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A descriptive analysis of the immigrant population with a rare disease in the Veneto region, Italy: Utilisation of healthcare services.

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SUMMARY

Introduction: Rare Diseases (RDs) constitute a rather heterogeneous group of disorders that can affect any system. Most RDs are genetic disorders which are often severely disabling, substantially affect life expectancy and impair physical and mental abilities. The number of RD patients in Italy is estimated between 1 and 2 millions. In Italy RDs have been one of the priorities in the policy agenda since 1998. There is a significant body of legislation on the issue of RDs not only on a national level but on a regional level, as well. There is little research on the field of RDs and immigrant population. In general, immigrants face discrimination in various degrees when accessing the healthcare system of the host country due to their ethnicity, religion, age, sex or low socio-economic status. This social exclusion affects their health status directly and indirectly. It is rare for European countries to collect data on ethnic groups. The main challenge in measuring migrant health is defining the term migrant. At least five groups of immigrants have been identified in international literature. Students, economic migrants, asylum seekers, irregular/undocumented migrants and displaced persons. According to the Statistical Report 2011 of the Veneto region, 11.3% of immigrants in Italy have settled in the region, making it the third most attractive destination for immigrants in the country. The foreign residents in Veneto are currently 480,616 making up 9.8% of the population in the region. There is a paucity of information regarding the utilization of the Italian healthcare services by the immigrant population with a RD. To date, various studies have shown the trends of the healthcare utilization by immigrants in the Italian territory for numerous pathologies. However, they focus on diverse geographical areas of the Italian country and different time periods, or use different inclusion criteria for defining the immigrant population under study, or focus primarily on infectious diseases.

Objective: Our aim is to conduct a study on immigrants with a RD seeking healthcare in the Veneto region. Our objective is two-fold. Firstly we identify the immigrant population. On a second level a thorough description of the immigrant population is conducted. An effort to determine their demographic profile has been made. The exact number of RD migrant subjects, their age, gender, legal status, nationality, RD diagnosis are displayed. Simultaneously a description of the Italian RD patients will be made resulting to a comparison between the two populations. The variables used to describe the immigrants are also used for the description of the Italian population. The second objective is to describe the utilisation of the healthcare services by immigrants with a RD. One aspect is whether immigrants use the healthcare system for RDs, to what extent and for which diseases. Another aspect is to show the impact of the immigrant population on the Veneto healthcare services.

Materials & Methods: We accessed the Istat website (http://demo.istat.it) and we used data on foreign citizens (Cittadini Stranieri) who are residents in Italy. This data categorization and analysis led to the depiction of the presence of foreign citizens in the Veneto region, as well as the possible changes of their number during the course of time. In addition we showed the alterations in the percentage of the foreigners for each continent residing in the Veneto region every year. Data starting from 2001 until October 2011 were taken from the registry of the Rare Diseases, pertaining to patients who are certified with a RD in the Veneto region. Information on the demographc profile of the immigrant population was extracted. From the Health Discharge Records, information used were the dates of admission and discharge from the hospital, duration of hospitalisation, hospital ward, principal diagnosis as well as further diagnosis made during hospitalisation.

Results: The temporeal trend of the presence of immigrants in the Veneto region was firstly designed. The augmentation of the immigrant population, and especially of the female one, was highlighted. The Heath Discharge Records demonstrated that the utilization of healthcare services does not change much between the Italian and the immigrant population. The results of the Registry underline the use of the healthcare services by different populations in the Veneto region (immigrants vs. Italians and residents of the Veneto region vs. non residents), as well as the pathologies which are more prevalent in the migrant population.

Discussion: Comparison of data between the Health Discharge Records and the Registry of the Veneto region was conducted. The recorded RDs in the Registry differ substantially from the ones recorded in the Health Discharge Records. This may be because the most prevalent diseases in the Registry do not require a strict medical supervision over time. On the contrary the most prevalent diseases in the Health Discharge Records require a systematic medical attention. Furthermore it is highlighted that the percentage of the affected individuals residing outside the Veneto region is greater than the percentage of the subjects residing in Veneto for specific conditions, such as blood disorders. Last but not least, the underlying reasons behind the elevated prevalence of some RDs (palatoschisis, anemias, precocious puberty) were searched and analysed.

1. INTRODUCTION

1.1. Definition of Rare Diseases

Rare Diseases (RDs) constitute a rather heterogeneous group of disorders that can affect any system. Most RDs are genetic disorders which are often severely disabling, substantially affect life expectancy and impair physical and mental abilities.[1] There are 5,000 recognised RDs of which some are rarer, such as muscular dystrophy and haemophilia and some even ultra-rare, such as Hutchinson-Gilford syndrome and Whipple's disease.[2] According to the European Organisation for Rare Diseases (EURORDIS), RDs are estimated between 6,000 and 8,000 and 50% of them affect children. There is no existing effective cure for these conditions and because relatively common symptoms can hide underlying RDs, the medical staff may come up with a misdiagnosis.[3] Eighty per cent of RDs have identified genetic origins involving one or several genes or chromosomal abnormalities. Other causes of RDs may be environmental (chemicals, radiation), infections (bacterial or viral) or allergies. The cause of some RDs is sometimes the combination of genetic and environmental factors.[4] Moreover RDs are becoming less and less rare due to scientific advancements which allow the precise categorisation of diseases into smaller entities. As a result approximately 250 new RDs are described every year.[5]

1.2. History of orphan drugs and rare diseases

The category of rare diseases first appeared in the United States with the 'Kefauver-Harris Amendments' of 1962 based on the 'Food, Drug and Cosmetic Act' of 1938. According to these amendments, the pharmaceutical products required proof of their efficiency. This left two options to the pharmaceutical industry; the pharmaceuticl products should be either adequately reviewed to meet the new standards or they should be withdrawn from the market. There was, however, a certain category of drugs which was neither reviewed nor withdrawn and remained available in hospital pharmacies. These drugs had no legal therapeutic authorization and were described as being 'for chemical purposes, not for drug use'. They were called 'orphan' or 'homeless'. In the late 1960s the term orphan drug was extended to all categories of drugs which were poorly addressed by the pharmaceutical industry. In the mid-1970s orphans were considered as drugs for single usage, drugs for chronic diseases, drugs with anticipated legal liability, drugs for use in disease endemic to third world countries and unpatentable drugs. [6]

What should be underlined is the role of patients in mobilising the public opinion about their condition. In the USA, the amendments of Kefauver-Harris in combination with the refusal of the

industry to engage in the production of drugs that it considered non-profitable, had deprived patients with a RD of their treatment. Some affected individuals chose to purchase it illegally in Canada and later informed their political representatives and the federal administration of their situation. The focus on patients as drug consumers is a specificity that had a major consequence in the USA. The gathering of people who both had a RD and had been suddenly deprived of their drug induced a crucial and long-lasting shift in the debate that turned from the issue of drug withdrawal to the issue of the unmet needs of people with a RD. In the US at the time the orphan drugs that were discussed were unavailable but existing drugs.[6]

Until the late 1960s the rarity of a disorder was mentioned only as a characteristic that a clinician should keep in mind when facing a delicate diagnosis, related, for instance, to an organ. In most cases, medical publications addressed one RD only. The term "rare diseases", in plural form and without any further details appeared in the United States in the mid-1970s and was established by the Orphan Drug Act.[6] The USA was the first country to get involved in the field of rare diseases, as we define them today, in the 1980s. In 1982 the Orphan Drug Act was passed as an amendment to the Federal Food, Drug and Cosmetic Act. It created government incentives to encourage academic researchers to participate in research on drugs for the treatment of rare diseases and to encourage the pharmaceutical industry to invest in the development and marketing of such drugs. From 1982 to 2006, 282 orphan drugs and biologic products were produced in the USA, compared to only 10 treatments for rare diseases which were approved by the Food and Drug Administration (FDA) in the decade before 1982.[7] The example of the US was followed by Singapore in 1991, Japan in 1993, Australia in 1998 and the EU in 1999 by introducing initiatives regarding rare diseases.[8]

When studying the history of RDs in Europe, one should take into consideration the significant role of the public administration and patients' groups, who strongly supported the adoption of this category. The perspective of a common European drug market and the American experience of the Orphan Drug Act elicited the interest of the European pharmaceutical industry, followed by the French public administration and patients' groups. On the other hand physicians in France, where the subject of RDs was first addressed, were not involved in this cause, unlike their American counterparts.[6]

A RD is precisely defined by a maximum prevalence threshold, respectively five persons out of 10,000 in Europe, 7.5 in the United States and four in Japan. The contemporary category of RDs thus resulted from a regulatory measure based on a precise statistical definition, which is known to

fulfil an ideal of communicability, a key feature of a boundary object. According to Huyard the category of RDs is a boundary object, but not a category that could be qualified as medical i.e. a category that has been initially defined by health providers or users alone, in relation respectively to their work or their experience of illness. A boundary object contributes to the co-ordination of different social worlds, combining both a blurred meaning in its common use and a specific meaning in its local uses. "Boundary objects are both plastic enough to adapt to local needs and constraints of the several parties employing them, yet robust enough to maintain a common identity across sites. They are weakly structured in common use, and become strongly structured in individual-site use. They may be abstract or concrete. They have different meanings in different social worlds but their structure is common enough to more than one world to make them recognisable means of translation."

Regarding the use of the name of RDs, competing categories existed in Europe; orphan diseases on one hand and genetic diseases on the other. By contrast with the adopted category, neither was related to precise public health measures, and both were more difficult to define. Thus the greater adequacy of the category of "rare diseases" regarding both the means and the needs of public bodies and the alignment with international health regulation, could be an explanation, along with the support that people with a RD gave for the adoption of this category. Last but not least, France was about to take the rotative presidency of the EU and wanted to seize the opportunity to push its own agenda. This short timetable most probably contributed to the decision of drawing on pre-existing answers instead of designing new ones.[6]

Concluding, we should bear in mind that the category of RDs itself was created with the intention of restoring collaborative relationships between stakeholders who were unable to find common ground. On the contrary it was not meant to provide a strong incentive to pharmaceutical innovation, but rather to settle a conflict between patients and the pharmaceutical industry and bring back existing orphan drugs to the market.[6]

Once the Orphan Drug Act was passed in the US, the Food and Drug Administration (FDA) approved the use of products which were tested in small trials. For instance, the product which has been approved for the smallest population is bovine pegademase (Adagen) for the treatment of severe combined immunodeficiency syndrome (SCID) of the adenosine deaminase type. The clinical trial for that product involved 8 patients and one can claim that this study sample is unusually small even for an orphan drug. One should remember that rare disease patients are not

only few but also generally geographically dispersed; therefore recruitment of patients for studies of orphan drugs is often difficult.[6]

Orphan drugs must go through the same development process as any other drug and must be shown to meet the same standards for effectiveness and safety as a drug for a common condition. Because of the small number of patients available to be enrolled in clinical trials of orphan drugs, these products must be even more effective than the average drug if a statistically significant benefit is to be established. As for safety, since 85 to 90% of known rare diseases are serious or life-threatening, patients and physicians may be willing to accept a slightly higher level of risk than they would for a treatment for a less serious disease. But the limited number of patients plays a role here as well: although there have been no reports of serious adverse reactions to any orphan drug thus far, when a product is tested in a very small population, our knowledge of the safety profile may not be as complete as it can be for a treatment for a more prevalent condition.[6]

1.3. Rare diseases in the European Union

Rare Diseases (RDs) are life-threatening or chronically debilitating conditions which are defined as a priority in the field of public health in the European Union (EU).[9] According to the European Parliament's and Council's Decision No. 1295/99/CE the prevalence of RDs in the EU is less than 5 per 10,000 people. Despite the fact that the number of patients with a RD is low compared to more common diseases, if taken together they affect a significant percentage of the general population.[10] There are however European countries which define rare diseases with a much lower prevalence; Denmark and Sweden with a prevalence of 1/10,000 and the United Kingdom with a prevalence of 1/50,000.[8] According to EURORDIS, RDs in the EU affect around 30 million citizens,[3] whereas the European Commission estimates that 6% - 8% of the EU population is affected by RDs, translating this to 27 – 36 million people.[11] Surveys conducted in the European context show that rare diseases are not as uncommon as they are considered to be; more than half of French doctors in emergency departments had treated a patient with a RD in a year's interval, and almost one out of ten doctors had treated more than 10 RD patients.[12]

1.4. Orphan drugs

RD patients are treated with medicinal products which are called orphan drugs, according to the Regulation No. 141/2000 of the European Parliament and Council. These medicinals are provided to patients who suffer from a chronic condition even when the prevalence of the specific condition is higher than five per 10 thousand.[9] The above regulation resulted in the creation of the Committee

for Orphan Medicinal Products (COMPT) which has the task of reviewing applications for drugs which wish to qualify for the label orphan.[13] Incentives should be provided by the EU for research on orphan drugs since their production is not profitable for pharmaceutical companies. These incentives may be market exclusivity up to ten years, tax credits and fee reductions, accelerated marketing procedures and scientific and technical support. Pharmaceutical companies sometimes seek orphan status for a drug which is already in clinical use for a more common disease in case it is proven that this drug is efficacious with the RD, as well.[5] The drawbacks regarding the Regulation No. 141/2000 concern the absence of obligation to market the products in all Member States, the lack of public funding of clinical trials for RDs, differences in approval of added therapeutic value of orphan drugs and the need to increase the fee reduction and protocol assistance.[14] In addition, Europe has been criticised in the past regarding the orphan-drug legislative system for being idle and not generating sufficient interest for the pharmaceutical industry. However the European Commission awarded 369 orphan-product designations and approved marketing for 21 orphan products from 2000, which is when the European legislation on orphan drugs was initiated, until 2005.[15]

1.5. Initiatives regarding rare diseases on a European context

1.5.1. Eurordis

Some of the main European organizations concentrating on the field of RDs are Eurordis, Orphanet and the Rare Diseases Task Force (RDTF). The objective of Eurordis is to build a strong European network of patients' organisation and people living with rare diseases, to express their needs at the European level and to fight against the impact of rare diseases on their lives. EURORDIS' main activities are empowering RD patient groups, advocating RDs as a public health issue, raising public RD awareness and also that of national and international institutions, improving access to information, treatment, care and support for people living with RDs, encouraging good practices in relation to the above, promoting scientific and clinical RD research, developing RD treatments and orphan drugs, improving quality of life through patient support, social, welfare and educational services.[3] Eurordis was founded in 1997 and federates 1673 patients' organisations on a European level, along with national alliances in 8 European countries.[13] It is supported by the French Muscular Dystrophy Association (AFM), the European Commission, corporate foundations, the health industry and its members.[3]

1.5.2. Orphanet

Orphanet is an internet site of free access whose aim is to inform physicians and patients on rare diseases and high quality services in Europe. It contains information about more than 5,000 rare diseases.[16] It was established in 1998 in France by the Ministry of Health and the French Health and Research Institute (Inserm). After years of presence on the internet, it has reached the first place among sites which deal with rare diseases and orphan drugs. Twenty thousand users per day in 6 languages consult the site acording to data of December 2006. Twenty percent of its visitors are French, while the remaining 80% comes from more than 150 different countries. A researcher has the necessary resources at any given moment to conduct an extensive literature study and the doctor himself, may have access to information directly relevant to him.[8]

Each RD is described by a principal name and its synonyms, and it is indexed to give us direct access to references of international articles on the disease. The total list of RDs is directly accessible. Every disease interfaces with other sites of information around the world as well as with one encyclopaedia documenting more than 2,000 RDs composed by internationally renown experts and validated by a European peer Committee. Orphanet data are systematically added in French and English, and the resumes of articles are translated in German, Italian, Spanish and Portuguese. For the RDs which are less rare, the articles are written by international experts. Orphanet has undertaken the production of an encyclopaedia for the public in cooperation with RDs information services, referral centres and RD associations. The Directory of specialised Services in Europe provides information on more than 2,000 consultating experts, on diagnostic laboratories offering the specialised tests, on current research projects, on cinical trials, registries and patients'associations. This list of services provides information on all the different services offered, on a vast catalogue of French professionals, from which one can seek medical advice regarding rare disease, and on the most suitable laboratories for each case, among others.[8]

1.5.3. The Rare Diseases Task Force (RDTF)

The Rare Diseases Task Force (RDTF) was founded in 2004 by the European Commission Public Health Directorate. At the moment RDTF has 36 members, comprising current and former project leaders of European research projects related to RDs, member state experts and representatives from relevant international organizations. It mainly focuses on advising and supporting the European Commission Public Health Directorate in its task to promote the optimal prevention, diagnosis and treatment of RDs in Europe. Furthermore it provides a forum for discussion and exchange of views and experience on issues regarding RDs.[17]

In the past years, the RDTF and related projects have undertaken numerous initiatives to improve data collection. In particular, efforts have been aimed to the creation of a better classification system for RD, which can unmask the presence of RD in hospital discharge charts and death certificates. To this aim the RDTF working group 'Coding and classification of RD' is currently acting as Advisory Group to the WHO in the ICD - International Classification of Diseases – revision process, from ICD-10 to ICD-11. Specific initiatives toward a better classification in the field of rare tumours have been carried on by the projects EuroCare and RARECARE, among others. Part of the work of the RDTF is directed towards the creation and establishment of quality standards of databases and registries, so as to facilitate comparability of data for epidemiological and public health purposes.

RDTF has an expert working group providing recommendations to the European Commission regarding Public Health Indicators for RDs. The categories of health indicators are the following:

a. Contribution of RD to morbidity and mortality
b. Socio-economic impact
c. Availability of appropriate Health Services
d. Information, research, technology development
e. Monitoring of geographical differences in Europe
f. Surveillance of status/trends over time [18]

Sources of indicators include:

- Death certificates
- Registries (national/regional, international)
- Hospital charts
- Scientific/clinical databases
- Dedicated web portals
- Patients' organizations
- Ad hoc clinical studies/ad hoc surveys
- Surveillance systems
- Literature

Information in healthcare is a main objective of the EU policy for the coming years and indicators are the necessary information tools to guide and evaluate health policies interventions, where important values such as equity and fight against discrimination are to be fulfilled, such as the field of RDs.

1.6. Health Indicators

Health indicators are a set of parameters to evaluate the health status of a population and the impact of health policies on this status. Indicators should be informative over the health status and sensitive to changes over time. The development of valid and relevant information is a prerequisite for planning efficient health interventions, health services and allocation of resources. The main purposes of health indicators for RDs are to measure RD globally and individually as a public health issue, enable surveillance of status and trends and provide efficient and consistent reporting mechanisms.

The field of RDs needs indicators that are particularly sensitive. An indicator is as sensitive as its ability of revealing changes in the issue of interest. For example, indicators such as mortality rates can have low sensitivity to change in very rare diseases due to the small numbers involved. However, the same indicators can become more sensitive in the presence of e.g. a very effective treatment or prevention action. In the field of RD, information tools have to be tailored to the specific needs and problems of this field. Due to the heterogeneity of RDs, the low number of patients and the geographical spread, main indicators used for more common diseases, are not applicable. In the RD field, coordination and pooling of resources are the necessary basis to generate indicators.

According to the European Committee health indicators are sets of data (tables, graphs, maps) on health status, determinants and care in EU Member countries. They allow for monitoring and comparison, and serve as a basis for policymaking. Out of a complete list of 88 health indicators, there are over 40 core European Community Health Indicators for which data is readily available and reasonably comparable.

The need of health indicators for RDs is crucial for the assessment of the present situation of RD and the monitoring of health policies in this field. Furthermore, the Communication, which constitutes an important legal basis for RD initiatives at EU level setting the main priorities in this field, pays significant attention to the visibility of RD also through the use of indicators,

encouraging the compilation of existing sources, as well ‘as the definition of a realistic and meaningful set of indicators in the areas of orphan drug availability and accessibility, centers of expertise, and RD policy initiatives at the Member States (MS) level’. Legal basis for health indicators is provided by several actions of the past Programme of Community Action in the Field of Public Health 2003-2008 and in the New Health Strategy 2008-2013.

1.7. Rare diseases in Italy

The number of RD patients in Italy is estimated between 1 and 2 millions.[19] Since 1998 RDs have been one of the priorities in the policy agenda of the country. In 2001 the Ministerial Decree 279/2001[20] established the national network for RDs in order to facilitate patients who suffer from RDs and define cost exemptions for related healthcare services. The main aim of the Decree is to set rules for cost exemptions for services included in the essential care levels *(LEA: livelli essenziali di assistenza)* and to identify specific protective measures for rare diseases patients. The National network consists of regional and interregional referral centres and foresees the creation of qualified centers which are responsible for the prevention, monitoring, diagnosis and treatment of RDs. Universities, hospitals and medical institutes are involved in the research on RDs, as well as, in providing support to patients with a RD through all the phases they are cared for.[21,22] However these centres of expertise are unevenly distributed across Italy, making the implementation of the Ministerial Decree difficult. Especially areas of Southern Italy lack high quality services and RD patients encounter difficulties in receiving diagnosis and treatment. The network, in theses cases, needs to ensure that an adequate and uniform coverage of the whole territory is applied.[21] This Decree applies to all patients registered in the national health system, including the foreigners who have residence or domicile in the Italian territory.

The National Registry of Rare Diseases was founded by the Istituto Superiore di Sanità which is the technical-scientific body of the national health system. In particular, the National Center has the following tasks: *to standardise and diffuse diagnostic procedures and therapeutic and health care guidelines for selected RDs; to ensure quality assurance and standardization of diagnostic genetic tests in the Country; to elaborate the inventory of orphan drugs; to promote and organise training and continuous education for health workers with particular emphasis on uniformly accepted standard guidelines of health interventions; to produce information for health workers, patients and their families, and the general population; to establish and run the ISS web-site dedicated to RD.*[23]

Moreover the National Register of Rare Diseases is where all the epidemiologic data is kept, arriving from the regional and interregional centres.[21] There are also International Registries established in Italy which collaborate with other centres of expertise around the world. They do not only constitute a repository of clinical data but also a collection of precious biological samples. In this way the patients' data and samples travel, and not the patients themselves. This reinforces the idea that rare disease patients seldom need to move, especially abroad, because Italy has all the expertise needed for almost any single rare disease.[24]

In addition the National Health Service fully reimburses orphan drugs. Italy is one of the European countries which compares the price of an orphan drug requested by the pharmaceutical company with the price in other countries. In this way companies are given the incentive to introduce an orphan drug first in countries where a favourable price and reimbursement are relatively easy to obtain. Last but not least, Italy has delineated procedures governing compassionate use of orphan drugs.[25]

1.7.1. Italian legislation on rare diseases

The most important legislation in Italy regarding RDs is the following:

- Ex article 26 Law 833/78.[19] Patients with physical, mental or sensory disabilities are provided with health services targeted at the functional recovery by the Local Health Units *(Aziende Sanitarie Locali)*. In case the Local health Unit is not able to provide these services to the patient, it should come to an agreement with institutions in the region where the patient lives, or even in other regions, to have the patient taken into care.

