SPECIAL COLLABORATION

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IMPLEMENTING A POPULATION-BASED RARE DISEASES REGISTRY IN SPAIN: NAVARRE´S EXPERIENCE(*)

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ABSTRACT

In 2012, the Spanish Rare Disease Registries Research Network (Spain-RDR) was consolidated with the aim of creating a Spanish population-based Rare Diseases Registry. In order to achieve this, each of the 17 Spanish Regions had to develop its own regional registry with a common agreed methodology. The Population-based Rare Disease Registry of Navarre was created in 2013 and, since then, its implementation is being carried out.

Navarre assumed the agreed list within the Spanish Network, which included 934 codes of the International Classification of Diseases, 9th Revision, Clinical Modification. Initially, the main data source used to capture cases was the Assisted Morbidity Registry of Navarre, which includes the Minimum Basic Data Set of every regional hospital discharges (both public and private). New data sources were added and ongoing validation studies of captured cases were developed.

Population-based rare diseases registries are fundamental for the study and quantification of this type of diseases since the classification and coding systems used in the current healthcare information systems are very nonspecific. The analysis and cross-referencing of data among multiple data sources is essential to maximize case detection capacity. Due to the low prevalence of these diseases, a high false positives rate among the detected cases greatly affects the estimation of epidemiological indicators, which makes it necessary to validate the cases by verifying the diagnoses.

Key words: Rare diseases, Registries, Information systems, Epidemiology, Prevalence.

RESUMEN

Implementando un registro poblacional de enfermedades raras en España: la experiencia de Navarra

En 2012 se consolidó la Red Española de Registros de Enfermedades Raras para la Investigación (Spain-RDR) con el objetivo de crear un Registro poblacional español de Enfermedades Raras. Para conseguirlo, cada Comunidad Autónoma tenía que desarrollar su propio registro autonómico con una metodología común consensuada. El Registro Poblacional de Enfermedades Raras de Navarra se creó en 2013 y, desde entonces, se está desarrollando su implementación.

Navarra asumió el listado consensuado dentro de la Red, que incluye 934 códigos de la 9ª revisión de la Clasificación Internacional de Enfermedades (modificación clínica). Inicialmente, la principal fuente de información utilizada para la captación de casos fue el Registro de Morbilidad Asistida de Navarra, que recoge el Conjunto Mínimo Básico de Datos de las altas hospitalarias (de centros públicos y privados) de la Comunidad Foral. Posteriormente se fueron añadiendo nuevas fuentes de información y desarrollando continuos estudios de validación de los casos captados.

Los registros poblacionales de enfermedades raras son fundamentales para el estudio y cuantificación de este tipo de enfermedades ya que los sistemas de clasificación y codificación utilizados en los actuales sistemas de información sanitaria son muy inespecíficos. El análisis y cruce de datos entre múltiples fuentes es esencial para maximizar la capacidad de detección de casos. Al tratarse de enfermedades muy poco prevalentes, una tasa alta de falsos positivos entre los casos detectados afecta en gran medida la estimación de indicadores epidemiológicos, lo que hace necesario validar los casos verificando los diagnósticos.

Palabras clave: Enfermedades raras, Registros, Sistemas de información, Epidemiología, Prevalencia.

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INTRODUCTION

Conceptual framework in Europe. In the framework of the European Union (EU), a Rare Disease (RD) is defined as that presenting a prevalence lower than 5 cases per 10,000 inhabitants[1]. The complexity of these diseases and the specific requests of the groups of patients that suffer from them, represent a challenge for health systems classically oriented to the care of high prevalence diseases[2].

During the last decade, several European actions have taken place in order to approach RD, and one of the biggest achievements was the development of the *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. "On Rare Diseases: Europe´s challenges"*, published in November 2008[3]. The objective of this communication was to establish a comprehensive EU strategy to support the Member States to perform an effective and efficient recognition, prevention, diagnosis, treatment, care and research of RD in Europe. Such Communication declares the "Registries and Databases" as key instruments for the knowledge and the research on RD, and was complemented with the promulgation of the "Council Recommendation, of June 8th, 2009, on a European action in the field of rare diseases"[4], in which all Member States agreed to develop a national action plan or strategy in the framework of RD by 2013.

Background in Spain. In this context, on April 22nd, 2009, the Spanish Ministry of Health and Social Policy presented the Rare Diseases Strategy of the Spanish National Health System (NHS), approved on June 3rd, 2009 by the Inter-territorial Council of the Spanish NHS[5]. This Strategy, reviewed in 2012[6] and updated on June 11th, 2014[7], highlighted: on one hand, the need to estimate the incidence and prevalence of each disease; and, on the other hand, the need of improving knowledge of the natural history of RD in order to adapt actions on health care issues and to be able to better monitor them.

