserta	Traditional antipsychotics	Trazodone	Valproic acid
	Napoli 1	Traditional antipsychotics	Trazodone	Paroxetine
	Napoli 2	Traditional antipsychotics	Trazodone	Sertraline

Table 5.32 – Most frequently prescribed drug or drug classes with SL score ≥3, in 2016

	LHU	1°	2°	3°
Lombardy	Bergamo	Traditional antipsychotics	Trazodone	Sertraline
	Lecco	Traditional antipsychotics	Trazodone	Sertraline
	Monza Brianza	Traditional antipsychotics	Trazodone	Sertraline
	Mantova	Traditional antipsychotics	Trazodone	Sertraline
Campania	Avellino	Traditional antipsychotics	Trazodone	Valproic acid
	Caserta	Traditional antipsychotics	Trazodone	Valproic acid
	Napoli 1	Traditional antipsychotics	Trazodone	Paroxetine
	Napoli 2	Traditional antipsychotics	Trazodone	Sertraline

5.4 APPROPRIATE DRUG USE ANALYSES

As describes in Methods section, adherence was assessed applying two different approaches; results for the annual adherence evaluation on prevalent users are reported in the **Appendix IV** section.

Overall, mean proportion of days covered (PDC) for the four selected drug classes was less than 60% in all the LHUs (**Table 5.33**).

New users of antidiabetic drugs had less than half of their first treatment year covered by the therapy, with the exception of Bergamo and Napoli 1, which showed the highest values (52.52% and 57.00%, respectively). Regarding antihypertensive drugs, four out of eight LHUs (Bergamo and Mantova in Lombardy and Napoli 1 and Napoli 2 in Campania) had a mean PDC greater than 50%. Mean adherence to bisphosphonates was highest for Napoli 2 (56.05%), while for statin none of Campania LHUs showed a PDC higher than 50%. This value was reached only for two LHUs in Lombardy (50.34% for Bergamo LHU and 50.74% for Mantova area).

Table 5.33 – Mean levels of adherence (as proportion of days covered) to selected drug classes in incident users aged ≥40 years

	LHU	Antidiabetic drugs	Antihyper-tensive drugs	Bisphospho-nates	Statins
Lombardy	Bergamo	52.52%	54.39%	46.89%	50.34%
	Lecco	38.00%	36.90%	33.10%	35.56%
	Monza Brianza	38.68%	36.22%	33.64%	34.56%
	Mantova	49.34%	52.33%	43.48%	50.74%
Campania	Avellino	46.95%	46.55%	39.46%	41.83%
	Caserta	43.75%	42.39%	34.31%	36.98%
	Napoli 1	54.67%	50.27%	44.21%	44.89%
	Napoli 2	57.00%	52.94%	56.05%	46.75%

Chapter 6

DISCUSSION

Over the last decade, national health systems have faced growing common challenges: increasing cost of healthcare, population ageing associated with a rise of chronic diseases and multi-morbidity leading to greater demand for healthcare, shortages, and uneven distribution of health professionals, health inequalities and inequities in access to healthcare.
All these factors have contributed to rise even serious medication-related problems, including mis-, under- and over-utilization and consumption of drugs, prescription of unnecessary drugs and multi-prescription drugs in elderly patients *[Spinewine, 2008]*. Although there is evidence of a growing awareness of the issue *[Mannucci et al, 2014; Franchi et al, 2016]*, in Italy there is a lack of official policy statements or regulatory guidelines on management of inappropriate prescribing and not-rational use of medicines.

6.1 HOW TO MEASURE APPROPRIATENESS

Medication prescription is one of the most powerful tools for GPs in the prevention and treatment of disease and the alleviation of symptoms. However, medication-related adverse events are an important source of patient morbidity, many cases of which could be prevented by the highest-quality prescribing and medicines management *[Howard et al, 2003; Howard et al, 2007; Howard et al, 2008; Pirmohamed et al, 2004].*
Good indicators are needed for a valid and reliable measurement of the quality of prescribing. This implies the need of measurable elements in the care provided for which there has to be consensus and which can be used to estimate and improve the quality of care provided *[Lawrence et al, 1997].* Evaluation of prescribing practice should be single, integrated process that allows to demonstrate that doctors meet current professional standards, are up-to-date, and fit to practise.
There have been many attempts over recent years to develop prescribing indicators, such as those based on the interrogation of prescriptions issued

by GPs (for example, using prescribing analysis and cost tabulation data). Other indicators required very detailed analysis and assessment of clinical records (for example, the medication appropriateness index), which would not be feasible for the large-scale assessment of all GPs *[Bregnhøj et al, 2005]*.

The evidence base for developing quality indicators for appropriate prescribing is limited; however, systematically combining available evidence with expert professional opinion using a consensus methodology can create quality indicators in areas where it would not otherwise be possible *[Campbell et al, 2002]*. Moreover, with developments in methods for interrogating electronic medical records, there is now the opportunity to develop and use sophisticated indicators that can give an assessment of the quality and safety of prescribing by individual GPs *[Batty et al, 2003]*. The indicators currently described in the literature with respect to the prescription of drugs are mainly formulated on the basis of general recommendations; they are rarely derived from existing, general practice guidelines that are more specific for GPs. Such evidence-based guidelines are now available in several countries.

Quality indicators are increasingly used to facilitate regulation, ensure accountability, and improve quality. In recent years there has been considerable interest in using high level indicators to compare the performance of different health systems. However, developing lower level clinical quality indicators is an expensive and time consuming process, and there is currently little evidence to suggest that the process can be facilitated by transferring indicators developed for the health system in one country to another country *[Marshall et al, 2003]*. Notably, indicators cannot simply be transferred directly between countries without an intermediate process to allow for variation in professional culture or clinical practice.

In Italy, AIFA (*Agenzia Italiana del Farmaco*), the main authority for drugs in Italy, has adopted four tools for the appropriateness of drug prescriptions, that are outlined in **Box 6.1**, and defined a set of indicators

focused on prescription behaviours, consumption of medicines, and compliance to prescribed therapies *[OsMed Report 2014]*. Despite this, there still is a paucity of studies investigating this phenomenon in the Italian population *[Allegri et al, 2017].*

Box 6.1 – Tools adopted by AIFA *[Garattini et al, 2017]*

(1) the so called 'AIFA notes', which define the reimbursement regimens for many drugs and encourage physicians to limit prescriptions to the indications with proven efficacy

(2) price caps for single drugs or therapeutic classes within managed entry agreements contracted with pharmaceutical industry

(3) 'therapeutic plans', which state the clinical conditions for reimbursement and limit it only to labelled therapeutic indications

(4) 'monitoring registries', which track the eligibility of patients and the complete flow of treatments according to approved indications

In this research project, we defined a set of explicit indicators for potential inappropriate prescription and drug use and we adapted them to the Italian drug formulary, providing tools specifically tailored to the Italian context. Secondly, using administrative health-care databases from two Italian regions, Campania and Lombardy (4.8 million and 4.7 million of adult subjects included, respectively), we retrospectively assessed the rates of the selected indicators of inappropriate prescribing and drug use among community dwelling adults, during the period 2014-2016.

The set of indicators proposed in the present thesis was developed to provide an explicit and meaningful measure of the quality of prescribing in a real-world setting. Particularly, the set assessed three main domains, including drug consumption (polypharmacy, DID calculation for selected drug classes), appropriateness of prescription (potential drug-drug interactions, therapeutic duplication, drug to be avoided in the elderly, anticholinergic and sedative load in the elderly), and adherence to chronic treatments, identifying the occurrence of risky or erroneous prescriptions

and suboptimal prescribing practice and drug use. An important area of application for these prescribing indicators is their use as an instrument to estimate and improve the quality of pharmacotherapeutic care. Another use of the prescription indicators can be found in research into clarifying variables for differences in prescribing behaviour. In a multivariate analysis, the prescription indicators, or reliable sum scores of these, can be used as independent variables alongside patient and practice characteristics and other clarifying variables which are thought to be correlated with prescribing, such as degree of urbanisation, type of practice, work pressure experienced, etc.

The definition of these indicators specific for the Italian context allows us to estimate the appropriateness of therapies that are actually available and traceable in our country. In addition, as shown in this thesis, it allows to make temporal comparisons and between different geographical areas.

However, as the prescribing indicators were calculated using pharmacy databases, the link with individual prescription decisions is lacking for prescribers, and the indicators are limited to what is measurable in the pharmacy databases. Moreover, it should be noted that pharmacy databases do not register the drugs prescribed but the drugs supplied to the patient. The supply may be influenced by the pharmacist; he could advise patients and prescribers and intervene in the case of drug-related problems and in partnerships with GPs.

A source of bias in the calculation of the indicators from pharmacy databases is the effect of the patient who, depending on the type of prescription, does not always submit all drug prescriptions to the pharmacist. As a consequence, an indicator might give an incorrect estimate of the degree to which prescribing is in accordance with the guideline; however, this effect is probably limited *[Beardon et al, 1993]*.

6.2 EVALUATION OF DRUG CONSUMPTION

6.2.1 Polypharmacy

Polypharmacy, commonly defined as taking five or more medications, resulted to be extremely common in the EDU.RE.DRUG population. In Campania LHUs, about 45-50% and 20-25% of older people (≥65 years) received 5-9 drugs and at least 10 drugs, respectively. These percentages were lower for Lombardy LHUs: less than 40% and less than 10%, respectively. In comparison with other studies on older adults, Campania LHUs showed higher prevalence of polypharmacy, while Lombardy LHUs were characterized by lower prevalence rate. For example, in the study of Onder and colleagues, around 49% and 11% of Italian people aged 65 years or over reported a concomitant dispensing of 5-9 drugs and ≥10 drugs, respectively *[Onder at al, 2014].* These data are in accordance with findings from a registered-based study performed in a large population of older adults in Sweden (44% of subjects with 5-9 drugs and 11.7% with ≥10 drugs) *[Morin et al, 2018]*. Another study on Irish primary care showed a polypharmacy (5-9 drugs) rate of 30% in adult aged 45-64 years and 60% in the elderly, while about 8% on those aged 45-64 years and 21% of over 65's patients received a simultaneous prescription of 10 drugs or more *[Moriarty et al, 2015]*. This expected evidence was observed also in our study, where younger adults (40-64 years) reported a lower prevalence for both the categories of polypharmacy. Two Italian studies conducted in community-dwelling elderly people reported that 46% *[Nobili et al, 2011]* and 31% *[ARNO Project Report, 2001]* were exposed to 5 or more drugs.

All these data are particularly alarming, because polypharmacy increases the likelihood of adverse drug events (ADEs). It was estimated that the risk of ADEs increases from 13% in a person taking two medicines to 58% when taking five and 82% when taking seven or more *[Prybys et al, 2002]*. In another study, the number of regular prescribed medications correlated with risk of ADEs: subjects taking 5 to 6 medicines, taking 7 to 8 medicines,

and 9 or more medicines showed 2 times, 2.8 times, and 3.3 times higher risk, respectively *[Field et al, 2001].* This is particularly true in older adults, often characterized by the coexistence of many chronic diseases and multiple therapies *[Field et al, 2004; Wauters et al, 2016]*. First, because a higher number of drugs comes with a higher risk of harmful drug–drug interactions *[Johnell et al, 2007]*. Second, because the aging process is associated with physiological, pharmacokinetics, and pharmacodynamics changes that make older adults more prone to adverse drug reactions *[Sera et al, 2012; Hubbard et al, 2013].* Third, because the high prevalence of chronic multimorbidity in old age leads to an enhanced risk of drug–disease interactions *[Mallet et al, 2007; Fortin et al, 2012]*.

Moreover, polypharmacy contributes to non-adherence *[Stoehr et al, 2008]*, to drug-related hospitalizations *[Marcum et al, 2012],* and consequently, to higher health care costs. According to the Geriatrics Working Group of AIFA, 1.3 million elderly Italians take more than 10 daily drugs, with the age group between 75 and 84 years recording the highest intake: 55% take between 5 and 9 drugs per day, 14% take 10 or more. In terms of expenditures, the older citizens absorb 60% (15.7 billion Euros) of the total cost of drugs (26.3 billion) *[OsMed Report 2014]*.

Beyond the prevalence of multiple concomitant disease, the reason why polypharmacy is so widespread can be partially found in the application of published guidelines that hardly take into account the presence of multimorbidity, especially in older patients *[Hilmer et al, 2009]*. Physicians tend to follow the guidelines available for each of the multiple diseases that affect the elderly, and hence prescribe all the drugs recommended for each disease *[Manucci et al, 2014]*. The management of comorbid conditions with multiple medications is indeed one of the greatest prescribing challenges in geriatrics *[Bernabei et al, 2011]* that can be summarized by the observations of two eminent geriatricians: Dr Jerry Avorn observed that "medications are probably the single most important healthcare technology in preventing injury, disability, and death in the geriatric population" *[Avorn et al, 1995]*. On the other hand, the risk associated with use of medications in the elderly is expressed in the warning by

Gurwitz et al. that "any symptom in an elderly patient should be considered a drug side effect until proved otherwise" *[Gurwitz et al, 1995].* Another reason stems from the fact that patients, especially the elderly, are followed at the same time by different specialists, in addition to their general practitioner. The poor information flow, the lack of habit of a medication review, and the reluctance to implement deprescribing, all contribute to increasing the prevalence of polypharmacy. Deprescribing has been defined as 'the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes'. This is particularly relevant to patients with polypharmacy, because the risk of harm caused by medication increases with the number of medications a patient is prescribed. Stopping or reducing the dose of medications requires careful clinical consideration, with a need to balance issues such as potential loss of clinical benefit and increased patient anxiety, against reductions in medication errors, adverse reactions and drug burden *[Reeve et al, 2015]*. Factors that influenced decisions of whether or not to deprescribe include a sort of clinician inertia, whereby the clinician is aware of the potential harmful effects of medications but chooses not to act on this knowledge neither to stop the medication. Reasons for this included not wanting to generate more work (e.g. having to monitor the effects of stopping medications or overcoming logistical issues such as making changes to dosette boxes), and avoiding conflict with other healthcare professionals who may have started the medication *[Anderson et al, 2014]*.

Polypharmacy, therefore, constitutes an important and well-known issue in all care settings, but still remains not widely addressed in Italy, as well as in some European countries, as reported by recently published data from the SIMPATHY Project and showed in **Figure 6.1** *[McIntosh et al, 2018]*. However, some efforts have been made to implement polypharmacy management initiatives in primary care, including guidelines to perform medication reconciliation and review or alert system pointing out complex chronic patients in electronic medical record. Certainly, a multidisciplinary approach implemented in multiple settings, such as

primary care, community pharmacies and hospitals, and involving not only GP and pharmacists, but also authorities of health-care systems and patients' families, is the key point to manage polypharmacy issue successfully *[Hosseini et al, 2018; McIntosh et al, 2018].*

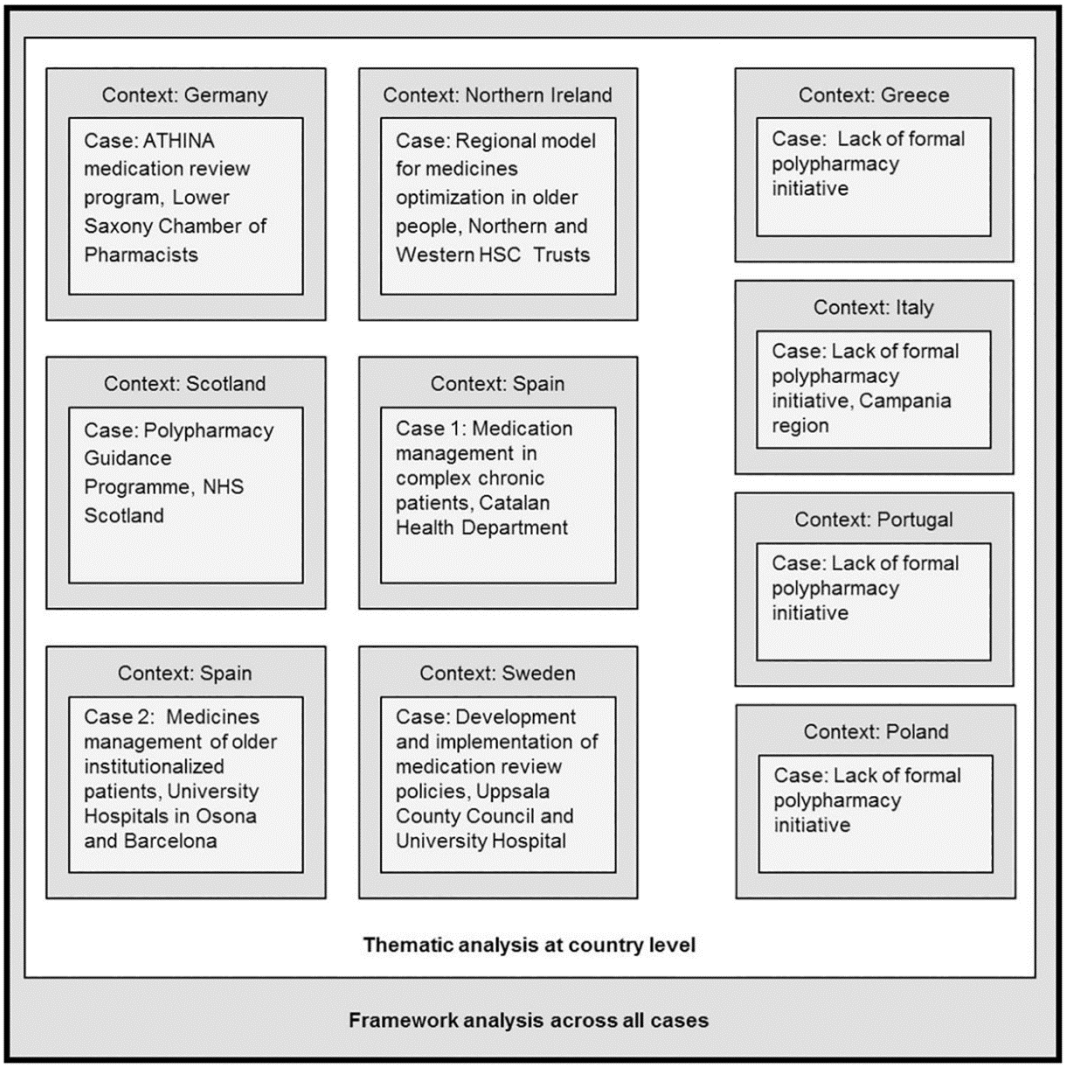


Figure 6.1 – SIMPATHY Project: a case study of polypharmacy management in nine European countries *[McIntosh et al, 2018]*

6.2.2 Consumption of selected drug classes

Proton pump inhibitors (PPIs) are among the most commonly prescribed and used drugs globally: the favourable benefit/risk ratio traditionally

attributed to PPIs, combined to their high cost-effectiveness, has increased their use, up to fall into the problem of over-utilization. In fact, in one study looking at elderly patients discharged from hospital in Italy, 30% were receiving a PPI with no clear indication *[Schepisi et al, 2016]*. Also in our study, for older people, time trend in PPI consumption (in terms of DID) increased from 2014 to 2016 in all LHUs, apart from Avellino and Caserta LHUs. Notably, the amount of PPI DID consumed by elderly in Lombardy LHUs was far lower than in Campania LHUs. A smaller difference between the two regions was found for patients aged 40-64 years (again, higher levels for Campania with respect to Lombardy), for whom a definite time trend cannot be described. It is important to keep in mind that, in Italy, PPIs are dispensed also without prescription. Thus, our data may underestimate real amount of PPI consumption or confound the real trend over time. Despite this, the problem of PPI over-prescription and use remained. Yet studies consistently show that PPIs are being overprescribed worldwide in both primary and secondary care *[Naunton et al, 2000; Walker et al, 2001; Bjornsson et al, 2006; Grant et al, 2006; Batuwitage et al, 2007]*. Furthermore, overprescribing is more common in patients with comorbidities and polypharmacy, likely due in part to a belief that PPIs have greater benefits and safety profiles than have actually been demonstrated *[Walker et al, 2001]*.

It is clear that actions are needed to curb and reduce PPI over use. Reeve and colleague outlined the steps to achieve the purpose: recognition of the problem; use of alternative approaches to manage conditions currently treated "by default" with PPIs; education regarding appropriate indications and durations for their use; and enhanced drug stewardship akin to that employed widely for antimicrobials, mandating better documentation around PPI prescriptions and regular review. Patient involvement and shared decision-making are also essential *[Reeve et al, 2014]*. In addition, Farrell and colleagues, developed an evidence-based guideline to help clinicians make decisions about when and how reduce the dose of or stop PPIs (**Figure 6.2**) *[Farrell et al, 2017]*. To note, an Italian version of this algorithm by Maio and colleagues is available *[bal.lazio.it website]*.

Figure 6.2 - Proton pump inhibitor deprescribing algorithm *[Farrell et al, 2017]*

Another drug class that has raised concerns for over-prescription is antibiotics. A 2016 report by Centers for Disease Control and Prevention (CDC) estimates that at least 30% of antibiotics prescribed in US outpatient settings are unnecessary *[Harris et al, 2016]*. Several studies show that the Italian consumption of systemic antibiotics is higher than the European average, both in hospitals and in the outpatient population *[Adriaenssens et al, 2011; Morgan et al, 2011]*. Reasons cited by doctors for overprescribing antibiotics include diagnostic uncertainty, time pressure on physicians, and patient demand. Physicians are pressured by patients to prescribe antibiotics. It may be easier for the physician pressed for time to write a prescription for an antibiotic than it is to explain why it might be better not to use one *[*Schwartz *et al, 1997].* These aspects, together with socio-demographic (eg, urbanization), socio-economic (eg, financial and well-being) and cultural (eg, education level) factors *[Russo et al, 2018]*, can explained the great variability in antibiotic consumption in our study.

Indeed, there was a wide difference in amount of DID consumed between Lombardy and Campania, where it was about two times higher in both age classes (younger and older adults). Moreover, for the elderly, in some LHUs (such as Avellino, Bergamo, Caserta and Mantova), antibiotic consumption decreased over time. On the contrary, Lecco and Monza Brianza show a small increase that was more marked for Napoli 1 and, even more, for Napoli 2.

Although universal agreement that antibiotic overprescribing is a problem, more changes in clinical practice are warranted *[Fiore et al, 2017].* Besides this, there is also strong evidence that when physicians decrease antibiotic prescribing, antimicrobial resistance (which has reached alarming levels worldwide) follows suit *[Seppälä et al, 1997; Guillemot et al, 2005; Butler et al, 2007; Baur et al, 2017]*. However, some early intervention programs (**Box 6.2**) directed at reducing antibiotic prescribing demonstrated success *[Gonzales et al, 1999; Perz et al, 2002; Meeker et al, 2016].*

Box 6.2 – Examples of practice- and system-level interventions that can decrease antibiotic prescribing

1) Monthly e-mails to physicians that compare their antibiotic prescribing to set goals or "top performers" within the organization.

2) Electronic medical record "prompts" that require physicians to provide an "antibiotic justification note" when a potentially inappropriate antibiotic is prescribed for a particular diagnosis.

3) Distribution of patient information that explains the limitations and potential harms of overprescribing antibiotics to patients.

6.3 APPROPRIATENESS OF PRESCRIPTION

Data on appropriateness of prescribing are not exhaustive in the general population; however, there is relevant literature regarding the inappropriateness in certain categories of patients, such as the elderly, who are certainly the most exposed individuals to potentially inappropriate prescriptions (PIP). As already mentioned, the age-related physiological changes, the higher incidence of multiple chronic diseases and the greater number of prescriptions they receive, make this population more prone to medication-related problems *[Morin et al, 2018]*. In order to give a quantitative estimate of this phenomenon in Italy, in the present study we measured the prevalence of some indicators among over 65 patients, including rate of drugs to be avoided in the elderly, anticholinergic burden and sedative load. Notably, in our study we also estimated the prevalence of potential drug-drug interactions (pDDI) and therapeutic duplicates (TD) in the whole cohort of adult patients, aged 40 years and over.

6.3.1 Appropriateness of prescription in adult patients

A range between 10 and 15% of residents in Lombardy LHUs were exposed to severe pDDI; in Campania the percentage was about two times higher

(between 21 and 25%). Evidence obtained for Lombardy LHUs are in accordance with a previous study conducted using the administrative prescription database of the LHU of Lecco, where 16% of elderly patients had at least one severe pDDI in 2003 *[Nobili et al, 2009]*. This percentage is slightly higher comparing to results for Lecco LHU in our study (nearly 11%), probably due to the different age of patients included, or to the time elapsed between theirs and our evaluation. In fact, the elderly constitutes a population at high risk of serious pDDIs because of the high rate of drug prescription. Accordingly, in another Italian study among patients aged 65 years or older recruited at hospital admission 18.9% were exposed to at least one severe pDDI *[Pasina et al, 2013]*. Another study on registered-based population in Sweden reported even higher percentages (31%) for people aged ≥75 years *[Johnell et al, 2007]*. Moreover, in a recently published study, among elderly patients in primary care, nearly 55% were found to have pDDIs *[Gören et al, 2017].* By contrast, in Swedish people aged 15–95 years, the prevalence of potential DDIs has been estimated to be about 14% *[Merlo et al, 2001],* more in accordance with Lombardy data, while lower in comparison with Campania results.

There is a great variability of pDDI prevalence between studies, that is strongly influenced by the type of population (patients' age and the severity of the diseases) and care setting examined and by the type of interactions investigated. In some studies, in fact, not all the possible drug interactions were examined, but only some of the most clinically relevant pairs *[Malone et al, 2004; Gagne et al, 2008; Tragni et al, 2013]*. In a study conducted in Italy the most commonly observed pDDI was warfarin-NSAID combination *[Gagne et al, 2008].* By contrast, in our study, the most frequent pDDI were hydrochlorothiazide-ibuprofen and pantoprazole-levothyroxine in Lombardy LHUs, and hydrochlorothiazide-diclofenac in Campania LHUs. The anti-inflammatory properties of NSAID therapy appear to result from their common ability to inhibit the biosynthesis of prostaglandins, which are involved in the modulation of blood pressure. The administration of ibuprofen or diclofenac has been shown to produce small increases in systolic and mean arterial blood pressure in older

subjects with hypertension controlled with hydrochlorothiazide. More than five days of treatment with both drugs are normally required for the interaction to manifest. Although the changes in blood pressure resulting from this interaction are typically small, some patients can experience substantial elevations in both systolic and diastolic blood pressure. Patients subjected to antihypertensive treatment should undergo closer blood pressure monitoring at the start of analgesic treatment *[Koopmans et al, 1987; Gurwitz et al, 1996].* Concerning pantoprazole-levothyroxine interaction, studies have shown that gastric acidity enhances the dissolution of levothyroxine tablets. Thus, PPIs, which suppress gastric acid secretion, might be expected to inhibit absorption of levothyroxine delivered as a tablet *[Vita et al, 2014]*.