- Law n. 648 of 23rd December 1996.[26] Conversion into law of the decree-law of 21 October 1996, n. 536, laying down measures for the containment of pharmaceutical costs and the restatement of the expenditure ceiling for the year 1996. This law permits the use of drugs which are already marketed abroad, in Italy, and the use of drugs which are not yet authorised but are subject to clinical trial and the off-label use of drugs.

- Law n. 94 of 8th April 1998.[27] Conversion into law, with amendments, of Decree-Law of 17 February 1998 n. 23, concerning urgent provisions on clinical trials in oncology and other health measures. In certain cases, doctors can use drugs in a compassionate way, especially when there is no official therapy for a RD.

- Legislative Decree n. 124 of 29th April 1998.[28] Exemption is provided according to the following criteria: clinical severity, degree of disability and the burden of the costs of its treatment.

- Decree of the Italian Council of Ministers of 9th July 1999.[29] According to this decree, newborns have to undergo screening tests for three rare conditions: phenylketonuria (which is a RD), congenital hypothyroidism and cystic fibrosis. The early identification of patients affected by these diseases before the clinical onset of symptoms, could allow for treatments that prevent the evolution of these diseases into severe disabilities.

- Ministerial Decree n. 279 of 18th May 2001.[20] Regulation of establishment of a national network of rare diseases and exemption of RD patients from health service costs. In order to identify a RD, a code has been formed. The first character is an "R" which stands for Rare. The second character corresponds to the group of diseases that the International Classification of Diseases-9 (ICD-9-CM) has appointed to each nosological category. The third character is either the number "0" in case of a single disease, or the letter "G" when the code refers to a group of diseases. The remaining three characters demonstrate the numerical progression of the disease or the group of diseases in every nosological category.

- Decree of the Italian Council of Ministers of 29th November 2001.[30] It defines the essential care levels *(livelli essenziali di assistenza)*, based on an agreement between the state and the Italian regions.

- Circular n. 13 laying down the indications for the application of Regulations relating to the exemption for rare and chronic diseases.[31]

- Ministerial Decree of 8th May 2003.[32] According to this MD a drug which is not authorised yet, but is subject to Phase II or III of clinical trials for the same therapeutic indication and seems to be efficient and safe, can be prescribed to patients on the costs of the producer.

- Ministerial Decree of 15th April 2008.[33] A list of the interegional centres which are specialised in RDs with a low prevalence is designed.

We present a Table with the categorized RDs according to the Ministerial Decree 279/2001.

Table 1: Nosological categories and codification of exemption according to the Ministerial Decree 279/2001.

Code	Nosological categories
RA****	Infectious and parasitic diseases
RB****	Tumours
RC****	Endocrine glands disorders and nutritional, metabolism and immune disorders
RD****	Disorders of blood and hematopoietic organs
RF****	Disorders of the nervous system and sense organs
RG****	Disorders of the circulatory system
RI****	Digestive disorders
RJ****	Diseases of the Genitourinary
RL****	Diseases of skin and subcutaneous tissue
RM****	Disorders of the musculoskeletal system and connective tissue
RN****	Congenital malformations
RP****	Some morbid conditions of perinatal origin
RQ****	Symptoms, signs, and ill-defined morbid conditions

1.8. International Classification of Diseases (ID-9-CM)

Apart from the classification of RDs by the Ministerial Decree of 2001, the ICD-9-CM is used to classify all diseases, including RDs, in Italy. The Health Discharge Records has to conform with ICD-9-CM in order to categorize diseases, chirurgical operations, diagnostic and therapeutic procedures. The ICD9 classification is the latest in a series which has its origins in the 1850s. The first edition, known as the International List of Causes of Death, was adopted by the International Statistical Institute in 1893. WHO took over the responsibility for the ICD at its creation in 1948 when the Sixth Revision, which included causes of morbidity for the first time, was published. The World Health Assembly adopted in 1967 the WHO Nomenclature Regulations that stipulate use of ICD in its most current revision for mortality and morbidity statistics by all Member States.[34]

The ICD is the international standard diagnostic classification for all general epidemiological purposes, many health management purposes and clinical use. These include the analysis of the general health situation of population groups and monitoring of the incidence and prevalence of diseases and other health problems in relation to other variables such as the characteristics and

circumstances of the individuals affected, reimbursement, resource allocation, quality and guidelines.[34]

ICD-9 is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.[34]

The version ICD-9-CM stands for 'International Classification of Diseases, 9th Revision, Clinical Modification' and its main difference from ICD-9, which primarily dealt with causes of mortality, is that it focuses on causes of morbidity. A more precise classification of analytical and diagnostic procedures is designed with the introduction of a fifth character on all codifications.

1.9. Legislation regarding the Veneto region

Most significant legislation regarding the Veneto region and RDs.

- Regional Committee Resolution n. 741 of 10 March 2000 has established the Regional Centre of reference for the rare diseases and the Regional Registry of Rare Diseases. With the additional Regional Committee Resolution n. 204 of 8 February 2002 the regional referral centres for the Rare Diseases were identified.

- Regional Committee Resolution n. 204 of 8 February 2002.[35] It has established the identification of referral centres for RDs. The network of these centers certifies RDs patients with a relative diagnosis. As a consequence the patient obtains a certification of exemption from the healthcare expenses related to his condition, which is released by the Local Health Unit of his residence.

- Regional Committee Resolution n. 2706 of 10 September 2004.[36] Agreement among the Veneto region, the Friuli Venezia Giulia region, the autonomous province of Bolzano, autonomous province of Trento regarding rare diseases. According to this agreement, collaboration in the area of RDs was achieved for the homogenisation of the welfare approach, as well as for the modalities and typologies of access at the specific benefits for every pathology. A single network of Referral centres for RDs for all the above mentioned

regions was established *(Area Vasta)*, as well as a single monitoring system, the one already in use by the Veneto region. This accord was ratified on 11 October 2004 by the Veneto region with a Regional Committee Resolution.

- Regional Committee Resolution n. 2046 of 3 July 2007.[37] Agreement among the Veneto region, the Friuli Venezia Giulia region, the autonomous province of Bolzano, autonomous province of Trento for the realisation of the *Area Vasta* in the field of rare diseases. Identification of interregional referral centres of the *Area Vasta* for rare diseases. As already mentioned on the title of the Resolution, the identification of the common centres of reference for the above regions and autonomous provinces is completed. Each region and autonomous community has to implement the Area Vasta agreement with a Regional Committee Resolution and this one applies to the Veneto region.

1.10. Definition of Immigrants

According to Amnesty International, an *immigrant* is a person who moves from one place to another. This individual may be forced to leave his country of origin because he is afraid for his own sake and his family's well being or because of famine or other natural disasters. Such an individual can also decide to move voluntarily. As a human being he has human rights; the right to life, to freedom from arbitrary detention, to freedom from torture as well as to a satisfactory standard of living. The number of immigrants globally is currently around 175 million.[38] At the international level however, no universally accepted definition for "migrant" exists. The term migrant is usually understood to cover all cases where the decision to migrate is taken freely by the individual concerned for reasons of personal convenience and without intervention of an external compelling factor; it is therefore applied to persons and family members, moving to another country or region to better their material or social conditions and improve the prospect for themselves or their family. The United Nations defines migrant as an individual who has resided in a foreign country for more than one year irrespective of the causes, voluntarily or involuntarily, and the means, regular or irregular, used to migrate.[39]

For the purpose of this study, the term immigrant or foreigner will be used from now on in order to identify the persons who do not have the Italian citizenship but reside in Italy and have access to the healthcare services for RDs. Since the group of immigrants is a rather heterogeneous one, we find it useful to refer to some categories of migrants. One can find the terms refugee, asylum seeker and irregular/undocumented/illegal immigrant in the literature. In our research the term undocumented

immigrant in the form of STP *(Straniero Temporaneamente Presente)* will be used; therefore we present the following definitions in order to clarify the differences among these terms so that the any confusions are avoided.

According to the UN Convention for refugees which has been signed by 140 countries, a *refugee* is someone who must leave his country of origin because he is in danger of having his human rights violated due to his identity or his convictions. He cannot or he does not wish to return to his country because his country of origin cannot or does not wish to protect him. Because of the prosecution that he may face upon return, a refugee is entitled to be protected from an involuntary return to his country of origin. A refugee is entitled to all the rights that all individuals have, as well as the protection from prosecution for illegal entrance to a foreign land. He is also entitled to identification and travelling documents and access to a long-term solution to his situation; this may be his integration into the country which offers asylum, re-establishment to a third country, or his repatriation, as long as his security and dignity are guaranteed. It is estimated that there are currently approximately 10.6 million refugees worldwide.[38]

An *asylum seeker* is a person seeking protection as a refugee even if he has not been officially recognised as one. Often this term is used when a person awaits to be granted refugee status by the government of the country he has entered.[38] In case of a negative decision, the person must leave the country and may be expelled, as may any non-national in an irregular or unlawful situation, unless permission to stay is provided on humanitarian or other related grounds.[39]

Irregular or undocumented or illegal migrant is a person who, owing to unauthorized entry, breach of a condition of entry, or the expiry of his or her visa, lacks legal status in a transit or host country. The definition covers inter alia those persons who have entered a transit or host country lawfully but have stayed for a longer period than authorized or subsequently taken up unauthorized employment. The term "irregular" is preferable to "illegal" because the latter carries a criminal connotation and is seen as denying migrants' humanity.[39]

Stateless person is a person who is not considered as a national by any State under the operation of its law, according to the 1st Article of the UN Convention relating to the Status of Stateless Persons, 1954. A stateless person lacks those rights attributable to nationality: the diplomatic protection of a State, no inherent right of sojourn in the State of residence and no right of return in case he or she travels.[39]

1.10.1. Immigrants' background

Immigrants may, as a group, have especially increased health care needs. The mode of travel and legal status of the migrant are two factors which determine the migrant's health status at various stages of the migration cycle. The migration process has three main phases: the pre-departure phase from the point of origin, the transit phase, and the phase of arrival and sojourn in the destination country. In addition migrants may derive from different backgrounds and once they migrate their status often changes dramatically. Different categories of migrants may have very different experiences. Determinants of migrants' health are shaped by their experiences in the country of origin, transit and destination.[40]

In reference to the pre-flight conditions, many immigrants come from countries where health care is restricted. In these countries there is lack of health care infrastructure, lack of well trained medical staff and lack of financial resources. In addition, a difficult to identify percentage of these individuals has been exposed to extreme health risks, such as political or religious persecution, torture, imprisonment, famine, or lack of shelter.[41] Hence they enter the new country severely damaged. Furthermore, the journey to the receiving country might be a burdensome experience. Due to the hardships of travelling and entering the country, sometimes illegally, immigrants may have accumulated further illnesses since their emigration. They are usually transferred in boats, packed in large numbers under dreadful conditions.[42,43] If they manage to survive drowning, they have to suffer from the total absence of sanitation. Basic needs such as the intake of food, water and sleep are completely disregarded.[43]

Other immigrant categories encounter much more milder conditions during the migration process. There are individuals who migrate for economic reasons seeking better job opportunities and improved working conditions. They are usually looking for an enhanced healthcare system, a more advanced educational system or have family ties in the host country i.e. chain migration (*pull factors).*[44,45] Other motives such as unstable political situations and social upheavals; persecution for political, social and religious beliefs; war or forced recruitment; child abuse constitute the so called *push factors*. Push and pull factors may be presented simultaneously.[46]

In the host country, the environmental factors, health behaviours, community resources and the migrant's income play a significant role in shaping his health status. One environmental factor is residential segregation; individuals who are members of racial/ ethnic minority groups run higher risk of having lower socioeconomic status and living in racially and economically segregated and

stressful environments which lack resources, such as employment, high quality food, safe places in which they can socialize and be physically active. Their neighbourhoods are also more likely to have higher rates of deliquency. Access to medical care in low socioeconomic neighbourhoods is also poor. Not only do they present high rates of uninsurance and sicker populations, but they also have healthcare services which are proven to be inadequate for the needs of the specific population. The resources are limited and disproportionately lower in order to meet people's needs. Last but not least, racial disparities in the amount and quality of medical care exist even for similarly insured patients. Therefore initiatives to eliminate health disparities should go beyond equalizing insurance coverage.[47]

Immigrants face discrimination in various degrees due to their ethnicity, religion, age, sex or low socio-economic status. This social exclusion affects their health status directly and indirectly.[48,52] Directly, since they have restricted choices regarding their health behaviour. Healthy choices are proven to be expensive; therefore an immigrant might not be able to follow what is better for him but rather what he can afford. Indirectly as they may face elevated psychological stress and demoralised feelings. Being on the margins of a new society for a second time, after one has left his home country, could be devastating for a person. The majority of immigrants are young adults who wish to contribute to their new environment, and are eager to work and ameliorate their standard of living. Their rejection from the social surroundings is an additional psychological burden which should not be underestimated.

1.10.2. Immigrants' mental health care needs

Apart from the pre-flight and flight conditions, one should also consider the after-flight ones. Once a migrant arrives at his destination country, he encounters several difficulties. Everything that surrounds him looks different. Factors such as the language, climate, family and social relations, as well as status alter. Migration is a psycho-social process characterized by loss and change. According to the psychiatry of migration the term used for this condition is the one of *grief process*, which may present different intensity and length depending on the individual. Difficulties in expressing grief can cause psychological problems.[49] The demanding process of integration makes the migrant more susceptible to mental health problems; however migrants rarely use the mental health services compared to the native population. This lower rate of utilization of care may be due to cultural and linguistic barriers. Even when migrants do decide to use the mental healthcare services, they present significant delay in seeking professional help or they are hardly ever being referred by their physicians. Furthermore they usually encounter problems with the police and the

emergency services resulting in their compulsory and secure-unit admission, a factor which aggravates their already blighted situation.[50]

1.10.3. Language and cultural barriers

The immigrants' limited proficiency in the language of the host country constitutes a great obstacle to healthcare access. Lack of a satisfactory command of the majority language discourages immigrants who are in need of medical care to ask for a professional's help. Linguistic barriers are associated with longer visit time per clinic visit, less frequent clinic visits, a low level of communication between the physician and the patient, increased number of laboratory tests, an augmented number of emergency care, less follow-up and low levels of satisfaction regarding healthcare services.[50] The healthcare staff has repeatedly highlighted the problems posed by the inability to communicate with foreign patients. Doctors cannot have a thorough picture of the history of the patient, and patients are reluctant to visit a doctor who does not understand them.

Cultural beliefs and practices are also another issue that should be taken into consideration. Immigrants come from a different socio-political background and have different perceptions about life and health.[53] Religious beliefs may act as a resource for health and religious taboos and traditions may have both positive and negative effects on health. Religion practices influence everyday life and hygiene practices.[51] Migrants' culture and traditional norms often differ from those of the host community. This is particularly a challenge for women migrants who adhere to traditional norms and have limited contacts outside their communities.[40] Health care personnel might be unfamiliar with the norms and practices of these populations. A culturally insensitive medical staff can put off immigrants from seeking care; this means that a part of the immigrant population may reach the hospital only in case of an emergency.

Interpretation facilities are not always available in order to facilitate communication between the migrant and the medical staff. Bilingual health workers assist with the delivery of healthcare to migrants; however professional interpretation services are needed in most cases. Interpreters should combine considerable medical knowledge and in-depth knowledge of patient's social and cultural background. This role is fulfilled by *cultural mediators* who are also called *consultants* or *brokers*. The concept of cultural differences has been used in order to identify problematic areas in the delivery of healthcare services to immigrants since the 1980s. The term *cultural sensitivity* was used in the past, referring to the knowledge of the characteristics of other cultures (beliefs and customs related to health, as well as, rules of interaction, values and norms). This approach, however,

resulted in preparing manuals for healthcare staff which categorized people according to their ethnicity and were limitative in a way. This approach has fewer supporters nowadays because it is believed that cultures are heterogeneous and subject to ceaseless change. In this way attention shifted to cultural self-knowledge. Healthcare staff is now encouraged to focus critical attention on their own old views, values and implicit presuppositions. Managers in particular have to accept that there are no shortcuts to providing good care to diverse populations; time and resources have to be invested in getting to know the patients and building trust.[52]

1.10.4. Bureaucratic obstacles

The challenges immigrants have to face when accessing health care commences with their lack of knowledge about the healthcare system of the receiving country. The procedures and the bureaucracy may be difficult to be followed by someone who has just entered a new country. Moreover, the language barrier can add more strain to the struggle of an immigrant to find his way in the healthcare system.[53] Furthermore there is no coordinated European approach to integrating migrants' needs into national health and welfare system. The approach of different countries to integrating migrants' health depends on various factors, including the particular patterns of migration and migrants entering the country, as well as the type of welfare state and legal system. In some countries migrants are entitled to a variety of services. However even where such policies exist, it is not always clear how well they are implemented in practice and whether all the relevant actors, including health and non-health providers and administrators are well informed about legal provisions.[40]

This, for instance, is a problem which has been identified in Italy where health coverage is provided by law to all migrants, including those who lack legal documents. Yet, NGOs criticize that implementation of the law differs significantly between regions and within regional health centres and hospitals. In rural areas access to health services for migrants tends to be rather restricted. Moreover the level of information amongst health and other key service providers may also vary. In some cases it has been found that local health administrators have asked migrants for documents even though it is not required by law[54] or have denounced irregular migrants to the police.[55]

1.11. Challenges in measuring migrant health and health care utilisation

The notion of public health has changed the way research and policy making, approach migrant health. In the past, immigration studies mainly focused on communicable diseases and the risk that immigrants might pose on the health of the autochtonous population. However, recent public health

perspective takes into consideration not only the possible burden of contagious diseases of immigrants, but also the noncommunicable and chronic diseases of this population. The interest on immigrant health is equal for the health of the majority population as well as for immigrants themselves.[56] Taking this idea one step further, one could say that the interest on immigrants with a rare disease is fully justified by public health's holistic approach.

Researchers face the difficulty of considering both the concepts of ethnicity and migration in their studies. Migrants are sometimes classified according to their country of origin but this variable is not an adequate proxy for ethnicity; a single country might provide shelter to many ethnic groups, while a single ethnic group might be scattered along many countries. In addition there is focus on migrants only and not on their descendants who are being overlooked, whereas health problems in later generations might be even greater than those in the first.[52]

It is rare for European countries to collect data on ethnic groups, with the exception of UK, Sweden and Netherlands. Recently, Germany, Belgium and Spain have initiated introducing migration questions in health surveys. The main challenge in measuring migrant health is defining the term migrant. At least five groups of immigrants have been identified according to the Health Protection Agency. Students, economic migrants, asylum seekers, irregular/undocumented migrants and displaced persons.[57]

Measurement of migrant health and health care utilisation is challenging for a variety of technical and political reasons; medical research favours homogeneous samples, resulting in ignorance about the effectiveness of treatments on ethnic minorities; recording ethnicity in clinical records can be perceived as discriminatory; ethnic minorities often have low response rates in epidemiological surveys; monitoring undocumented immigrants is difficult; information is not validated, and thus its accuracy is unknown; immigrant mortality in the population may be underestimated in register-based studies because sizeable numbers of immigrants who subsequently leave their new homeland (the host country) fail to register this fact with the national registration authorities.[58]

If surveys do include migration variables, they mostly depend on a broad "social science" definition of immigrant status, employing country of birth, parental country of birth and length of stay in the host country as indicators to identify this population. Conceptually there are two main problems with this. First, the paradigm incorporates important subcategories of individuals, sush as refugees, who may experience specific non-random patterns of health and health care that differ to those of

non-refugee immigrants. Second, the paradigm does not capture legal status, which may affect access to and utilisation of health services, and which in turn may also affect patterns of disease in a non-random manner. To make these indicators relevant to health research, an understanding of the way immigration law relates to eligibility in accessing public services is important. This may become complex when legal criteria for the eligibility of immigration subcategories change over time.[59]

1.12. Immigration in Europe

According to EUROSTAT the total population of the 27 Member States on January 1st 2009 was 499.7 million people. Since 1960 the European population follows a trend of continuing growth. The population of the EU-27 grew by 4.1 per 1000 inhabitants in 2008 due to a natural increase of 1.2 per 1000 inhabitants and net migration of 2.9 per 1000 inhabitants. In 2008 the population increased in 20 Member States, including Italy, and declined in the other seven. Net migration is the third determinant of population change after fertility and mortality. As the EU's inhabitants are having fewer children than they used to do and the total fertility rate has declined from around 2.5 live births per woman in the early 1960s to 1.60 for the period 2006-2008, net migration plays an important role in maintaining the size of the population. Furthermore, migration contributes indirectly to natural growth because migrants have children. Migrants are also younger compared to the native population and have not yet reached the age at which the probability of dying is higher. In some EU-27 regions, northern and central regions of Italy included, negative natural change has been offset by positive net migration.[60] The median age of non nationals living in the EU in 2009 was 34.3 (36.9 for the EU non-nationals and 33.0 for third-country nationals). The lowest median age for foreign citizens in the EU Member States, around 32 years old, was observed in the United Kingdom, Denmark and Italy.[61]

1.12.1. Unemployment, income gaps & social exclusion

In absolute numbers, the largest numbers of non-EU-27-born persons reside in Germany, France, the United Kingdom, Spain and Italy. For more information see table 1. The widest income gaps both in absolute and relative terms between foreign-born and native-born persons are observed in Iceland, Austria, Cyprus, Belgium and Italy. Higher levels of unemployment hamper the integration of migrants into the labour market. Male and female migrants, regardless of their educational level, suffer from higher unemployment levels. In addition migrants have a lower level of income and particularly those from outside the EU have a significantly increased risk of poverty or social exclusion, even if they are in employment. In 2008, the at risk of poverty or social exclusion rate

among foreign-born persons was highest in Greece, followed by Belgium, Italy, France, Sweden, Spain, Austria, Finland and Denmark, where the proportions of migrants at risk of poverty or social exclusion were above 30%. Last but not least, the situation of second-generation migrants with a foreign background, while being more positive than that of first-generation migrants, still shows disadvantages compared to the situation of persons with a native background.[61]

The proportion of foreign citizens with tertiary and low educational attainment levels differs significantly across the EU. The highest shares of tertiary educated foreign citizens (over 40%) can be noted in Ireland, Sweden and Norway. However there are Member States with large numbers of non-nationals who have a low educational level. In the southern Member States (Portugal, Greece, Italy and Spain), France and Germany, as well as in Iceland, more than 40% of non-nationals have a low level of educational performance.[61]

1.12.2. Overqualification of immigrants

The term overqualification refers to the state of being more skilled or educated than it is necessary for a job. According to EUROSTAT the overqualification rate is defined as the share of persons with tertiary education working in a low or medium skilled job among employed persons having achieved tertiary education. The overqualification rate for foreign citizens was 39% compared to 19% for nationals. Foreign citizens were thus twice as likely to be overqualified as nationals. This gap indicates a potential misuse of migrants' skills and qualifications. This issue was particularly acute for third-country nationals, for whom overqualification reached 46%. This may be a consequence of the greater difficulties encountered by third-country nationals in having educational qualifications and skills earned abroad recognised in the receiving country. This mismatch can also result from the lack of networks, limited access to information and discrimination from employers. This inequality between foreign citizens and nationals could be particularly marked in Greece, Italy, Portugal, Cyprus, Spain and Estonia, where there were overqualification gaps in excess of 25 percentage points (in Italy there were overqualification gaps of almost 50 percentage points between foreign citizens and nationals. The magnitude of the overqualification gaps between nationals and third-country nationals reached 60 percentage points).[61]

1.12.3. Historical migrational trends in Europe

European countries present a different approach regarding immigration depending on their history, culture and the idea of welfare state they have formed over the years. UK and France have a long immigration history with colonies in Africa and Asia.[62,63] In addition Germany, Austria,

Switzerland, Denmark and Sweden, which did not have colonies, were also familiar with immigration flows. In the late 50's and early 60's they implemented guest-worker policies in order to augment their workforce. In the case of Germany the first workers came from southern Europe and steadily the country expanded its bilateral agreements with Turkey and North Africa.[64] This phase of economic boom lasted from 1945 to 1973, when the "Oil Crisis" took place.[63] The last two decades however the immigration trends have changed and apart from the traditionally European destinations, new countries such as Italy have become appealing to immigrants who are coming from outside the European Union (EU).[61,62] The most prevailing reasons for this influx to the European territory are the collapse of the Soviet Union, the conflicts in the Middle East and Africa, as well as the hope of immigrants for better living conditions in Europe.[62]

The migratory behaviour of Member States is, however, heterogeneous: the northern zone (United Kingdom, Finland and Sweden) has been quite dynamic as far as migratory movements are concerned; the central zone (Belgium, Denmark, Germany, France, Luxembourg, Netherlands and Austria) is the main focal point of attraction of immigration headed for Europe; the Mediterranean zone (Italy, Spain, Portugal and Greece) has undergone a radical change, given that this zone, once provider of emigrants for the central zone, is now a receiver of immigrants coming largely from North Africa.[65]

A substantial burden is posed upon the mechanisms, infrastructure and legislation of countries which experience a significant influx of immigrant population. At the same time the international community is concerned about how to tackle this humanitarian crisis, especially in the field of human rights and protection. The EU has realized that immigration is a common challenge for all Member States and has mobilised its legislative and executive institutes as well as its financial resources in order to develop a harmonised immigration policy. For this reason the EU has launched an initiative for a Common European Asylum System (CEAS) since 1999 and created the European Refugee Fund in 2000.[11]

This large number calls for attention and the Member States of the European Union are currently moving towards this direction. Initiatives for common immigration and asylum policies are now under way but the massive numbers of foreigners reaching Europe from inland and the coasts on a daily basis is a burden for the national coastlines and borders.