In parallel, the Spanish Rare Diseases and Sample Bank Registry was launched from a practical point of view, officially created and declared to the Spanish Agency of Data Protection in 2005 by the Rare Diseases Research Institute (IIER), which is part of the Institute of Health Carlos III (ISCIII)[8]. It is a patient registry in which any affected person by a RD, or their legal guardian, can register voluntarily.

In 2011, the ISCIII joined the International Rare Diseases Research Consortium (IRDiRC). This consortium pretends to promote research facilitating international cooperation in every area of interest related to these diseases, the Rare Diseases Registries (RDR) being one of the most strategic of them. The ISCIII launched an internal call from the IRDiRC for Spain and finally, the Spanish Rare Disease Registries Research Network-SpainRDR, was consolidated. This project raised funds for a 3-year period (2012-2015) and it had the participation of the Health Departments of every Spanish Region, coordinated and led by the IIER.

The main objective of SpainRDR Network was to create a nationwide population-based RDR in Spain, gathering the population-based registries of each Spanish Region as well as the specific registries of patients. In order to achieve this, each of the 17 Spanish Regions had to develop a regional population-based RDR that could work in coordination with the rest of registries to establish a nationwide registries network. Once the project Spain-RDR was finished (June 2015), the Ministry of Health, Social Services and Equality (MSSSI) decided to continue this work with the creation of the Spanish Registry of Rare Diseases (ReeR), currently in force.

Rare Diseases Registries. Health registries are very valuable tools in the field of RD due to their low prevalence, the dispersion of the information and the lack of knowledge about RD[5]. In this regard, one of the main objectives of the strategy is, precisely, the creation of a Spanish population-based RDR. The aim of the registry is to promote etiological and clinical research and, at the same time, to contribute to the resource planning that health services must provide for the attention to those affected and their families. This registry would also provide, on one side, adequate information in order to facilitate the development of social and health policies such as prevention, diagnosis and treatment, and on the other side, it would promote RD research. Obviously, the final objective would be to provide a higher life quality and to increase the possibilities of intervention for those affected, facilitating preventing strategies, early diagnosis and, if possible, their cure. Furthermore, patients associations have been demanding the creation of these registries for a long time (at regional and national level) in order to achieve the implementation of epidemiological studies that would allow knowing the number and location of patients and would also help to plan assistance and research[9].

The challenges facing a population RDR are numerous, one of the most important being the great difficulty of establishing a closed list of RD, which is due to numerous factors:

– The definition of RD is not universal since each country uses different prevalence cut-off points[10].

– It is estimated that there are between 6,000 and 8,000 different RD (or more), between 75 and 80% of them genetic in origin, and new mutations on human genome are continually discovered. Their clinical consequences have to be investigated and also, they give place to the description of new clinical entities in the scientific literature[2,11].

– The different degrees of specificity used when classifying clinical entities also affect the number of rare diseases[12].

– An effective but not curative treatment can turn a rare disease into a common one; and, conversely, an effective prevention can turn a common condition into a rare disease[13].

– An increase in new scientific data, which is generated mainly by the massive use of novel high-throughput technologies, is resulting in a great amount of traditional phenotypes being split into different diseases[10].

As an example, the RD inventory of the European website 'Orphanet' went from having 7,786 phenomes in 2010 to collect 9,799 different phenomes in 2015, including: diseases, malformative syndromes, morphological abnormalities, biological abnormalities, clinical syndromes, particular clinical situations in a disease or syndrome, groups of phenomes, etiological subtypes, clinical subtypes and histopathological subtypes[14].

Other difficulties faced by RDR are: the "invisibility" of these types of conditions in conventional Health Information Systems (HIS), which rarely assign specific codes to some diseases[10], often leaving RD clustered in nonspecific codes[15,16,17,18]; and traceability of the recordable cases, due both to the need for unique identification of affected people, and the utilization of different disease classification systems in the different HIS that can provide new cases[19].

The aim of this article is to describe the implementation of the population-based Rare Diseases Registry of Navarre (RERNA) within the framework of the *Spanish Rare Disease Registries Research Network (Spain-RDR)*.

METHODOLOGY

The Spain-RDR working group considered the following methodological aspects for the design of the regional RDR: case definition, list and coding of RD, and Minimum Common Dataset. All these aspects, among others, are gathered in a manual of procedures developed in consensus within the Network.

Case definition. SpainRDR Network recognizes the definition of RD established by the EU, also used by the RD Strategy of the Spanish NHS: low prevalence disease (less than 5 cases per 10,000 inhabitants), which in turn is chronic, debilitating and life-threatening[1]. Therefore, anyone suffering from any of these so defined RD should be considered as a justified case to be registered.