Although the estimation of the prevalence of pDDIs varies greatly from study to study, it is understandable that pDDIs represent an important issue in clinical practice. Several studies demonstrated that the exposure to pDDIs can lead to serious problems, such as adverse events, and increase the risk of hospitalizations and length of stay in the intensive care unit *[Hamilton et al, 1998; Juurlink et al 2003; Rodrigues et al 2017]*. However, pDDIs are not the same as actual DDIs *[Seymour et al, 2011]*. Even if we only included potentially clinically relevant type C DDIs (which may require at least dose adjustment) and potentially serious type D DDIs (which should be avoided), we have no way of verifying whether the concomitant prescription of two potentially interacting drugs resulted in their actual concomitant intake, nor whether it is hesitated in relevant clinical consequences. In addition, we could not know if GP who has prescribed two interacting drugs at the same time, has also explained to the patient to postpone or to suspend one of the them.

Our study indicates a relatively low prevalence of patients with at least one TD, defined as overlapping prescription of two drugs with same ATC code at the fourth level but different ATC code at the fifth level. In particular, it counts for 2-3% and 5-7% of adult residents in Lombardy LHUs and in Campania, respectively. Also in the study by Azoulay and colleagues

involving patients aged ≥65 years in Iran, prescribing medications having the same ATC fourth level was regarded as TD. Out of this study's population, 25% had prescriptions with medication duplications *[Azoulay et al, 2005]*. The large discrepancy between the latter and our results is mainly due to the source of data used in our study. It should be remembered that the evaluation of therapeutic duplicates, as well as of the other indicators, was limited to the drugs prescribed under the reimbursement regime. Of note, the most prevalent drug-class duplication was NSAIDs (32.8%), a class of drugs particularly prone to duplicate. Indeed, in Italy, medications containing NSAIDs could be prescribed by physicians but also freely purchased by the citizen (over the counter drugs), who often does not know their composition. In addition, it may be partially due to the different characteristics of patients included. With regard to therapeutic duplicates, it is difficult to make comparison with previous studies, because of the variety of TD definition, besides the heterogeneity of settings and populations studied. In a national-based study in Austria, for about 13-15% of subjects treated with antihypertensives, hypoglycemic, or lipid-lowering medication at least one occurrence of TD was reported *[Heinze et al, 2016]*. In this study, TD was defined as the overlapping prescription of the same substance with the same route of administration by two different prescribers to the same patient. Our findings appear to be in accordance with those reported in a study conducted among home healthcare patients in US *[Meredith et al, 2001]*, as well as in another study performed in Belgium's Flemish County pharmacies in 2001 that showed that 5.4% of patients had TD *[Leemans et al, 2003]*, even if, in the latter study, TD was defined as "two or more medicines containing the same medicinal compound". In the same year, in a study conducted in 112 European community pharmacies (across Austria, Denmark, Germany, The Netherlands, Portugal and Spain) drug duplication was found in 2.2 % of patients *[Paulino et al, 2004]*.

6.3.2 Appropriateness of prescription in elderly patients

Over the past two decades, several lines of evidence demonstrated an increasing prevalence in prescribing potentially inappropriate medications in the elderly, determined by a variety of different screening tools across a number of different jurisdictions and health care settings. In this regard, we developed a list of inappropriate drugs in the elderly, called EDU.RE.DRUG list or ERD-list, specifically adapted to Italian drug formulary.

Also in this case, findings from our study showed differences in prevalence and time trend between the two geographical areas in Italy: out of the elderly population (1.7 million in Lombardy; 1.6 million in Campania), around 25-35% in Northern LHUs and between 50 and 65% in the South received prescriptions of at least one inappropriate drug/drug class included in the ERD-list. The results for Lombardy region are consistent with a cohort study conducted in elderly outpatients of Parma LHU (Emilia-Romagna region, Italy), using pharmacy database *[Maio et al, 2010]*. In the mentioned study, about 26% of elderly people received a prescription for at least one drug included in the list the authors developed by adapting the Beers 2003 criteria to Italian context. Of note, a previous study by the same author showed a lower percentage (18%) of elderly outpatients, in Emilia-Romagna region, affected by PIP *[Maio et al, 2006]*. However, in the latter study the update Beers 2003 criteria, originally developed in the US, were used. The same criteria list was utilized in two other studies conducted in Italy *[Landi et al, 2007; Ruggiero et al, 2010]*: in the first one nearly 26% of elderly population (≥80 years), while in the second one 48% of older people (≥65 years) living in 31 nursing home across Italy, were exposed to PIP. In addition, the prevalences reported in our study for Lombardy region, unlike Campania region, are in accordance with several Italian studies conducted among in-hospital older adults *[Onder et al, 2003; Onder et al, 2005; Pasina et al 2014; Di Giorgio et al, 2016]*. Results found in Campania region are even more alarming if we look at other European countries. In a study published in JAMA, the prevalence of

inappropriate drugs was studied in a sample of patients aged ≥80 years receiving home care services in 11 European countries, including Italy *[Fialová et al, 2005]*. The authors observed that, overall, about 20% of patients received the prescription of at least one inappropriate drug, with wide differences between the various countries. Italy (26.5%) was second only to the Czech Republic (41.1%). Similarly, a systematic review, that included fifty-two manuscripts evaluating the prevalence of PIP in community-dwelling older adults across Europe, reported un overall prevalence of 22.6% *[Tommelein et al, 2015].*

Among the most prevalent ERD criteria, there were the PPI therapy for more than 8 weeks. PPIs are a class of medications used to treat acid-related disorders and, as already described (see paragraph 6.2.2), their use has significantly increased over the last few decades. Since they have been on the market, a number of post-marketing studies have been published demonstrating associations between longer duration of PPI therapy and a number of adverse effects that are a concern in older adults. PPIs have been associated with an increased risk of a number of adverse effects including osteoporotic-related fractures, *Clostridium difficile* infection, community-acquired pneumonia, vitamin B12 deficiency, kidney disease, and dementia, demonstrated by a number of case-control, cohort studies, and meta-analyses. Older adults should be periodically evaluated for the need for continued use of PPI therapy *[Maes et al, 2017]*. In addition to PPIs, prescriptions of diclofenac and ketoprofen were found in elderly. It can put you at risk for falls and other dangerous events. In general, NSAIDs can cause extreme sleepiness, confusion, dizziness, loss of balance, and severe stomach problems in the elderly *[Hughes, 1991]*.

In our study we found a relatively low prevalence of anticholinergic burden, estimated as defined by Anticholinergic Cognitive Burden (ACB scale) *[Boustani et al, 2008; Campbell et al, 2013]*, which is the most frequently validated expert based anticholinergic scale on adverse outcomes *[Salahudeen et al, 2015]*; the proportion of older study population with an ACB score of 3 or higher ranged between 4.6% and 9.3% in all the LHUs.

Indeed, in a study among a cohort of older adults attending primary care clinics, Boustani and colleagues stated that the percentage with at least one medication with ACB score of 3 was 20% *[Boustani et al, 2008].* Moreover, in a population of community-dwelling adults 65 years or older in the US, an ACB score of 3 or greater was identified in 47.8% of patients *[West at al, 2013]*. This discrepancy may be due to the fact that we evaluated only drugs reimbursed by Italian NHS, which do not comprise some medications with anticholinergic properties, such as antihistamines, or antiemetics. However, a more recent study, involving community dwelling Australian men aged 70 years and over, showed that 8% of subjects was exposed to high (≥3) anticholinergic exposure according to the ACB *[Pont et al, 2015]*, being comparable with our results. In another English community-based study a high burden of anticholinergic drug use was reported in 4% of older people included *[Fox et al, 2011].* Unfortunately, making comparison with other countries is quite chancy, because of multiple local-related variables. Yet, there is not great availability of Italian literature in this regard. Only one study was conducted in primary care, but the author used another classification for the ACB scale by Cai et al. *[Cai et al, 2013]*, defining a high score as ACB ≥2; 13.6% of adult patients (≥45 years) with first cognitive impair reported a high ACB score *[Grande et al, 2017].* In a multicentre study conducted in Italy in adults over 40 years with intellectual disabilities, 11.3% of the total population showed an ACB score ≥3; of these only 10% were over 65 years old *[De Vreese et al, 2018].* Finally, Pasina and colleagues, determined the ACB score in a cohort of hospitalized elderly patients; of these, nearly 8.5% had an ACB score of 3 or greater. Moreover, they found a dose-response relationship between total ACB score and cognitive impairment, thus suggesting that the ACB scale can be a useful tool for a rapid identification of drugs potentially inappropriate in the elderly. In line with other similar studies, among participants with ACB scores ≥3, paroxetine (score 3), furosemide (score 2), and warfarin (score 1) were the most frequently used medications on the ACB scale *[Green et al, 2016]*.

We also found extremely low prevalence of sedative load, assessed as defined by the Sedative Load (SL) Model *[Linjakumpu et al, 2003]*. In the elderly population of the EDU.RE.DRUG study less than 2% showed a high SL score (≥3), with no remarkable variation depending on the geographical area. The epidemiology of sedative load as SL score has been studied only in another Italian study conducted in primary care setting: about 21% of older people had elevated SL score *[Allegri et al, 2017]*. Such a difference might be explained, again, to the limited drug formulary included in our analysis. In fact, numerous drugs with sedative effects, first of all benzodiazepines, are not currently reimbursed by Italian NHS. Lower percentage of subjects with high SL score with respect to the previous discussed study (8%, still higher than our results) was found in a cohort of community-dwelling patients aged 75 years and older in Finland *[Taipale et al, 2012].* Another Finnish study among community-dwelling elderly (64 years or over) reported that 12% had a sedative load ≥3 *[Linjakumpu et al, 2004]*. The same study investigated the factors associated with sedative load, reporting that older age (≥80 years) and female sex were associated with sedative load ≥3. Despite the different setting, a very similar percentage of people having high SL (12.2%) was found among residents with dementia living in residential aged care facilities in Ireland *[Parsons et al, 2011].* Accordingly, a study comparing sedative load between those with and without dementia in the same study population found that residents with and without dementia had a similar sedative load (SL mean 3.0 versus 2.7) *[Bell et al. 2010]*. All in all, these data suggest that the use of drugs with sedative properties is widespread also among patients without established cognitive impairment, thus confirming that our results may be affected by an underestimation of this indicator.

Unlike the prevalence of the other indicators of appropriateness, which are quite stable over time, the percentage of elderly patients with of high ACB score and SL score showed some increase over time. As regards the prevalence of high ACB score, a slight increase can be observed over time (with the exception of Bergamo and Caserta), up to around +11-12% for

Lecco, Monza, and Napoli 1. For high SL score, with the sole exception of Caserta area, which showed a slight decrease, in all LHUs the percentages increased from 2014 to 2016, with increments of 40% for Lecco and Monza and even higher for Napoli 1 and Naples 2 (+65% and +54%, respectively). These trends could be secondary to an increased prescription of selected serotonin reuptake inhibitors (as we observed in the consumption analysis by DID) and of antipsychotics among elderly. Indeed, based on AIFA data, Lombardy and Campania regions recorded an increase of antipsychotics consumption from 2014 to 2016 *[OsMed Report 2017]*.

6.3.3 Factors associated with prescribing practice

Our study found differences between the two regions involved in the study. In general, compared to Lombardy LHUs (in the North of Italy), Campania LHUs (in the South of Italy), reported higher prevalence for most of the indicators of quality prescribing evaluated in this study. Previous studies have showed that geographical location and other sociodemographic and socioeconomic factors, such as urbanization, low wages, education level and social deprivation, have been associated to an increased risk of potentially inappropriate prescribing *[Zhang et al, 2012, Holmes et al, 2013; Lund et al, 2013; Beuscart et al, 2017].* In a study conducted in Italy, patient living in rural areas (hill and mountain locations) were found to be more likely to be prescribed potentially inappropriate medications *[Maio et al, 2006].* Moreover, for some indicators we found differences between LHUs within the same region. This is consistent with another study conducted in Lombardy region *[Nobili et al 2011].* However, Lombardy region is quite homogeneous in terms of clinic-epidemiological factors, and there are no significant differences in relation to the age distribution of patients. For this reason, and in light of the fact that a strong correlation was found between the overall prescription prevalence rate and exposure to chronic drugs and chronic polypharmacy, the authors concluded that the

quantitative and qualitative differences between LHUs might therefore be due not to differences in the epidemiology of disease, but to different prescribing habits between physicians.

In fact, there have been several factors that influence the prescribing behavior of GPs (**Figure 6.3**), that can be summarized in five different classes *[Prosser et al, 2003; Muijrers et al, 2005; Mason, 2008; Spurling, 2010]*:

- GP factors – education, clinical knowledge, experience, confidence, risk aversion, evidence-based medicine skills;
- patient factors – compliance, ability to pay, specific request;
- clinical factors – need, previous adverse events, comorbidities;
- medication factors – safety, cost, efficacy;
- systems factors – marketing, pharmaceutical representative visits, clinical information sources.

All these variables may further complicate the process of properly choosing a drug. All of this must then be adequately contextualized in the daily work of the GP, which is not always able to fit into an optimal diagnostic-therapeutic process.

6.3.4 Interventions aimed at improving prescribing practice

Ameliorated decision-making about drug prescribing by clinicians could lead to significant improvements in patient outcomes and effective use of healthcare expenditure. There is a significant body of literature about interventions designed to change the behaviours of health professionals in order to decrease inappropriate prescribing. Of these, interventions that rely solely on passive information transfer appear to be ineffective; conversely, active knowledge translation strategies (such as audit and feedback involving comparison with peers, educational outreach, and "real-time" reminders) are usually effective *[Ostini et al, 2009]*. Finally, multifaceted interventions, that incorporate two or more strategies, are more likely to work than single ones *[Sumit et al, 2003]*.

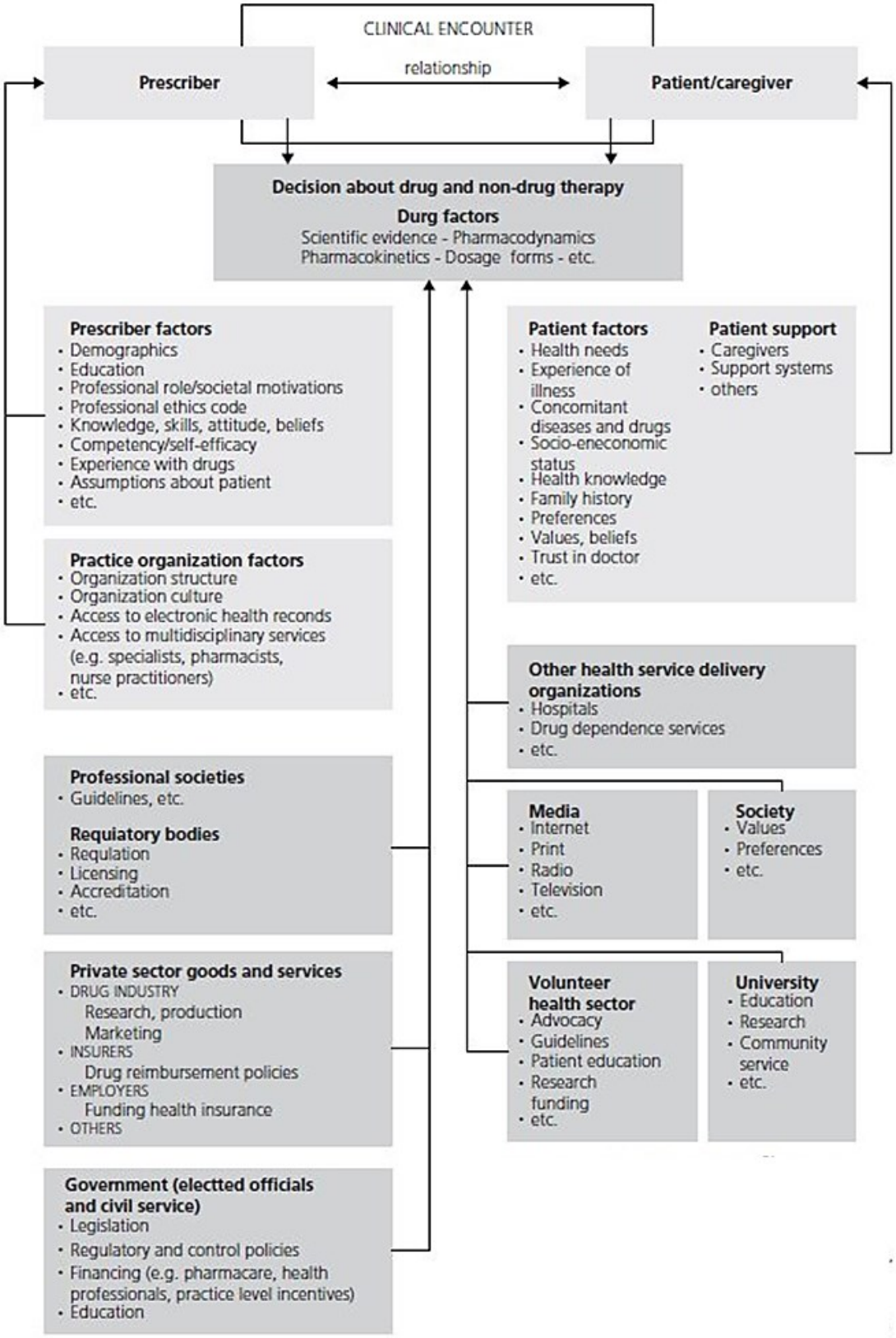


Figure 6.3– Factors affecting prescribing in clinical practice *[Sketris et al, 2007]*

Besides GP-related strategies, also patient education to improve medication compliance turned out to be effective in reducing inappropriate prescribing and adverse events *[Kaur et al, 2009].* Additionally, particular emphasis should be placed on the emerging role that pharmacists play in moderating medication appropriateness in primary care. Indeed, pharmacist-led interventions involving access to medical notes and medication reviews conducted in physician practices with feedback to physicians may improve prescribing appropriateness in community-dwelling older adults *[Riordan et al, 2016]*.

A systematic review by Garcia specified five ways to reduce inappropriate prescribing in the elderly: (i) obtain pharmacist recommendations; (ii) use computerized alerts; (iii) review patient medications; (iv) consider using Beers' criteria; and (v) educate patients to improve compliance *[Garcia et al, 2006].* In a recent publication also, the authors outlined a list of strategies to prevent inappropriateness of prescribing that is reported in **Box 6.3** *[Varghese et al, 2019].*

Box 6.3 – Strategies to prevent inappropriate drug prescribing

- Maintain an accurate medication list and medical history and update whenever possible.
- Encourage patients to bring all medications including prescription, OTC drugs, supplements, and herbal preparations.
- Review any changes with patient and caregiver and if possible, provide all the changes in writing.
- Use the fewest possible number of medications and the simplest possible dosing regimen.
- Try to link each prescribed medication with its diagnosis.
- Discontinue all unnecessary medications.
- Screen for drug-drug and drug-disease interactions.
- Use a team approach if possible, involving the caregiver or family and pharmacist (community pharmacist).
- Avoid starting potentially harmful medications; use Beer's criteria.
- Try to start a new medication at the lowest dose and then titrate slowly.
- Avoid starting medications to combat the potential side effects of other medications.
- Careful medication reconciliation during transitions of care including proper communication handoffs to accepting providers. Ensuring a close post discharge follow up for updating medical history and medications can help in preventing medication errors, treatment failures, and rehospitalizations.
- Consider goals of care and life-expectancy of patients when assessing medication appropriateness.

6.4 ADHERENCE TO CHRONIC TREATMENTS

Adherence was defined as the extent at which a person's behaviour –taking medication, following a diet, and/or executing lifestyle changes- corresponds with agreed recommendations from a health care provider *[WHO, 2003].* Measurement of adherence to chronic treatment provides useful information regarding the patient's actual behaviour towards drug therapies. This is extremely important because chronic therapies are widespread: in Italy, 50% of older patients (about 6.8 million of subjects) had at least one chronic therapy, such as diabetes, osteoporosis, and hypertension. Unfortunately, it was estimated that adherence averages only 50% among patients suffering long-term diseases *[WHO, 2003]*. Poor medication adherence is exactly the first cause for unsuccessful pharmacological treatment *[Haynes et al, 2002]*, being consequently associated with higher risk of hospitalization, increased morbidity and mortality *[Vermiere et al, 2001; Sokol et al, 2005]*. On the other hand, high rates of adherence not only have a positive impact on patient's health status, but it is also related with economic benefits. In fact, the PGEU (Pharmaceutical Group of the European Union) report showed that, in Europe, low medication adherence and inappropriate drug use cause 194,500 deaths and cost 125 billion Euros for related hospitalizations every year *[PGEU annual report, 2012]*. In Italy, it was estimated that up to 11.4 billion Euros per year would be spared with higher adherence to chronic therapy, and, therefore, fewer adverse events, lower admission to first aid and hospitalizations and lower pharmaceutical expenditure *[Centro Studi SIC-Sanità in Cifre- website]*.

In the light of these data, having an estimation of adherence to chronic therapies is extremely important to understand the magnitude of this problem and to manage it.

In our study, we evaluated the adherence level, as proportion of days covered (PDC), among new users of four different chronic therapies (antidiabetic and antihypertensive drugs, bisphosphonates and statins).

For antidiabetic drugs, mean PDC ranged between 38 and 57%, with great

differences between all LHUs. Mean adherence to antihypertensives and bisphosphonates was between 36 and 54% and between 33 and 56%, respectively. New statin users had less than half of their first treatment year covered by the therapy in all the LHUs (range: 34.5-50.7). Overall, for all the long-term therapies analysed, a suboptimal adherence level was observed (standard PDC threshold is 80% -the level above which the medication has a reasonable likelihood of achieving the most clinical benefit).

Our data describe a critical situation, which is not too far from that referred to the entire Italian population. In 2016 in Italy, only 57.7% of patients adhered to antihypertensive treatments, 63.4% to hypoglycemic drugs for the treatment of diabetes, 46.9% to statins and 52.1% to treatments for osteoporosis *[OsMed Report 2016].* The percentage reported in a study conducted in Southern Italy was even lower: only 39% were adherent to therapies, according to the MMAS-4 (Morisky Medication Adherence 4-item Scale), that is used as self-reported adherence measure *[Napolitano et al, 2016]*. Another study conducted in Southern Italian primary care, showed that 43% of new statin users had an optimal medication adherence (defined as MPR ≥80%) after 6 months, while 26% after 4-years of follow-up *[Ferrajolo et al, 2014]*. In the study by Mazzaglia and colleagues, involving about 400 GPs across Italy and their patients aged 35 years and over, only 8% of newly diagnosed hypertensive subjects were classified as having high adherence levels (PDC ≥80%) after 6 months from the first prescription. The percentage of patients with low adherence levels (PDC ≤40%) was about 51%.

Although it is difficult to make a comparison with our results, because of the difference in the methodologies used for adherence estimation in the discussed studies, poor medication adherence to long-term therapies represents a common problem. It is also a complex problem, as it is simultaneously influenced by several factors, including social and economic aspects, the health care team/system, the characteristics of the disease, disease therapies and patient-related factors. For this reason, a multidisciplinary approach is needed in order to make progress in this area,

requiring coordinated action by health professionals, researchers, health planners and policy-makers *[WHO, 2003].* Recently, some efforts have been made to address this issue and to improve the ability of patients to follow treatment plans in an optimal manner. **Figure 6.4** depicts the level of involvement of institutions in promoting medication adherence in chronic disease care in Italy, in 2018. According to the data, 38% of local healthcare centres and pharmaceutical companies encouraged the implementation of activities aimed at improving therapeutic adherence among patients suffering from chronic diseases *[Federfarma Report 2018].*

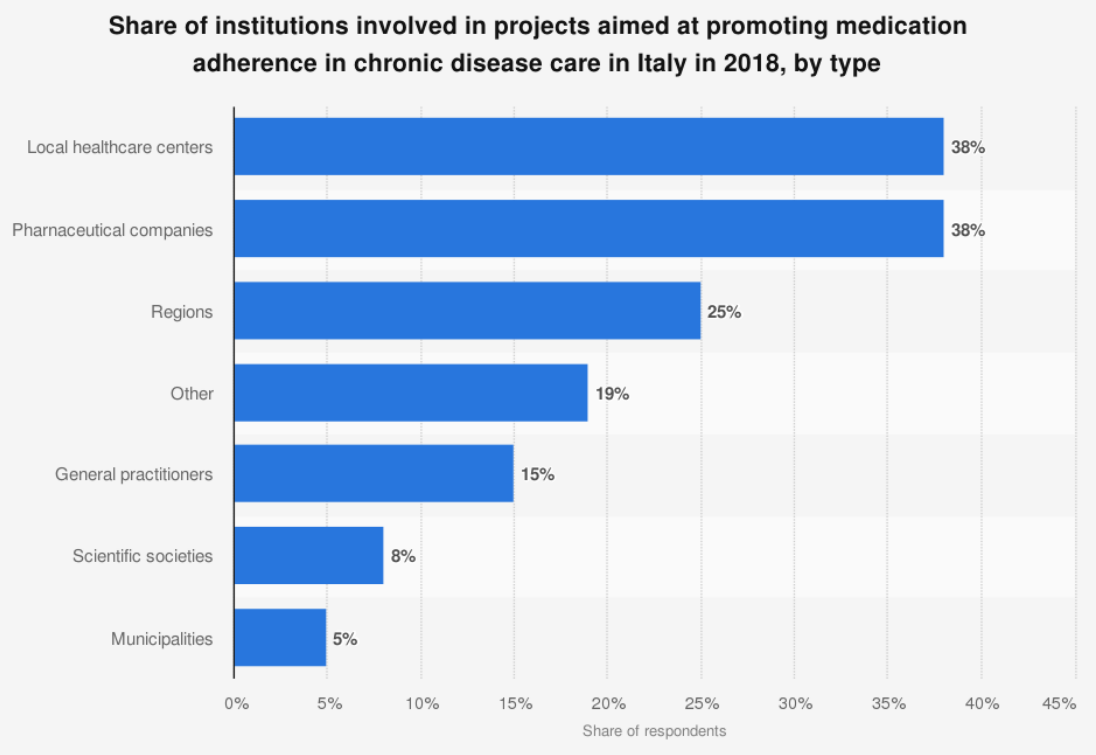


Figure 6.4 – Level of involvement of institutions in promoting long-term medication adherence

6.5 STRENGTHS AND LIMITATIONS

This project has contributed to explore inappropriate drug prescription and use, thus addressing a critical concern of great epidemiological, clinical and

socio-economic impact. The investigation was not only at qualitative level, but also quantitative. In fact, we define and develop prescribing appropriateness indicators, specifically adapted to Italian setting, that could be used both by the physician in the daily prescription activity and by the LHU for the activities of evaluation and monitoring of the prescriptive performance. This provides benefits both for GPs' activity and for health policy. On one hand, healthcare providers can target patients, evaluate patient's medication list and make appropriate changes to decrease polypharmacy and adverse events; and considering that the majority of drug-related adverse events can be preventable, a set of indicators for detecting prescribing inappropriateness, especially in the elderly, is crucial to improve the patient's quality of healthcare and to enhance safe prescribing practices. On the other hand, a useful tool is available for the evaluation of prescription appropriateness by LHU. These procedures could be applied to other specific sub-populations and to other regions or at national level, thus reducing the costs associated with inappropriate/unnecessary prescribing. Unfortunately, they cannot be applied to other countries, because there may be differences in national drug formularies or local policies. We have also to acknowledge that all our analyses were conducted through the automatic application of explicit criteria, that can yield false-positive. As already mentioned, the rationale for prescribing or starting medications was not known and patients might be wrongfully classified as being prescribed an inappropriate drug, because their medication history was not known. Despite the potential of prescription database analysis, the appraisal of the appropriateness in prescription cannot rely on the use of explicit criteria only. It must be embedded within a patient's global assessment of his/her clinical status, the complete pharmacological history and his/her preferences and needs. In this study we used secondary data, as they are routinely gathered at individual level for administrative purposes and as a part of the healthcare system in Italy. The use of existing data represents a powerful and relative low-cost research tool; however, drugs traced in these databases are limited to those that are reimbursed by Italian NHS, probably leading to

underestimation of PIP prevalence. Furthermore, our analyses did not assess important areas of suboptimal prescribing, such as benzodiazepines with long half-life or some drugs with anticholinergic properties, which are not reimbursed by the Italian NHS.