1.13. Immigration in Italy

As of January 1st 2010, the resident population in Italy was equal to 60,340,328 people, with a presence of 4,235,059 people with non-Italian citizenship, equal to 7.0% of the total population.[66] During the last decade there has been a massive influx of people from Asia, Africa and Eastern Europe. According to the International Organization for Migration, Italy's migrant annual growth rate is the highest in Europe along with Spain.[67] The total number of new registrations at the Registry Office from abroad between 2002 and 2009, that is, people who established their own permanent residence in Italy for a period of at least 12 months, was calculated at an average of more than 400,000 people per year.[66] The official estimate is that the number of immigrants in the country is more than 4.000.000 people.[68] Of these, 47.061 are refugees and 722 are stateless persons. In 2008 Italy received 37,000 immigrants from Morocco. An interesting fact is that in 2008, Italy received more female migrants than male. In particular, women outnumbered men among citizens of Romania (the biggest group of immigrants in Italy), Ukraine, Moldavia, Poland and Russia.[61]

1.13.1. Challenges regarding migrants' influx in Italy

The sudden rise of the migration flows poses a great challenge in the function of the state and has activated healthcare staff in order to see to the newly arrived people's needs.[42] The number of people arriving by sea, especially in southern Italy has alarmed the state mechanisms and has tested the efficiency of the coastal guards.[66,69] According to the European Migration Network, debarkations primarily take place in the regions of Calabria, Apulia, Sardinia and Sicily, which have coasts along the southern meditteranean sea. The increase of people arriving in Sicily the last years, can be partly explained by Spain's restrictive policies which shifted the pressure onto Italy, by closing the Ceuta and Melilla passages.

Italy has paid special attention to the pursuit of increasing border controls and preventing illegal entries and stays. In 2009, a new strategy was implemented to contain migrants arriving by sea. It was based on a specific interpretation of EU and international regulations by Italian authorities. Boatlands of migrants were pushed back into international waters with the aim of preventing them from mooring in Italian ports, while at times migrants were transferred to onto coastal ships which arranged for the immediate transfer to Libya. This interpretation of the non refoulement principle, provided for under the Geneva Convention of 1951, sparkled off a heated debate between the government and some international organizations such as the ACNUR, as well as numerous pro-migrant and ecclesiastical associations. In addition to the refusals cited above, a joint patrolling

effort along the Libyan coast was simultaneously launched, accompanied by the delivery of six patrol boats to the Libyan navy, as per article 19 of the Italy-Libya "Treaty on Friendship, Partnership and Cooperation" dated August 30th 2008 (ratified with Law n. 7 of February 6th 2009). The fight against unauthorizes immigration, as well as that against trafficking in human beings, was also a point in the Italy-Nigeria collaboration agreement signed in Abuja at the beginning of 2009, as was in the agreement signed on July 22nd 2009 in Algiers between the Algerian and Italian police forces to reinforce cooperation on the field.[66]

Refusal rates continued to decrease in 2009, dropping to 3,700 people compared to 9,394 in 2007 and 6,405 in 2008. A partial explanation of a trend going back some years consists in the exclusion of Bulgarian and Romanian citizens from the statistics; before the EU joining, in fact, they were among the largest communities to be refused. Another explanation is the absence of border control at land borders due to the entry of Slovenia (December 2007) and Switzerland (December 2008) into the Schengen agreement.[66]

A great complication Italy has to cope with is the fact that the Western European countries, by applying the Dublin Regulation, manage to refuse stay to a great number of refused asylum seekers, whom Italy is obliged to receive instead. The Dublin Regulation specifies that the refused asylum seekers, who frequently enter Italy on their way to other European destinations when arrested in their territory, are forced to return to the first European country they entered i.e. Italy. Germany and Sweden describe this process as 'burden sharing' whereas mediterranean countries as 'burden-shifting'.[70]

1.13.2. Immigrants' healthcare utilisation in previous Italian studies

There is a paucity of information regarding the utilisation of the Italian healthcare services by the immigrant population with a RD. To date, various studies have shown the trends of the healthcare utilisation by immigrants in the Italian territory for numerous pathologies. Despite the fact that they focus on diverse geographical areas of the Italian country and different time periods, or use different inclusion criteria for defining the immigrant population under study, or focus primarily on infectious diseases, they still depict the current situation regarding immigrants and their access to the national health system.

It is interesting to list the conclusions drawn by reading these studies. Firstly, the number of female immigrant patients utilizing the healthcare services exceeds that of male ones. A partial explanation

for the notable presence of women at hospitals can be attributed to obstetric reasons (especially childbirth and abortion).[71,72,73]

Secondly, it should be taken into consideration that immigrants adopt the western lifestyle of the host country and its accompanying risk factors (tobacco, high fat diet, lack of exercise). As a result non- communicable diseases such as coronary heart disease, cancer, diabetes and mental disorders are becoming prevalent in the migrants' group. The healthy migrant effect according to which the healthiest and youngest people choose to migrate in search of better living conditions seems to be confirmed; however the health condition of the migrant population may be subject to rapid deterioration due to lifestyle changes or prolonged exposure to risk factors, such as the difficulty of integrating with the social fabric of the host country, poverty and discrimination with regard to access to social and health services. In addition chronic diseases present a higher incidence in the immigrants' population due to changes in demographic profile (aging and population) and to attenuation of the healthy migrant effect, as a consequence of forced migration and family reunions.[71,73,74]

Thirdly, infectious diseases present a higher percentage in the group of immigrants compared to the group of Italians, but communicable diseases are not as high as they are thought to be for immigrants. Communicable diseases rank relatively low on the pathologies for which migrants seek help to Italian hospitals. Mostly irregular migrants present more elevated percentages of communicable diseases. Injuries and traumas rank the first place in hospitalization for immigrant males. The hypothesis is that a significant fraction of traumatic accidents takes place at the work environment where immigrants might be exposed to hazardous duties, have insufficient training and get less tutelage, especially if they work casually. Regarding women and reproductive health, the utilisation of the healthcare services for induced abortions is of vital importance. The reproductive phase for immigrant women commences earlier compared to the native counterparts. It seems that family planning interventions which target the female migrant population are essential.[71,73,75]

Fourthly, many studies are based on health discharge records, which do not provide direct measures of disease occurrence, but only the frequency of admissions among immigrants and Italians. Therefore, the question, whether the reduced use of hospital services by foreign people observed in these studies is to be attributed to better health or to a lower access to healthcare or both, has to be adequately examined.[71,73,75]

1.14. The Veneto region

In general terms, the Veneto region is a prosperous region which offers professional opportunities, a rich and versatile economy and social policies. In 2010 Veneto consolidated its second place in Italy's regional rankings for the total value of exports (45.6 billion euro, a 13.5% share of the national total). The leading sector remained the mechanical industry (18.9% of regional exports) followed closely by fashion (18%). Some products, such as furniture, jewellery and sporting goods, had a share of 13.4% of Veneto's exports, while metal products accounted for a little more than 11%. In addition, the value of Veneto's agricultural production was estimated to have earned 4.8 billion euro. It recovered substantially compared to 2009, maintaining its leading position in the national rankings for both the domestic and international markets. Forests cover about 23% of the Veneto region; this percentage increases in the mountains and hills, where coverage can reach 60%. Since the 1951 census, mountain areas have continued to record a decrease in population. This has led to a reduction in agricultural activities .Although the mountains have been recognized in recent years as an important resource for all, the geographical challenges these areas present, continue to lead to a difference in costs compared to life on the plains.[76]

However there are numerous challenges which the region has to face. Regarding labour policy, Veneto's employment rate for 20-64-years-old was 68.7% in 2010, therefore fulfilling the target set by the Lisbon Strategy, which calls for an employment rate of 69% for the European Union by 2010. Italy however was distant, as it recorded a rate of 61%, more than seven percentage points below the EU27 figure. The labour market is discriminative for certain categories such as women, young people and older people and migrants. The female employment rate is equal to 53.3% in Veneto compared to 46.1% at national level. The population aged 55 to 64 performed well in terms of employment. In the last 10 years, employment in this bracket has increased by 10 percentage points and stood at 35.4% in 2010. The gap between foreign and Italian workers is still too wide, especially as far as unemployment rate and contract conditions are concerned. Moreover, few migrants are employed on open-ended contracts compared to Italian workers. Many of them are also employed in jobs for which they are overqualified. Finally in Veneto the migrant unemployment rate is 11.5% compared to 3.9% for Italian workers.[76]

Poverty is a multifaceted phenomenon that includes other forms of exclusion not necessarily linked to income, such as job insecurity and the difficulties of daily life, which are determined by the inability of households to access certain goods and services. The number of people at risk of poverty or social exclusion reaches 14.8 million in Italy. If on national level, nearly one quarter of

the population lived in conditions of poverty or of social exclusion, the percentage decreases to 14.1% for Veneto, one of the lowest levels of the Italian regions, after Trentino Alto Adige, Valle d'Aosta and Emilia Romagna. However, this means that there are 688,000 people who cannot fulfil their basic needs adequately.[76]

Today Veneto has more than 975,000 over 65s, 20% of its population. This number will grow by 45% in the next twenty years, and forecasts state that this rise will be as high as 67% for the over 80s. The areas where the population is falling and is mainly elderly will have to review their supply of basic public goods and services, such as health, transport and residential care; they will also have to take into account changing family situations and an increase in the number of elderly people living alone. The elderly are vulnerable in financial terms. In Veneto 16.5% of elderly people are at risk of poverty, more than the overall population (9.7%). Elderly women are at greater risk (one in five) as on average they have lower pensions. Although average life expectancy is longer, it is also true that in the last part of their lives, elderly people will not be self-sufficient; indeed, the time between loss of self-sufficiency and death is set to grow longer as time goes by. In Veneto, 68% of over 75s have at least two chronic degenerative illnesses, while 46% of people aged 65-74 years old have a number of chronic illnesses.[76]

Europe is clearly worried about the vulnerability of Italy's public finances, especially since it has an ageing population. In the next few decades factors such as low birth rates, increased life expectancy and a plummeting working-age population will only be partially counterbalanced by migratory flows; therefore the age of Europe's population will change. All of these factors will have major repercussions on public finances and on the social and economic situation.

1.14.1. Immigration in the Veneto region

The majority of immigrants are concentrated in northern Italy (62%) while only 25% in central and 12% in southern Italy. According to Caritas, in the Veneto region the number of foreign citizens is around 450,000.[68] It ranks the second place among Italian regions which receives the largest number of foreign population, after Lombardy. This means that immigration is an important issue that definitely affects the region. The majority of immigrants come from Romania, Morocco and Albania.[68]

According to the Statistical Report 2011 of the Veneto region, 11.3% of immigrants in Italy have settled in the region, making it the third most attractive destination for immigrants in the country.

The foreign residents in Veneto are currently 480,616 making up 9.8% of the population in the region; on a national level this percentage is 7.0%. The last four years the phenomenon of migration has exploded in the region as from 2006 to 2009 the number of immigrants increased by 120,000. Females account for 49.2% and males for 50.8% of the migrant population. Immigrant minors are also highly represented in the region; they are 24.3% compared to 22% which is the average for the rest of Italy.

A study on obstetric hospitalizations in the Veneto region showed that regular immigrants were 10.0% of Veneto female residents and accounted for 20.0% of deliveries. Delivery rates were 36.5 and 79 per 1,000 among Italian and immigrant residents, respectively.[77] The total fertility rate in the Veneto region decreased from 2.7 in 1964 to 1.45 in 1980 and 1.07 in 1994. An increase that reached 1.42 was noted in 2007, partly accounted by immigrant women. It is predicted that as the native population continues to become old, the contribution of immigrant women will be even more fundamental to sustain the demography, society (many are employed in the care of the elderly) and the economy of the Veneto region.[77]

1.15. Italian Legislation on Immigration and Citizenship

- Law n. 91 of 5th February 1992. Italian citizenship is primarily based on the "right of blood" – *ius sanguinis*. This means that a child born to an Italian mother and father is Italian. Dual citizenship is also recognized by the Italian legislation. According to Law n. 91, citizenship is also granted to a foreign or stateless person who is married for at least two years to an Italian citizen. In addition the foreigner's legal residence must be in an Italian municipality for at least two years following the marriage. The term legal residence means that the applicant must be enrolled in the municipality's registry and should hold a valid permit to stay, as well. In case the spouses reside abroad, then the application for citizenship should be lodged after three years following the marriage. The above periods are reduced by half if the spouses have natural or adopted children. Other cases in which citizenship is granted are the following: To aliens who have legally resided in Italy for at least 10 years, to nationals of EU Member States who have legally resided for at least 4 years on the Italian territory, to refugees or stateless persons who have legally resided for at least 5 years on Italian territory. Acquisition "by birth on the territory" – *iure soli* is given in two cases: To an alien whose father or mother or one of his grandparents had been citizens by birth, or to an alien who was born on the Italian territory and who has been legally residing there for at least 3 years. To an alien of full age adopted by an

Italian citizen and who has legally resided on the Italian territory for at least 5 years after the adoption.

- Law n. 40 of 6th March 1998[78] (Legge Turco-Napolitano). Article 31 refers to the Committee for Foreign Minors whose role is to protect and promote the rights of all foreign minors located in the Italian state. Article 33 regarding access to healthcare states that minors should access the healthcare services as this is foreseen by the CRC. Emergency care, vaccination, interventions for international profilaxis and communicable diseases are accessible to all foreign citizens regardless of their status on the Italian territory.

- Law n. 189 of 30th July 2002 (Legge Bossi-Fini).[79]It refers to permit to stay on the Italian territory, expulsions, to family reunification as well as to permit to stay for family reasons.

1.16. Registry of Rare Diseases of the Veneto region

The Veneto Region has taken on specific planning policies to provide health care for a regional system of care for people with rare diseases since 1999. Since then it has gradually structured a support network for patients with RDs, through the identification of the network of regional centers for patients with a RD, the activation of a computerized system of certification, exemption and registration of patients, provision of special benefits, such as the free provision of dietary foods and medicines, which are considered essential for patients.

The Regional Coordinating system for rare diseases was established by the Regional Committee Resolution n.2169 of 8/08/2008, with a mandate to perform the following functions:

- Management and inter-regional registry of rare diseases
- Exchange of information and documentation on rare diseases with other inter-regional centers-Coordinators and other relevant bodies
- Coordination of the referral centers of the network in order to ensure early diagnosis and appropriate treatment if any, through the adoption of specific protocols agreed
- Advice and support to doctors in the NHS in relation to rare diseases and the availability of appropriate drugs for their treatment
- Co-training activities of health workers and volunteers and collaboration with preventive initiatives

- Dissemination of information to citizens and associations of patients and their families with regard to rare diseases and the availability of drugs

The activities of the regional registry of rare diseases in 2010 was divided according to different areas of activity. On the one hand, the work involved the management of the current registry, on the other hand, new activities were developed. In particular, its actions aimed at simplifying care pathways for patients, delivering care levels consistent throughout the regional level, the identification of means of access to available treatments, in collaboration with other services of regional authorities.

1.17. Immigrant status and entitlement to healthcare in Italy

Immigrants in Italy have access to different healthcare services depending on their status in the Italian territory. Regular immigrants who are registered in the national healthcare system (Sistema Sanitario Nazionale - SSN) are treated exactly as Italian citizens. They are entitled to emergency care, primary care, ambulatory care, hospital care and rehabilitation. Asylum seekers obtain temporary access to the healthcare system while their application for asylum is under examination. In case they are granted refugee status, they gain the same access to health services as the autochthonous population. Irregular or undocumented immigrants can apply for a card (Stranieri Temporaneamente Presenti - STP) which guarantees their anonymity and provides them with restricted access to the healthcare system. They are only entitled to emergency care and specific care such as maternal and child health care, health care for minors (less than 18 years old), vaccination and international preventive treatments, prophylactic services, diagnosis and care for infectious diseases, as well as ambulatory and hospital care. Prisoners who are also immigrants are registered in the SSN for the period they are in prison.[80]

International bibliography demonstrates that patients with a RD face a series of impediments when accessing the healthcare system. They usually have their diagnosis made after long and risky delays and the lack of scientific knowledge does not allow them to be treated with the appropriate therapeutic methods and products. In addition patients with a rare disease usually need the expertise of diverse medical staff since their condition is complex. Reaching advanced medical expertise and follow a thorough therapeutic plan might be difficult for patients. Physicians do not have the sophisticated knowledge required and the innovative treatments conducted in the EU are hard to access. The costs of orphan drugs and care can be overwhelming for families who cannot afford such high costs meaning that rare disease patients face health inequities.[4] Taking into consideration

the fact that the obstacles mentioned above are ncountered by all patients with a rare disease, one might wonder whether immigrants who suffer from a rare disease are even more excluded by the healthcare system.

The data show that immigrants are on the increase in Italy and are possibly in need of healthcare. Previous studies have pinpointed the fact that some of them might suffer from a rare disease making their treatment more difficult due to their vulnerable position. Their access to healthcare might be hindered by the lack of knowledge of the language, lack of the bureaucratic procedures and the lack of education and information. In addition, their condition demands high expertise from the medical and pharmaceutical fields. It is of vital importance that the medical staff is familiar with immigrants who have a rare disease so that they can meet their elevated needs.

At this point we should make a distinction among different categories of foreigners with a rare disease who seek medical assistance in the region. Firstly, the immigrants who permanently live in the Veneto region. Secondly immigrants who live permanently in another Italian region but obtained a RD certification in the Veneto region. Thirdly, foreigners with a RD who practice health immigration. This means that patients come from abroad to Veneto in order to receive treatment for a limited time and then they return to their home countries. Fourthly, there is a group of immigrants whose status is uncertain and their application is still pending. They are the ones who are provided with the *codice fiscale provvisorio* until their status is determined. In this caregory, another subgroup could be the people with a codice *Straniero Temporaneamente Presente (STP)*. These people are irregular immigrants and are given this card for a period of 6 months. After the end of this period they can renew this card. It is important to highlight these different and heterogeneous groups of foreigners in Italy as the they have different ethnic backgrounds, socioeconomic status and are entitled to different healthcare services. Especially the third group which practices health immigration lives in a different setting and receives diverse health care on a daily basis compared to the immigrants permanently residing in Italy.

2. OBJECTIVE

Our aim is to conduct a study on immigrants with a RD seeking healthcare in the Veneto region. Our objective is two-fold. Firstly we identify the immigrant population. The term 'immigrant' applies to persons, and family members, moving to another country or region to better their material or social conditions and improve the prospect for themselves or their family. The term migrant is usually understood to cover all cases where the decision to migrate is taken freely by the individual concerned for reasons of 'personal convenience' and without intervention of an enternal compelling factor. However, there are various categories of immigrants such as asylum seekers and refugees who are forced to leave their country of origin. Other categories are: economic migrants and students. In this study the target group includes all the different categories of immigrants. Our sources are the Registry of Rare Diseases and the Health Discharge Records. From these two sources we can recognize the different types of immigrants, such as legal, irregular, residents of the Veneto region and residents outside the Veneto region. We can also obtain information regarding health migration.

On a second level a thorough description of the immigrant population is conducted. An effort to determine their demographic profile has been made. The exact number of RD migrant subjects, their age, gender, legal status, nationality, RD diagnosis are displayed. Simultaneously a description of the Italian RD patients will be made resulting to a comparison between the two populations. The variables used to describe the immigrants are also used for the description of the Italian population.

The second objective is to describe the utilisation of the healthcare services by immigrants with a RD. One aspect is whether immigrants use the healthcare system for RDs, to what extent and for which diseases. Another aspect is to show the impact of the immigrant population on the Veneto healthcare services. It is possible that with the augmentation of the immigrant population in the Veneto region, a possible increase in their healthcare needs will occur, as well. In this way the use of the healthcare services by immigrants will be amplified, too. This demand for healthcare services may pose a challenge to the existing infrastrusture, the healthcare personnel and the economic resources. Additionally, a comparison between Italian and immigrant RD patients is conducted in reference to their use of the Veneto healthcare services.

Our aim is to record and classify all the patients regardless of their nationality and place of residence. The same procedure is followed in our study in reference to the Italian affected individuals. In this way we obtain a clear picture of the subjects accessing the Veneto healthcare system for a RD treatment. The immigrant group is rather heterogeneous because of immigrants' diverse backgrounds. Our study includes all the foreign subjects who are recorded in the Registry of Rare Diseases in combination with the information extracted from the Health Discharge Records. It is crucial to pinpoint that we refer to all the different group of immigrants regardless of their legal status, age, religion, nationality and sex, in order to conduct this study. Immigrants are a part of a vast number of affected individuals seeking healthcare in the Veneto area. Some of these subjects already reside in the Veneto region while the others arrive from other Italian regions or abroad. An aspect we are interested in is to explore whether there is health migration towards the Veneto region. Concluding, assumptions can be made regarding whether the Veneto region is an attractive destination for RD patients.