In addition, these administrative databases do not contain information on the patient clinical history (together with other lifestyle and sociodemographic factors that could drive the choose of drug prescriptions), on GP instructions, on dose and times of administration, nor on indication for treatment. To note, the only source for diagnoses is the hospital discharge database.

Finally, another great limitation is represented by the lack of information on patient real adherence to prescribed/dispensed drugs: a dispensed drug from pharmacy does not necessarily mean that the patient will take the medication, and will actually follow GP's instructions. In this regard, it must keep in mind that the DDD (defined by WHO) is a fixed unit of measurement and does not necessarily reflect the recommended or prescribed daily dose for a specific patient. Doses for individual patients and patient groups are based on patient characteristics (e.g. age and weight) and pharmacokinetic considerations, and thus may differ from the DDD. As a result, DDDs provide only a rough estimate of drug utilization, useful for comparisons between countries, LHUs, etc.. These limitations, however, are less relevant if we look at the results from the point of view of the appropriateness of the prescription habits of physicians.

Despite these limitations, large population administrative databases would have several advantages, such as the detection of different patterns of prescribing in real world setting and the analysis of the complexity of drug prescriptions. They are a great source of information on drug utilization and GPs' behaviors in routine clinical practice. Indeed, different types of information deriving from different sources (including pharmacy drug dispensation data, patients' and GPs' registry) can be combined through record linkage processes.

More details about advantages and limitations of administrative databases are outlined in **Table 6.1**.

Table 6.1 – Advantages and limitations of administrative databases

PROs	CONs
Time and cost saving	Great variation depending on the context
Regional/national coverage	Uncomplete or missing data
Free from recall bias	Information only on outpatient prescription drugs reimbursed by NHS or only on events leading to hospital admission
Information on dispensed drugs or hospital admissions	No information on lifestyle factors or other risk factors
Standardized coding	No information on prescribed dose and instructions for use
Possibility of record linkage between different sources	No information on adherence to prescriptions

6.6 CONCLUSIONS AND FUTURE PERSPECTIVES

Being able to prescribe appropriately is a complex task that is difficult to accomplish in daily clinical practice. The prescriber must take into account at least five fundamental elements: therapeutic indication, the real benefit that the patient will get from taking the drug (effectiveness), the risk of adverse drug reactions, the interactions with other drugs and the cost of treatment.

In our study, using administrative health-care databases from two Italian regions, we highlight a high drug consumption rate, a high prevalence of inappropriate drug prescriptions, and a suboptimal level of adherence to chronic therapies in primary care setting. Despite any possible clinical justification, potentially inappropriate prescription has been associated with adverse outcomes in many previous studies, thus suggesting that our project describes and highlights a real and worrying situation, characterized by drug-related issues. For this reason, it would be extremely important to implement strategies promoting proper prescription and drug use. To the best our knowledge, relatively few trials have focused on interventions to improve appropriate prescribing in primary care. In Italy

GPs have a key role in prescribing drugs, in summarizing pharmacological recommendations from specialists, and in carrying out the therapeutic reconciliation after a hospital discharge. Therefore, they are the preferred target of an intervention aimed to optimize drug management. The intervention implemented during this study and addressed to GPs, could thus be extremely important for showing the impact of different approaches targeting the quality of prescribing. However, since the prescribing practice is entrusted to the GP and is based on GP final judgment, any intervention cannot necessarily impose decisions, but only educate and inform the doctors, supporting their activity.

Moreover, the prescribing process relies on the relationship between GP and patient. The patient, in fact, is the first actor in his own health care and, nowadays, the availability of informatic and social media makes the self-medication, defined as the selection and use of medicines by individuals to treat self-recognized or self-diagnosed conditions or symptoms *[WHO, 1998]*, the most common form of medicine use worldwide. For this reason, in our study, we also implemented a strategy of intervention addressed to patients, believing that multidimensional interventions are required for the integration of some improved decision-making processes into the daily prescribing practice.

Although we did not observed a unique time trend for the measured indicators during 2014-2016, due to the large variability between different geographical areas, the prevalence of indicators on inappropriate prescribing is noteworthy, and deserves to be targeted by harmonized interventions, that addressed not only the general practitioners but also all those involved in the prescriptive process, and the patients themselves.

Chapter 7

APPENDICES

APPENDIX I

PROGETTO EDU.RE.DRUG

Efficacia di un intervento informativo/educativo, indirizzato ai medici di medicina generale e ai loro pazienti, finalizzato al miglioramento dell'uso appropriato dei farmaci

REPORT

MEDICO: M00247

Macroarea: Lecco (ATS Brianza)

Distretto: 002

a cura di:

SEFAP	**SEFAP** – ***Centro di Epidemiologia e Farmacologia Preventiva*** *(Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari)*
CIRFF	**CIRFF**– ***Centro Interdipartimentale di Ricerca in Farmacoeconomia e Farmacoutilizzazione*** *(Università degli Studi di Napoli)*
UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA	**DiSMeQ** – ***Dipartimento di Statistica e Metodi Quantitativi*** *(Università degli Studi di Milano-Bicocca)*

Gentile Dr/Dr.ssa

Il presente Report ha l'obiettivo di evidenziare le potenziali aree di inappropriatezza prescrittiva attraverso la misurazione di specifici indicatori.

Per quanto riguarda gli indicatori di performance, l'analisi delle prescrizioni è stata ristretta a specifiche categorie terapeutiche: inibitori di pompa protonica (abbreviato in PPI) (ATC: A02BC); antibiotici (ATC: J01); antiasmatici (ATC: RO3); statine (ATC: C10AA); ACE-inibitori (ATC: C09AA); sartani (ATC: C09CA); inibitori selettivi del *reuptake* della serotonina (abbreviato in SSRI) (ATC: N06AB); inibitori della ricaptazione della serotonina-norepinefrina (abbreviato in SNRI) (ATC: N06AX). Per ciascuna di queste categorie, nelle fasce d'età 40-64 anni e ≥65 anni, viene riportato il numero di pazienti trattati e i volumi di prescrizione misurati in termini di DDD (*Defined Daily Dose* o dose definita giornaliera, vedi box) per 1000 assistiti die.

Sono successivamente descritti alcuni indicatori di inappropriatezza. Nello specifico, su tutti gli assistiti over 40 anni sono state valutate le prescrizioni a rischio di interazione farmacologica (pDDI, limitatamente alle potenziali interazioni di rilevanza clinica controindicata/maggiore) e le prescrizioni concomitanti di farmaci appartenenti alla stessa classe chimico-terapeutica, ovvero duplicati terapeutici (livello 4 dell'ATC; ad es. statine C10AA). Sugli assistiti over 65 anni sono stati analizzati indicatori di inappropriatezza specifici per la popolazione anziana, quali prescrizioni di farmaci non indicati o controindicati negli anziani (sulla base di una lista [ERD-list] derivante dall'armonizzazione di tre diversi criteri espliciti Beers, STOPP e EU(7)-PIM limitatamente ai farmaci disponibili in Italia e prescritti in classe A), prescrizioni concomitanti di farmaci ad elevato carico anticolinergico (AntiCholinergic Burden [ACB] score ≥3) e prescrizioni concomitanti di farmaci ad elevato carico sedativo (Sedative Load [SL] score ≥3). Per ciascun indicatore, è riportata nei grafici la percentuale di pazienti coinvolti e sono elencati dettagliatamente i farmaci o le classi di farmaci più frequentemente interessate all'inappropriatezza.

DEFINIZIONI

Dose definita giornaliera *(Defined Daily Dose, DDD):* rappresenta la dose di mantenimento per giorno di terapia, in soggetti adulti, relativamente all'indicazione terapeutica principale della sostanza (si tratta di una unità standard e non della dose raccomandata in ciascun singolo paziente). Il numero di DDD giornaliere prescritte, rapportato a 1000 assistibili, è un indice standardizzato di consumo.

Numero trattati: indica il numero di soggetti che hanno ricevuto almeno una prescrizione nel periodo considerato.

CARATTERISTICHE GENERALI

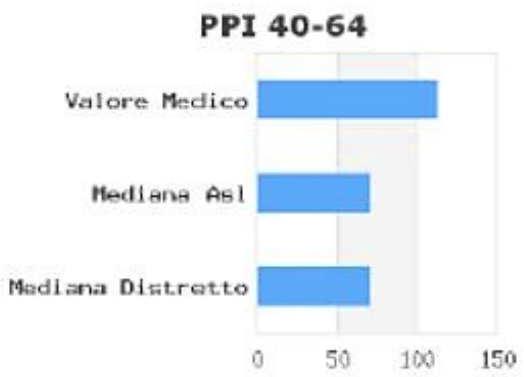
MEDICO	
Assistiti	**1559**
Numero (%) assistiti con età 40-64 anni	668 (42,8)
Numero (%) assistiti con età ≥65 anni	371 (23,8)
DISTRETTO	
Assistiti	**105.644**
Numero (%) assistiti con età 40-64 anni	44.896 (42,5)
Numero (%) assistiti con età ≥65 anni	26.052 (24,7)
MACROAREA	
Assistiti	**300.215**
Numero (%) assistiti con età 40-64 anni	126.847 (42,3)
Numero (%) assistiti con età ≥65 anni	75.631 (25,2)

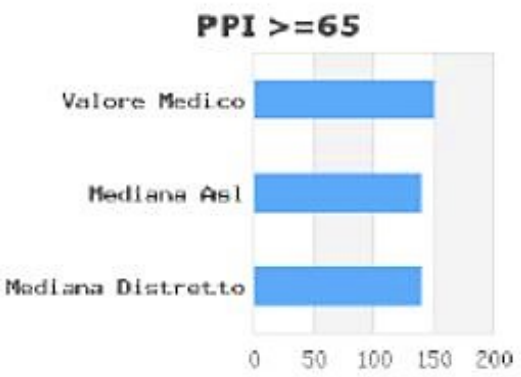
	Distribuzione per classi di politerapia (%)		
	1-4 farmaci	**5-9 farmaci**	**≥10 farmaci**
MEDICO			
Tra gli assistiti con età 40-64 anni	54,9	13,9	2,7
Tra gli assistiti con età ≥65 anni	44,7	30,5	5,4
DISTRETTO			
Tra gli assistiti con età 40-64 anni	52,8	8,0	0,7
Tra gli assistiti con età ≥65 anni	42,0	31,1	5,8
MACROAREA			
Tra gli assistiti con età 40-64 anni	53,3	8,3	0,8
Tra gli assistiti con età ≥65 anni	41,6	32,1	6,2

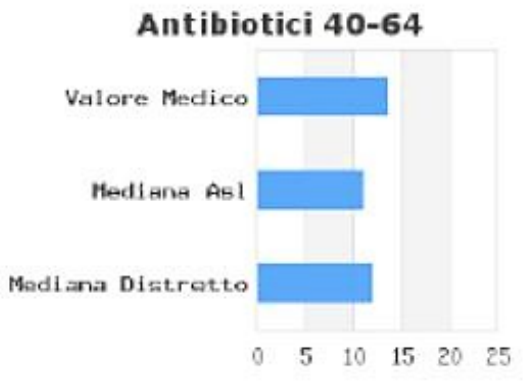
INDICATORI DI PERFORMANCE PRESCRITTIVA

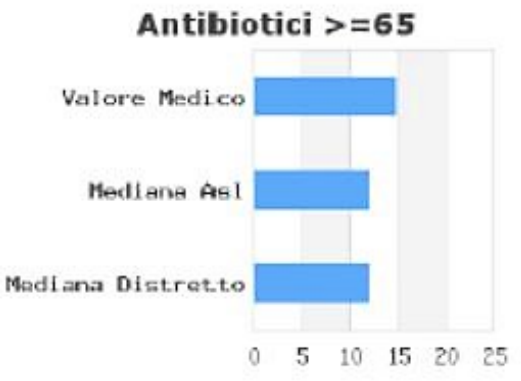
	Percentuale di trattati sul totale assistiti		
	Medico	Distretto	Macroarea
Inibitori di pompa protonica (ATC: A02BC)			
Tra gli assistiti con età 40-64 anni	22,6	14,0	14,6
Tra gli assistiti con età ≥65 anni	32,9	32,4	32,5
Antibiotici (ATC: J01)			
Tra gli assistiti con età 40-64 anni	40,1	28,1	27,9
Tra gli assistiti con età ≥65 anni	39,9	33,2	33,3
Antiasmatici (ATC: RO3)			
Tra gli assistiti con età 40-64 anni	5,5	7,2	7,4
Tra gli assistiti con età ≥65 anni	8,4	10,1	10,5
Statine (ATC: C10AA)			
Tra gli assistiti con età 40-64 anni	12,9	7,6	6,8
Tra gli assistiti con età ≥65 anni	29,6	25,2	24,0
Ace-inibitori (ATC: C09AA)			
Tra gli assistiti con età 40-64 anni	5,1	6,8	7,0
Tra gli assistiti con età ≥65 anni	9,2	17,7	19,4
Sartani (ATC: C09CA)			
Tra gli assistiti con età 40-64 anni	7,2	5,2	4,4
Tra gli assistiti con età ≥65 anni	17,3	12,8	12,1
SSRI (ATC: N06AB)			
Tra gli assistiti con età 40-64 anni	4,0	3,6	3,6
Tra gli assistiti con età ≥65 anni	3,2	5,9	6,1
SNRI (ATC: N06AX)			
Tra gli assistiti con età 40-64 anni	2,4	1,3	1,3
Tra gli assistiti con età ≥65 anni	4,0	3,2	3,1

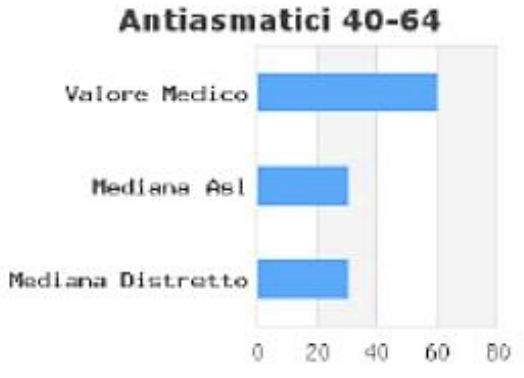
DDD/1000 ab die per le principali categorie terapeutiche nelle classi di età 40-64 anni e 65 anni: confronto medico vs distretto vs macroarea

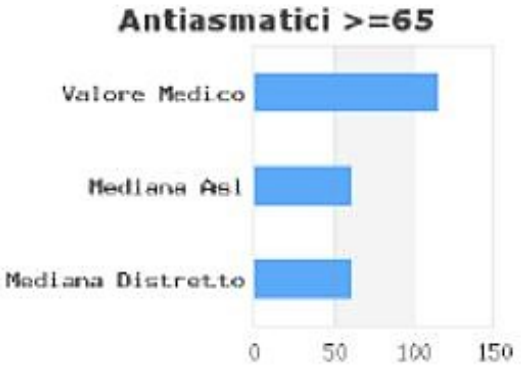


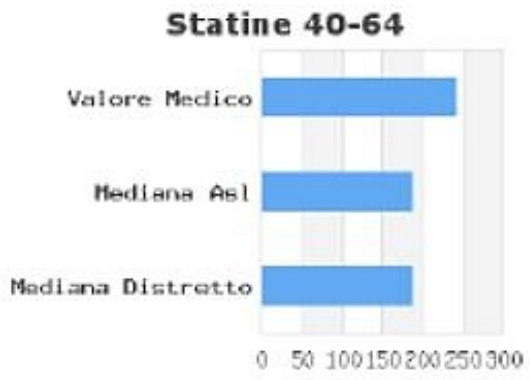











Statine 40-64
Valore Medico
Mediana Asl
Mediana Distretto
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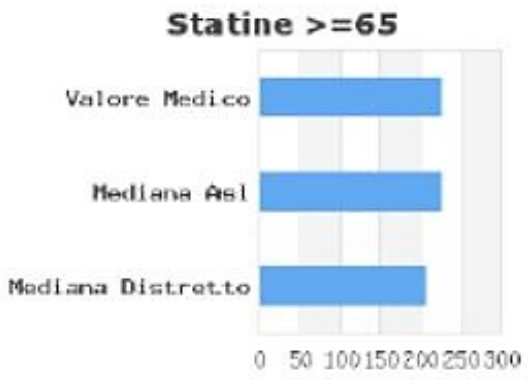
Statine >=65
Valore Medico
Mediana Asl
Mediana Distretto
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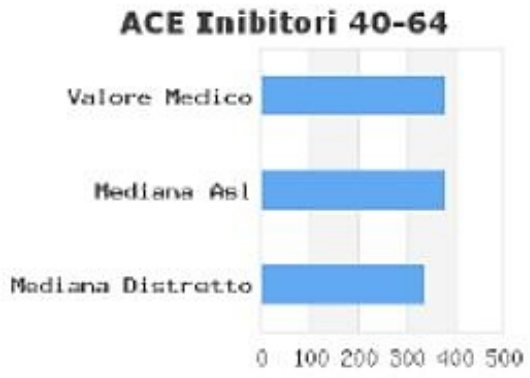
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Valore Medico
Mediana Asl
Mediana Distretto
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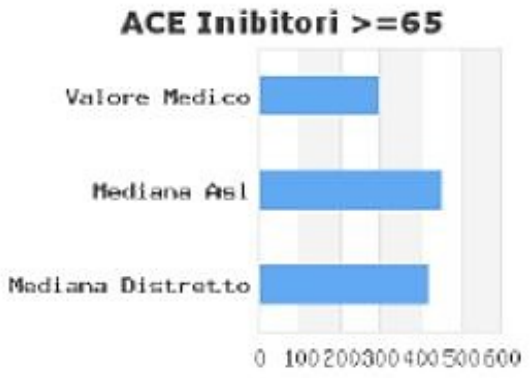
ACE Inibitori >=65
Valore Medico
Mediana Asl
Mediana Distretto
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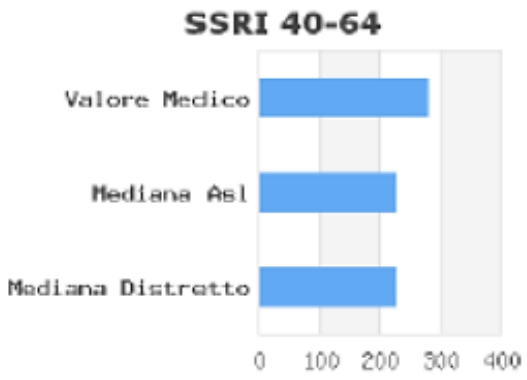
Sartani 40-64
Valore Medico
Mediana Asl
Mediana Distretto
0 100 200 300 400 500


Sartani >=65
Valore Medico
Mediana Asl
Mediana Distretto
0 100 200 300 400 500


SSRI 40-64
Valore Medico
Mediana Asl
Mediana Distretto
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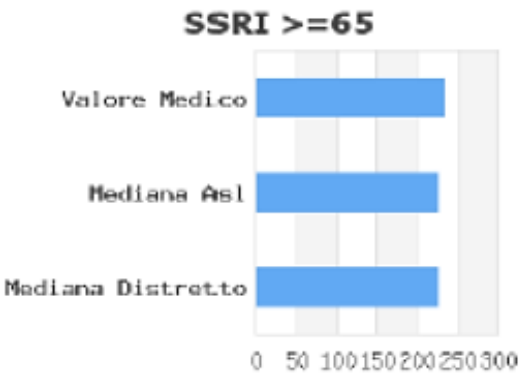
SSRI >=65
Valore Medico
Mediana Asl
Mediana Distretto
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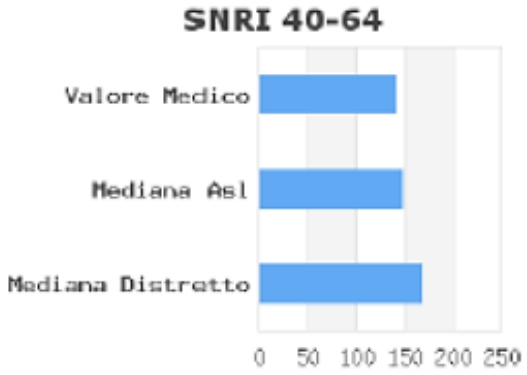
SNRI 40-64
Valore Medico
Mediana Asl
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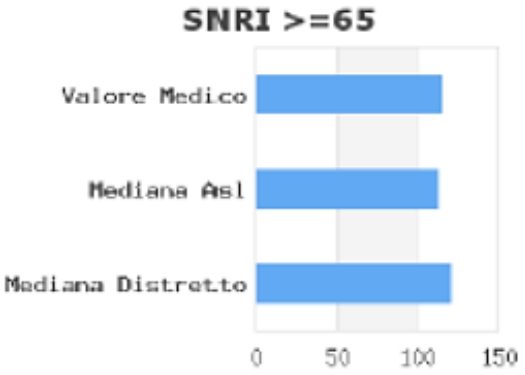
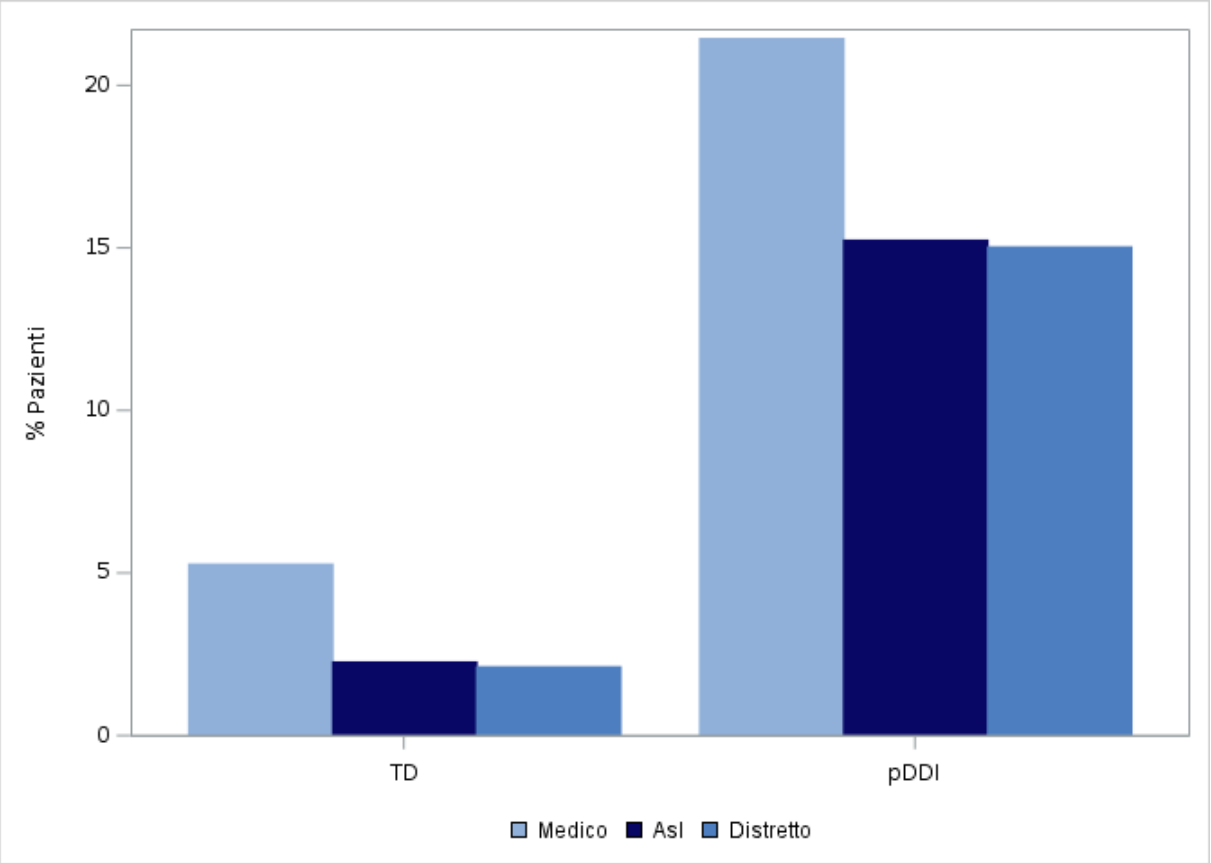

SNRI >=65
Valore Medico
Mediana Asl
Mediana Distretto
0
50
100
150

INDICATORI DI APPROPRIATEZZA PRESCRITTIVA NEI PAZIENTI OVER 40

Percentuale di pazienti con almeno una prescrizione di farmaci a rischio di interazione farmacologica (pDDI) o di duplicati terapeutici (TD): confronto medico vs distretto vs macroarea



N soggetti con prescrizione di coppie di farmaci potenzialmente interagenti (pDDI) = 223

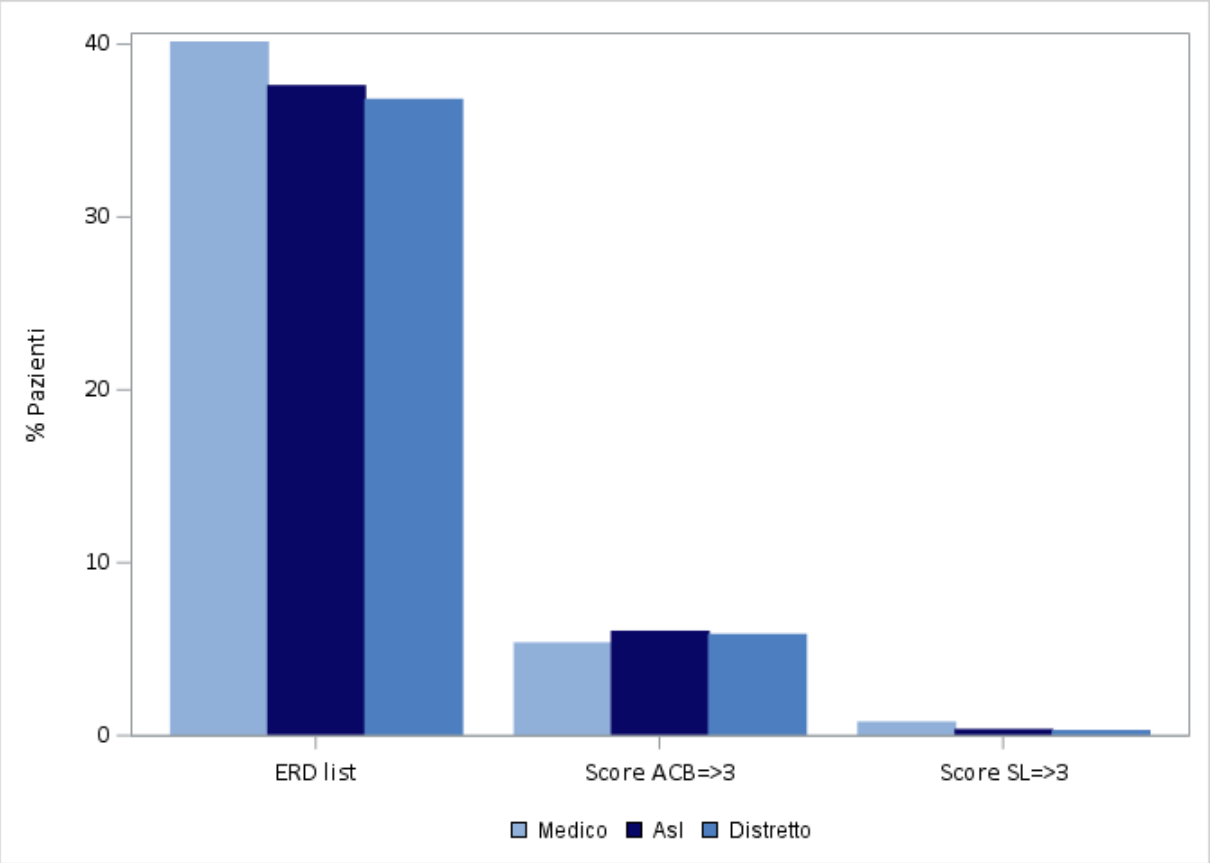
Prime 3 per frequenza	N di assistiti interessati
PREDNISONE-MELOXICAM	33
DESAMETASONE-DICLOFENAC	17
IDROCLOROTIAZIDE-DICLOFENAC	10

N soggetti con prescrizione di duplicati terapeutici (TD) = 55

Primi 3 per frequenza	N di assistiti interessati
INIBITORI DELLA POMPA ACIDA (A02BC)	8
GLICOCORTICOIDI (H02AB)	7
INIBITORI DELLA HGM COA REDUTTASI (C10AA)	6

INDICATORI DI APPROPRIATEZZA PRESCRITTIVA NEI PAZIENTI OVER 65

Percentuale di pazienti con almeno una prescrizione inappropriata per farmaci non indicati o controindicati negli anziani (ERD-list), con prescrizioni concomitanti di farmaci ad elevato carico anticolinergico (ACB score ≥3) e prescrizioni concomitanti di farmaci ad elevato carico sedativo (SL score ≥3): confronto medico vs distretto vs macroarea



N soggetti con prescrizione di farmaci presenti nella ERD-list = 149

Primi 3 per frequenza	N di assistiti interessati
ETORICOXIB	20
MELOXICAM	17
CELECOXIB	15

N soggetti con prescrizione di farmaci con elevato carico anticolinergico (ACB score ≥3) = 20

Primi 3 per frequenza	N di assistiti interessati
PAROXETINA	6
PREDNISONE	6
FUROSEMIDE	5

N soggetti con prescrizione di farmaci con elevato carico sedativo (SL score ≥3) = 3

Primi 3 per frequenza	N di assistiti interessati
QUETIAPINA	2
ACIDO VALPROICO	1
AMITRIPTILINA	1

APPENDIX II

CORSO ECM-FAD: Appropriatezza prescrittiva in medicina generale: aspetti teorici e pratici.

PRIMO MODULO

Obiettivi: presentazione del progetto e introduzione generale all'appropriatezza prescrittiva, al paziente anziano e a casi tipici di prescrizione inappropriata in questa popolazione, con esempi pratici

1. Presentazione del progetto: aspetti generali – Elena Tragni
2. L'appropriatezza prescrittiva nella medicina generale: concetti generali – Ettore Saffi Giustini
3. Il paziente anziano: invecchiamento, cronicità, multimorbilità – Marco Visconti
4. Il paziente anziano: modificazioni fisio-patologiche della farmacocinetica e della farmacodinamica – Alberto Corsini
5. Il paziente anziano: politerapia e criticità – Marco Visconti
6. L'aderenza alla terapia – Alberto Aronica
7. Inappropriatezza prescrittiva nell'anziano: farmaci inappropriati (Criteri di Beers, criteri START, il carico anticolinergico; epidemiologia e casi clinici) – Alessandro Nobili (Luca Pasina)
8. Inappropriatezza prescrittiva nell'anziano: overuse, duplicazione terapeutica, interazioni tra farmaci (epidemiologia e casi clinici) – Alessandro Nobili (Luca Pasina)
9. I medication errors – Manuela Casula
10. La farmacovigilanza: concetti generali – Annalisa Capuano

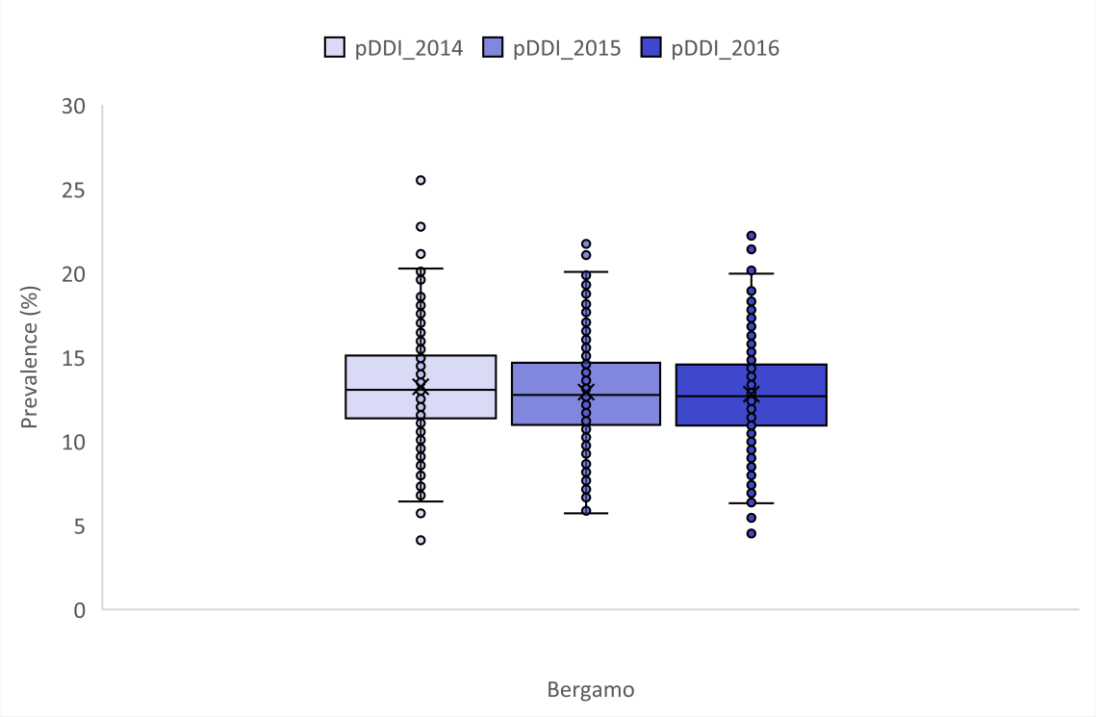
SECONDO MODULO

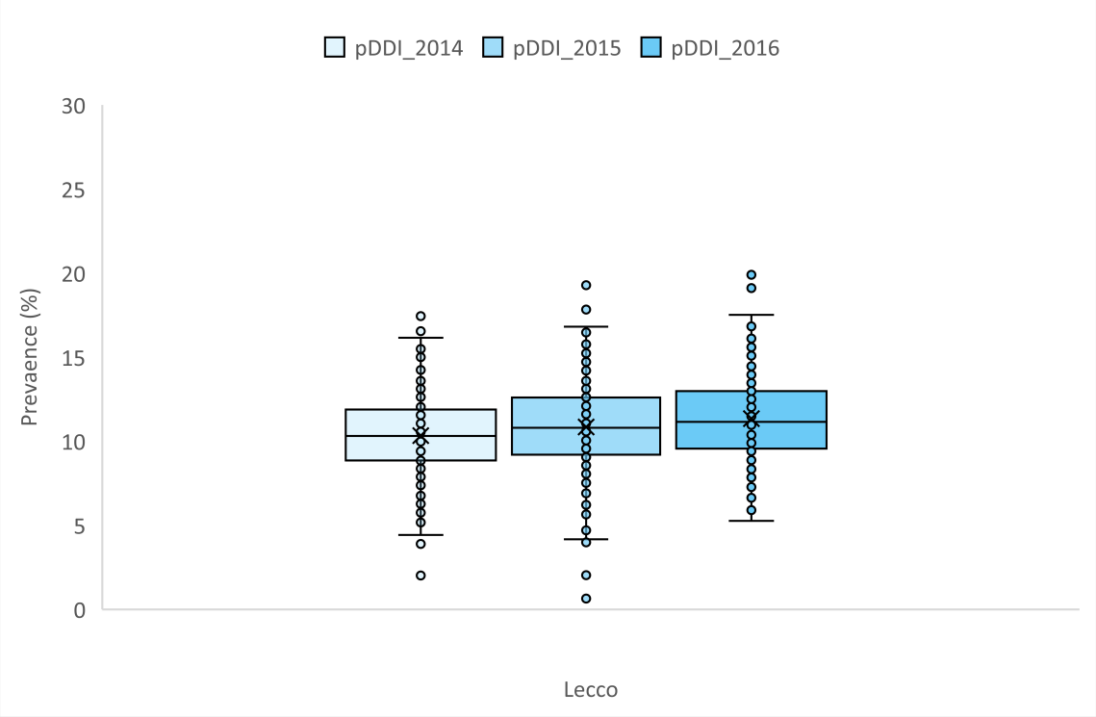
Obiettivi: spiegazione degli indicatori e della reportistica; presentazione di strumenti per il miglioramento della gestione del paziente anziano

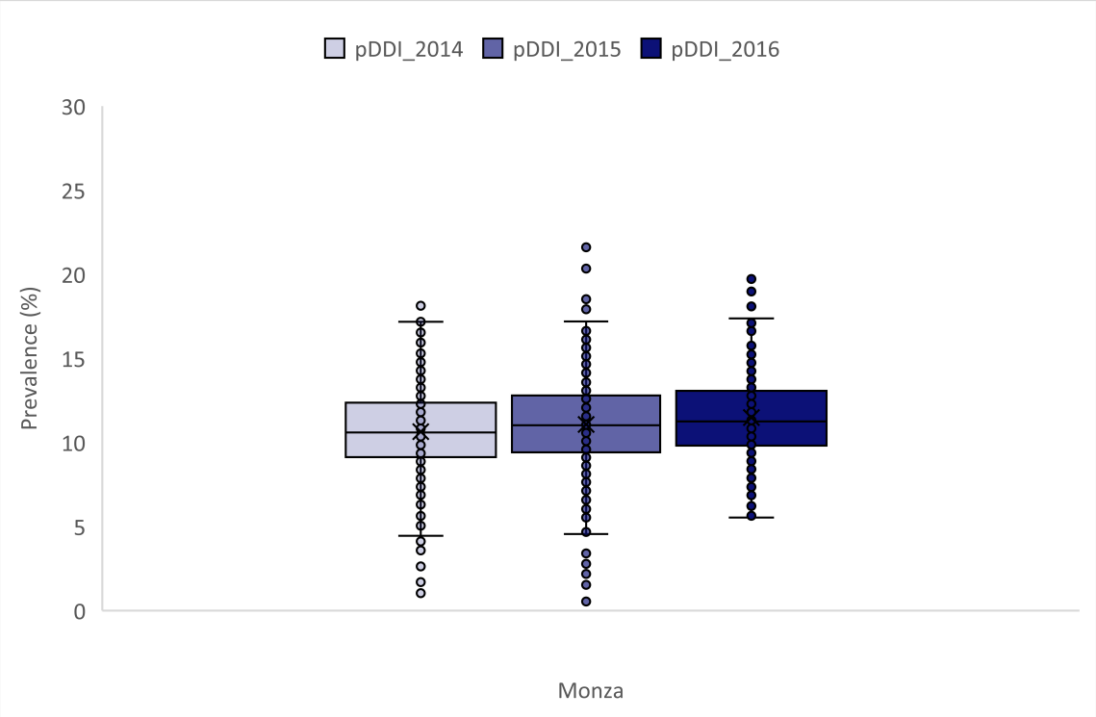
1. Come misurare l'appropriatezza: gli indicatori di performance – Enrica Menditto
2. Come misurare l'appropriatezza: gli indicatori espliciti – Manuela Casula
3. Come misurare l'uso appropriato dei farmaci: aderenza e persistenza alle terapie croniche – Lorenza Scotti
4. La reportistica del progetto: una lettura critica – Davide Lauri
5. L'approccio al paziente anziano: valutazione multi-dimensionale e diagnosi differenziale – Graziano Onder
6. La comunicazione medico-paziente: l'importanza, le strategie, gli strumenti – Silvia Muggia
7. Raccomandazioni per la prescrizione al paziente anziano complesso – Graziano Onder
8. Medication review, riconciliazione terapeutica e deprescribing – Paolo Longoni
9. Reazioni avverse ai farmaci nell'anziano: ADR prevenibili e migliorabili – Annalisa Capuano
10. La gestione del paziente anziano complesso: prospettive future – Ettore Saffi Giustini

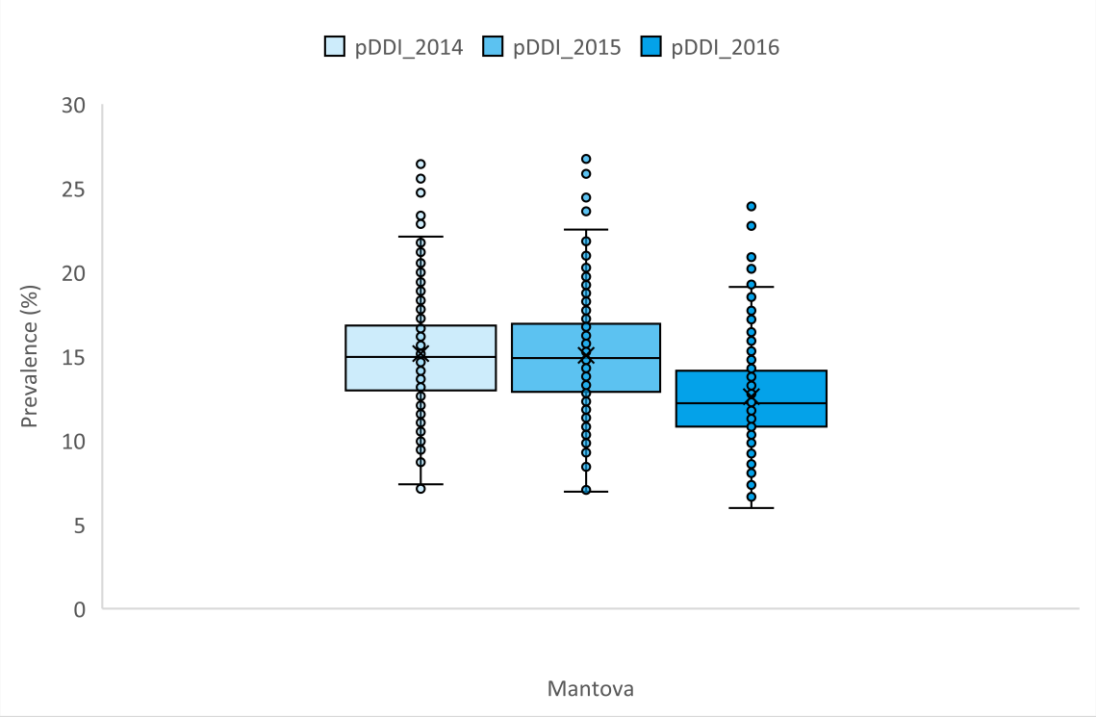
APPENDIX III

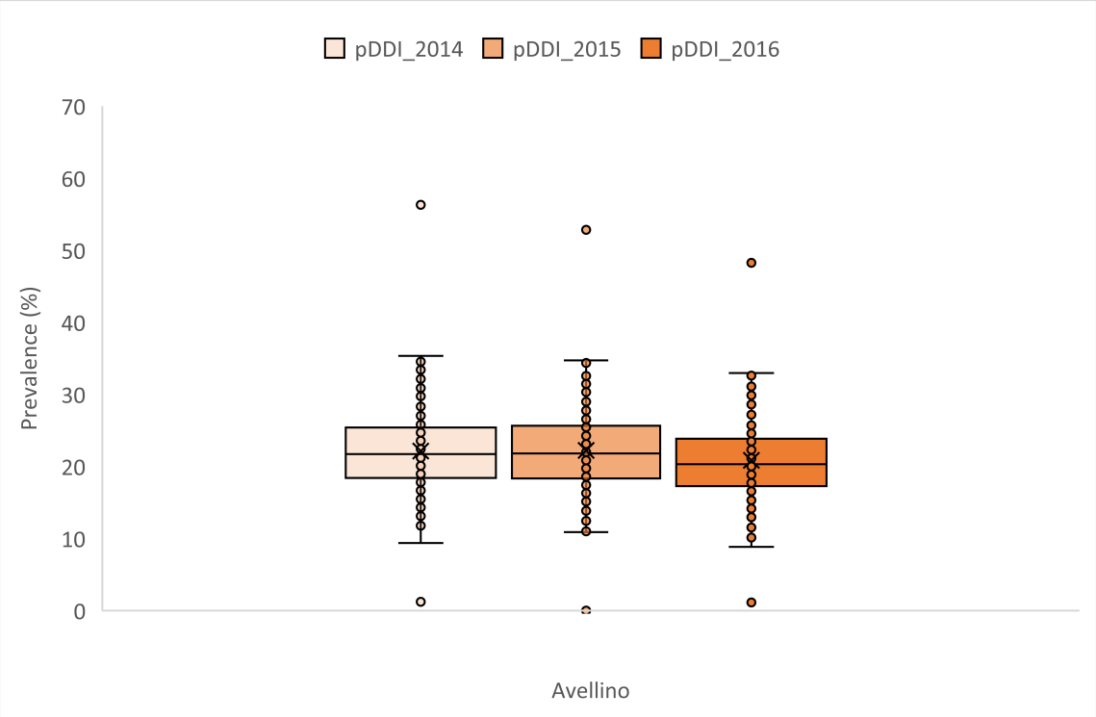
Potential DDI, GP distribution 2014-2016