3. MATERIALS & METHODS

The aim of this study is to identify the group of immigrants who seek healthcare for RDs in the Veneto region. In order to reach our goal we used two sources: The first one is the Registry of Rare Diseases and the second one is the Health Disharge Records. It was a significant challenge to define the immigrant population by the existing data. Delicate and in-depth work was performed in order to obtain these results.

The difficult task of this particular study is to identify the immigrants and to distinguish them from the native population. Why such a seemingly simple task is so difficult? Firstly, in the Registry of Rare Diseases the element of citizenship is not included. The lack of this piece of information prevents us from classifying the affected individuals into Italians and immigrants. Secondly, even when the citizenship is provided, as in the case of the Health Discharge Records, the problem of the definition of ethnicity arises. For example, a foreign subject who has obtained in the course of time the host country's citizenship i.e. the Italian citizenship, or the example of a native subject whose parents are of different ethnic origin but one of them being native. Therefore once more we should highlight that initially we categorize our subjects according to bureaucratic factors and official documentation and not on ethnic criteria.

3.1 ISTAT

ISTAT stands for the Italian National Institute of Statistics and is the main provider of official statistical information in Italy since 1926. It provides high-quality information on various domains such as economic and social dimensions and Italy's environment. Its main focus however, is on the conduction of censuses regarding the population, the industry and services, as well as agriculture. Since 1989 the role of ISTAT has increased since it has undertaken the responsibility of planning, directing and providing technical assistance and training within the National Statistical System (Sistan), as its co-ordinator. Sistan is a network of 10,000 statistical operators which collaborate in order to produce reliable data and involves the statistical departments of the Italian Ministries, regions, autonomous provinces, provinces and municipalities among others.

3.1.1. Methodology used for ISTAT

Data from the ISTAT database were used. We accessed the Istat website (http://demo.istat.it) and we used data on foreign citizens (Cittadini Stranieri) who are residents in Italy. Under the title 'Population residing in Italy' (Popolazione residente) we clicked on every single year from 2003 to

2011. We found data regarding the age and sex of each foreigner residing in the Veneto region for each year.

Afterwards, under the title 'Demographic Balance' (Bilancio demografico) we clicked on every single year from 2002 to 2010. We found data regarding the citizenship and sex of the foreign population residing in the Veneto region for each year. We did not use the classification information according to the country of origin as it is shown in the tables. We altered the categories and we formed new ones according to continent of origin. This classification resulted in six new categories:

1. European Union
2. Other European countries
3. Africa
4. America
5. Asia
6. Oceania

Thus, we numbered the five continents (European Union countries, Africa, America, Asia and Oceania) and we created an additional category under the name of 'other European countries', resulting in six categories in total. So, a number from 1 to 6 was appointed to every foreign subject according to its citizenship. In the end, we added up the total number of subjects for each continent. We followed this process separately for men and women. It was important to distinguish European Union citizens from the rest of the Europeans because of the difference spotted in their way of entry and in their access to the healthcare services in a Member State of the EU.

This data categorization and analysis led to the depiction of the presence of foreign citizens in the Veneto region, as well as the possible changes of their number during the course of time. In addition we want to know the alterations in the percentage of the foreigners of each continent residing in the Veneto region every year.

3.2. Registry of Rare Diseases

The Registry of Rare Diseases of the Veneto Region was established by the Ministerial Decree n. 279 of 2001. According to this Decree, all Italian regions should be involved in the following three activities: providing certifications for diseases which is a task of the accredited centres of the region, providing certifications for exemptions which is a task of the ASL of the patient's residence and registering every patient which is a task of the intra-regional registries. The goal of the Registry

of Rare diseases of the Veneto region is to join the three activities (certification, exemption, registration) in order to have one regional database, where all the information regarding the patient and his pathology are included.

3.2.1. Activities of the Registry of Rare Diseases

The activities of the Registry of Rare Diseases of the Veneto Region can be classified in three main categories.

1. The creation of a supporting database in assistance to the information site of the Registry of Rare diseases in the Veneto region; the continuous updating of the information sheets on rare diseases included in the decree (in english and italian). Direct contact with patients who have requested information on specific diseases; centers or specialists where they can refer to. The creation and development of software for the web sites providing information and as well as certifications and exemptions (only accessible from the regional intranet). Management of network services identified by the Regional Resolution regarding accreditation (accredited centres, operating units, ASL). Furthermore constant support is provided to qualified operators; definition and allocation of access to the system of certification-exemption-monitoring.
2. Continuously updated publications of the information sheets database on rare diseases on the web; update of the supporting information and its dissemination (accredited regions, laws and regulations, research and development, treatment and orphan drugs).
3. Management of programs designed for the uploading of patients' data, certification and attestation of exemption; continuous updating of the lists of diseases and their synonyms; including diseases in indicated groups of the ministerial decree and their synonyms; Continuous update of the structural changes or of the accredited operators; management of permissions and access control, resolution of problems and errors by operators; management of the patients' data input.

3.2.2. Methodology used for the Registry

Data starting from 2001 until October 2011 were taken from the registry of the Rare Diseases, pertaining to patients who are certified with a RD in the Veneto region. The Registry of the Veneto region is part of the *Area Vasta* and this means that the Veneto, the Friuli Venezia Giulia region and the autonomous provinces of Bolzano and Trento are using a single monitoring system. The registry

has access to information to all the above regions and provinces but we merely selected certified patients of the Veneto region.

For the purpose of this study, three variables were chosen in order to categorize our subjects seeking healthcare in the Veneto region.

1. Tax code (Codice fiscale)
2. Country of birth (for foreigners) or municipality of birth (for Italians).
3. Place of residence

The *first variable* is the ***Codice Fiscale***. It consists of 16 characters (numbers and letters) and it includes the surname, name, date of birth, country of birth or Italian region for Italian citizens, and a last character to differentiate between subject with the same data. An example of the Codice Fiscale and its decoding is presented (see figure). In order to identify the foreign population in the region the first step is to select the Codice Fiscale which have in the first 3 items the letters STP and the rest of the Codice has only numbers. STP, as mentioned above, stands for *Straniero Temporaneamente Presente* which is a temporary status of 6 months for immigrants and is renewable. In order to obtain it, a person has to declare his personal details and the absence of sufficient economic resources to support himself in any Local Health Unit *(Azienda Sanitaria Locale - ASL)*. This form of Codice Fiscale applies only to third-country citizens while foreigners from EU countries may have another form of Codice fiscale. It must be underlined that out of the STP cases there may also be Italians whose surname presents the characters in the first 3 items of the Codice Fiscale. These cases are excluded from the group of immigrants and are included in the group of Italians. The second step is to select the subjects whose Codice Fiscale has the letter Z in the 12^{th} place. All subjects born in a foreign country have the letter Z at the 12^{th} position of their Codice Fiscale, followed by the identifying 3 digits of the country's codification.

We have placed the affected individuals into three categories with the following symbols: **"0"** for subjects born in Italy, **"1"** for subjects born abroad and **"."** for subjects whose tax code (codice fiscale) is missing. This symbolization applies to all three variables.

The *second variable* is the specific ***municipality*** of birth for subjects born in Italy and the ***Country of Birth*** for subjects born outside of Italy. It may have three possible forms:

1. Born in the Veneto region
2. Born in another Italian region

3. Born abroad.

If the patient is born in Italian territory we use the code from ISTAT, which has six characters. The first three characters correspond to the province and the other three correspond to the municipality. For the subjects born abroad we use the code "999" in the place of the code of the province, followed by three characters defining the foreign state, according to the Ministry of Interior and ISTAT. All the relevant codes are available at the folowing webpage: http://www.istat.it/strumenti/definizioni/

The Rare Diseases Registry provides information on the municipality of birth and subsequently the region for subjects born in Italy. On the other hand, we obtain information only for the country of birth for subjects born abroad. It is crucial for the researcher that the Registry of RDs provides information on the specific Italian region where each subject was born. We are able to photograph all the different categories of Italians who have access to the Veneto region health services and it proves to be a useful tool in order to distinguish the Italian Veneto residents from the rest of Italians.

The *third variable* is the ***place of Residence***. Again the distinction for this factor was the following:
1. resident in the Veneto region
2. resident in Italy
3. resident abroad.

The *Place of residence* corresponds to the municipality of residence for Italians, or to the foreign state, where the patient legally resides. If the patient is resident in Italian territory we use the code of six characters provided by ISTAT. For patients who reside abroad we use the code "999", followed by the code of the foreign state according to the Ministry of Interior and ISTAT. For stateless or individuals without fixed domicile, we use the code "999" followed by the code "999". The mother's municipality of residence must be indicated for newborns as foreseen by the law n.127 of the 15th May 1997.

The immigrant population with a RD was grouped into countries of origin in order to see the most populous ones and whether they conform with the most prevalent groups of immigrants in the region. Patients were grouped not only according to the country of origin but also in six larger groups with geographical and political criteria. The division was the following:

1. European Union (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lettonia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom)
2. Other European countries (Albania, Andorra, Armenia, Azerbaijan, Belarus, Bosnia-Herzegovina, Georgia, Lichtenstain, Moldova, Monaco, Norway, Russia, San Marino, Serbia, Switzerland, Ucraine, Vatican city) included the candidate states for entering the EU (Croatia, Former Yogaslavic Republic of Macedonia, Iceland, Montenegro and Turkey)
3. Africa
4. America
5. Asia
6. Oceania

This classification was performed in order to facilitate the study; comparisons can be made between different continents which will help in the descriptive part of the results. The first division between EU and non EU countries, although not geographical, is of vital importance because EU citizens are entitled to different healthcare services. The other geographical divisions were deemed appropriate in order to better identify RD patients. Most RDs have a genetic background and are more prevalent in some parts in the world. We were interested to see if geographical distribution of RDs in our study is in accordance with existing literature and if the trends follow the norm.

3.3. Health Discharge Records

The Health Discharge Records *(Scheda Dimissione Ospedaliera – SDO)* form the instrument which gives us information on each patient who is dismissed by any public or private health entity on the Italian territory. They refer to the number of "events" of discharge and not at thenumber of individual patients. This means that a patient may have more than one hospitalisation in the course of a year, and the Health Discharge Records refer to every single hopitalization of the same subject. They were established by the Decree of the Ministry of Health on the 28th December 1991. The Decree of 26th July 1993 described the contents and the modalities of trasmission of the collected information. Since 1st January 1995, the Health Disharge Records have replaced the previous tool ISTAT/D10 which was used for hospitalization of patients. The Ministerial Decree n.380 f the 27th October 2000 updated the contents and the information included in the Health Discharge Records and set the general rules for the codification of information of clinical nature (diagnosis, surgical

operations and diagnostic-therapeutic procedures). In addition, it was decided that the updated version of ICD 9 CM would be used from now for the codification of diseases on the Health Dicharge Records.

The Health Discharge Records are filled in by the physician who treated the patient, both in case of his hospitalization or in case of "day hospital". The information gathered from the Health Dicharge Records refer to both clinical aspects of the hospitalization (diagnosis, symptoms, surgery, modality of the discharge) and organizational aspects (operational unit of the admission and discharge, internal transfers, subject who is responsible for the hospitalization costs).

3.3.1. Methodology used for the Health Discharge Records

Firstly we used the Health Dicharge Records information for the period 2000-2005. Five variables were chosen in order to categorize the affected individuals seeking healthcare in the Veneto region.

1. STP (Stranieri Temporaneamente Presenti)
2. Tax code (Codice Fiscale)
3. Place of birth (provincia di nascita)
4. Place of Residence (residenza)
5. Citizenship (Cittadinanza)

We have already discussed the first four variables in the Registry section. The fifth variable is the citizenship. We use the code "100" for subjectswith Italian citizenship. Foreigners are identified by a code with three characters corresponding to their country of origin, according to the Ministry of Interior and ISTAT. For stateless and indviduals without fixed domicile we use the code "999".
Information used was the duration of hospitalisation, hospital ward, principal diagnosis as well as further diagnosis made during hospitalisation.

The Health Discharge Records were reviewed for the years 2006-2008, as well. The three variables used are:

1. citizenship
2. place of birth
3. place of resedence

A limitation on these data is that we have information on the *citizenship, province and municipality of birth* were used, as the *name/surname/codice fiscale* are not provided by the database for these

years. For the Health Discharge Records of 2000-2005 we followed the same exact procedure as above for the Codice Fiscale, with an important addition. In the Health Discharfe Records for these years, we were able to identify the group of STPs, a fact that was not possible in the Registry neither in the HDR of the period 2006-2008. It should be noted that the results we get from the Health Discharge Records regard the recoveries in total. In order to quantify the hospitalisations into number of patients we used the last date of hospitalisation so as to see the status of the foreigner (citizenship, STP).

3.4. Statistical analysis

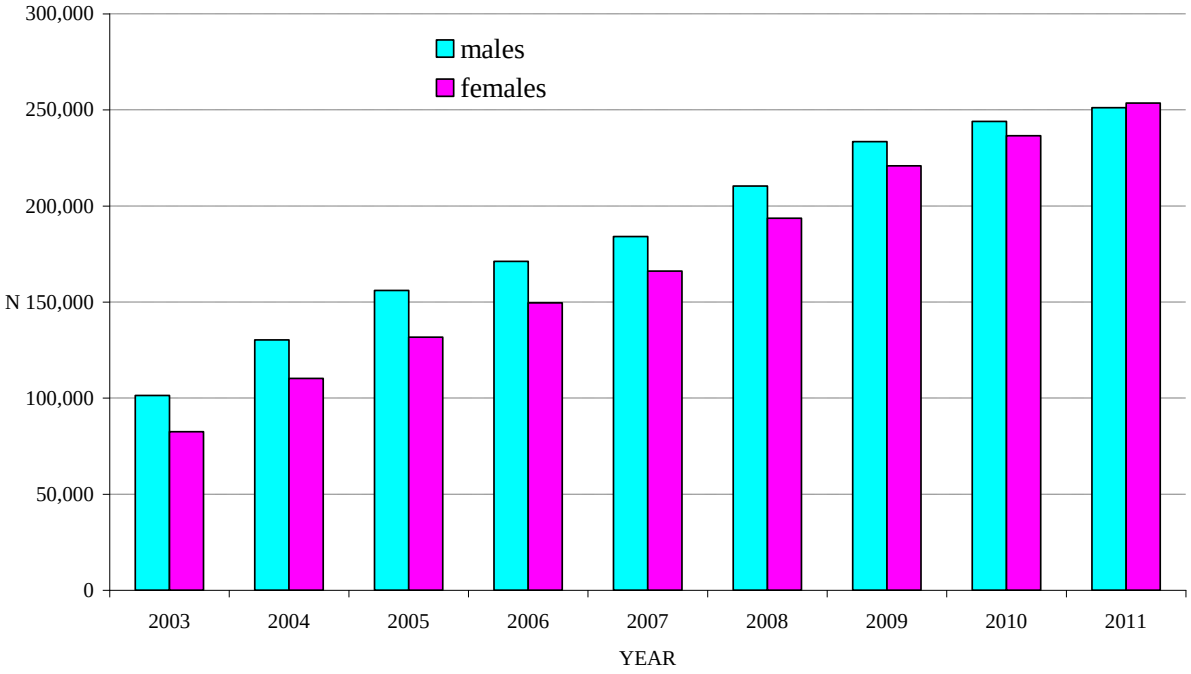
The programme SAS was used for the data analysis.[81] By analysing the data above on the SAS programme we will gain quantitative information regarding immigrants with a rare disease in the Veneto region. The information collected from these sources will provide us with the opportunity to see the trends of the use of healthcare services by immigrants, their special needs, and finally make comparisons between the health status of the native population with a rare disease and the immigrant one.

4. RESULTS

4.1. ISTAT

We traced the presence of all the immigrant population residing in the Veneto region, over the last decade, acording to the ISTAT database.

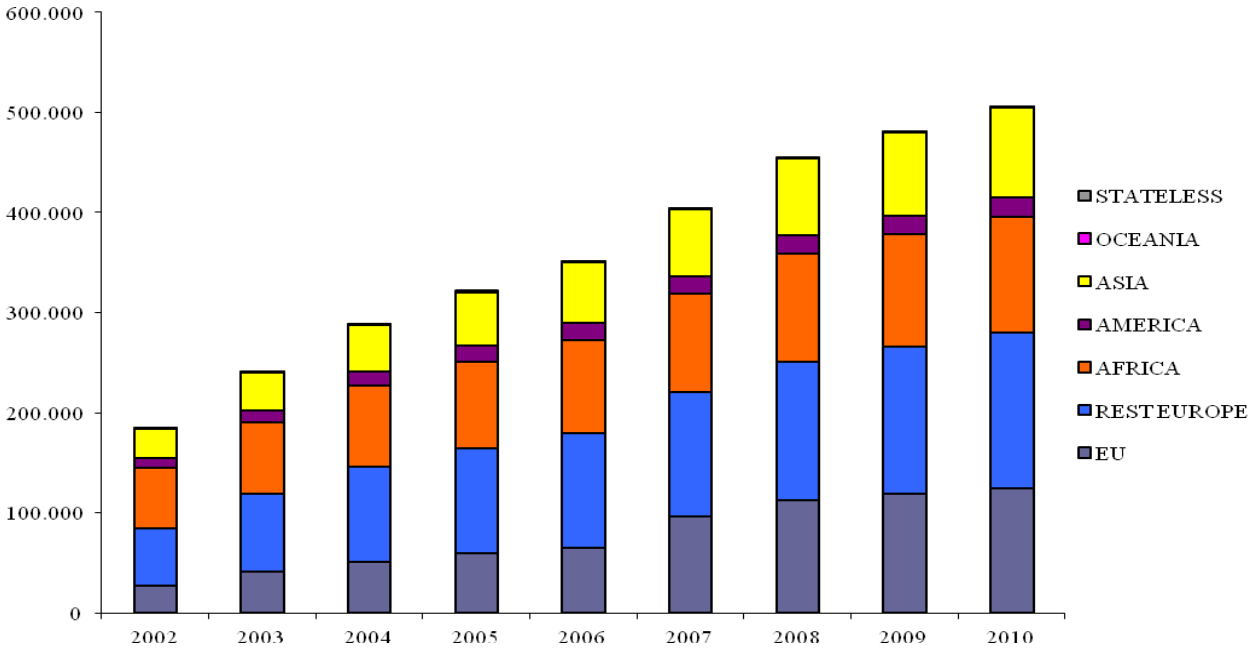
Graph 1: Temporal trend of the immigrant population in the Veneto region



In graph 1, the temporal trend for both male and female immigrants in the Veneto region has increased during the period 2003-2011. The female immigrant population is smaller in the beginning, but steadily rises and for the first time in 2011 outnumbers the foreign males. In addition, in 2011, the immigrant population exceeds for the first time the 500,000 persons.

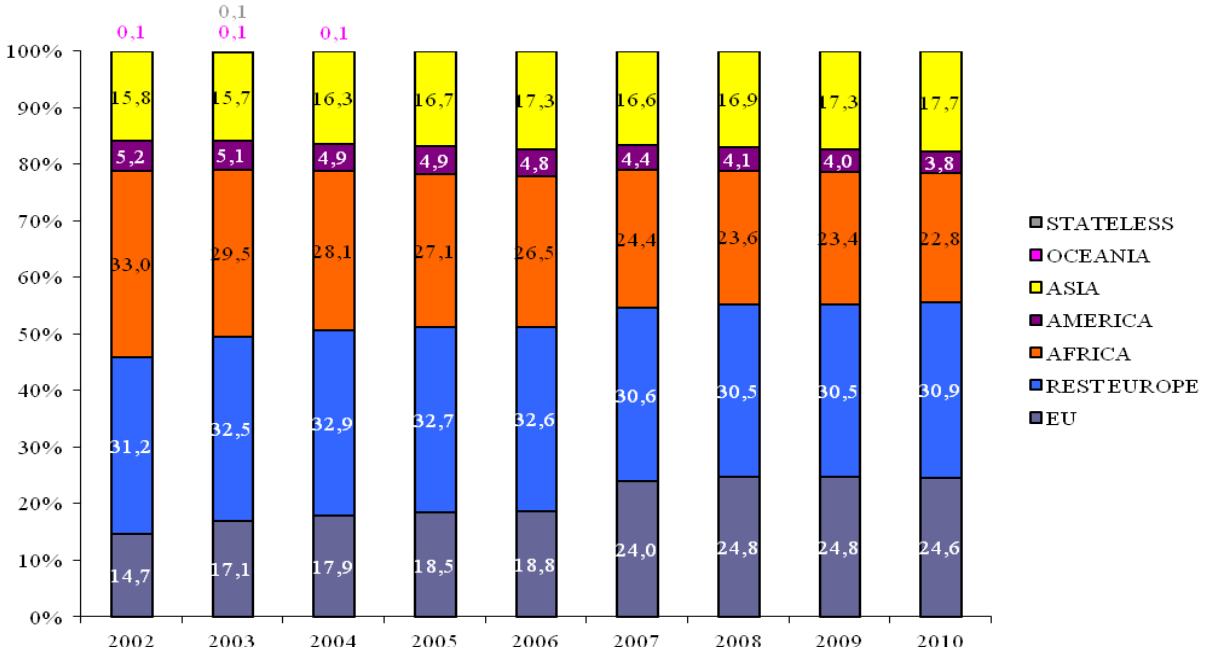
After having visualized numerically the number of immigrant population, we were interested in dividing it according to continent of origin.

Graph 2: Number of immigrants according to continent of origin



In graph 2, the influx of the immigrant population is on the increase during a nine-year period (2002-2010). In absolute numbers the immigrant population exceeds the 500,000 individuals in 2011. Notable increases are observed for immigrants coming from the EU, other European countries, Asia and Africa.