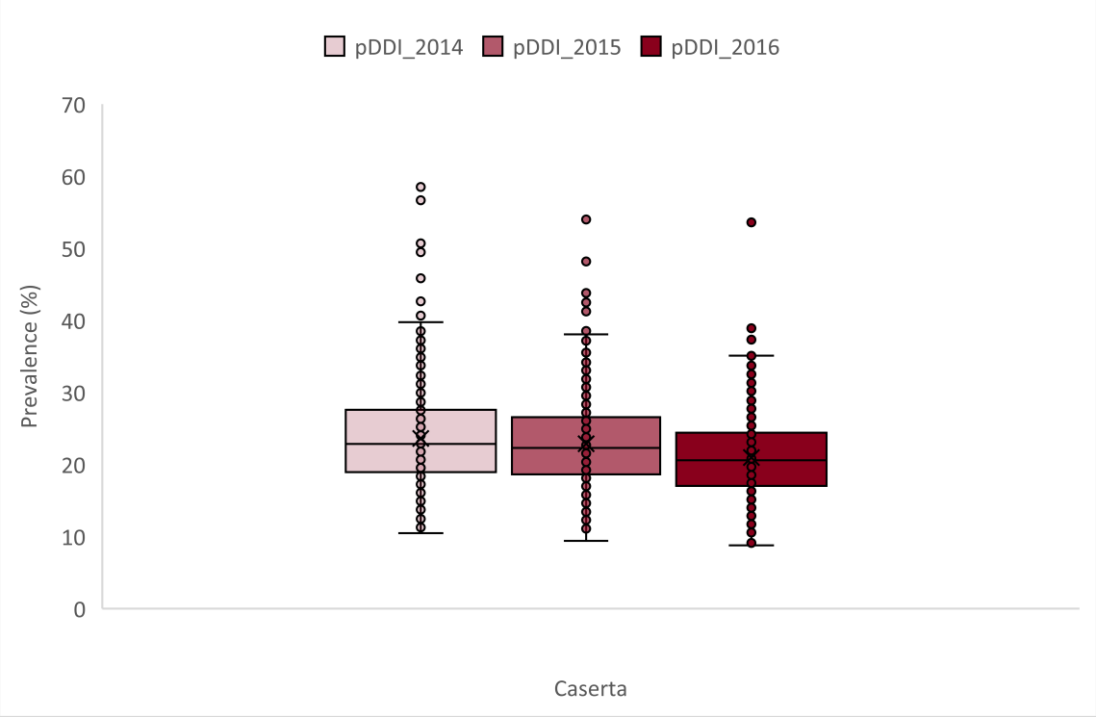


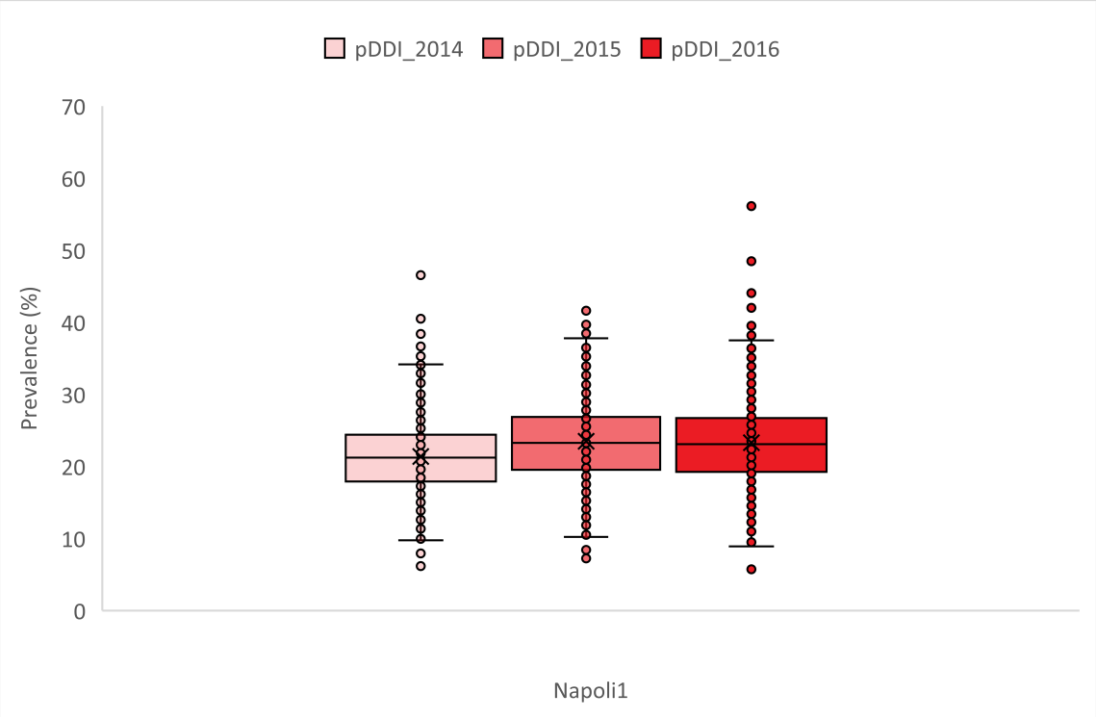


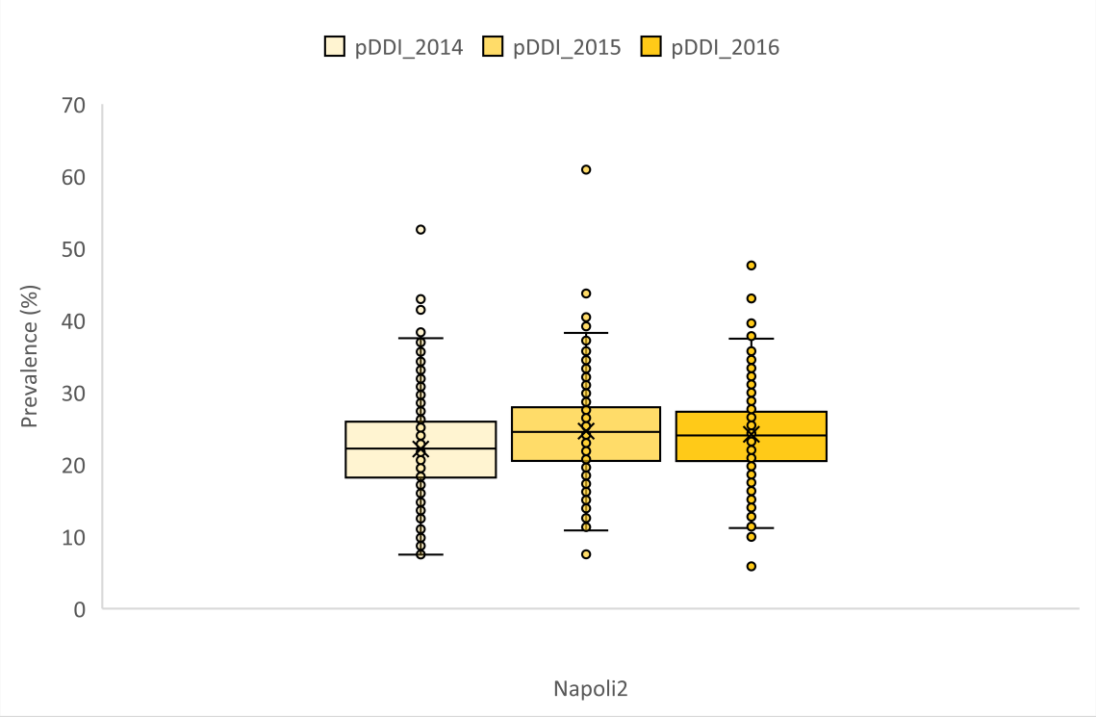

pDDI_2014
pDDI_2015
pDDI_2016
30
25
20
15
10
5
0
Prevalence (%)
Monza


pDDI_2014
pDDI_2015
pDDI_2016
30
25
20
15
10
5
0
Prevalence (%)
Mantova

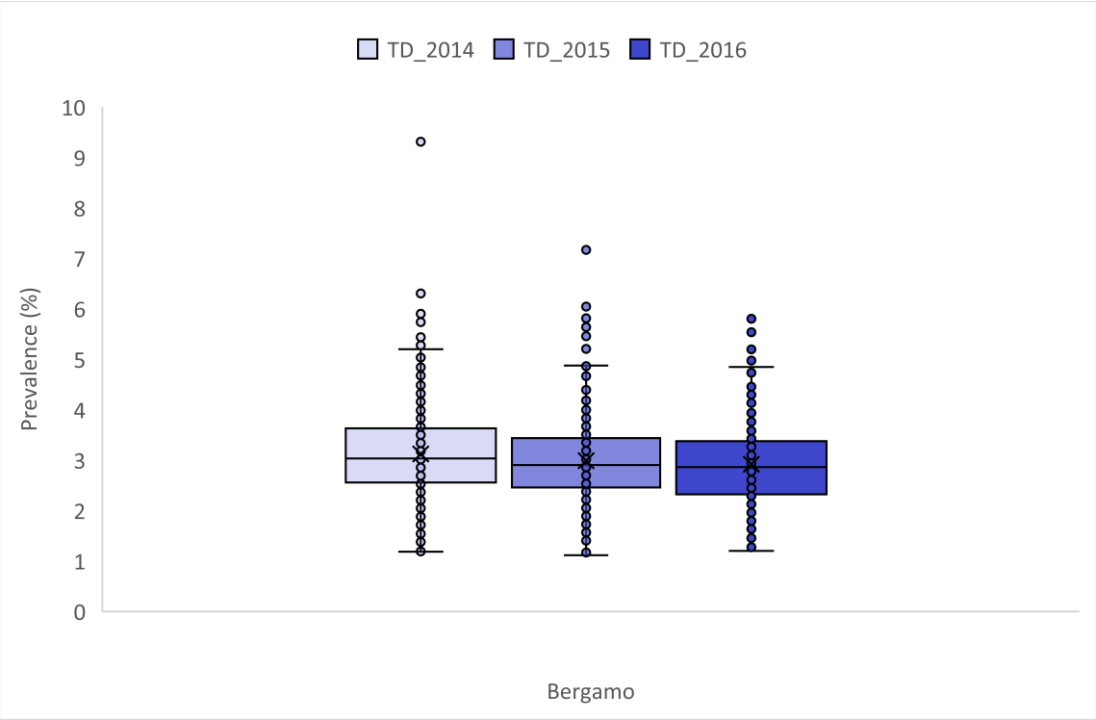

pDDI_2014
pDDI_2015
pDDI_2016
Prevalence (%)
70
60
50
40
30
20
10
0
Avellino

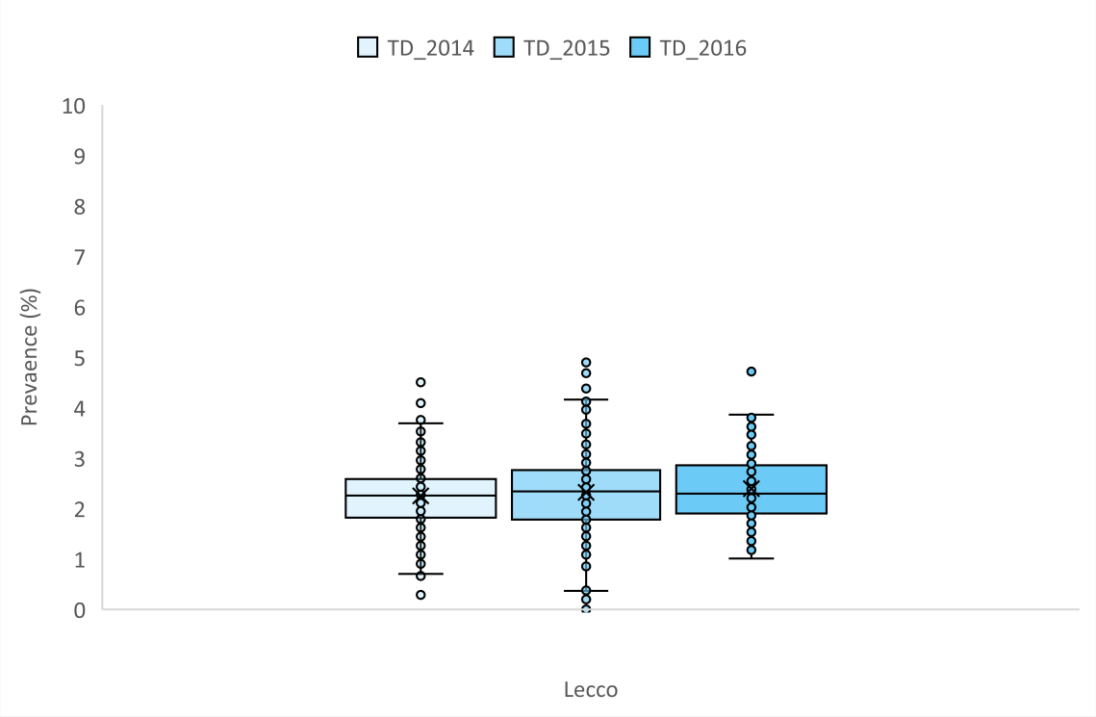

pDDI_2014
pDDI_2015
pDDI_2016
Prevalence (%)
70
60
50
40
30
20
10
0
Caserta

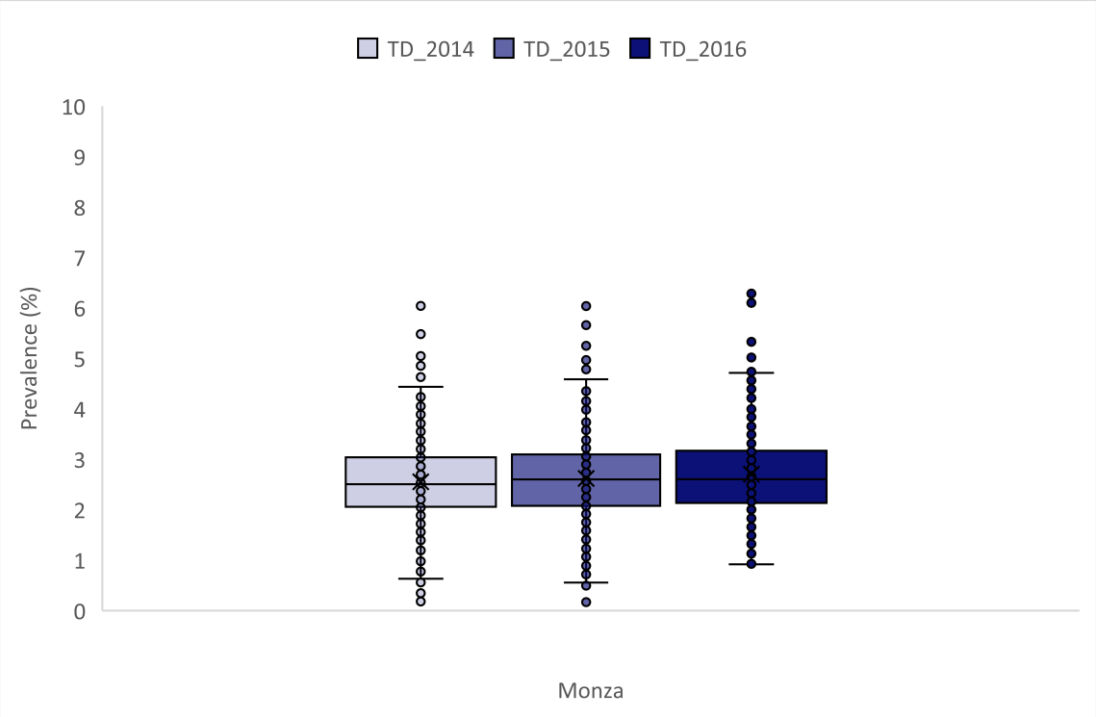

pDDI_2014
pDDI_2015
pDDI_2016
70
60
50
40
30
20
10
0
Prevalence (%)
Napoli1

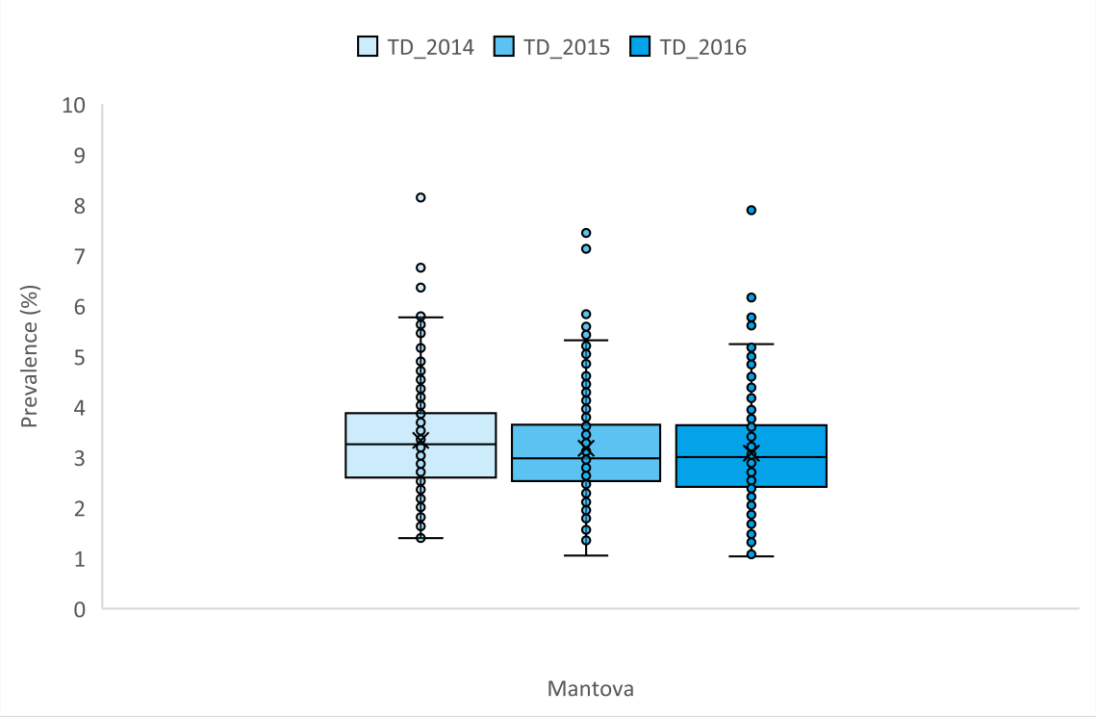

pDDI_2014
pDDI_2015
pDDI_2016
70
60
50
40
30
20
10
0
Prevalence (%)
Napoli2

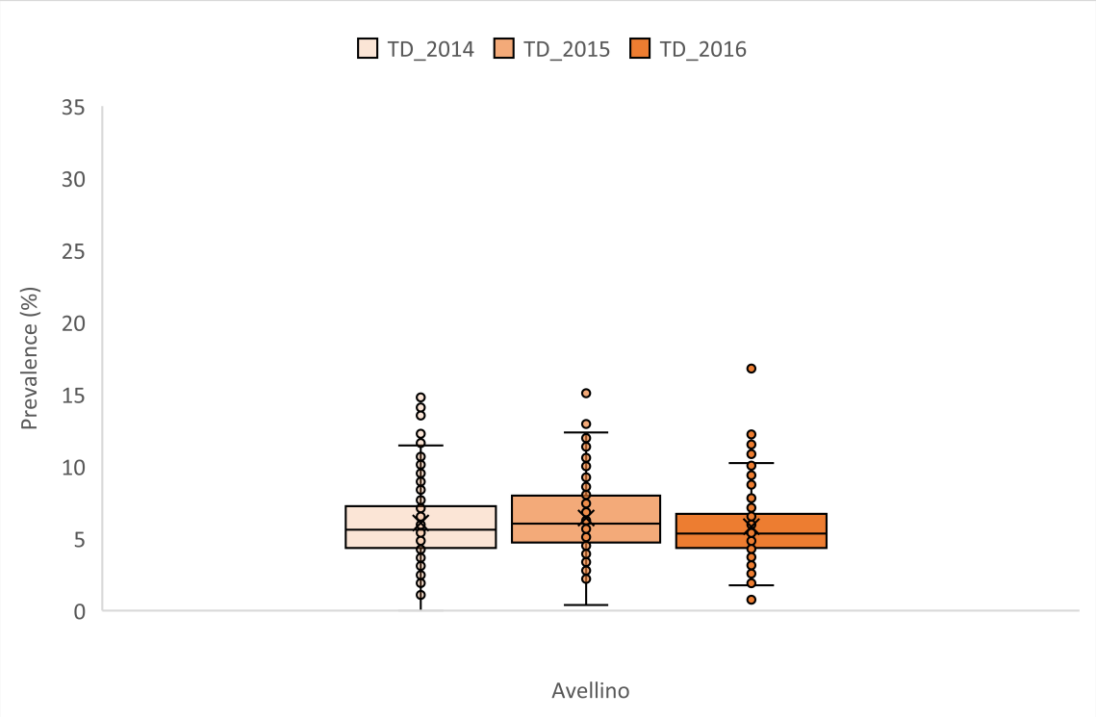
Therapeutic Duplicates, GP distribution 2014-2016

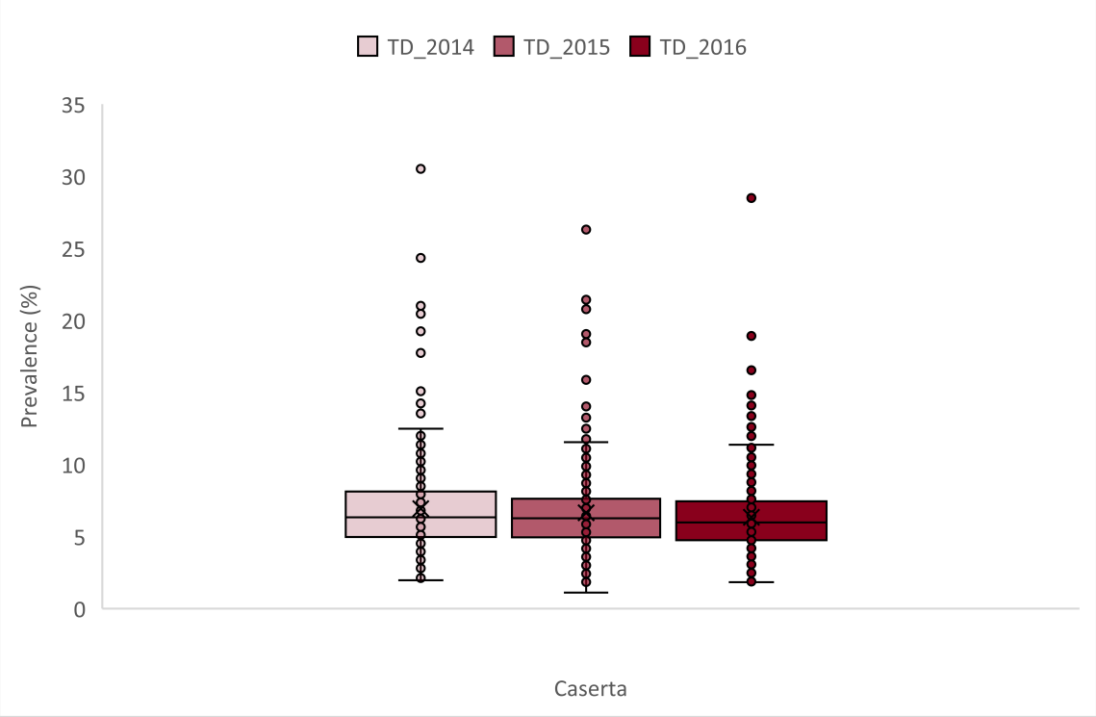


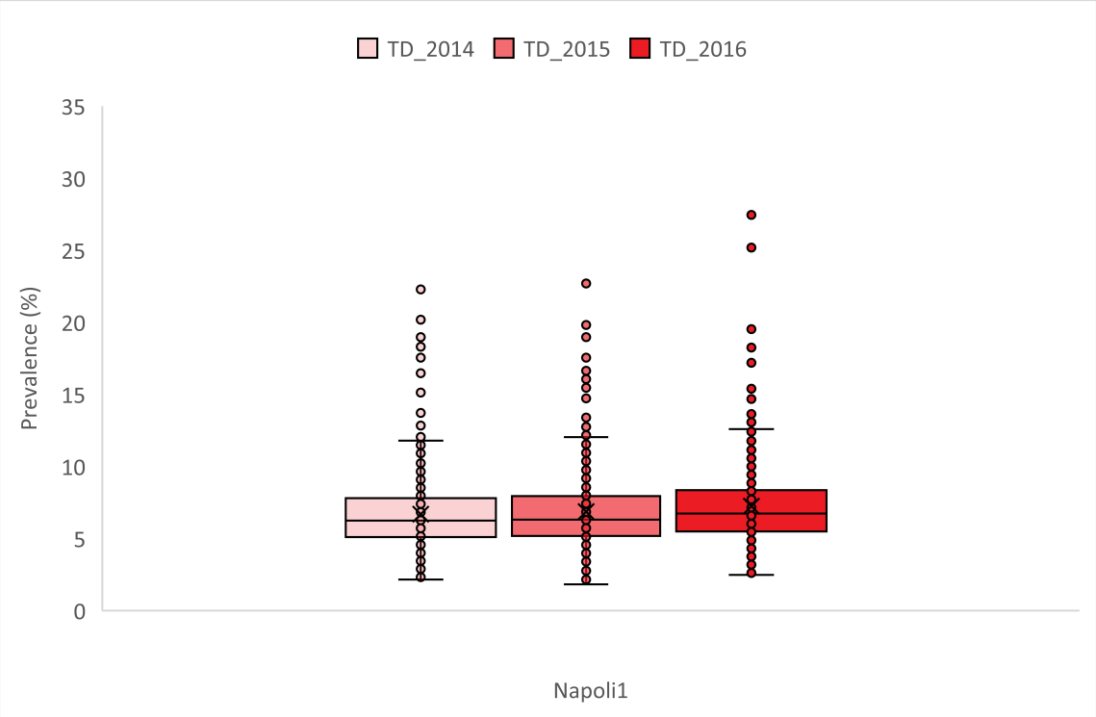


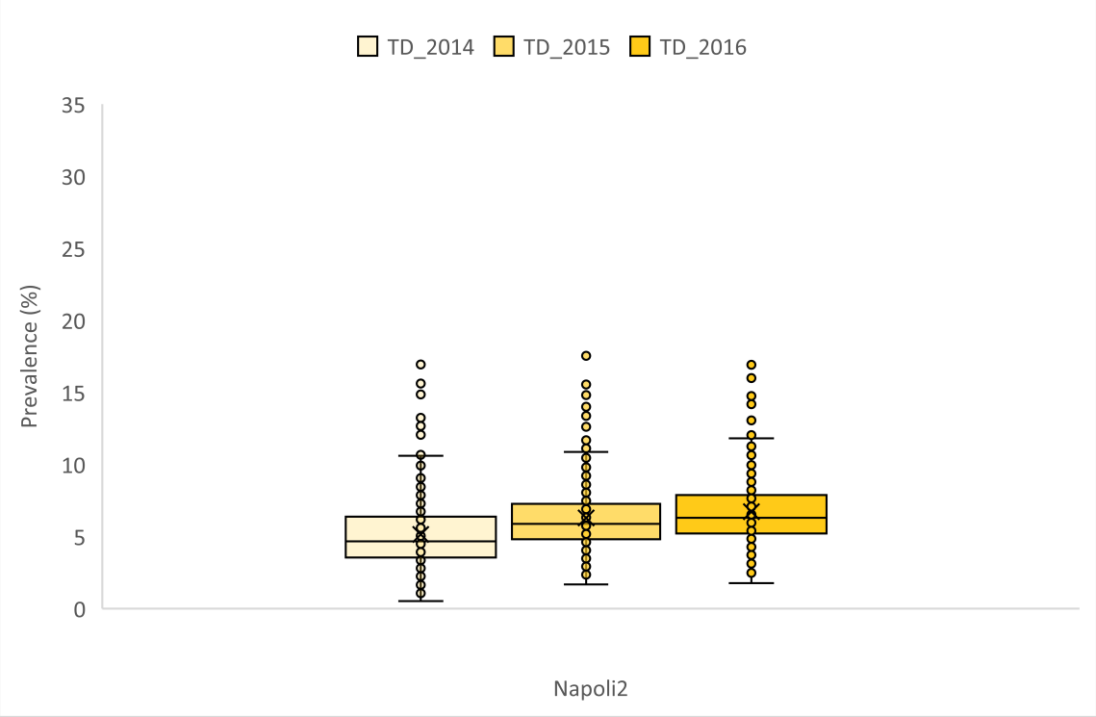

TD_2014
TD_2015
TD_2016
Prevalence (%)
10
9
8
7
6
5
4
3
2
1
0
Monza


TD_2014
TD_2015
TD_2016
Prevalence (%)
10
9
8
7
6
5
4
3
2
1
0
Mantova

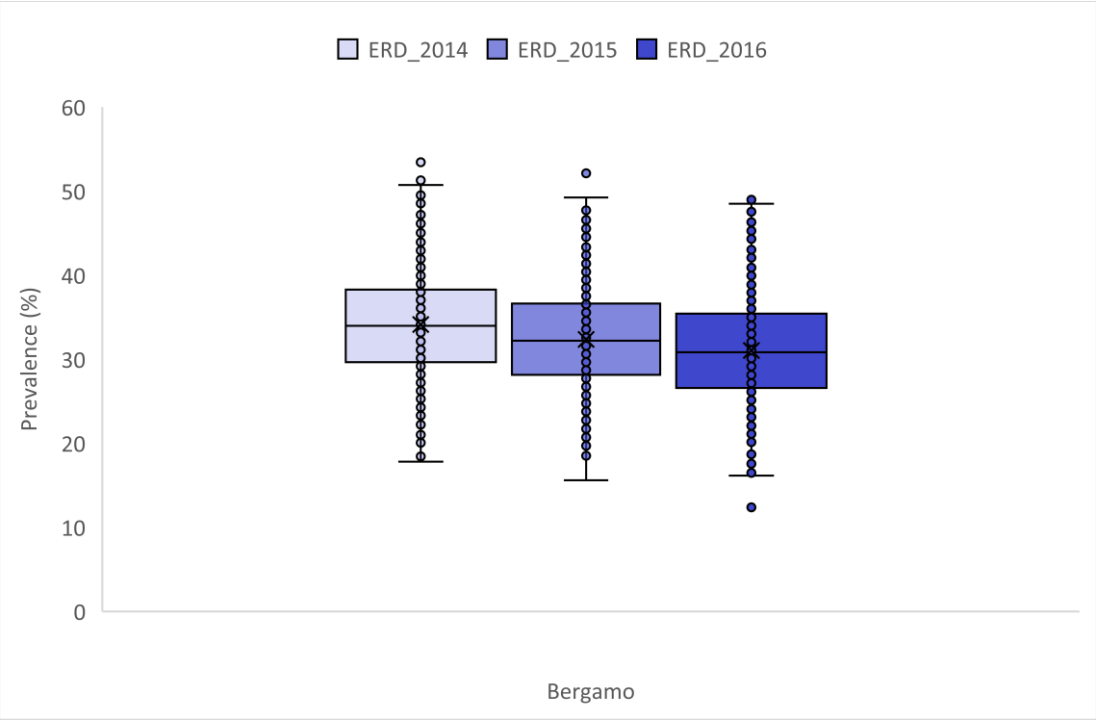

TD_2014
TD_2015
TD_2016
35
30
25
20
15
10
5
0
Prevalence (%)
Avellino

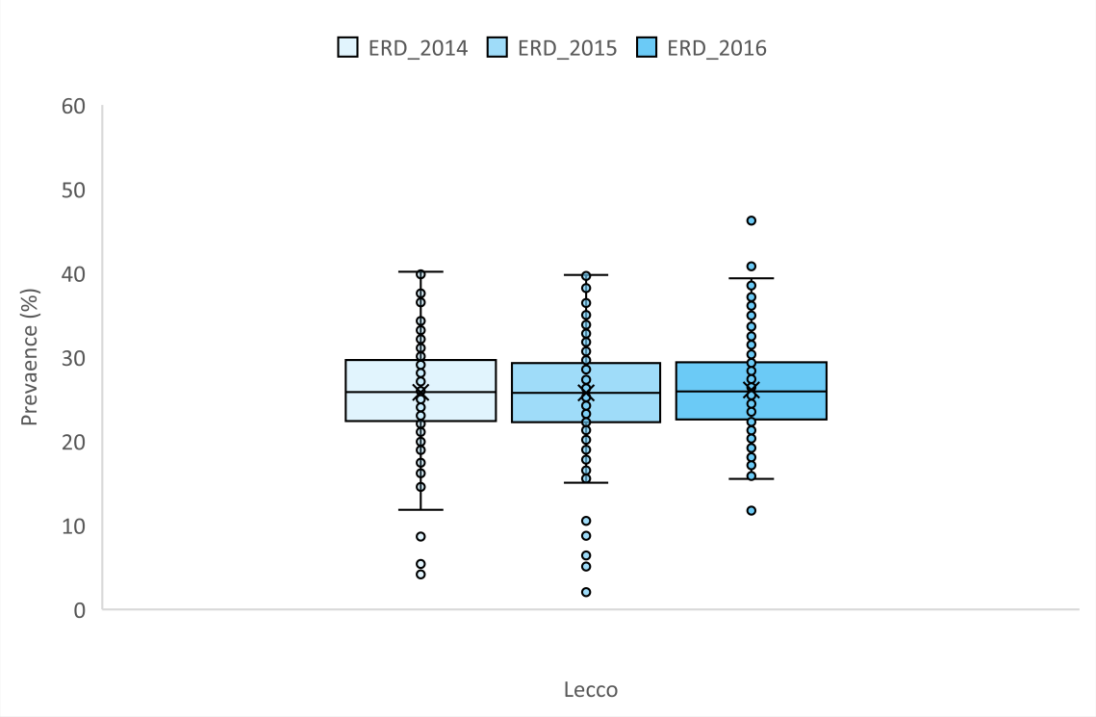

TD_2014
TD_2015
TD_2016
35
30
25
20
15
10
5
0
Prevalence (%)
Caserta

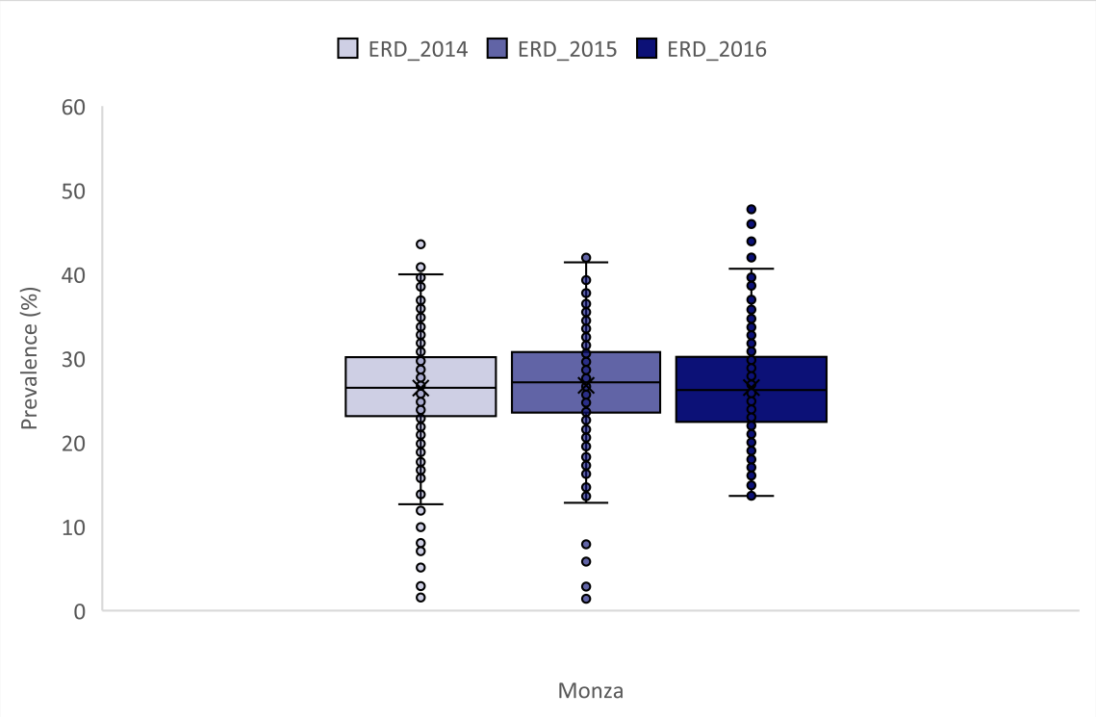

TD_2014
TD_2015
TD_2016
35
30
25
20
15
10
5
0
Prevalence (%)
Napoli1

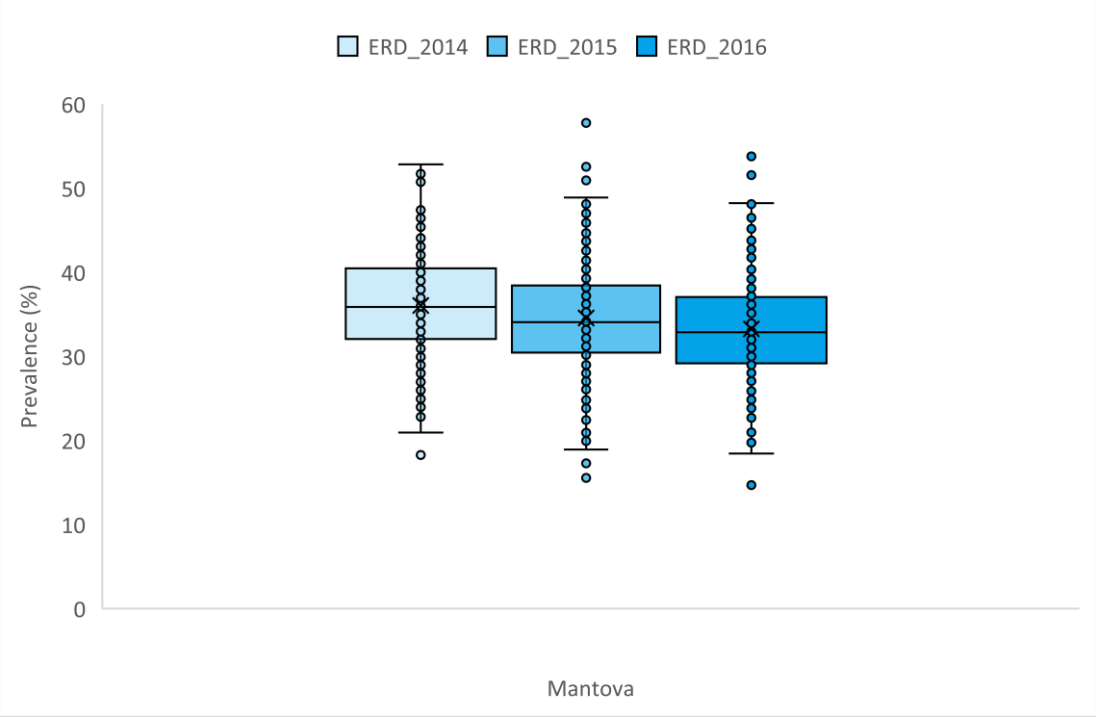

TD_2014
TD_2015
TD_2016
35
30
25
20
15
10
5
0
Prevalence (%)
Napoli2

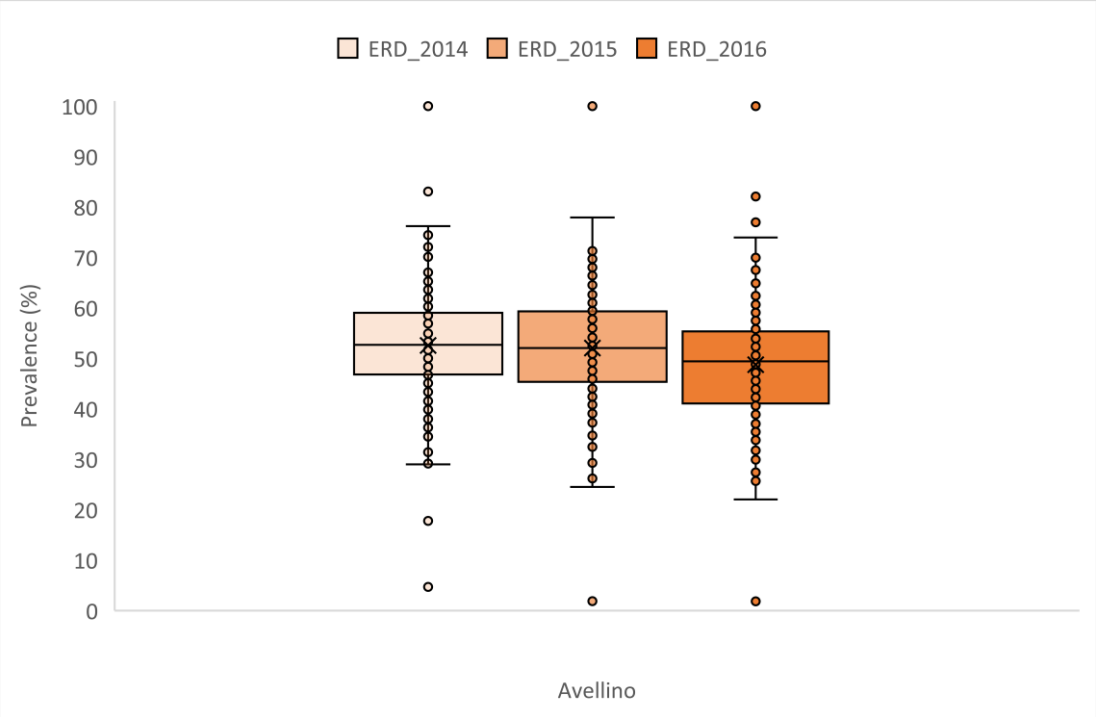
ERD-list, GP distribution 2014-2016

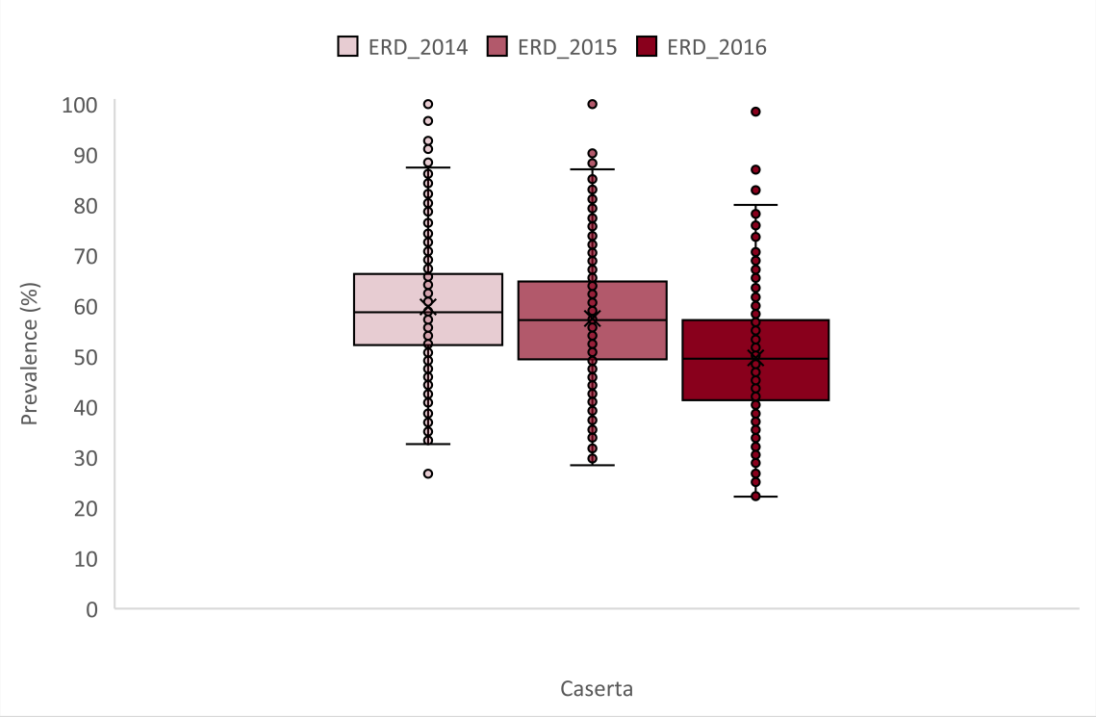


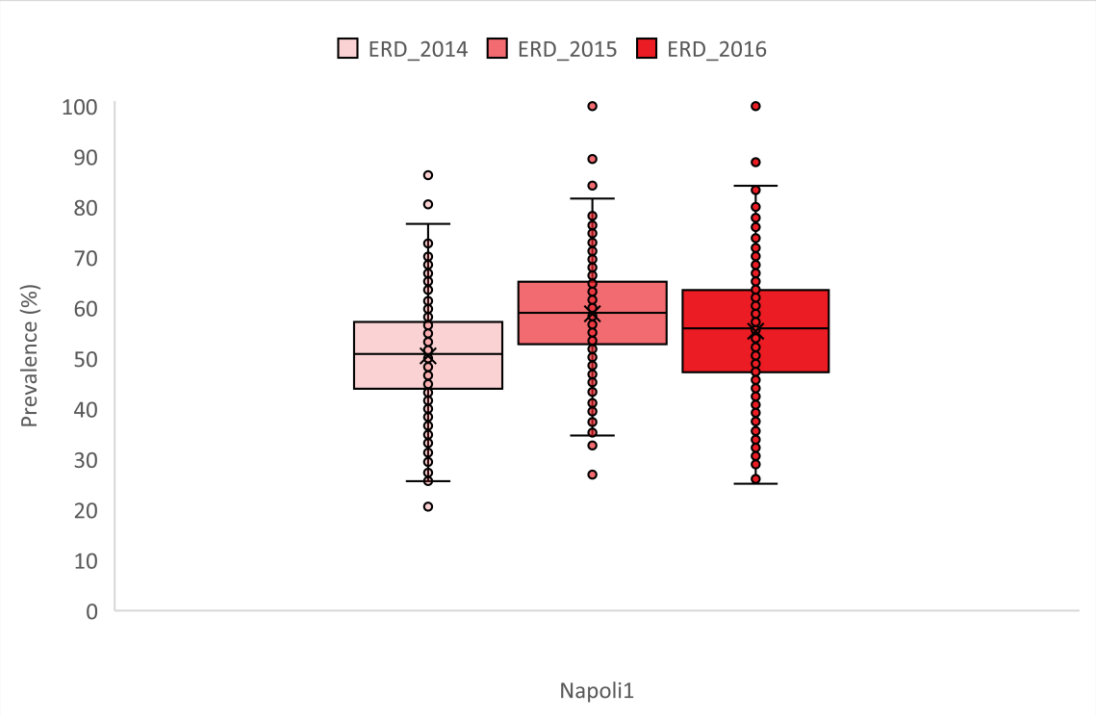


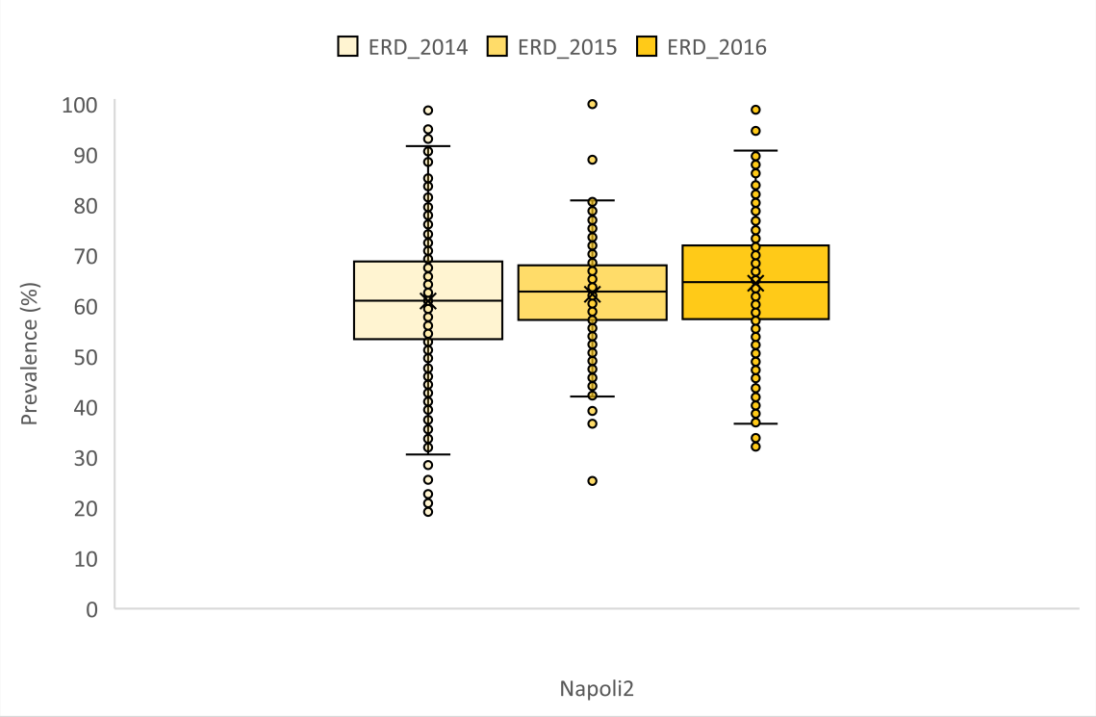

ERD_2014
ERD_2015
ERD_2016
60
50
40
30
20
10
0
Prevalence (%)
Monza


ERD_2014
ERD_2015
ERD_2016
60
50
40
30
20
10
0
Prevalence (%)
Mantova

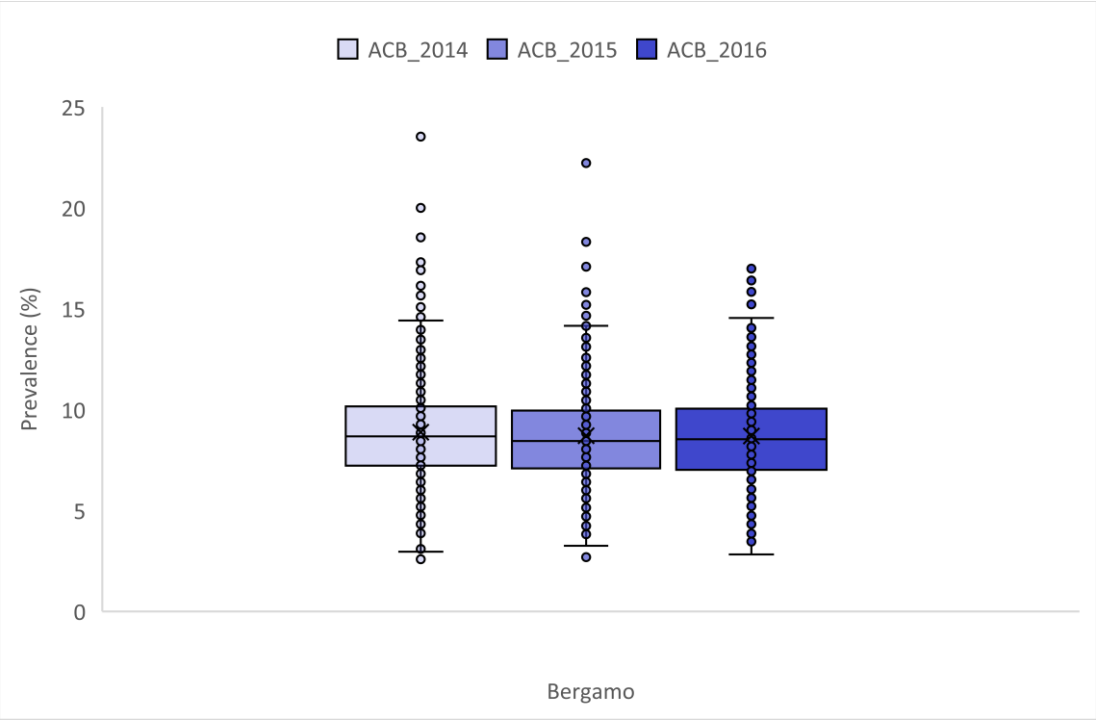

ERD_2014
ERD_2015
ERD_2016
100
90
80
70
60
50
40
30
20
10
0
Prevalence (%)
Avellino

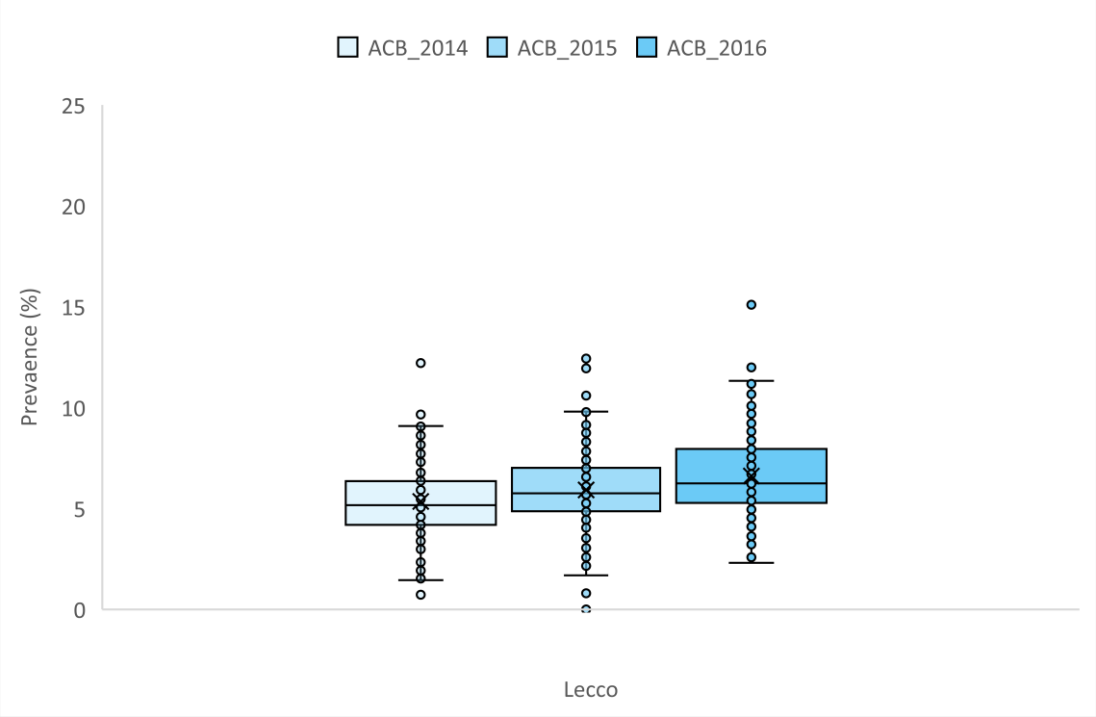

ERD_2014
ERD_2015
ERD_2016
100
90
80
70
60
50
40
30
20
10
0
Prevalence (%)
Caserta

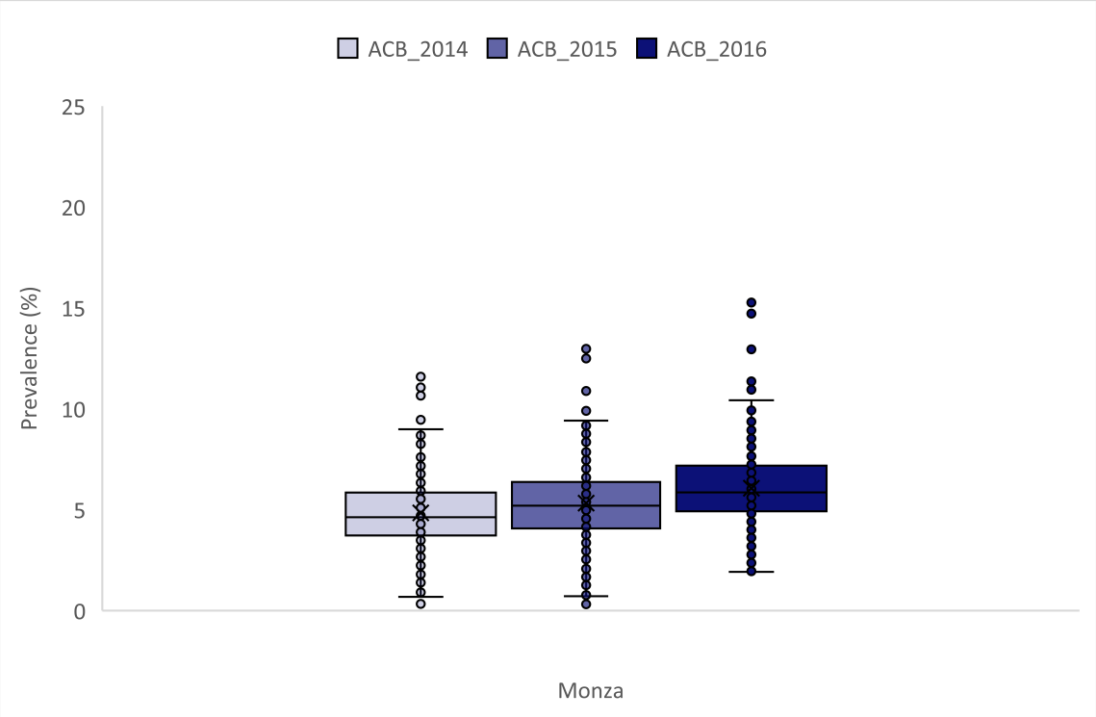

ERD_2014
ERD_2015
ERD_2016
Prevalence (%)
100
90
80
70
60
50
40
30
20
10
0
Napoli1

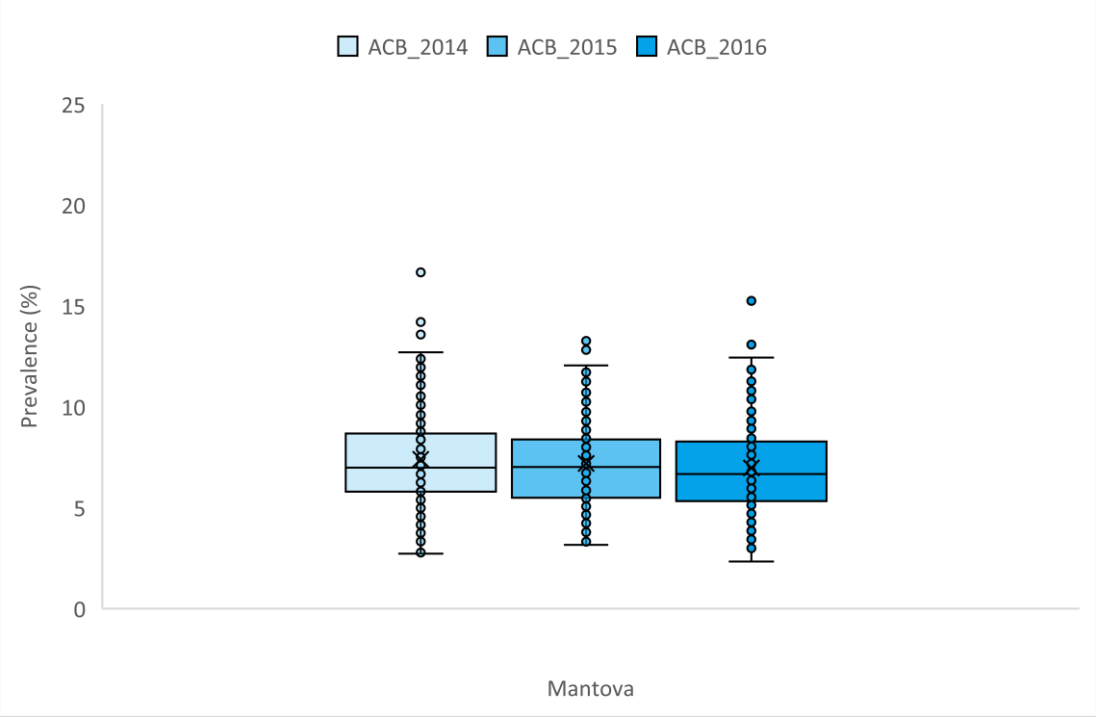

ERD_2014
ERD_2015
ERD_2016
Prevalence (%)
100
90
80
70
60
50
40
30
20
10
0
Napoli2