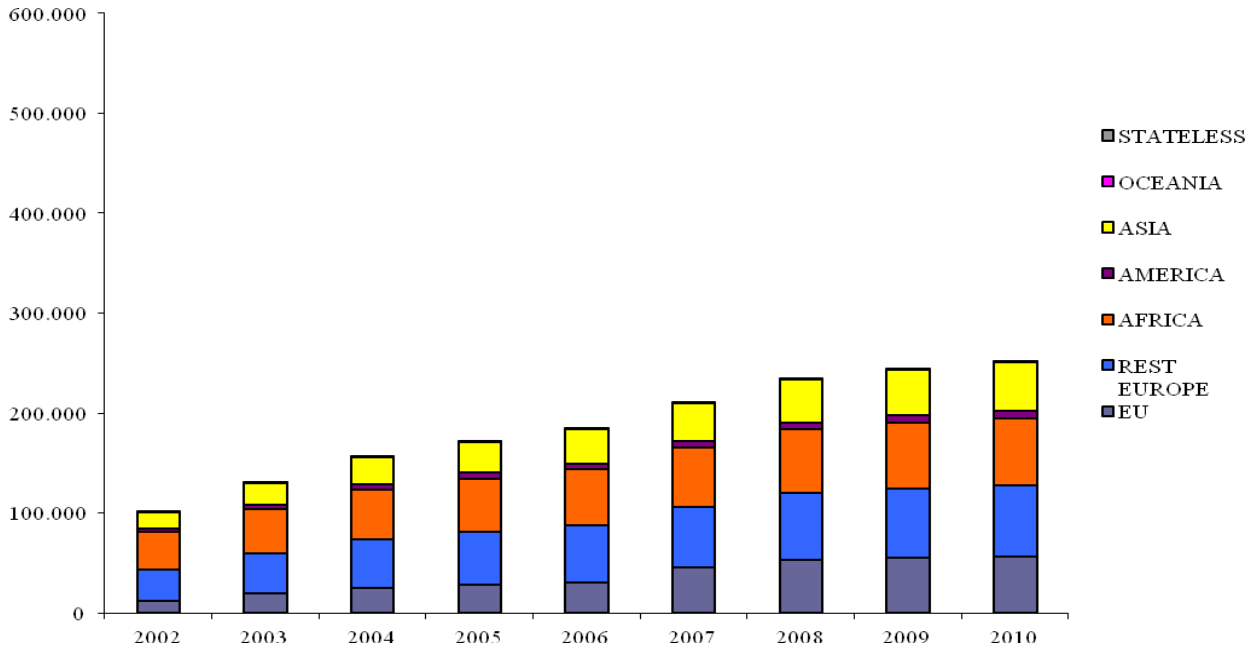
Graph 3: Percentage of Immigrants according to continent



In graph 3 the percentages of each immigrant population are presented, as shown over the course of nine years. In each year the percentages of each immigrant population are added to equal to 100%.

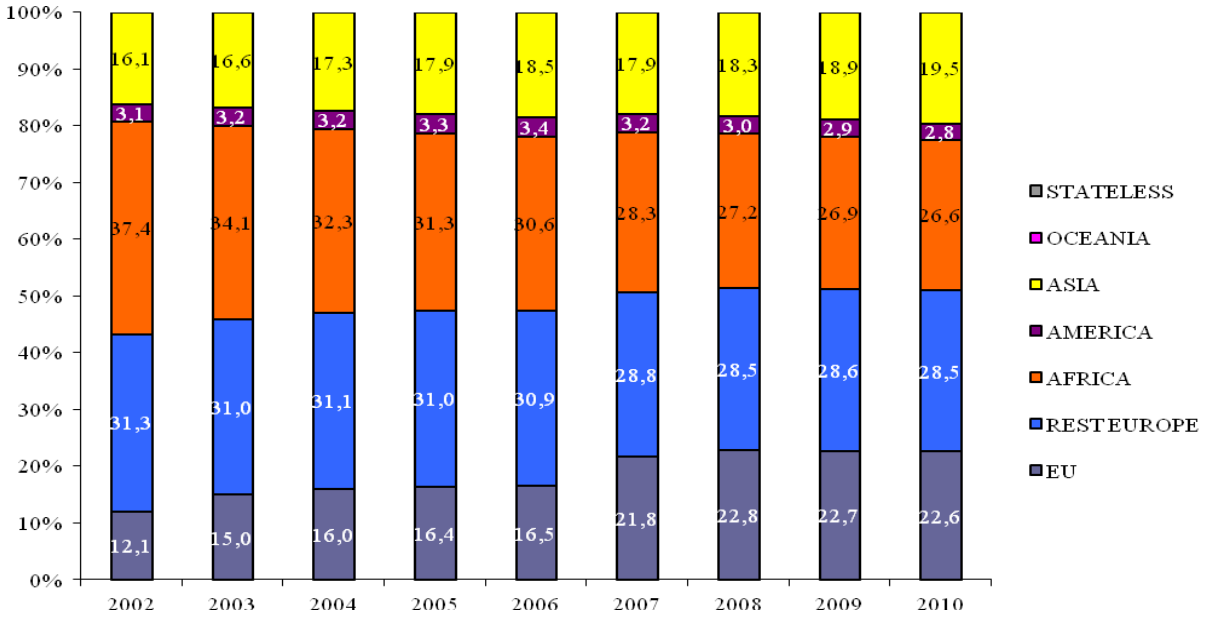
In this way we keep track of the alterations in the percentage of each group compared to the other groups over the course of time.

Graph 4: Number of male immigrants according to continent of origin



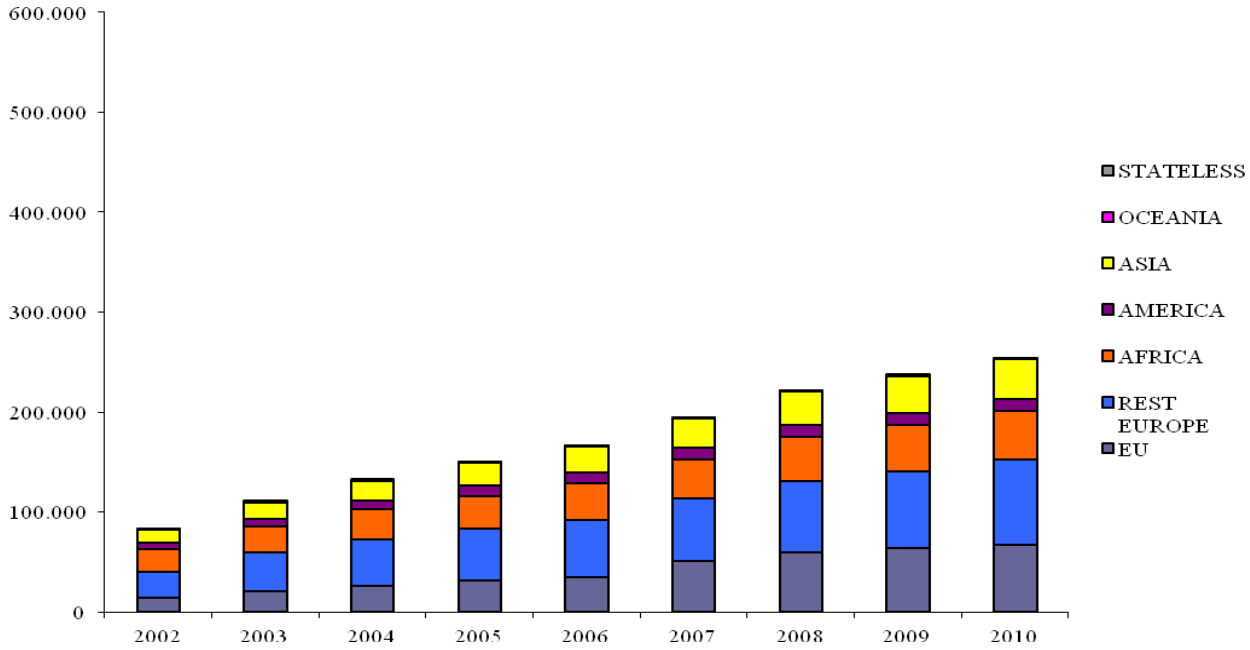
In graph 4, the distribution of male immigrants in absolute numbers is presented. An increase in all groups is observed.

Graph 5: Percentage of male immigrants according to continent



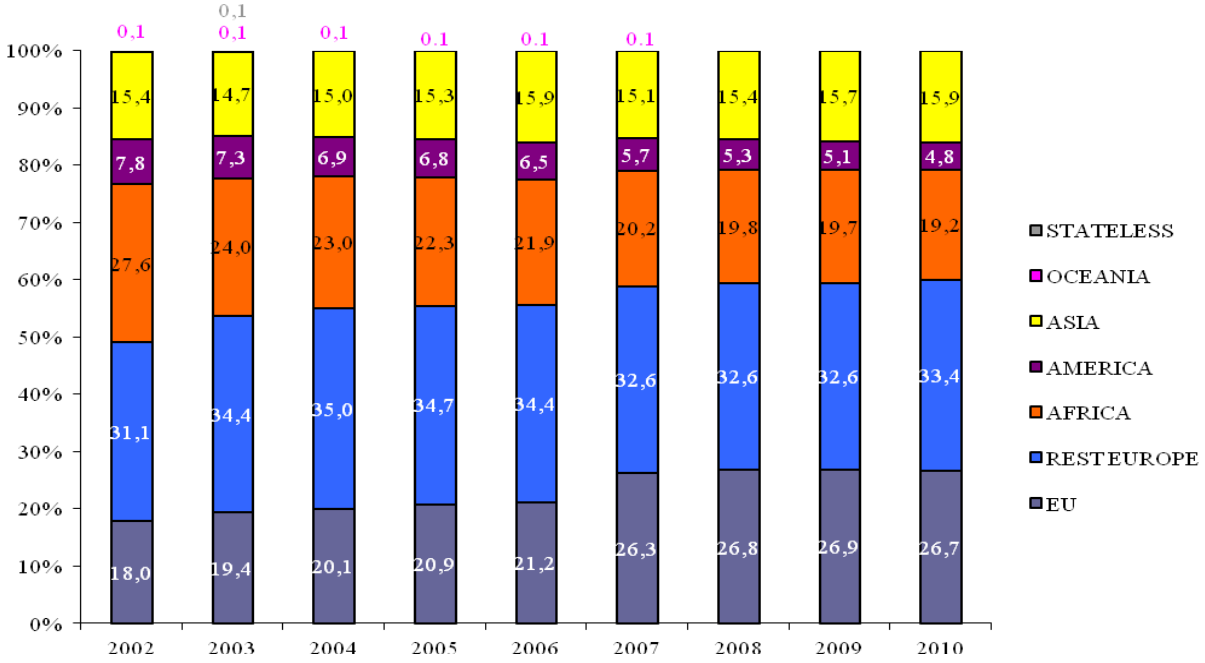
In graph 5, the percentage of males from the “Rest of Europe” group has decreased by almost three points; however, “Rest of Europe” countries still rank in the first place of immigrant presence in Italy. The steep decline in the percentage of African males is also noted over the decade.

Graph 6: Number of female immigrants according to continent of origin



The impressive rise of the female immigrant population in Italy is shown in graph 6.

Graph 7: Percentage of female immigrants according to continent

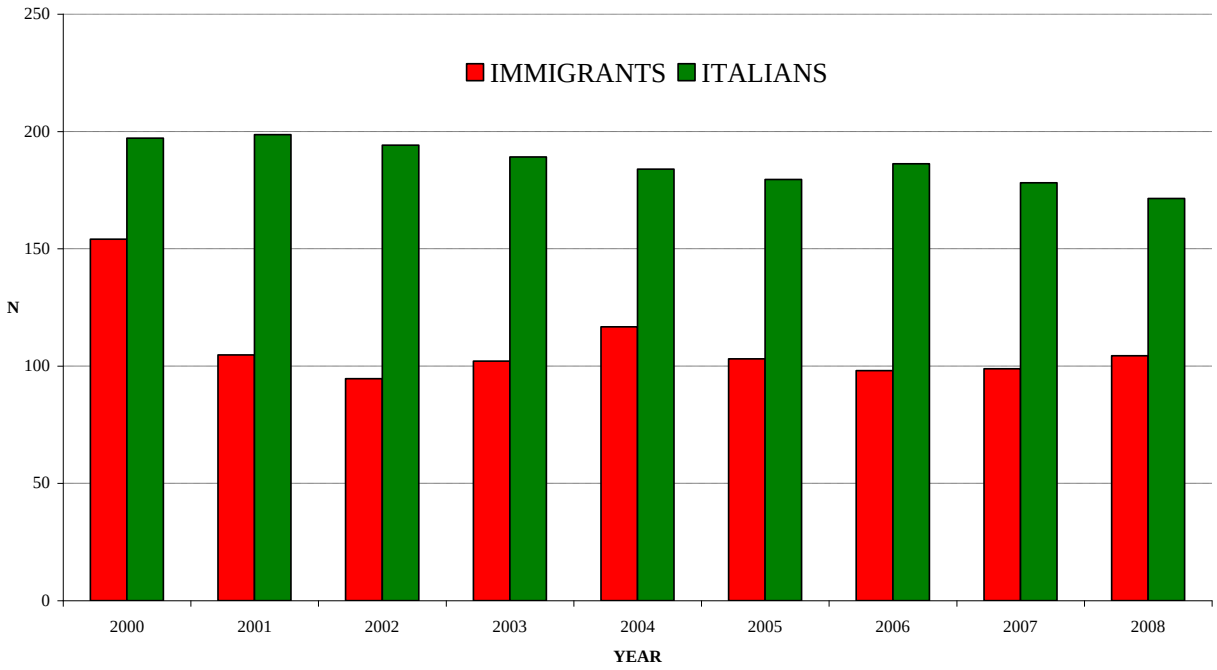


The percentage of females from the EU occupies a bigger part annually as seen in graph 7. Women from Asia display a slightly higher percentage over the course of years, while women from America and other European countries present a slight decline in their percentages. African females present major decline, losing more than 8%.

4.2. Health Discharge Records

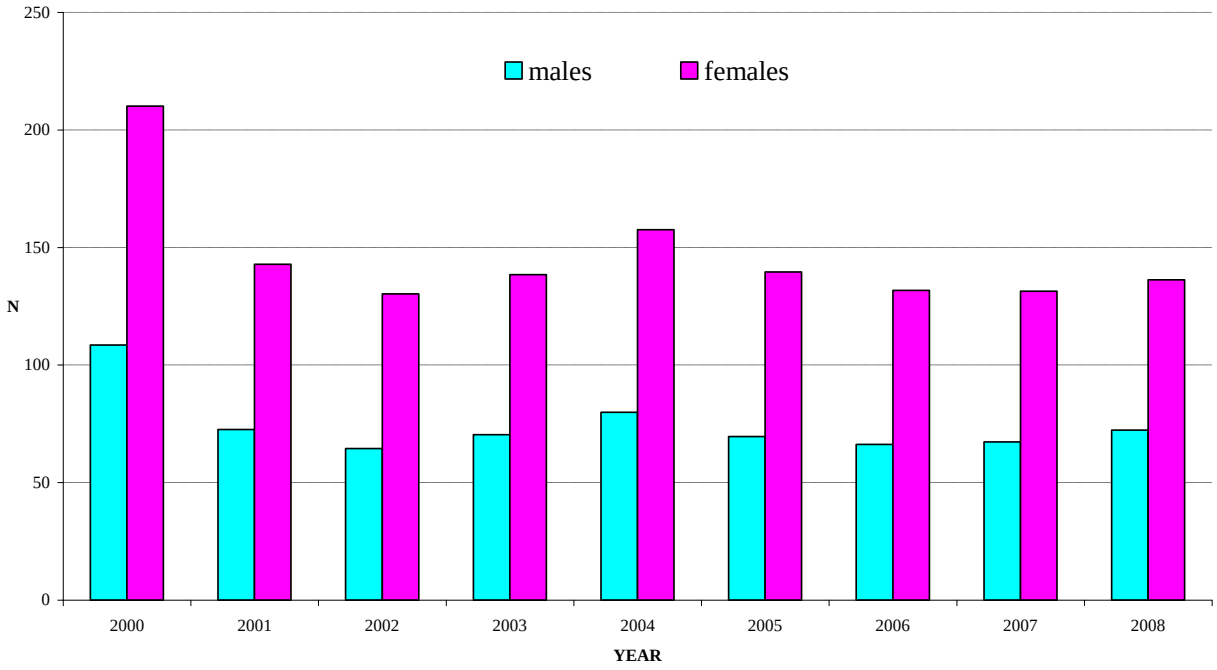
Prior to focusing on RDs, our interest is to examine the Health Discharge Records for all the pathologies/causes (hospitalizations and "day hospital"), for both Italians and immigrants.

Graph 8: The rate of hospitalizations of the Italian and immigrant population per 1,000 inhabitants in the Veneto region



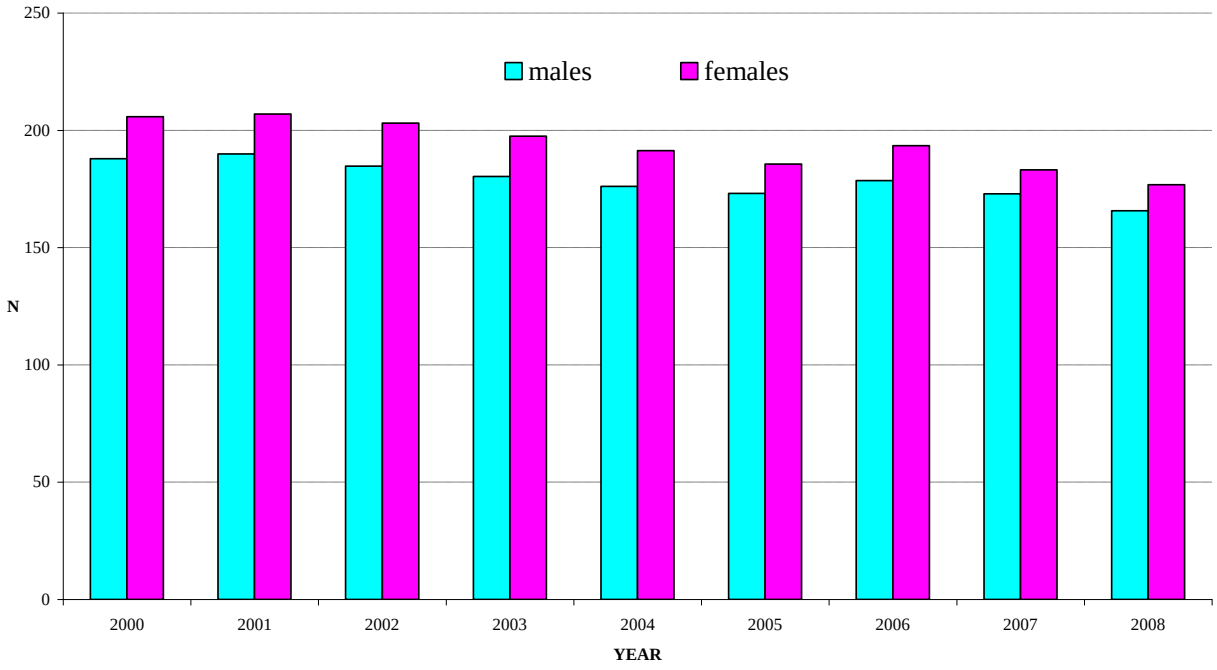
In graph 8, the immigrant population displays much less hospitalization rates compared to the Italians of the Veneto region. Apart from year 2000, there is a slight and continuous fluctuation until 2008 in the number of the immigrants' hospitalization records. The utilisation of the hospital services decreases slightly over time for Italians.

Graph 9: The rate of hospitalizations of the immigrant population per 1,000 inhabitants in the Veneto region, by gender



In graph 9, the percentage of females' Health Discharge Records exceeds that of males. In the first years the gap between women and men is larger, while this gap decreases over time.

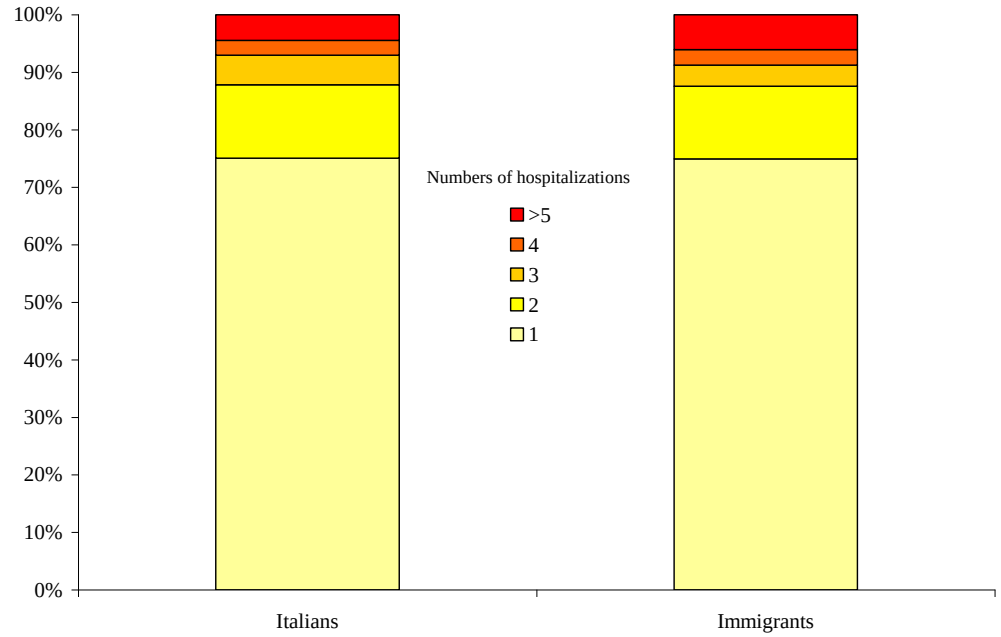
Graph 10: The rate of hospitalizations of the Italian population per 1,000 inhabitants in the Veneto region, by gender



In graph 10, the female and male Italian population uses almost eqaully the healthcare services. Women utilise the healthcare services slightly more than men. In addition, the trend for both groups decreases over time.

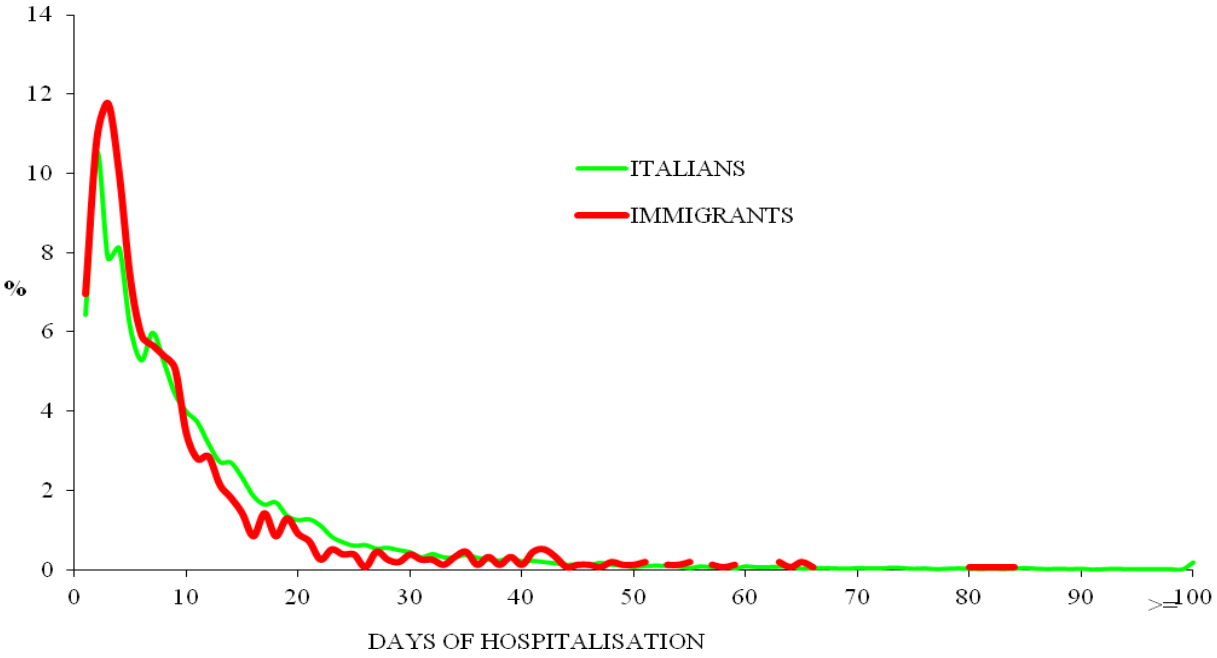
4.2.1. Health Discharge Records for RDs

Graph 11: Percentage of patients and period of hospitalization



The greatest percentage of Italians and immigrants are hospitalized for one night. We have excluded all patients who have made use of the hospital premises for "day hospital".