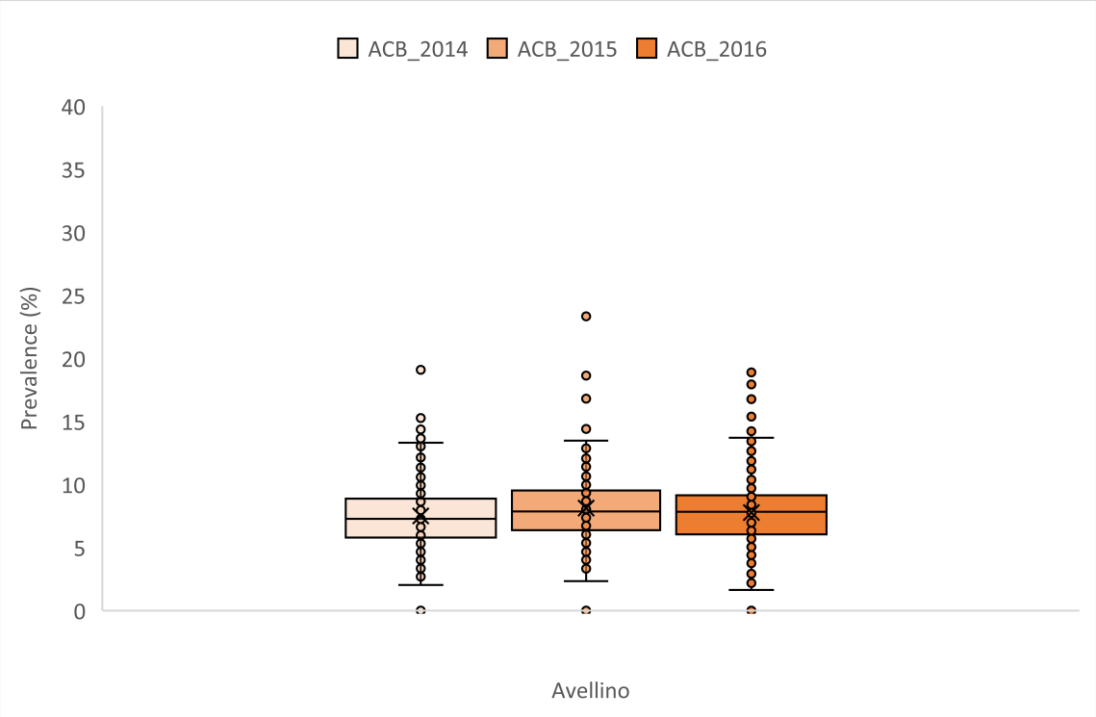
ACB Score, GP distribution 2014-2016

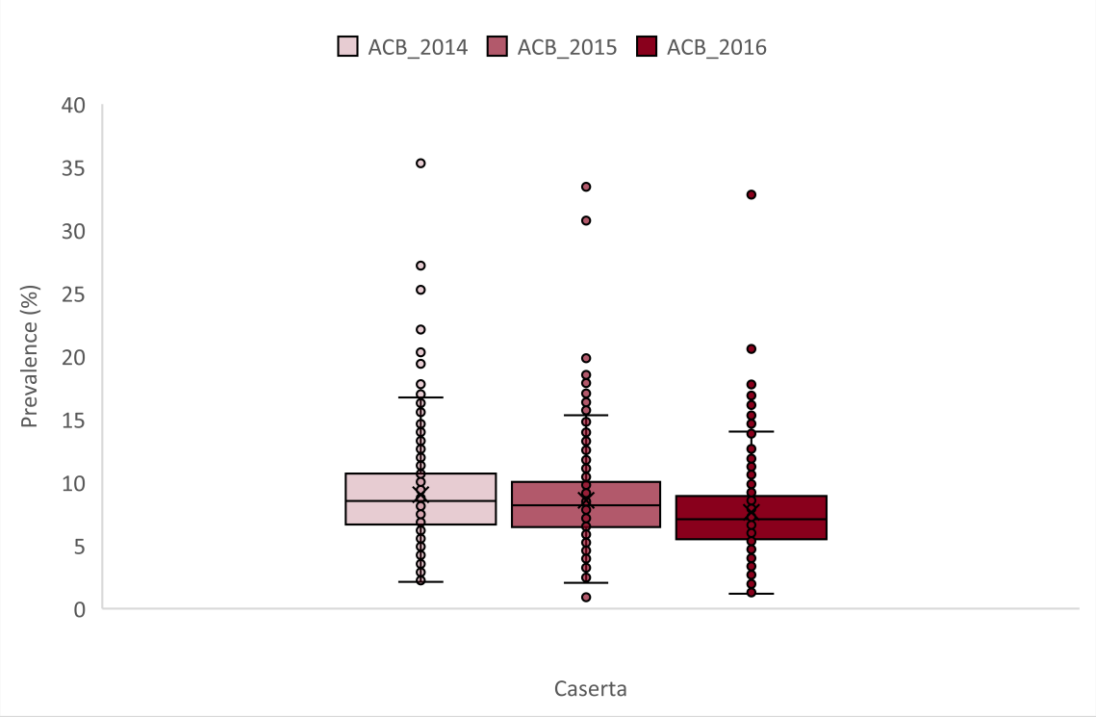


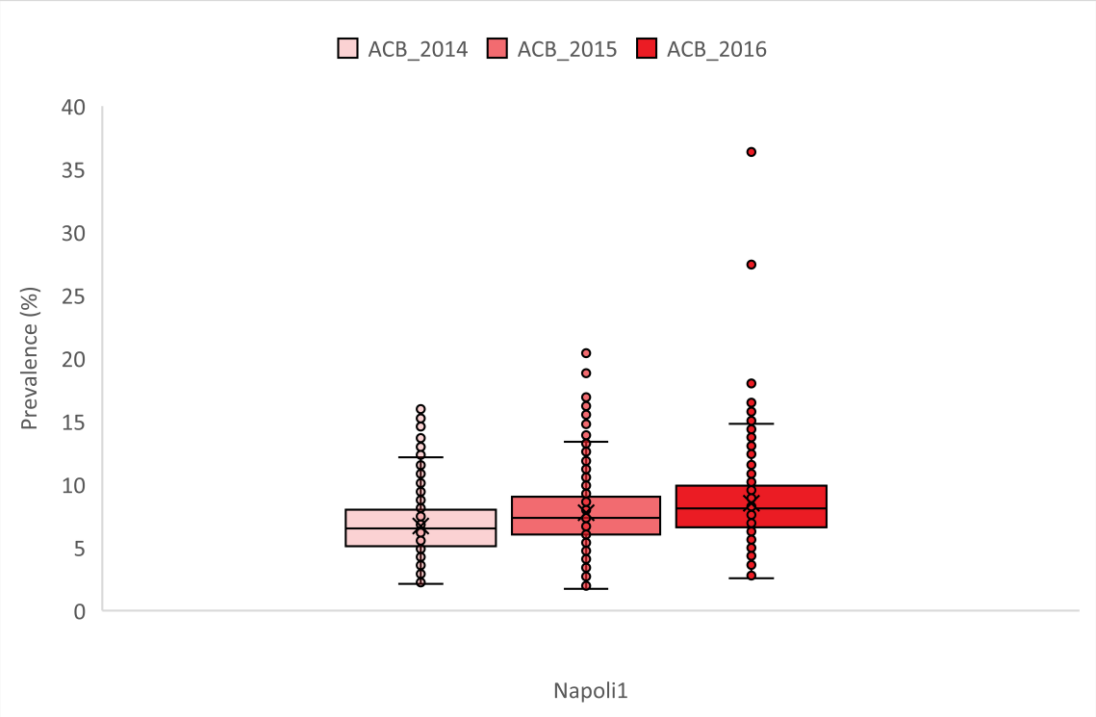


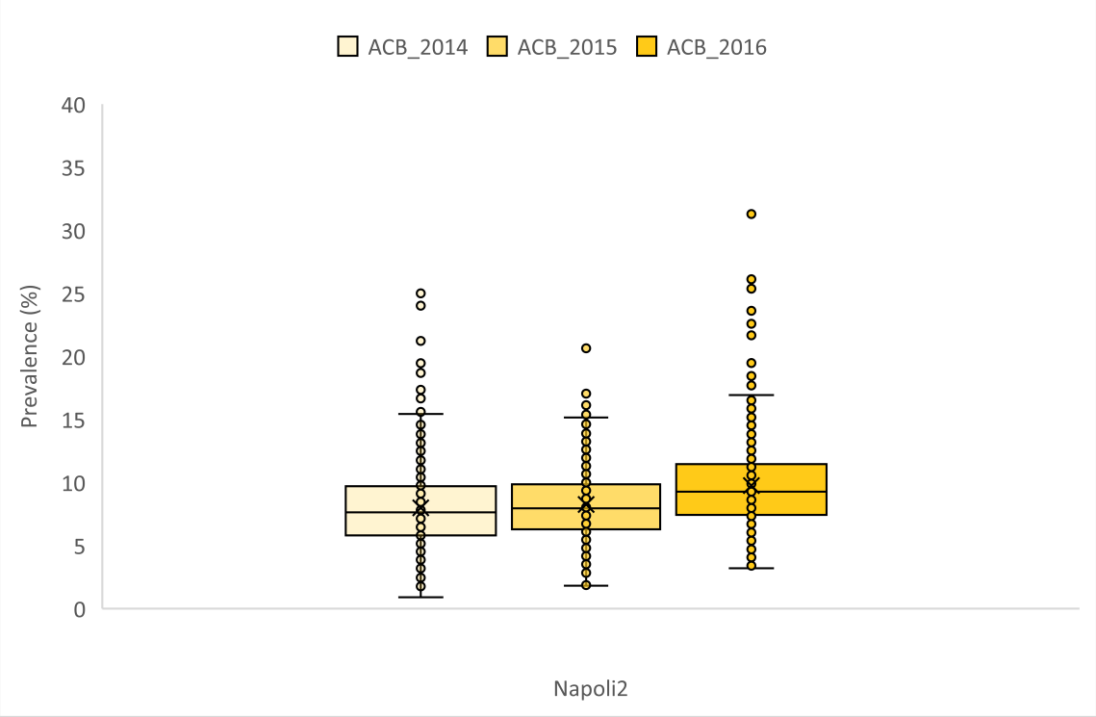

ACB_2014
ACB_2015
ACB_2016
25
20
15
10
5
0
Prevalence (%)
Monza


ACB_2014
ACB_2015
ACB_2016
25
20
15
10
5
0
Prevalence (%)
Mantova

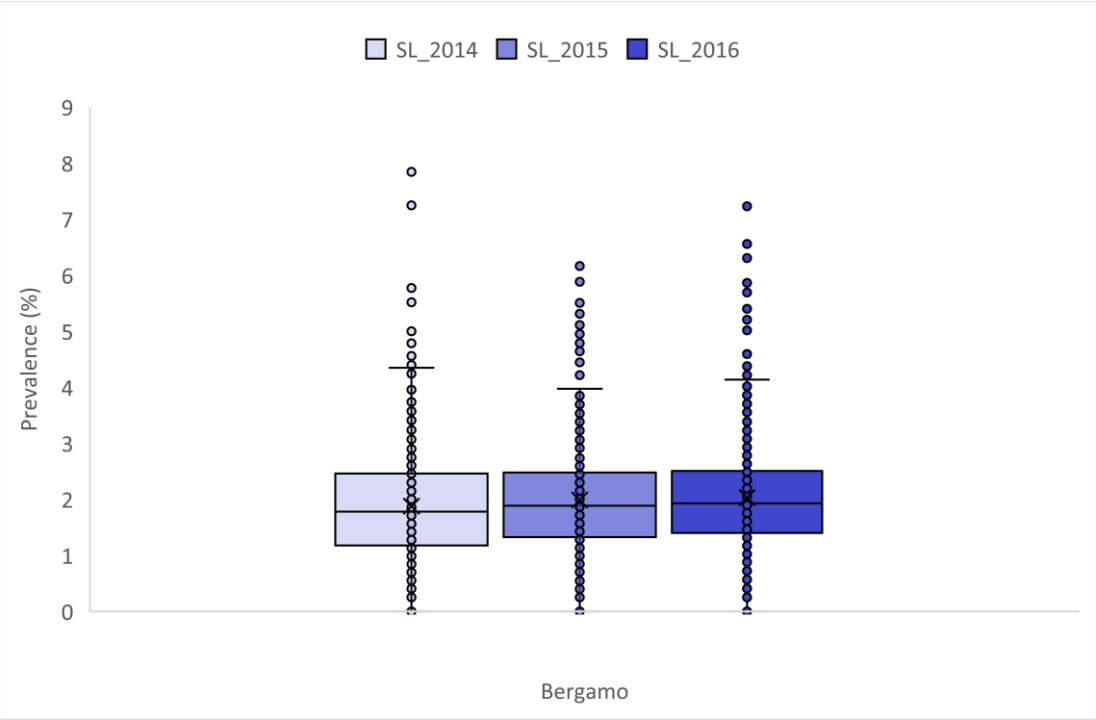

ACB_2014
ACB_2015
ACB_2016
Prevalence (%)
40
35
30
25
20
15
10
5
0
Avellino

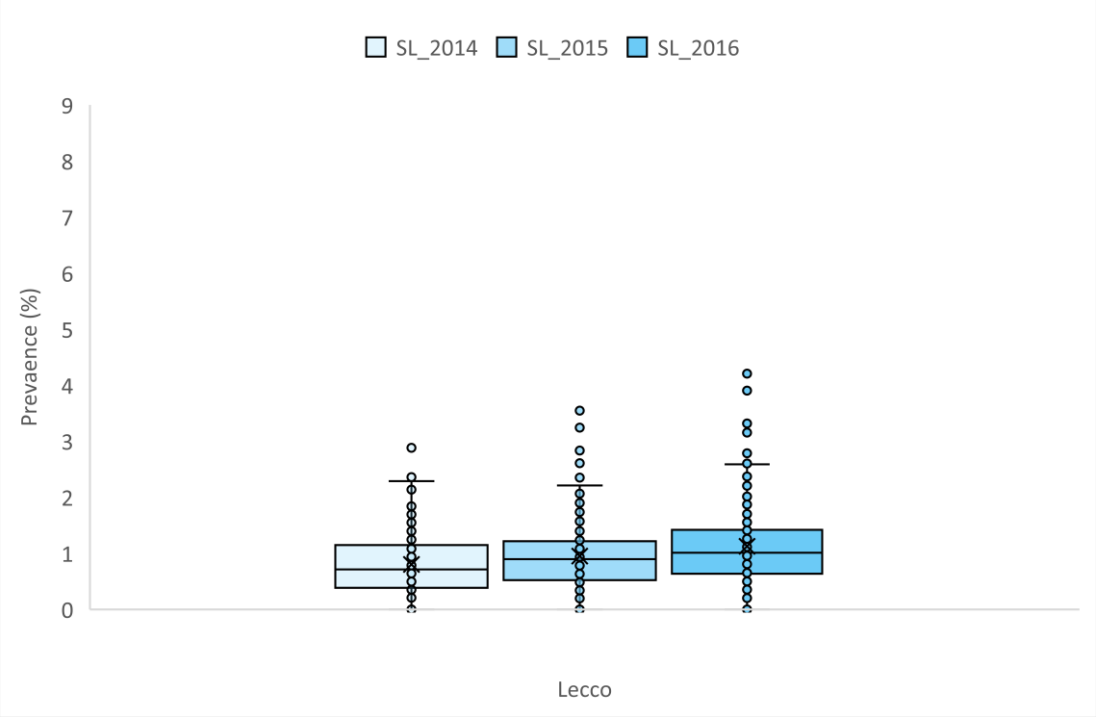

ACB_2014
ACB_2015
ACB_2016
Prevalence (%)
40
35
30
25
20
15
10
5
0
Caserta

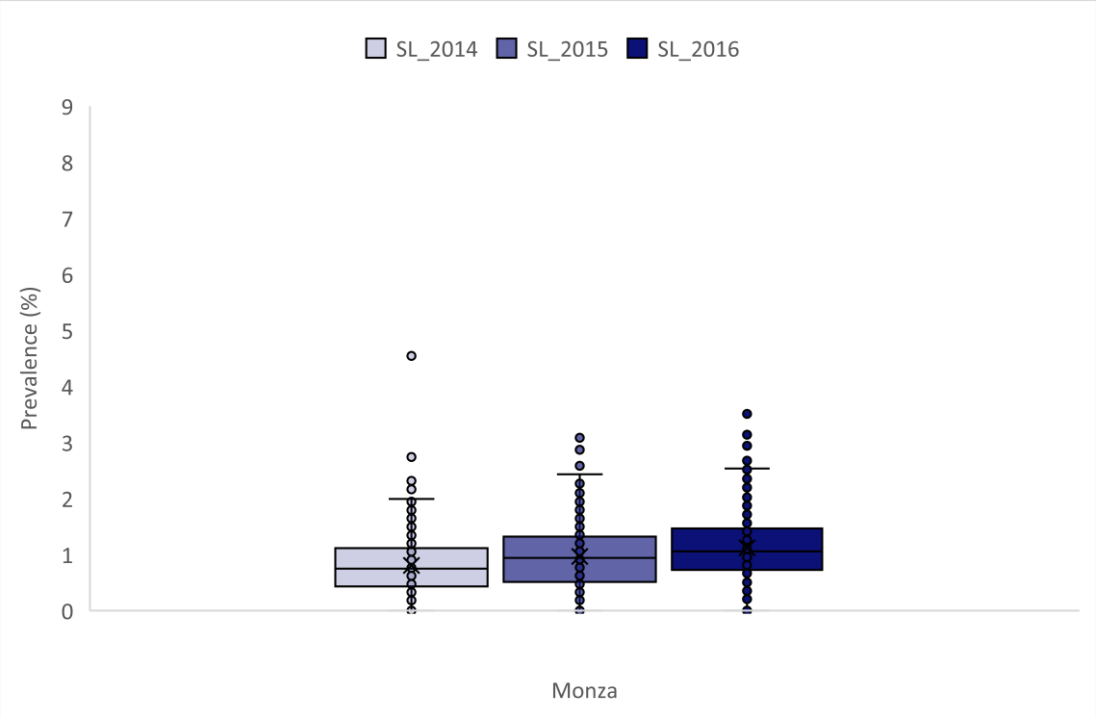

ACB_2014
ACB_2015
ACB_2016
Prevalence (%)
40
35
30
25
20
15
10
5
0
Napoli1

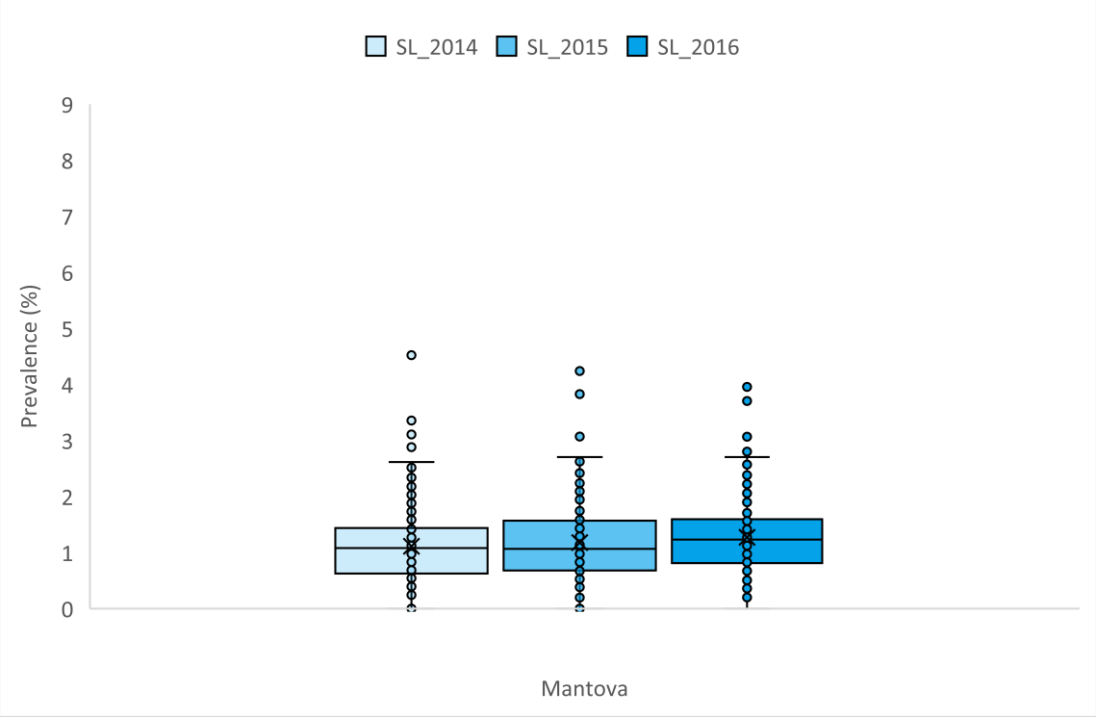

ACB_2014
ACB_2015
ACB_2016
Prevalence (%)
40
35
30
25
20
15
10
5
0
Napoli2

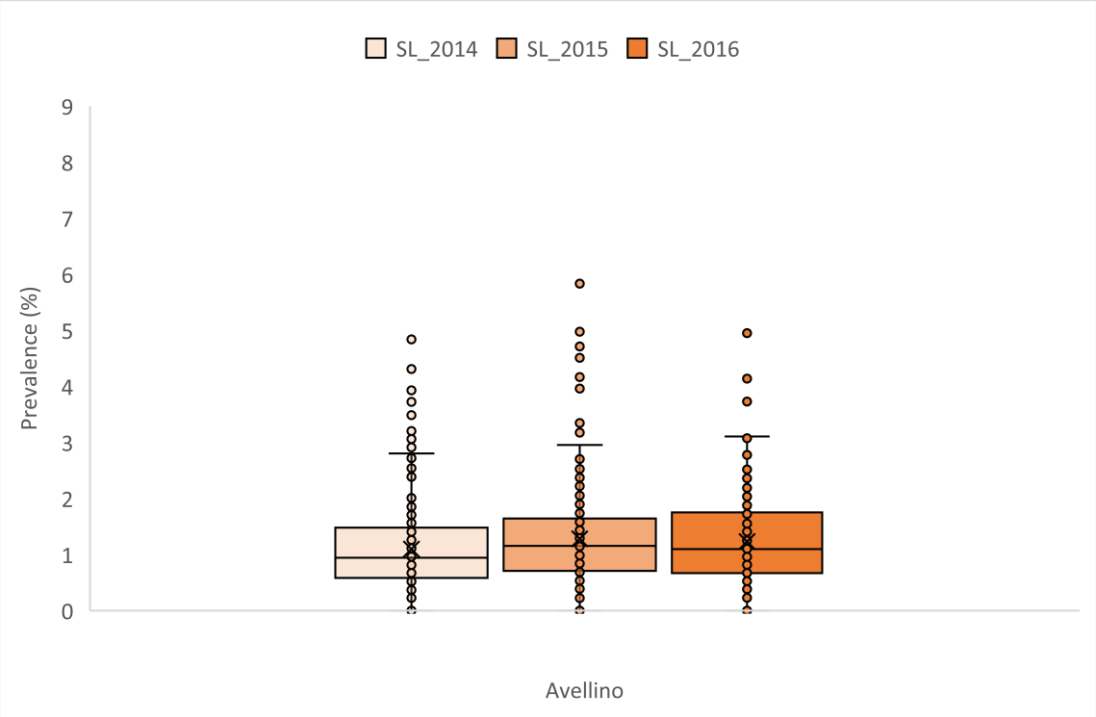
SL Score, GP distribution 2014-2016

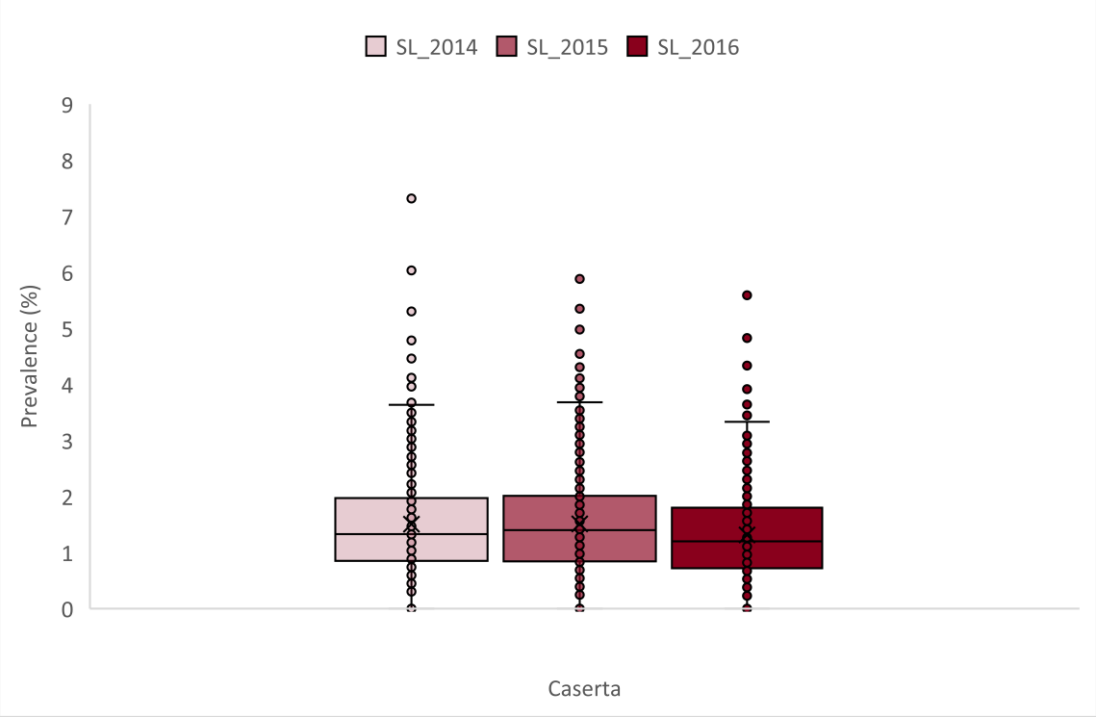


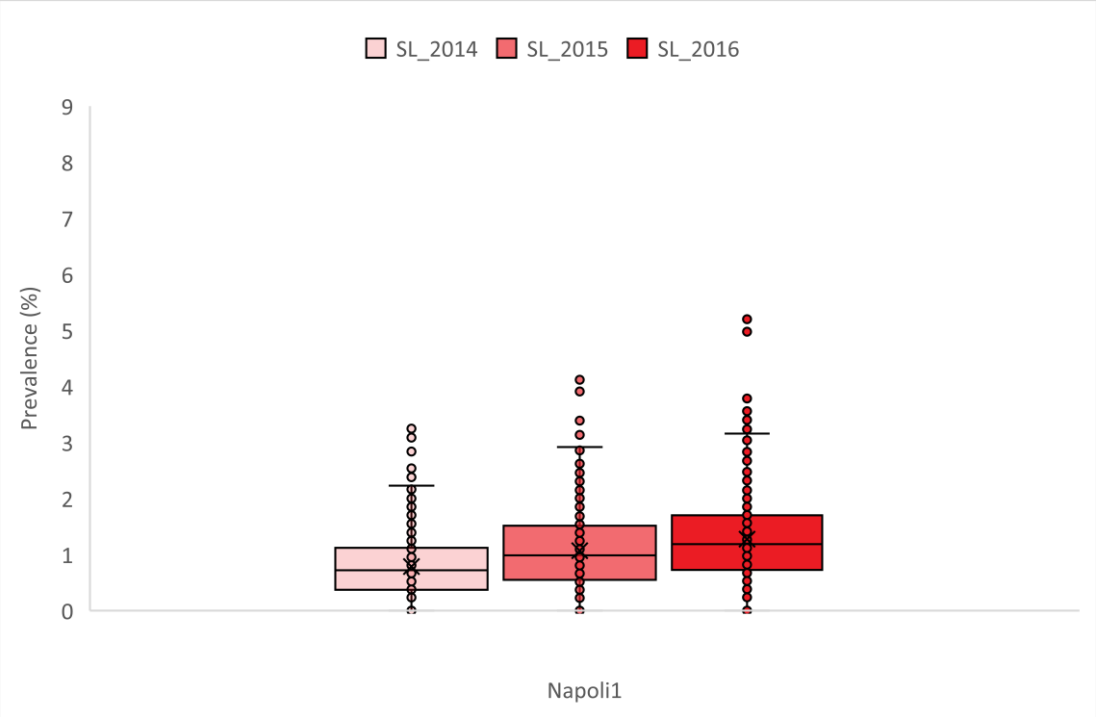


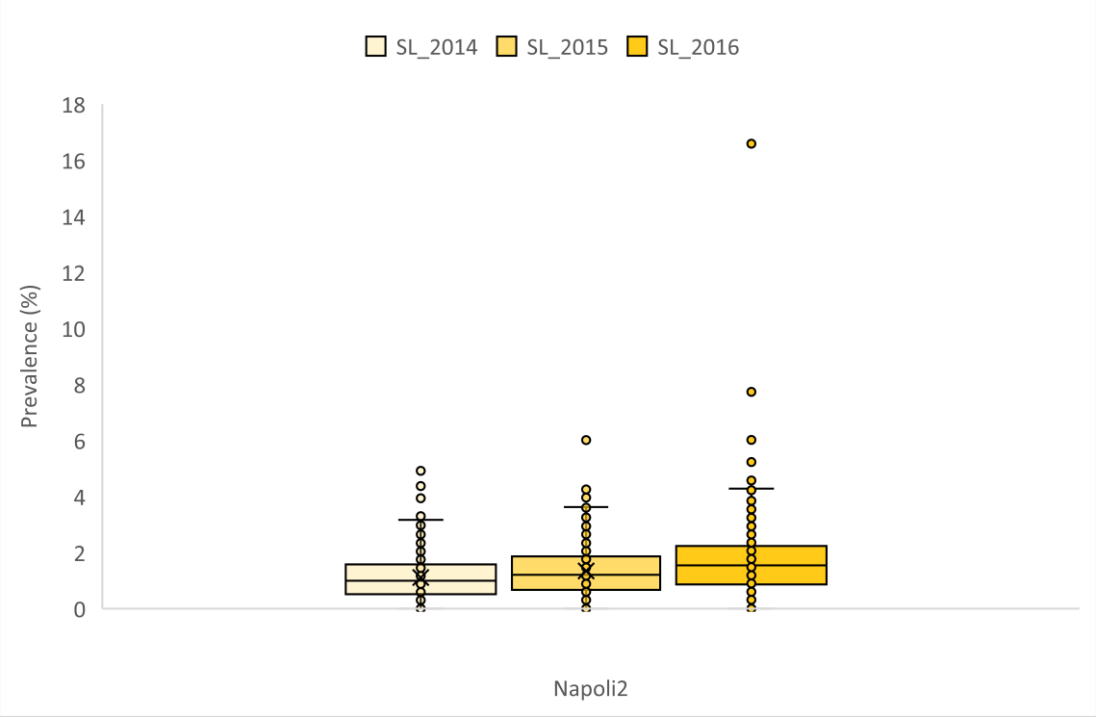

SL_2014
SL_2015
SL_2016
Prevalence (%)
0
1
2
3
4
5
6
7
8
9
Monza


SL_2014
SL_2015
SL_2016
Prevalence (%)
0
1
2
3
4
5
6
7
8
9
Mantova

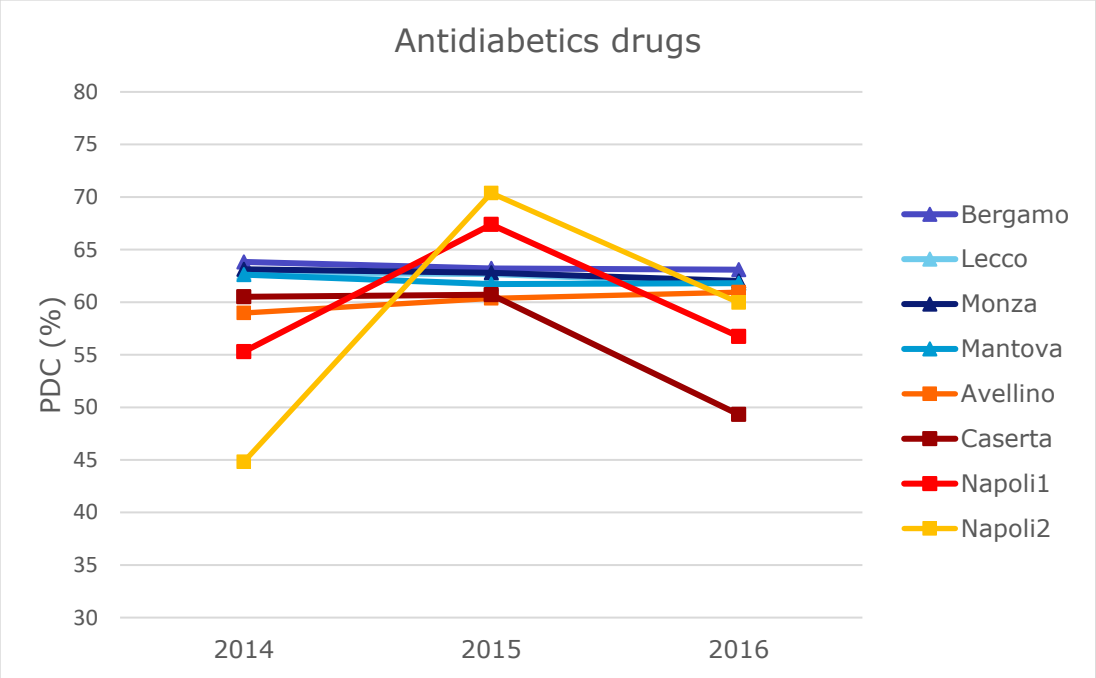

SL_2014
SL_2015
SL_2016
Prevalence (%)
0
1
2
3
4
5
6
7
8
9
Avellino


SL_2014
SL_2015
SL_2016
Prevalence (%)
0
1
2
3
4
5
6
7
8
9
Caserta

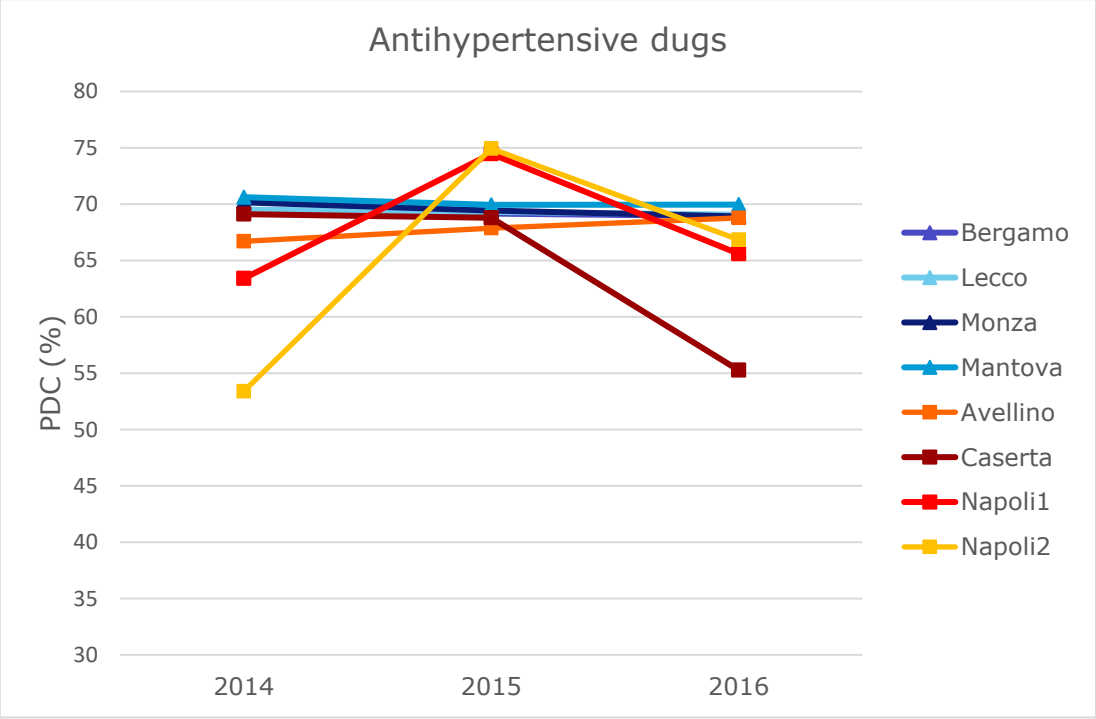

SL_2014
SL_2015
SL_2016
Prevalence (%)
0
1
2
3
4
5
6
7
8
9
Napoli1


SL_2014
SL_2015
SL_2016
Prevalence (%)
0
2
4
6
8
10
12
14
16
18
Napoli2

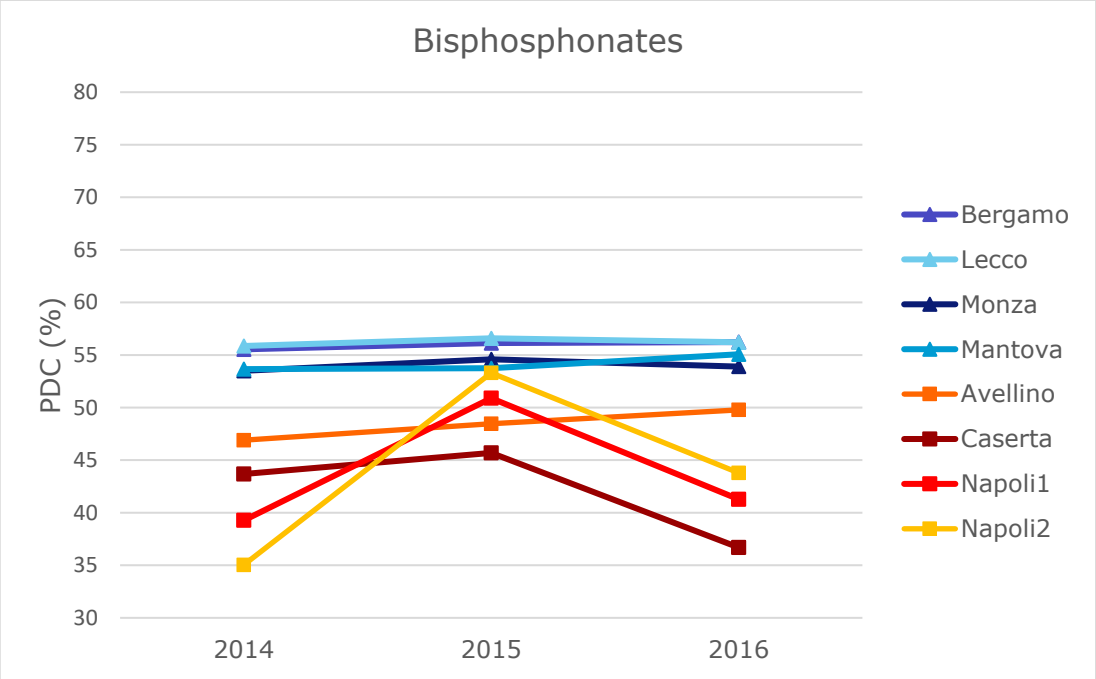
APPENDIX IV



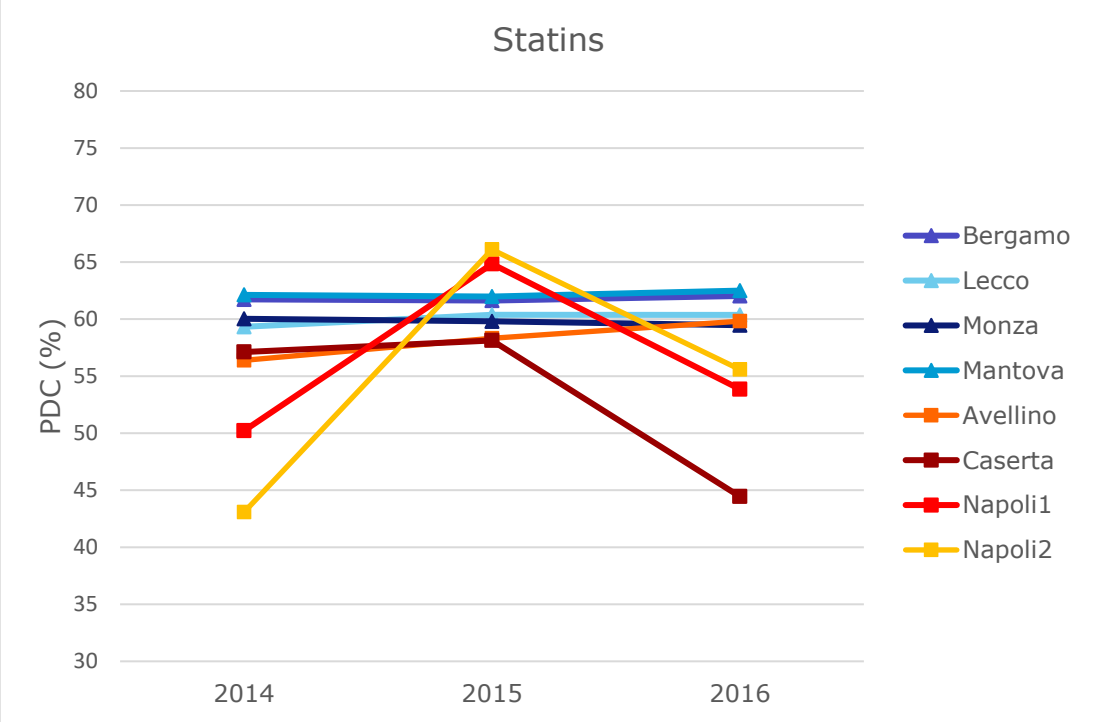
Annual adherence to antidiabetic drugs in prevalent users aged ≥40 years



Annual adherence to antihypertensive drugs in prevalent users aged ≥40 years



Annual adherence to bisphosphonates in prevalent users aged ≥40 years



Annual adherence to statins in prevalent users aged ≥40 years

Chapter 8

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DOCTORAL ACTIVITY REPORT

During my PhD programme, conducted at the Epidemiology and Preventive Pharmacology Service (SEFAP) of the Department of Pharmacological and Biomolecular Sciences, I have gain experiences and acquired skills related to:

- Bibliographic search, review of scientific literature (through PubMed, EMBASE and Web of Science databases) and interpretation of epidemiological data.
- Organization and management of large databases.
- Design, conduction and analysis of pharmacoepidemiology and pharmacoutilization (drug use profiles) studies, mainly through healthcare utilization databases.
- Assessment of drug prescribing quality and rational drug use by determining specific indicators (drug-drug interactions, therapeutic duplicates, off-label use, misprescribing/overprescribing in the elderly, medication adherence) through the analysis of administrative databases applying record linkage procedures.
- Development and implementation of educational/informative interventions for physicians on pharmacotherapy and appropriate prescription practices and of educative campaigns for the population on the proper use of medications.
- Evaluation of the risk/benefit profile of drugs in the context of real-world clinical practice, through the estimation of the association between their use and the reduction of the incidence of events (effectiveness) or the development of adverse events (safety), through both the use of databases (administrative, clinical or pharmacovigilance) and the application of meta-analytic methodologies based on the published results of clinical and/or experimental studies.
- Mentoring activity for student compilative theses.

I also acquired advanced knowledge of SPSS statistic software and good knowledge SAS and STATA software.

Most of my research activity was dedicated to the EDU.RE.DRUG project (Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients), that is the object of the present thesis. The protocol of this pragmatic trial, that is still ongoing, has been preparing for publication. We also planned a number of manuscripts concerning the baseline analyses, the results of which are showed in the present thesis.

Besides this project, during my PhD course, I have also collaborated with the research group of Professor Corrao, at the Department of Statistics and Quantitative Methods (University of Milano-Bicocca). In this context, I could gain experience in the design and the conduction of epidemiological studies aimed at evaluating the prevalence of risk factors and their correlation with cardiovascular diseases in the Italian population, through the analysis of healthcare data from regional administrative databases of the outpatient drug prescriptions. In particular, we conducted a case-control study investigating the association between proton pump inhibitors use and risk of hospitalization for cardio/cerebrovascular events that has been published in *Atherosclesosis*. We also performed a cohort study exploring the effect of the exposure to oral bisphosphonates on cardiovascular risk. The manuscript describing the latter study has been submitted for publication.

Furthermore, I spent a period of my PhD program at the Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care (University of Cambridge, Cambridge, UK), under the supervision of Professor Ference, where I could improve my skills in performing systematic reviews of scientific literature and meta-analysis of randomized controlled trials (RTCs) in the field of cardiovascular diseases. In this regard, we conducted a meta-analysis of RTCs investigating the association between apolipoprotein B levels and cardiovascular risk, which will be published soon (paper in preparation).

In this context, I have also enhanced my knowledge on genomic and pharmacogenomic topic related to the cardiovascular system, and experienced the conduction of studies based on the principles of Mendelian

randomization, to identify risk factors that have both a causal and a cumulative effect of the risk of disease, in an attempt to identify targets for early intervention, and to model "naturally randomized trials" that attempt to frame and answer clinical questions to fill evidence gaps when an actual clinical trial would be impractical or impossible to conduct.

List of publications:

Casula M, Scotti L, Galimberti F, Mozzanica F, Tragni E, Corrao G, Catapano AL. Use of proton pump inhibitors and risk of ischemic events in the general population, Atherosclerosis (2018).doi:10.1016/j.atherosclerosis.2018.08.035.

Casula M, Olmastroni E, Galimberti F, Tragni E, Corrao G, Scotti L, Catapano AL. Cardiovascular risk reduction with cumulative exposure to bisphosphonates: a population-based cohort study. [IN SUBMISSION]

Casula M, Menditto E, Galimberti F, Russo V, Olmastroni E, Scotti L, Orlando V, Corrao G, Catapano AL, Tragni E, on behalf of EDU.RE.DRUG Group. A pragmatic controlled trial to improve the appropriate prescription of drugs in adult outpatients: design and rationale of the EDU.RE.DRUG study.