Graph 12: : Percentage of patients and period of hospitalization



4.2.2. Health Discharge Records 2000-2005

The total number of hospitalisations for the years 2000-2005 regarding all medical conditions in the Veneto region is 5,722,650. It must be underlined that for each individual may have been recorded more than one hospitalizations. Table 1 shows the citizenship of the individuals and their place of residence.

Table 1: Heath Discharge Records for the period 2000-2005 for all medical conditions

Citizenship	**Residence**	**N**	***%***
STP	Italy	48	*0*
	Veneto	3,733	*0.1*
	Abroad	9,106	*0.2*
Foreign citizen (born in Italy)		1,864	*0.03*
	Italy		
	Veneto	52,513	*0.9*
	Abroad	2,505	*0.04*
Foreign citizen (born abroad)		7,308	*0.1*
	Italy		
	Veneto	139,658	*2.4*
	Abroad	34,860	*0.6*
Italians	Italy	425,745	*7.4*
	Veneto	5041272	*88.1*
	Abroad	3938	*0.1*
Total		**5,722,650**	***100***

Table 2: Number of Health Discharge Records for Italians and immigrants for all medical conditions

Citizenship	**N**	***%***
Italians	5,470,955	*95.6*
Immigrants	251,695	*4.4*
Total	**5,722,650**	***100***

From Table 1 we proceed to Table 2 in order to show the total number of Health Discharge Records for Italians and immigrants for all medical conditions.

Table 3: Number of individuals hospitalized for all medical conditions

Citizenship	Residence	N	%
STP	Italy	27	*0.0*
	Veneto	2,467	*0.1*
	Abroad	6,610	*0.2*
Foreign citizen (born in Italy)	Italy	1,097	*0.04*
	Veneto	33,249	*1.2*
	Abroad	1,834	*0.1*
Foreign citizen (born abroad)	Italy	4,866	*0.2*
	Veneto	81,405	*3.0*
	Abroad	25,415	*0.9*
Italians	Italy	252,178	*9.3*
	Veneto	2,287,580	*84.7*
	Abroad	2,878	*0.1*
Total		**2,699,606**	***100***

In Table 3 the number of hospitalized patients with various medical conditions is shown. Thus we can see that the total number of 5,722,650 hospitalizations corresponds to 2,699,606 patients. We reached this result by selecting the last Health Discharge Record for each patient.

Table 4: Number of Health Discharge Records for Italians and immigrants for all medical conditions

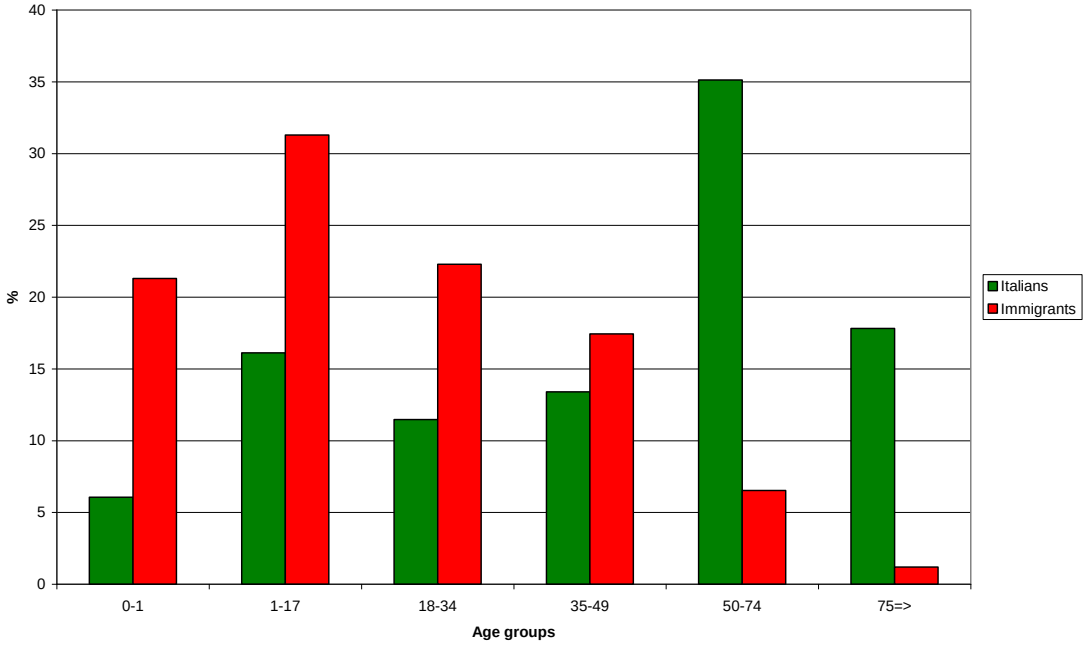
Citizenship	N	%
Italians	2,542,636	*94.19*
Immigrants	156,970	*5.81*
Total	**2,669,606**	***100***

We then focused on the Health Dicharge Records which are relevant to RD patients only. Again we followed the same process. Firstly we traced the total number of Health Discharge Records (Table 5) and then we identified the RD patients by group (Table 6).

Table 5: The total number of Health Discharge Records only for Rare Diseases for the period 2000-2005 by groups

Group	N	%
Italians	34,158	94.2
Immigrants	2,104	5.8
Total	**36,262**	**100**

Graph 13: Age distribution of Italians and immigrants according to the HDR 2000-2005



In graph 13 it is shown that immigrants until the age of 49 use the hospital services more often than the Italians. However, in the last two age categories, Italians exceed the number of immigrants regarding their use of hospital care.

Table 6: Number of RD patients according to the Health Discharge Records 2000-2005.

Citizenship	**Residence**	**N**	***%***
STP	Italy	1	*0*
	Veneto	13	*0.1*
	Abroad	30	*0.1*
Foreign citizen (born in Italy)	Italy	27	*0.1*
	Veneto	309	*1.5*
	Abroad	15	*0.1*
Foreign citizen (born abroad)	Italy	55	*0.3*
	Veneto	430	*2.1*
	Abroad	130	*0.6*
Italians	Italy	3,295	*15.7*
	Veneto	16,677	*79.4*
	Abroad	18	*0.1*
Total		**21,000**	***100***

Table 7: Number of RD patients by the Health Discharge Records 2000-2005

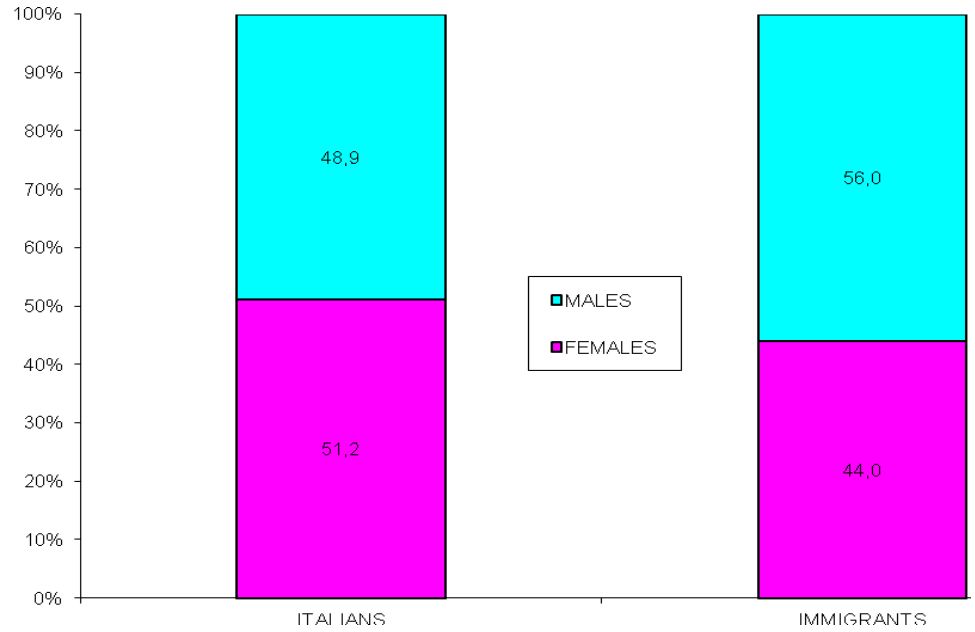
Group	N	%
Italians	19,990	*95.2*
Immigrants	1,010	*4.8*
Total	**21,000**	***100***

Table 8: Distribution of RD patients according to continent

Continents	N	%
1. European Union	124	*12.6*
2. Other European countries	213	*21.6*
3. Africa	478	*48.3*
4. America	48	*4.9*
5. Asia	123	*12.5*
6. Oceania	2	*0.2*
Total	**988**	***100***

Frequency missing: 22

Graph 14: Distribution of Italian and immigrant patients by gender according to HDRs 2000-2005



In graph 14, it is shown that the percentage of male immigrants is more that that of their female counterparts. On the other hand, in the Italian population, females are slightly ore than males.

Table 9: Most prevalent diagnosis for immigrants according to the Health Discharge Records

Most prevalent diagnosis for immigrants HDR 2000-2005	N	%
Anaemia due to disorders of glutathione metabolism	96	*9.5*
Sickle cell anaemia, unspecified	73	*7.2*
Hb (Hemoglobinopathy) - S disease with mention of crisis	33	*3.3*
Other Hemoglobinopathies	33	*3.3*
Achalasia and spasm of the cardia	27	*2.7*
Dwarfism, not elsewhere classified	21	*2.1*
Hereditary progressive muscular dystrophy	21	*2.1*
Microcephaly	20	*2.0*
Osteogenesis imperfecta	20	*2.0*
Other	20	*2.0*
S-hemoglobinopathy without mention of crisis	18	*1.8*
Sickle cell anaemia/Hemoglobinopathy -C	17	*1.7*
Other Sickle cell disease	17	*1.7*
Congenital deficiency of other clotting factors	17	*1.7*
Bechet's syndrome	15	*1.5*
Acute febrile mucocutaneous lymph node syndrome	15	*1.5*
Situs Inversus	15	*1.5*
Polymyositis	14	*1.4*
Atresia and stenosis of the small intestine	14	*1.4*
Atresia and stenosis of the large intestine, rectum and the channel	13	*1.3*
…	…	...

Table 10: Most prevalent diagnosis for immigrants according to the Health Discharge Records

Most prevalent diagnosis for Italians HDR 2000-2005	N	%
Amyotrophic lateral sclerosis	1,038	*5.2*
Achalasia and spasm of the cardia	1,011	*5.1*
Giant cell arteritis (GCA) or Temporal arteritis	709	*3.6*
Hereditary progressive muscular dystrophy	684	*3.4*
Pemphigoid	598	*3.0*
Endothelial dystrophy ofthe cornea	532	*2.7*
Congenital cystic disease of the liver	436	*2.2*
Osteogenesis Imperfecta	405	*2.0*
Disorders of the metabolism of sulfur amino acids	390	*2.0*
Gastric mucosal hypertrophy without mention of hemorrhage	389	*2.0*
Anaemia due to disorders of glutathione metabolism	372	*1.9*
Other	368	*1.8*
Von Willebrand disease	355	*1.8*
Congenital deficiency of other clotting factors	309	*1.6*
Neurofibromatosis type I (Von Recklinghausen's disease)	301	*1.5*
Chondrodystrophy	257	*1.3*
Pemphigus	251	*1.3*
Other hamartomas, not elsewhere classified	247	*1.2*

Polymyositis	243	*1.2*
With hydrocephalus, unspecified region	224	*1.1*
…	…	…

Graph 15: Distribution of RDs in the Italian and immigrant population according to the Health Discharge Records

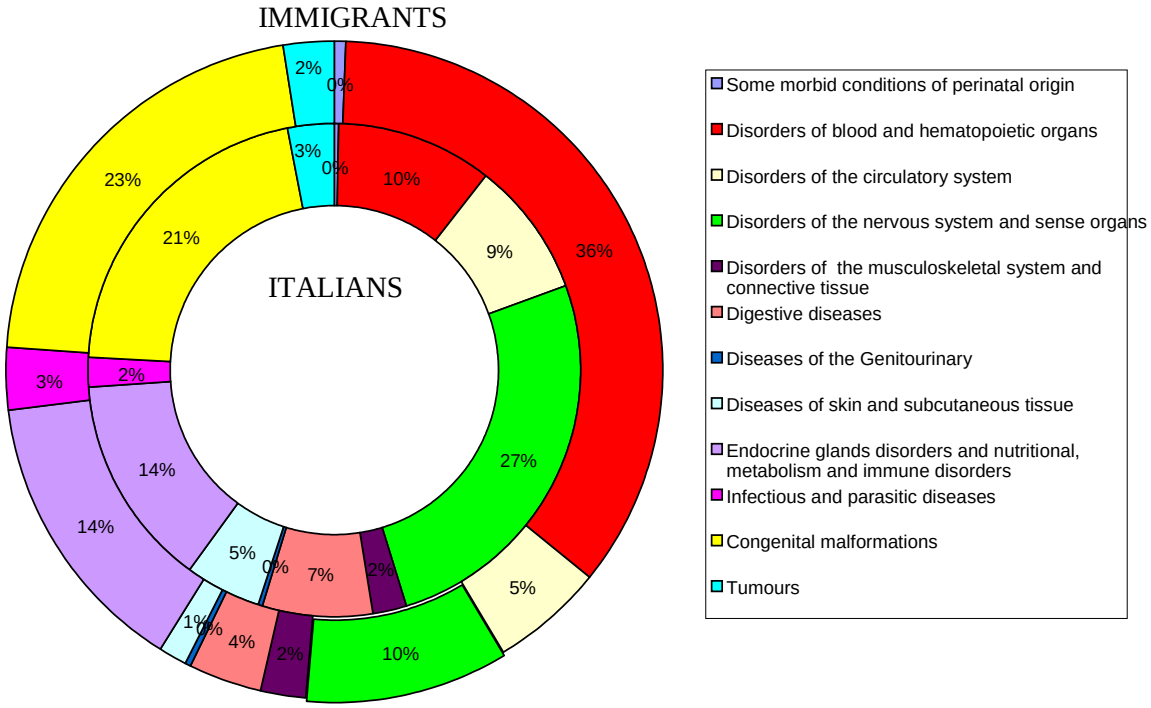


Table 11: The most highly used hospital wards by Italians (hospitalization and "day hospital)

Hospital wards	**N**	***%***
General Medicine	6,349	*18.6*
Paediatrics	5,563	*16.3*
Neurology	3,932	*11.5*
Recovery and Functional Rehabilitation	2,476	*7.3*
General Surgery	2,136	*6.3*
Opthalmology	1,337	*3.9*
Geriatric	1,034	*3*
Dermatology	924	*2.7*
Pulmonology	868	*2.5*
Orthopaedics and Traumatology	797	*2.3*
…	…	…

Table 12: The most highly used hospital wards by immigrants (hospitalization and "day hospital)

Recovery units (ord & DH) Immigrants	N	%
Paediatrics	755	*35.9*
General Medicine	298	*14.2*
Paediatric Hematological Oncology	231	*11*
Tropical and Infectious Diseases	87	*4.1*
Neurology	72	*3.4*
Nidotherapy (Nest)	69	*3.3*
General Surgery	64	*3*
Paediatric Surgery	42	*2*
Recovery and Functional Rehabilitation	42	*2*
Neonatal Intensive Care	42	*2*
…	…	…

Table 13: The most highly used hospital wards by Italians (only hospitalization)

Hospital wards	N	%
General Medicine	5,203	*20.8*
Paediatrics	3,327	*13.3*
Neurology	3,051	*12.2*
General Surgery	1,535	*6.13*
Recovery and Functional Rehabilitation	1,199	*4.79*
Geriatric	956	*3.82*
Pulmonology	761	*3*
Dermatology	759	*3*
Opthalmology	748	*3*
Orthopaedics and Traumatology	678	*2.7*
…	…	…

Table 14: The most highly used hospital wards by Italians (only hospitalization)

Hospital wards	N	%
Paediatrics	558	*36.3*
General Medicine	214	*13.9*
Tropical and Infectious Diseases	84	*5.5*
Paediatric Hematological Oncology	81	*5.3*
Nidotherapy (Nest)	69	*4.5*
Neurology	58	*3.8*
General Surgery	52	*3.4*
Neonatal Intensive Care	40	*2.6*
Obstetrics and Gynaecology	39	*2.5*
Paediatric Surgery	36	*2.3*

… … …

4.2.3. Health Discharge Records 2006-2008

Table 15: Heath Discharge Records for the period 2006-2008 for all medical conditions

Groups	Residence	N	%
Italians	Veneto	2,374,363	*86.3*
Italians	Italy	201,284	*7.32*
Italians	Abroad	1,584	*0.06*
Immigrants	Veneto	144,768	*5.26*
Immigrants	Italy	5,854	*0.21*
Immigrants	Abroad	23,352	*0.85*
Total		**2,751,205**	***100***

Table 16: Total number of Health Discharge Records for Italians and immigrants for all medical conditions

Groups	N	%
Italians	2,577,231	*93.68*
Immigrants	173,974	*6.32*
Total	**2,751,205**	***100***

Table 17: Number of Health Discharge Records for Italians and immigrants patients for all medical conditions

Groups	Residence	N	%
Italians	Veneto	1,387,788	*84*
Italians	Italy	133,272	*8.1*
Italians	Abroad	1,234	*0.1*
Immigrants	Veneto	105,488	*6.4*
Immigrants	Italy	4,330	*0.3*
Immigrants	Abroad	19,389	*1.2*
Total		**1,651,501**	***100***

Table 18: Number of Health Discharge Records for Italians and immigrants patients for all medical conditions

Groups	N	%
Italians	1,522,294	*92.8*
Immigrants	129,207	*7.8*
Total	**1,651,501**	***100***

Table 19: Number of Health Discharge Records only for RDs

Health Discharge Records for RDs			
		RD patient	
			Total
Groups	**N**		
Italians	**N**	15926	**15926**
	%	92.32	
Immigrants	**N**	1324	**1324**
	%	7.68	
Total	**N**	17250	**17250**

Table 20: Number of RD patients according to the Health Discharge Records

Number of RD patients			
		RD patient	
		1	**Total**
Italians	**N**	10,818	10,818
	%	93.94	
Immigrants	**N**	698	698
	%	6.06	
Total	**N**	11,516	11,516

Table 21: Numbers of RD patients according to the Health Discharge Records 2006-2008

Groups	**N**	***%***
Italians_res Veneto	9,003	*78.2*
Italiano_res Italy	1,805	*15.7*
Italiano_res Abroad	10	*0.1*
Immigrant_res Veneto	550	*4.8*
Immigrant_res Italy	56	*0.5*
Immigrant_res Abroad	92	*0.8*
Total	**11,516**	***100***

4.3. Registry of Rare Diseases of the Veneto region

According to the Registry, the certificates provided from 2001 until October 2011 from the Veneto region are in total 21,460. Of these certificates, 1,298 belong to foreigners (equal to 6.0%) and 20,162 belong to Italians. The 21,460 certificates correspond to 21,269 individual patients; this is because there may be cases of patients who present two or more rare diseases. In fact, there are 189 subjects who present 2 or 3 RDs (10 subjects are migrants and 179 Italians). Out of the 21,269 patients, 1,288 are foreigners and 19,981 are Italians.

Table 22: Distribution of RD patients accoding to the Registry

Group	**N**	**%**
Italians	19,981	*93.9*
Immigrants	1,288	*6.1*
Total	**21,269**	***100***

Table 23: Distribution of RD Italian and immigrant patients according to number of RDs

N. of RDs	**Italians**	**Immigrants**	**Total**
1	19,802	1,278	**21,080**
2	177	10	**187**
3	2	0	**2**
Total	**19,981**	**1,288**	**21,269**

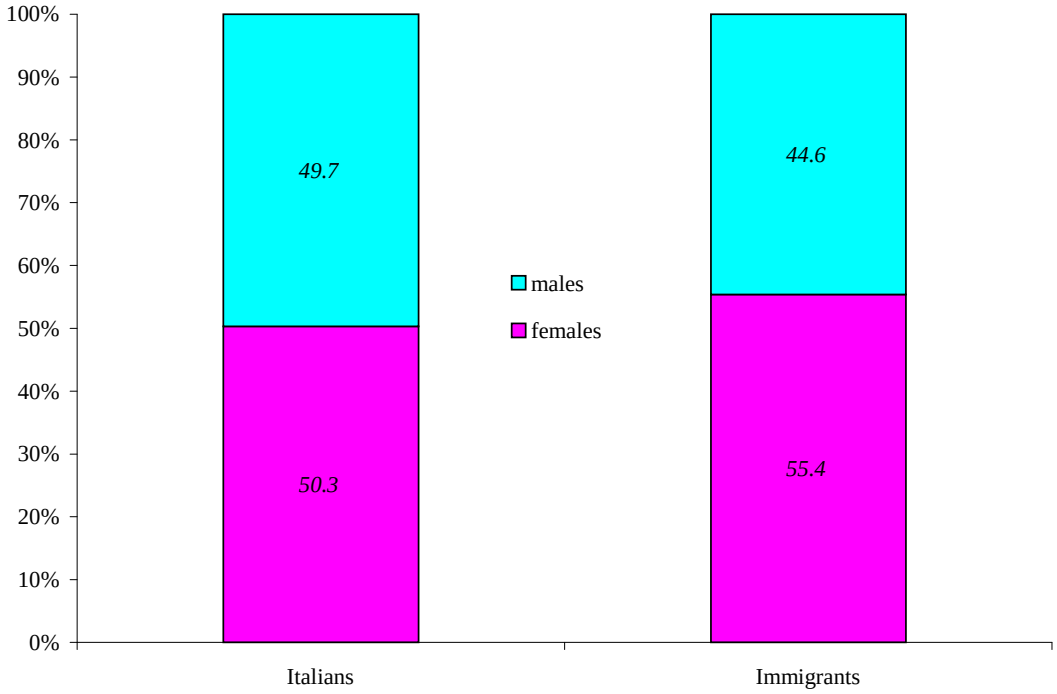
It should be underlined that there were no STP cases found in the Registry of RDs. Apart from the two main groups i.e. Italians and foreigners, we further categorize them into eleven subgroups. 7 pertain to the Italian and 4 to the foreign cases. We mention the four most numerous subgroups. The first subgroup is of Italians who were born and reside in the Veneto region (14,935 subjects corresponding to 70.22%). The second subgroup is of Italians who were born and reside in other Italian regions (3,205 subjects corresponding to 15.07%). The third group consists of Italians who who were born in other regions but are now residents of the Veneto region (1,667 subjects corresponding to 7.88%) and the fourth group is of subjects who were born abroad and reside in the Veneto region (1,113 subjects corresponding to 5.23%). All the subgroups are presented in table 4.

Table 24: Number of Italians and immigrants included in the Registry

Citizenship	Place of birth	Residence	N	*%*
Italians	Veneto	Veneto	14,935	*70.2*
		Italy	158	*0.7*
	Italy	Veneto	1,677	*7.9*

		Italy	3,205	*15.1*
		Abroad	1	*0.00*
	Abroad	Veneto	3	*0.01*
		Italy	2	*0.01*
Immigrants	Abroad	Veneto	1,113	*5.2*
		Italy	164	*0.8*
		Abroad	9	*0.04*
	Veneto	Abroad	2	*0.01*
Total			21,269	*100*

Graph 16: Distribution of Italians and Immigrants by gender.

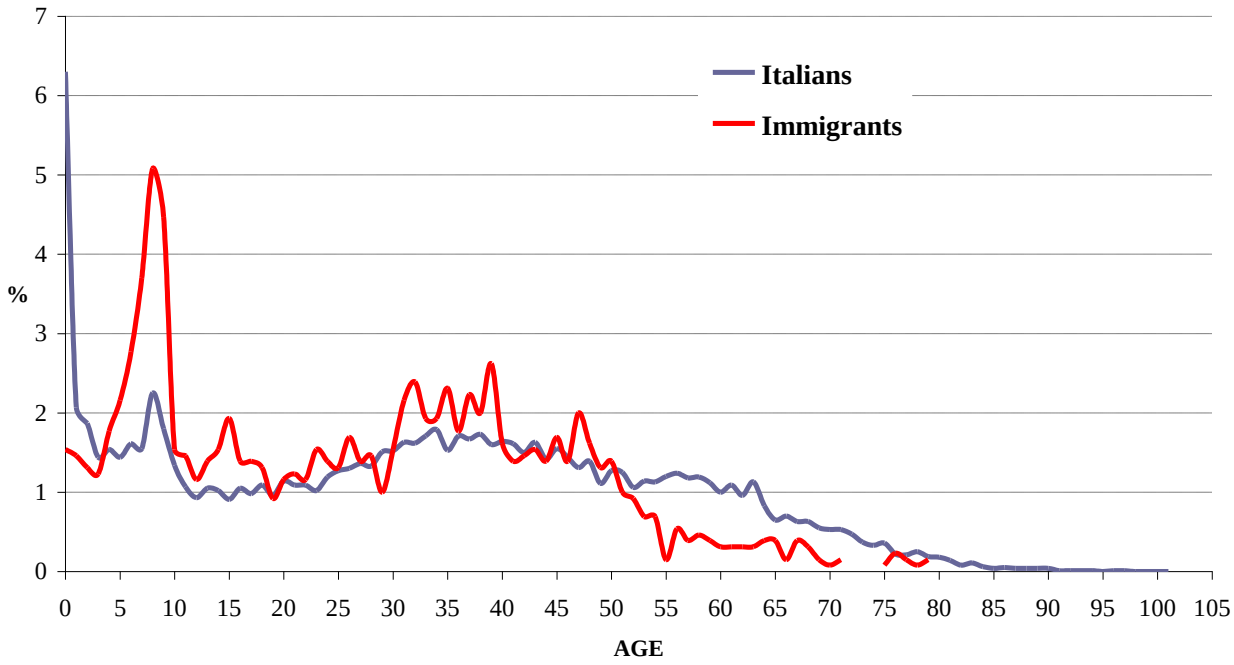


Graph 1 displays the gender distribution of Italians and foreigners. There are no big differences among the 2 groups regarding the gender. In both groups, female patients are more than their male counterparts. The percentage of Italian male and female patients is almost equal (50.28% females, 49.72% males), while female immigrants present an augmented percentage compared to their male counterparts (55.36% versus 44.64%).

Table 25: Age distribution of RD Italian and immigrant population

	Italians		Immigrants	
Age	N	%	N	%
0-1	1,257	6.3	20	1.6
1-17	4,740	23.7	457	35.5
18-34	4,523	22.6	330	25.6
35-49	4,582	22.9	341	26.4
50-74	4,448	22.3	127	9.9
75 >=	431	2.2	13	1.0
Total	19,981	100	1,288	100

Graph 17: Distribution of Italians & Immigrants with a RD according to age



Age distribution for Italians is much higher in the first year of life. The biggest differences are presented in the age group of 0-1 year old between the two groups. Italian babies present a four-fold higher percentage of being diagnosed with a RD than non-native babies (6.3% versus 1.6%). In the age group of 5-17 the Italians present a steep decrease of certification for a RD, while the immigrant group manifests a significant increase of diagnosed RD cases. A noteworthy difference is also presented in the age groups over 55 years old because immigrants' percentage is much lower than that of their Italian counterparts (22.9% Italians versus 9.86% foreigners).

Table 26: Distribution of Immigrant population according to continent

Continents	**N**	***%***
1. European Union	293	*22.8*
2. Other European countries	313	*24.3*
3. Africa	288	*22.3*
4. America	197	*15.3*
5. Asia	183	*14.2*
6. Oceania	14	*1.1*
Total	**1,288**	***100***

The majority of foreign RD patients come from European countries outside the EU (24.3%). EU Member States and Africa follow with 22.8% and 22.3%, respectively. America and Asia have similar percentage of representation in the Veneto region (15.3% and 14.2%). Last but not least, RD patients from Oceania make up only a 1.1% of total patients in the region.

Table 27: Distribution of migrants according to country of origin.

Continents	**Country**	**N**	***%***
EU	ROMANIA	114	*38.9*
	GERMANY	46	*15.7*
	FRANCE	39	*13.3*
	BELGIUM	21	*7.2*
	POLAND	16	*5.5*
	BULGARIA	15	*5.1*
	UK	13	*4.4*
	SPAIN	6	*2.1*
	AUSTRIA	5	*1.7*
	NETHERLANDS	5	*1.7*
	SLOVACCHIA	4	*1.4*
	HUNGARY	4	*1.4*
	GREECE	2	*0.7*
	CZECH REPUBLIC	1	*0.3*
	LUXEMBOURG	1	*0.3*
	SLOVENIA	1	*0.3*
Other European countries	ALBANIA	83	*26.6*
	SWITZERLAND	83	*26.6*
	EX-YUGOSLAVIA	50	*16.0*
	MOLDOVA	28	*9.0*
	FYROM	26	*8.3*
	UCRAINE	13	*4.3*
	BOSNIA HERZEGOVINA	9	*2.9*
	CROATIA	8	*2.6*
	SERBIA	6	*1.9*

	BELARUS	3	*1.0*
	ARMENIA	2	*0.6*
	KOSSOVO	1	*0.3*
Africa	MOROCCO	86	*30.4*
	ETHIOPIA	35	*12.4*
	GHANA	32	*11.4*
	SENEGAL	23	*8.1*
	NIGERIA	21	*7.4*
	TUNISIA	12	*4.2*
	LIBYA	9	*3.2*
	IVORY COAST	8	*2.8*
	ALGERIA	7	*2.4*
	CAMEROUN	7	*2.4*
	TOGO	7	*2.4*
	EGYPT	5	*1.8*
	BURKINA FASO	4	*1.4*
	REPUBLIC OF THE CONGO	4	*1.4*
	SUDAN	4	*1.4*
	TANZANIA	4	*1.4*
	ANGOLA	2	*0.7*
	ERITREA	2	*0.7*
	GUINEA	2	*0.7*
	KENYA	2	*0.7*
	SOMALIA	2	*0.7*
	SOUTH AFRICA	2	*0.7*
	BENIN	1	*0.4*
	BURUNDI	1	*0.4*
	MADAGASCAR	1	*0.4*
	SIERRA LEONE	1	*0.4*
America	BRAZIL	48	*24.4*
	COLOMBIA	25	*12.7*
	ARGENTINE	24	*12.2*
	USA	20	*10.2*
	CANADA	13	*6.6*
	VENEZUELA	13	*6.6*
	PERU	11	*5.6*
	DOMINICAN REPUBLIC	10	*5.1*
	CUBA	6	*3.1*
	ECUADOR	6	*3.1*
	HAITI	6	*3.1*
	COSTA RICA	3	*1.5*
	MEXICO	3	*1.5*
	URUGUAY	3	*1.5*
	CHILE	2	*1.0*
	BOLIVIA	1	*0.5*

	GUADALUPA	1	*0.5*
	PANAMA	1	*0.5*
	PARAGUAY	1	*0.5*
Asia	INDIA	52	*27.7*
	CHINA	30	*16.0*
	BANGLADESH	18	*9.5*
	RUSSIA	15	*8.0*
	SRI LANKA	11	*5.9*
	PAKISTAN	10	*5.3*
	EX USSR	8	*4.2*
	PHILIPPINES	7	*3.7*
	NEPAL	7	*3.7*
	TURKEY	5	*2.7*
	CAMBOGDIA	4	*2.1*
	IRAN	4	*2.1*
	SYRIA	4	*2.1*
	THAILAND	4	*2.1*
	JAPAN	2	*1.1*
	LEBANON	2	*1.1*
	VIETNAM	2	*1.1*
	SOUTH VIETNAM	2	*1.1*
	ISRAEL	1	*0.5*
Oceania	AUSTRALIA	13	*92.9*
	NEW ZEALAND	1	*7.1*

Looking at the countries, the majority of foreign RD patients come from Romania (8.9%), Morocco (6.7%), Switzerland (6.4%), Albania (6.4%), India (4.0%), ex-Yugoslavia (3.9%), Brazil (3.7%), Germany (3.6%), France (3.0%), Ethiopia (2.7%), Ghana (2.5%) and China (2.3%).

Table 28: The 20 most prevalent RD diagnosis for Immigrants are the following:

RARE DISEASES (20 MOST PREVALENT FOR IMMIGRANTS)	N	*%*
idiopathic precocious puberty	127	*9.8*
keratoconus	119	*9.2*
sickle cell anaemia	68	*5.2*
undifferentiated connective tissue diseases	58	*4.5*
palatochisis	52	*4.0*
retinitis pigmentosa	34	*2.6*
hereditary hemocromatosis	29	*2.2*
achalasia	28	*2.2*
hemophilia A	23	*1.8*
coeliac sprue/ celiac diseases	23	*1.8*
mixed connective tissue disease (MCTD)	21	*1.6*

behcet syndrome	20	*1.5*
drepanocytosis	18	*1.4*
neurofibromatosis type 1	18	*1.4*
turner syndrome	18	*1.4*
amyotrofic lateral sclerosis	16	*1.2*
von willebrand disease	15	*1.2*
inherited retinal dystrophy	12	*0.9*
klinefelter syndrome	12	*0.9*
protein S deficiency	11	*0.9*
…	…	...

Table 29: The 20 most prevalent RD diagnosis for Italians are the following

RARE DISEASES (20 MOST PREVALENT FOR ITALIANS)	N	*%*
keratoconus	2,294	*11.4*
undifferentiated connective tissue diseases	969	*4.8*
hereditary hemocromatosis	717	*3.6*
neurofibromatosis type 1	567	*2.8*
amyotrofic lateral sclerosis	561	*2.8*
achalasia	541	*2.7*
coeliac sprue/ celiac disease	474	*2.4*
von willebrand diseases	437	*2.2*
idiopathic precocious puberty	424	*2.0*
retinitis pigmentosa	392	*1.9*
palatochisis	363	*1.8*
hemophilia A	316	*1.6*
bullous pemphigoid	247	*1.2*
mixed connective tissue disease (MCTD)	241	*1.2*
turner syndrome	236	*1.2*
down syndrome	221	*1.1*
klinefelter syndrome	216	*1.0*
glucose-6-phosphate dehydrogenase deficiency	201	*1.0*
behcet syndrome	189	*0.9*
congenital adrenal hyperplasia syndrome	186	*0.9*
…	…	...

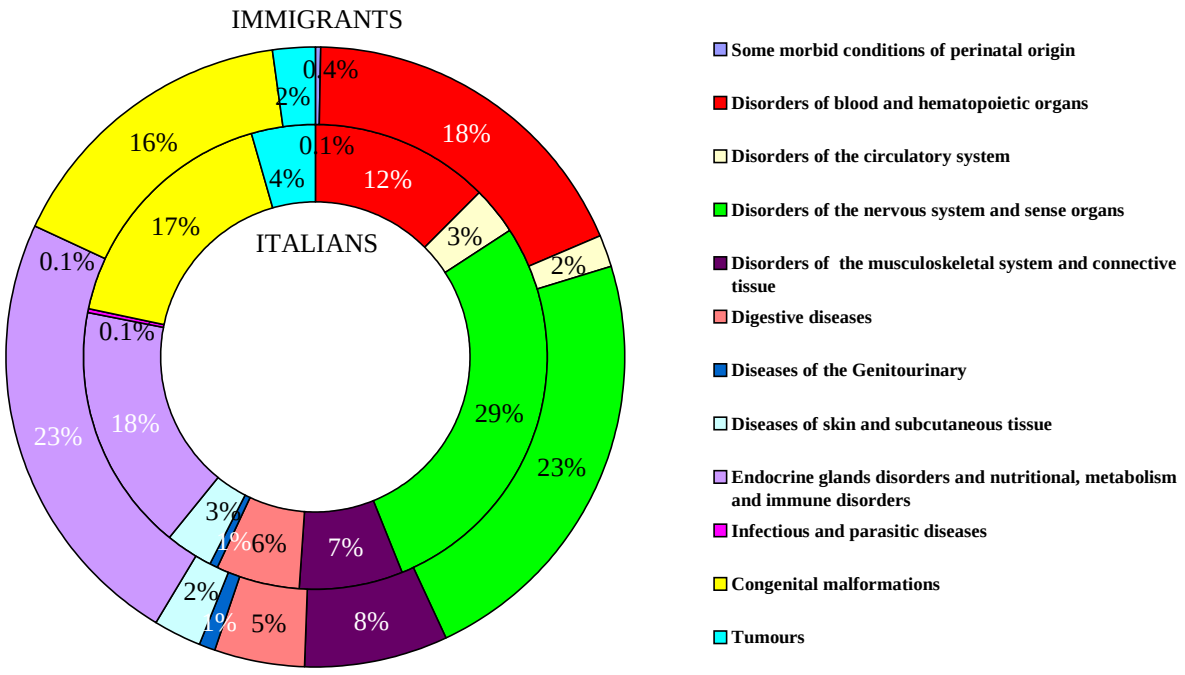
It is also interesting to see the distribution of the most prevalent diseases in the groups of immigrants by continent. **Table 30** shows the most prevalent diseases.

Continent	**Rare diseases**	**N**	***%***
EU	undifferentiated connective tissue diseases	21	*7.2*
	idiopathic precocious puberty	20	*6.8*
	keratoconus	19	*6.5*

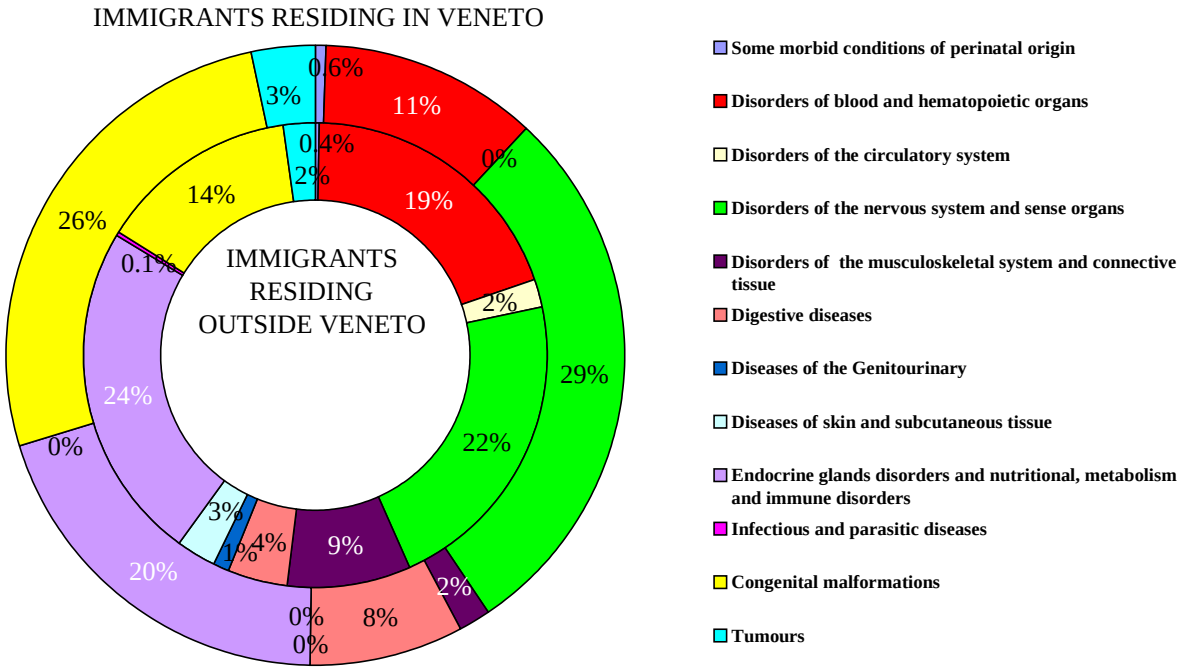
	hereditary hemocromatosis	13	*4.4*
	achalasia	11	*3.8*
	retinitis pigmentosa	11	*3.8*
	coeliac sprue/ celiac disease	11	*3.8*
	neurofibromatosis type 1	7	*2.4*
	palatoschisis	7	*2.4*
	interstitial cystitis	5	*1.7*
	von willebrand disease	5	*1.7*
	amyotrofic lateral sclerosis	5	*1.7*
	turner syndrome	5	*1.7*
	thrombophilia due to homozygosity for the factor V Leiden	5	*1.7*
		…	...
Other European countries	keratoconus	41	*13.1*
	palatoschisis	13	*4.2*
	undifferentiated connective tissue diseases	8	*2.6*
	retinitis pigmentosa	8	*2.6*
	coeliac sprue/ celiac disease	7	*2.2*
	achalasia	6	*1.9*
	sickle cell anemia	6	*1.9*
	protein S deficit	6	*1.9*
	hereditary hemocromatosis	6	*1.9*
	hemophilia A	6	*1.9*
	amyotrofic lateral sclerosis	6	*1.9*
	Ehlers-Danlos syndrome	6	*1.9*
	turner syndrome	6	*1.9*
	von willebrand disease	5	*1.6*
	autoimmune polyendocrinopathy type II	5	*1.6*
	polymyositis	5	*1.6*
	idiopathic precocious puberty	5	*1.6*
		…	...
Africa	sickle cell anemia	51	*17.7*
	idiopathic precocious puberty	31	*10.8*
	keratoconus	24	*8.3*
	drepanocytosis	17	*5.9*
	undifferentiated connective tissue diseases	13	*4.5*
	behcet's syndrome	9	*3.1*
	hereditary anemias	7	*2.4*
	glucose-6-phosphate dehydrogenase deficiency	6	*2.1*
	behcet's syndrome	6	*2.1*
	retinitis pigmentosa	6	*2.1*
	hemophilia A	5	*1.7*
		…	...
America	idiopathic precocious puberty	28	*14.2*
	keratoconus	23	*11.7*

	sickle cell anemia	8	*4.1*
	palatoschisis	8	*4.1*
	achalasia	7	*3.6*
	hereditary hemocromatosis	7	*3.6*
	mixed connective tissue disease	6	*3.1*
	undifferentiated connective tissue diseases	6	*3.1*
	retinitis pigmentosa	6	*3.1*
	inherited retinal dystrophy	5	*2.5*
		…	...
Asia	idiopathic precocious puberty	42	*23.0*
	palatoschisis	22	*12.0*
	undifferentiated connective tissue diseases	10	*5.5*
	hemophilia A	6	*3.3*
	behcet's syndrome	5	*2.7*
		…	...
Oceania	keratoconus	7	*50.0*
		…	...

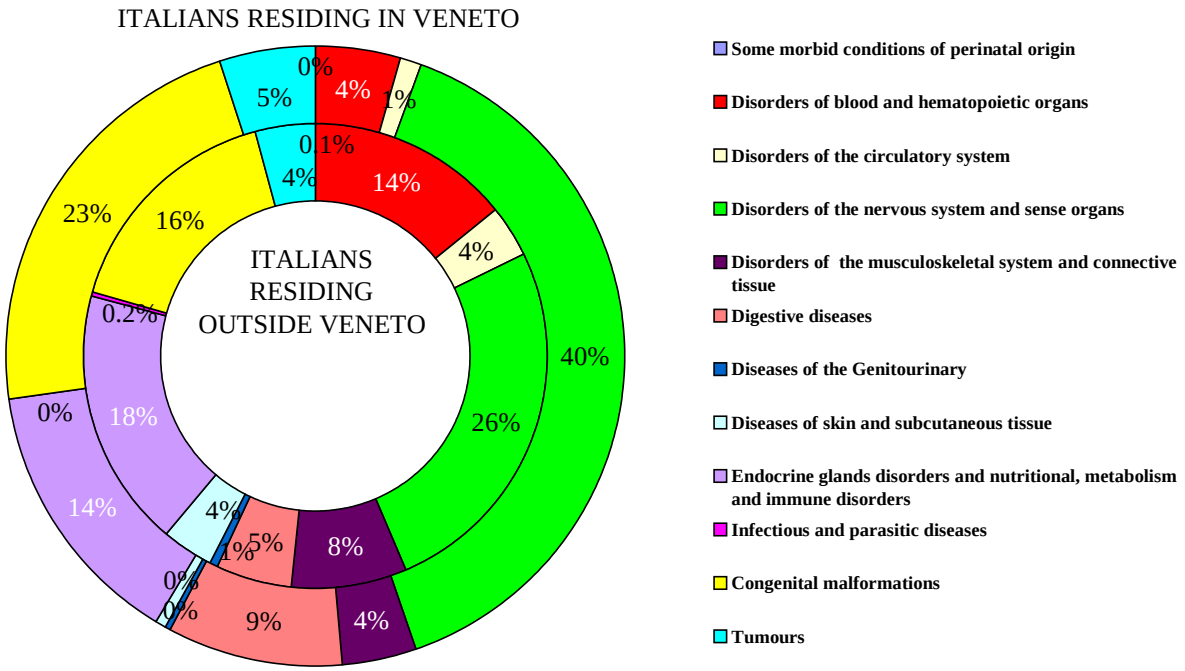
Graph 18: Distribution of RDs among Italians and Immigrants



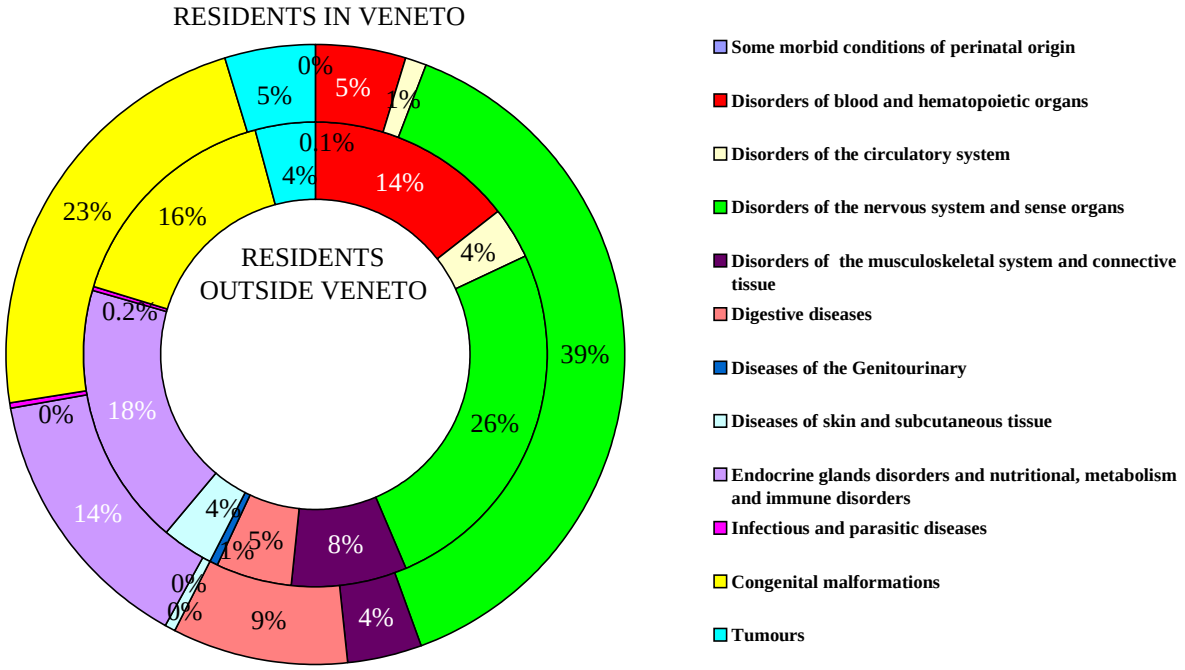
Graph 19: Distribution of RDs among Immigrants residing in Veneto and Immigrants residing outside Veneto



Graph 20: Distribution of RDs among Italians residing in Veneto and Italians outside Veneto.