[IN PREPARATION]

Galimberti F, Catapano AL, Cupido AJ, Katzmann JL, Kitch T, Snidermann AD, Ference BA. Association between apolipoprotein B lowering and cardiovascular risk reduction: a meta-analysis of randomized controlled trials.
[IN PREPARATION]

Others:

Galimberti F. Applicazione della randomizzazione Mendeliana allo sviluppo dei farmaci. GIFF 2019;11(2):12-18.

During my PhD programme, I attended a number of congresses (outlined below), at national and international level, in the belief that sharing experiences with other research groups working on the same topic of interest is a valuable key point to broaden knowledge and develop and optimize research practices.

Date	Title of contribution	Site
26-28 May 2019	**Use of bisphosphonates and risk of cardiovascular events: a population-based retrospective cohort study.** Science at a glance e-poster presentation	87th EAS Congress - Maastricht
5-6 October 2018	**Differenze di genere nell'aderenza alla terapia con statine.** Oral communication	XII Congresso Nazionale SITeCS - Milan
20-21 September 2018	**Inappropriate medication prescribing among adult patients in two Italian Regions.** Oral communication	XXI SIF SEMINAR ON PHARMACOLOGY for PhD students, fellows, post doc and specialist trainees – Bresso (Milan)
22-26 August 2018	**Association between PPI use and risk of cardiovascular events.** Poster **Inappropriate medication prescribing among elderly patients in Italy.** Poster **Monitoring of Italian pharmaceutical administrative databases: an assessment of prescriptive performance.** Poster	ISPE's 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management - Prague
3 July 2018	**Association between PPI use and risk of cardiovascular events** Oral communication	Next Step 9th ed: La giovane ricerca avanza - Milan
6-8 May 2018	**Use of PPI and risk of ischemic events in the general population.** Science at a glance e-poster presentation	86th EAS Congress - Lisbon
6-7 April 2018	**Use of PPI and risk of ischemic events in the general population.** Oral communication	SPRING meeting 2018. Novità nello studio dell'aterosclerosi e delle sue complicanze. Incontro tra giovani ricercatori SIIA, SIMI e SISA - Rimini
19-21 November 2017	**Use of proton pump inhibitors and risk of cardiovascular events in Lombardy.** Oral communication	31° Congresso Nazionale SISA - Palermo
25-28 October 2017	**Adherence to therapy with different second-line hypoglycaemic drugs in patients with type 2 diabetes mellitus.** Oral communication	38° Congresso nazionale SIF - Rimini
20-21 October 2017	**Rischio di eventi cardiovascolari associato all'uso di inibitori di pompa protonica nella popolazione lombarda.** Oral communication	XI Congresso Nazionale SITeCS – Milano
29 June 2017	**The LIPIGEN study: Dutch Lipid Clinic Network Score in Italian patients with FH.** Oral communication	Next Step 8th ed: La giovane ricerca avanza - Milan
23-26 April 2017	**Characterization of Italian patients with familial hypercholesterolemia: the LIPIGEN study.** Poster **LDL-cholesterol reduction with PCSK9 inhibitors: a meta-analysis of randomized controlled trials.** Poster	85th EAS Congress - Prague

	Characterization of metabolic syndrome in PLIC cohort. Poster	
7-8 April 2017	**Cardio-metabolic profile in a cohort from Lombardy region: the PLIC study.** Poster	SPRING meeting 2017. Novità nello studio dell'aterosclerosi e delle sue complicanze. Incontro tra giovani ricercatori SIIA, SIMI e SISA - Rome

Moreover, in the last three years, I followed a series of seminars, conferences and educational courses (listed below), in order to keep on training and updating my knowledge.

List of seminars, conferences and educational courses

2019. BHF Cambridge Cardiovascular Annual Research Symposium. Cambridge.

2019. External seminar: 'Identifying drug targets at scale using GWAS fine mapping and colocalization analyses'. Cambridge.

2018. EAS Advanced Course on Rare Dyslipidaemia and Atherosclerosis - Importance of Personalized Medicine and Differential Diagnosis. Cinisello Balsamo (Milan).

2018. Convegno Regionale SISA Lombardia, XVII Giornata Studio - Il soggetto ad alto rischio cardiovascolare: ricerca clinica e di base nell'ambito dell'aterosclerosi. Milan.

2018. International Conference on Pharmacoepidemiology & Therapeutic Risk Management Course: Precision Medicine with a Skills-based Focus for the Pharmacoepidemiologists. Prague.

2018. International Conference on Pharmacoepidemiology & Therapeutic Risk Management Course: Comparative Effectiveness Research: Real-World Evidence in Health Technology Assessment. Prague.

2018. International Conference on Pharmacoepidemiology & Therapeutic Risk Management Course: Propensity Scores in Pharmacoepidemiology. Prague.

2018. International Conference on Pharmacoepidemiology & Therapeutic Risk Management Course: Advanced Drug Utilization Research. Prague.

2018. 1° HOT TOPICS IN NUTRIZIONE – Linee guida nutrizionali e nutrizione personalizzata: una sfida per il futuro. Milan.

2017. XXVI Seminario Nazionale, Istituto Superiore di Sanità - La valutazione dell'uso e della sicurezza dei farmaci: esperienze in Italia. Rome.

2017. Convegno Regionale SISA Lombardia, XVI Giornata Studio- Il soggetto ad alto rischio cardiovascolare: ricerca clinica e di base nell'ambito dell'aterosclerosi. Milan.

2017. Convegno Istituto Superiore di Sanità – Le analisi sull'uso dei farmaci: metodi ed esperienze in Italia. Rome.

2017. Symposium - Lipids & Lipoproteins Atherosclerosis: from genes to therapy. Prague.

2017. Corso di formazione speciale e aggiornamento professionale – Prevenzione dei rischi chimico e biologico in laboratorio. Segrate (Milan).

2016. XXX Congresso Nazionale SISA. Rome.

2016. Convegno SifMed "Farmaco equivalente, Aderenza e Cronicità: una sfida per le Cure primarie". Milan.

2016. X Congresso Nazionale SITeCS. Milan.

2016. Convegno Regionale SISA Lombardia, XV Giornata Studio - Il soggetto ad alto rischio cardiovascolare: ricerca clinica e di base nell'ambito dell'aterosclerosi. Milan.

2016. Conferenza SIF-SITOX - Conferenza nazionale sullo Switch farmacologico. Milan.

Finally, in the awareness that transferring scientific knowledge within the scientific community and, above all, to the public is one of the hardest challenges of the "research world" nowadays, I have carried out information and dissemination activities. In particular, I am a member of SEFAPnews editorial-board, that provides monthly newsletters published on SEFAP website (www.sefap.it), on the topic of pharmacovigilance, pharmacoepidemiology, pharmacoutilization and health economy. Furthermore, I was involving in dissemination activity through RicercaMix blog of the Department of Pharmacological and Biomolecular Sciences of the University of Milan (www.ricercamix.org).