Graph 21: Distribution of RDs among residents in the Veneto region and residents outside the Veneto region.



5. DISCUSSION

5.1. ISTAT

The ISTAT data demonstrate a rapid increase of the immigrant population in the Veneto region the last decade. It seems that the Veneto has become an attractive destination and in 2011 the population legally residing in the region, has reached half a million. In percentual distribution, the "other European countries" keep the first place in population distribution over the years, while the EU countries have augmented their percentage rapidly. On the other hand, the percentage of African and American immigrants has decreased.

5.2. A first glance at the results from the Registry of Rare Diseases

The large ethnic groups of Romanians, Moroccans and Albanians constitute the greater percentage of RD patients in the Veneto region. They are of relatively young age and being in their working and most reproductive years, as highlighted by the existing literature.

The female immigrant population with a rare disease in the Veneto region is slightly higher than the male one; this data agrees with the current immigration trends in Italy. The number of female immigrants is increasing in Italy and female immigrants, in general, tend to seek healthcare more often than men do. The high utilization of healthcare services by women is found to be primarily due to the their need of obstetrical and mental healthcare services.[71,72,73,82]

Our study identified two groups of RD patients seeking healthcare in the Veneto region. The first one pertains to affected individuals arriving from abroad and the second deals with subjects arriving from other Italian regions. From the data, one can see that the percentage of Italians and foreigners who permanently live abroad and who both arrive in the Veneto region seeking RD treatment is minute. Patient mobility is a factor that cannot be always explained. There is not much research on this area and we can only speculate why the percentages of health migration from abroad towards the Veneto region are low. This may be due to the gravity of the condition of the RD patient. This conclusion brings us back to the healthy migrant effect. Patients with a RD may not be in position of travelling abroad to seek healthcare; as a result the healthiest individuals arrive in other countries as migrants. The majority of the migrant population which has arrived the last decade in Italy belongs to the first generation of immigrants. Once should wait to see the second generation of immigrants on the Italian territory. Foreign subjects with more severe and disabilitating diseases may be present in the following generations, born in Italy.

Subjects certified with a RD diagnosis, which are included in the groups below show us that the percentage of the affected individuals residing outside the Veneto region is greater than the percentage of the subjects residing in Veneto.

A. disorders of blood and hematopoietic organs

B. disorders of the muskuloskeletal system and connective tissue

C. endocrine glands disorders and nutritional metabolism and immune disorders

D. diseases of skin and subcutaneous tissue

E. disorders of the circulatory system

A logical explanation could be that the Veneto region attracts affected individuals from other regions due to its high level of expertise in these medical fields. Another explanation may be that the regions from which originate the RD patients, lack in healthcare services. A hypothesis could also be that these patients come from the Friuli Venezia region or the autonomous provinces of Bolzano and Trento composing the Wide Area of RDs, as mentioned above. Each region has its excellence centres where patients from the other regions of the Wide Area are referred to, and have access to the best possible services. Extensive research is needed on this field in order to highlight the underlying reasons behind these trends of healthcare utilisation by patients who come outside the Veneto.

The internal migration for obtaining healthcare services may have various reasons. For instance, a study was conducted in the Veneto region regarding Italian and foreign female residents. A significant percent of both groups of women preferred to perform elective procedures of pregnancy (induced abortion and part of cesarean sections) in other regions and not in Veneto. The data show that for the years 2006-2007, 1,477 women of Italian citizenship were hospitalized for abortion outside Veneto but only 532 women came to Veneto hospitals from other Italian regions. A possible explanation for that are the delays in obtaining these procedures in near hospitals. Waiting times in the Veneto region can exceed 4 weeks in 19% of cases (compared to 7% in nothern Italy).[77]

5.3. Comparison of data by the Health Discharge Records and the Registry of the Veneto region

We can see that the recorded RDs in the Registry differ substantially from the ones recorded in the Health Discharge Records. This may be because the most prevalent diseases in the Registry do not require a strict medical supervision over time. On the contrary the most prevalent diseases in the

Health Discharge Records require a systematic medical attention. The gravity between diseases registered in our two sources also differs significantly. In the first places of the Registry, milder conditions are recorded while in the Health Discharge Records more severe and acute pathological situations are shown. For example, three very prevalent diseases in the Registry (keratoconus, retinitis pigmentosa and celiac sprue) are not as prevalent in the Health Discharge Records.

Furthermore the STP patients could be only identified by the Health Discharge Records for the period 2000-2005. This is an interesting finding as it sheds light upon a number of RD patients who have irregular status. The Registry is an official entity which registers all RD patients legally residing in the Veneto or other Italian regions (Friuli Venezia and the autonomous provinces of Trento Alto Adige and Bolzano). However the Registry does not include undocumented patients on its list. This may occur due to the unwillingness of the immigrants to register in the Registry or because the Registry does not record undocumented immigrants or misclassifies them as regular ones.

This leads to a problematic situation because immigrants with a RD are deprived from their entitlement to make use of the healthcare services. Rare Diseases constitute a substantial economic and psychological burden for the patient and his family, which without the intervention of the state, it is impossible to handle it. Another implication is that their possible misclassification poses a significant financial burden for the healthcare system of the Veneto region. In this way affected individuals not registered and thus not entitled to have access to healthcare services, do use the allocated resources of the healthcare system

5.4. Most prevalent RDs in the immigrants' group

5.4.1. Precocious Puberty

Looking at the most prevalent RDs from the Registry of the Veneto Region, the following observations can be made. Idiopathic precocious puberty presents a five-fold higher percentage in the group of immigrants compared to that of Italians (9.8% versus 2.1%). The majority of affected individuals come from Asia, Africa, South America and Eastern Europe. India and Ethiopia present the majority of cases. Studies from Denmark have demonstrated that adopted Indian and South American girls, often present precocious puberty.[83]

The immigrant population presents almost five times more cases of precocious puberty than the Italian one. This is a notable difference. Additional evidence derives from the international

literature, where the following themes emerge. The cut-off limit of precocious puberty has been defined as 8 years for girls and 9 years for boys. There is data that the risk of precocious puberty (PP) significantly increases among adopted children in contrast to what is seen in children migrating with their families.[84,85 ,86] Different growth patterns and dietary habits between adoptees and children migrating with their families might contibute to explain these findings. Another possible explanation is that stressful psychological factors in infancy and childhood may lead to earlier pubertal maturation. In general adopted children have experienced several traumatic events in their life, and it may be speculated that these events alter the susceptibility for developing precocious puberty.[83]

Foreign children coming to Europe often present premature sexual maturation; however the etiology is not clear yet. Research has suggested that it is due to genetic/ racial differences, prenatal and postnatal growth patterns (including advancement in pubertal maturation after poor intrauterine growth and catch-up growth during childhood). Environmental factors, such as improved nutrition and exposure to endocrine disrupters, are also considered as major fators which trigger PP. Environmental influences include the suggested role of the dietary change, especially in adopted children, from low protein and low energy vegetarian diet to a balanced, ennriched diet after adoption. In addition the presence of estrogen-like substances in food (phytoestrogens) and other endocrine disrupters in their new environment influencing the pubertal development of adopted children needs to be furtherly examined. The improvement of nutritional status in children adopted at later stages in their life, may facilitate the onset of puberty by an increase in leptin levels. This augmentation may act as a permissive factor for the onset of puberty by interacting with several neuropeptides.[86]

5.4.2. Palatochisis

Palatoschisis is a nonsyndromic birth defect with a complex etiology and likely results from an interaction between genetic and environmental factors. Smoking has been identified as the most consistent environmental risk factor,[87] along with maternal drug intake, trauma and radiation. Gender, race/ethnicity and maternal age play a crucial role, as well.[88] Studies have also demonstrated that preterm infants are more than two times as likely to have cleft palate than term infants.[87]

Palatoschisis presents a significant difference in prevalence between Italians and immigrants. The ethnic groups which are more affected by palatoschisis in the Veneto region are Chinese (22.6%),

Romanian (7.6%) and Russian (7.6%). It is worth mentioning that the countries of the ex-Yugoslavia make up a 13.2% if their prevalence percentages are added up together. The findings on Chinese patients agrees with existing literature on cleft palate. It has been reported that the prevalence of cleft anomalies ranges between 6.9 and 23.5 per 10,000 births in Caucasians, between 1.8 and 8.2 per 10,000 in U.S. Afro-Americans, and between 16.5 and 27.1 per 10,000 births in Japanese.[89] In addition, earlier studies showed that Chinese, Japanese, and other Asian populations have the highest prevalence of Non Syndromic Cleft Lip Palate (NsCL/P), followed by Caucasians and then Afro-Americans.[90,91] Birth prevalence of all cleft types was also higher among Whites compared to Afro-Americans and Hispanics in a study conducted in the USA.[87]

Another interesting aspect is the reason why China presents the highest percentage of subjects with palatoschisis among the immigrant groups in the Veneto region. Literature demonstrated that in a country of 1.3 billion inhabitants, the ratio of pediatric surgeons per million of population varies substantially, depending on the area. Two big cities, Beijing which has 7 million inhabitants and Shanghai which has a 15 million population, have 100 and 130 pediatric surgeons respectively. Rural areas have the smallest ratio of 0.5 pediatric surgeons per million population, while urban areas have a ratio of above 2 surgeons per million population. Last but not least, the training for pediatric surgery varies across the country. Centers might request from 1 to 5 years for the specialisation in pediatric surgery.[92] Concluding, due to the fact that China is the most populous country in the world, combined with the fact that it presents a great difference between the quality of helthcare services from area to area, as well as a lack in medical staff, may partially explain the high prevalence of subjects with palatoschisis in the Veneto region.

The low percentages of palatoschisis in the group of Italians may be justified by the fact that palatoschisis is a malformation that is diagnosed immediately after birth. Usually new borns suffering from this condition are being operated upon a few days after their birth. As a result, physicians do not include the palatoschisis diagnosis in the medical records of the new-borns. Another possible explanation could be that nowadays in Italy there is a widespread use of prenatal diagnostic tools for congenital malformations. As a result future parents can decide on whether to terminate the pregnancy (TOP) for birth defects. Data from north-eastern France showed that during a 9 year study period, out of 207 cases of cleft lip palate or cleft palate, 5.3% of pregnancies were terminated after prenatal diagnosis of associated malformations.[93] Findings by King's College London Dental Institute showed that over a 5 year period, 23,577 live and still births took place in Cambridge, UK. Thirty of those had facial clefts, and 17 were detected by the antenatal ultrasound

screening (AUS). Out of these 17 pregnancies, 7 were terminated. With one exception, all terminations were in foetuses with multiple anomalies. The same study allows pre-pregnancy counselling of families previously affected by clefting about the reliability of AUS detection rates.[94] In addition data also demonstrate that prenatal diagnosis for foetuses' anomalies lead to induced abortions; 85% of Down syndrome foetuses were aborted in Paris, France,[95] 32% in Western Australia,[96] 75% in South Australia,[97] 80% in Taiwan.[98]

5.4.3. Amyotrophic lateral sclerosis

The findings regarding amyotrophic lateral sclerosis are also interesting. According to the Registry, the percentage of Italian patients exceeds the one of the immigrants. Out of the 16 foreign patients, 11 originate from Europe, 4 from South America and 1 from Africa. The ratio among male and female patients was 1.0.

Amyotrophic lateral sclerosis is a fatal neurodegenerative disorder, which involves the large motor neurons of the brain and the spinal cord. Its main characteristic is progressive paralysis resulting in death from respiratory failure.[99] Studies which have been conducted in Europe and the USA have shown that the incidence is rather similar between the western countries. The bibliography supports that the mean age of ALS is 60 years old, and is usually presented before the age of 65.[100,101] There are a few cases of subjects who present the onset of ALS in age less than 30 years old.[100] The lower prevalence of ALS among the immigrant patients could be attributed to the younger age of this group; age is a favorable factor contributing to the low levels of ALS prevalence among the immigrant population in the Veneto region. In addition a comparison between the Registry of Rare Diseases and the Health Discharge Records demonstrates that ALS patients are underpresented in the Health Discharge Records. A possible explanation could be that the duration of the disease is limited from 2 to 5 years [99,100] and the nature of the disease is degenerative and patients pass away before they manage to obtain a certification from the Registry for their condition.. Moreover the ALS diagnosis can be time-consuming because it is difficult to differentiate it from other pathologies which present similar symptoms (Kennedy's disease, cervical spondylotic myelopathies and multifocal motor neuropathy).[100] As a result ALS is often misclassified since it is difficult to obtain the diagnosis and we may see an underestimation of the ALS cases on the Health Discharge Records.

5.4.4. Blood disorders in the African population

Blood disorders, and hereditary anemias in particular, are most prevalent in the African population of the Veneto region. The percentage of patients diagnosed with anemia is almost the same among the African male and female subjects (51.1% males and 48.9% females). The majority of patients originates from Ghana (28.9%), Nigeria (20.0%), Senegal (10.0%) and Morocco another (10.0%). The ages at which Africans are diagnosed with blood disorders mostly belong to two age groups. The first one is from 1-17 years old (38.9%), and the second one is from 18-34 years old (37.8%). Furthermore there may be an underestimation of recorded patients in the first age group of Africans due to their false registration under the group of Italians. This occurs due to the lack of the element of citizenship in the Registry's database.

On the contrary, according to the data regarding the Italian patients diagnosed with blood disorders, there is a great difference between males (81.0%) and females (19.1%), who present this disorder. In addition the distribution of Italian patients is much broader among the different age groups, compared to the African ones, where the distribution is more concentrated. See table.

Both sources, the Registry of Rare Diseases and the Health Discharge Records, show that anemias rank in the first places among Africans. Existing literature also underlines the high prevalence of blood disorders in the Sub-Saharan Africa population (the indigenous population presents a carrier frequency of 20-25%), as well as the Caribbean, Eastern Mediterranean, Middle East and Indian tribal populations.[102,103] A study from the USA highlights that African Americans with sickle cell disease have less Caucasian admixture than African Americans who do not present the disease. The African Americans who suffer from sickle cell disease were found to have a genetic structure similar to the one of the African ethnicities of the Yorubans, Bantus and Mandenkas.[103] It has been also found that sickle cell disease and glucose-6-phosphate dehydrogenase deficiency (G6PD) are common in African subjects who are carriers of malaria as well. This is because patients with blood disorders are protected against malaria and present higher survival possibility compared to non carriers, and thus are more likely to survive and reproduce.[103,104,105]

Since a significant percentage of individuals with blood disorders come from Morocco, it would be interesting to have a closer look at their beliefs. The majority are of Muslim religion, known for rigidity towards induced abortion. In a qualitative study by Giordano and colleagues, Moroccans were interviewed regarding their attitude and beliefs towards hemonoglobinopathies and their implications. The majority of Moroccans responded that they would be least in favour of

terminating a pregnancy in case they were informed of being *at risk for a severely affected child.* One could wonder whether this response could be related to the high percentage of Moroccans with blood disorders. It seems that in this culture, religion plays a discouraging factor in conducting prenatal diagnostic tests and abortion. On the other hand, there is contradicting data that illegal abortions are a common practice in Morocco and are performed by midwives or in private hospitals.[106] Therefore a taboo theme such as abortion, may result in Moroccans giving a socially desirable response, hiding the fact that they do have abortions. More research is needed in this field in order to examine this culturally sensitive issues.

Strengths

To our knowledge, this is the first study that deals with immigrants who have a RD in the Veneto region. RD immigrants constitute a small and group and there is paucity of data regarding their healthcare needs and utilisation of healthcare services. To date, studies have focused on utilization of healthcare services by the immigrant population, but have neglected the specific group of immigrants with a RD. An attempt to bridge the gap of current literature is made; demographic profiles, RDs and utilisation of healthcare services were the main topics of this paper.

Limitations

As underlined by other studies, different considerations relate to the validity of the information on citizenship ,the key variable used to identify immigrants through the Health Discharge Records. The validity of this variable has not been demonstarted either by specific studies nor by its use. This could imply misclassification and biased results. Immigrants are more likely to be misclassified as Italians than vice versa. In this case, the effect of misclassification would be to undrestimate the number of immigrants receiving hospital treatment, with the risk of both biased rates and biased association measures.

Other flaws in the study may be related to both discharge and population data; due to irregular immigration, it is impossible to identify the total number of immigrants present at the Veneto region for the years under study. The data on the immigrant population legally residing in the Veneto region were taken from the Istat website. As a result, the immigrant population at risk may be underestimated.

Recommendations

Regarding the Registry of Rare Diseases, it should be noted that the absence of the citizenship variable is of vital importance. It is shown in our study that an underestimation of the foreign population is performed in the Registry due to the lack of the citizenship variable. The difference was emphasized when there was a comparison of the results with the Health Discharge Records. It is strongly recommended that the Registry should be updated, inserting the variable of citizenship in order to avoid misclassification of the immigrant group and reduce bias.

ANNEX

Figure 1. Data sheet of the Registry of Rare Diseases of the Veneto region.

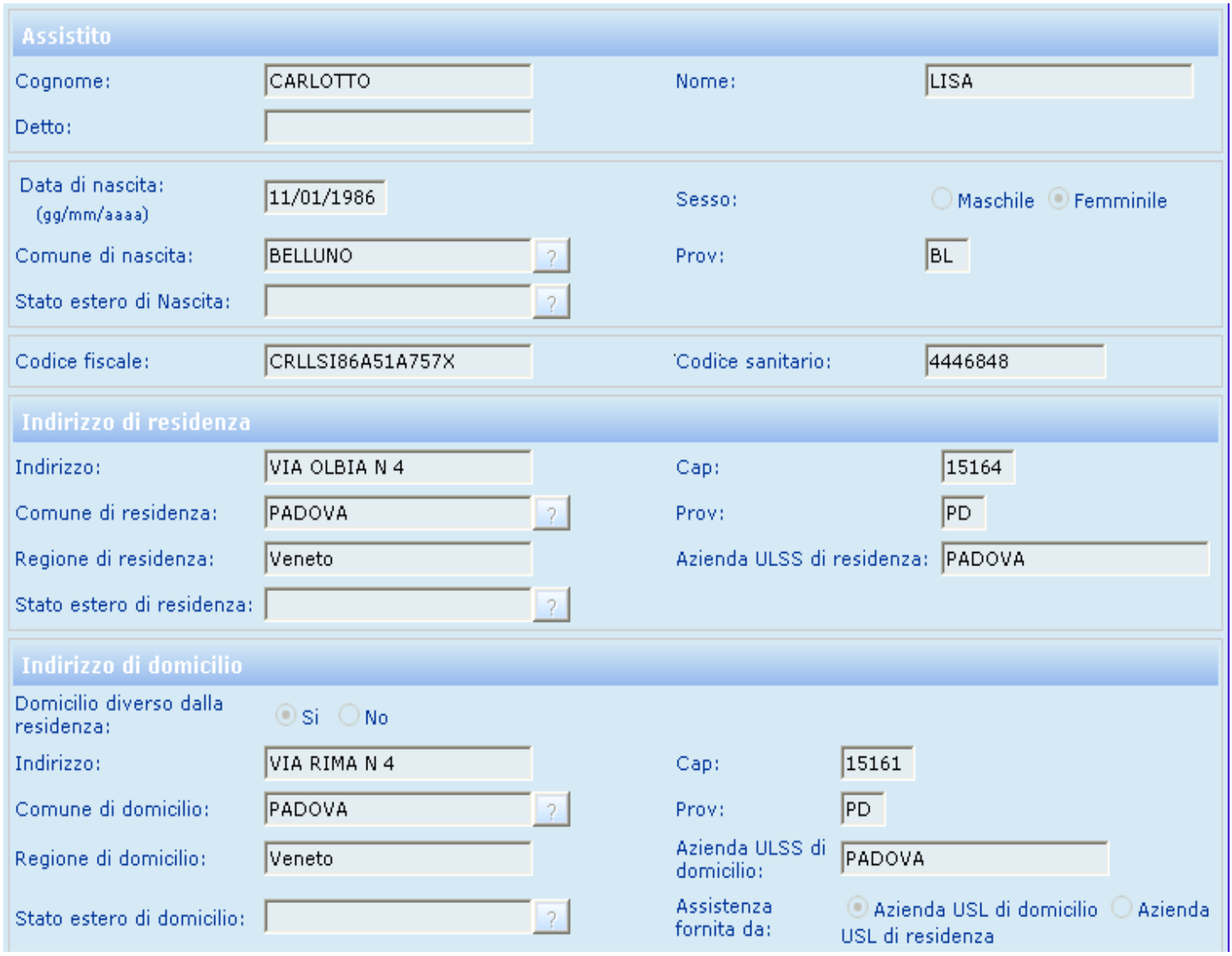


Figure 2. Disease Tab of the Registry of Rare Diseases of the Veneto region.

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