List of Rare Diseases and codification. As mentioned in the introduction, it is extremely difficult to establish a closed list of RD. Furthermore, this list should be flexible and it must have the capacity to adapt over time in order to include the future recommendations related to new classification and codification systems made by international consortiums and also, from the World Health Organization's working group on RD.

The classification system of diseases initially worked with within the Spain-RDR Network to code RD was the International Classification of Diseases (ICD), both the clinical modification of its ninth edition (ICD9-CM) and the tenth edition (ICD10).

On the other hand, renal diagnoses related to RD of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the ICD10-BPA extension of the British Pediatric Association were also analyzed. In addition, the correlations of codes between the different classification systems mentioned, as well as with the ORPHA numbers (Orphanet's own codes), were studied.

Minimum Common Dataset. SpainRDR Network has designed a Minimum Common Dataset (MCD) harmonizing its elements with the RD Strategy of the Spanish NHS and adopting the standardized definitions of each variable of the HIS. The aim of SpainRDR is to achieve the implementation of the agreed MCD by every regional population-based RDR, including the registries of the patients affiliated to this network, giving the possibility to incorporate other complementary variables according to the specific objectives of each registry. The MCD collects information related to the socio-demographic data, clinical diagnosis and follow up of patients.

Legal coverage. Disease registries handle highly sensitive information that needs to be kept under proper custody. Information systems must be endorsed by relevant regulations and they also must meet the Organic Law 15/99, of December 13th, on Protection of Personal Data[20], be guaranteed by all the regulations regarding personal and health data processing[21,22,23,24,25] and, in addition, the corresponding files must be registered in the Spanish Agency of Data Protection.

RESULTS

Study population. RERNA gathers every case of people residing in the Spanish region of Navarre suffering from a RD of those included in the agreed list.

Case definition. It is considered that a subject will likely be included in RERNA when suffering from a disease whose prevalence is less than 5 cases per 10,000 inhabitants, and that he/she resides in Navarre, whatever age, sex, region or country of origin could be.

The exclusion criteria are:

– Death date registered before 01/01/2010.

– Cases diagnosed in Navarre and/or that are included in any database of Navarre, but that do not officially reside in Navarre.

– Lack of minimum information for the correct and unambiguous identification of the subject: National Document of Identification (ID) or Social Security number or Healthcare Card number (regional or national).

Every single diagnosis of RD suffered by any recordable subject is considered a "case".

List of rare diseases. When starting RERNA, the list of RD agreed in the second half of 2012 within SpainRDR was assumed; it included 934 codes of the 9th Revision of International Classification of Diseases, Clinical Modification (ICD9-CM) and 1,370 ICD10 codes. The full resulting list allowed exploring the chosen codes in several health databases.

Design of the structure of the registered information. On one side, RERNA gathers a group of variables related to personal and socio-demographic data of cases, and on the other side, it collects a group of variables specifically related to the rare disease. Regarding the RD, RERNA records: the name of the RD; observations related to that name (synonymous names), diagnosis date, detection date (if the diagnosis date is not available), diagnostic basis, information sources and several codes from different classification systems (Orphanet code; ICD-9-CM; ICD-10; ICD-10-BPA; ICD-O; SNOMED-CT; OMIM; EDTA codes; and others).

Legal Coverage. At the beginning of the project, there was no legal frame at national level to regulate the creation of population-based RDR, so the first step given in Navarre to create and implement the regional registry was the writing and publication of the corresponding regulations to provide the legal coverage needed by RERNA: the *"Foral Order 69/2013, of June 19th, of the regional minister of Health, by which the population-based Rare Diseases Registry of Navarre is created and regulated, and its corresponding personal data file"*, published in the Official Gazette of Navarre number 130, of July 9th, 2013[26].

Once the SpainRDR Network was finished, the Ministry of Health, Social Services and Equality, published in the Official State Gazette (BOE) number 307, on December 24th 2015, the "Royal Decree 1091/2015, on December 4th, by which the National Registry of Rare Diseases is created and regulated"[27]. According to this Royal Decree, each region registry -which are all coordinated by the MSSSI- holds the commitment to provide information on their validated cases to the ReeR.

Data sources identification. The population-based registries require a systematic and active search of cases. For this reason, one of the first activities that were proposed within the SpainRDR network was the study of the different sources of information that could bring cases to the regional RDR. Taking into consideration that first analysis, the following data sources were identified in Navarre[28]:

– Individual Health Card, for demographic data (IHC)[29].

– Assisted Morbidity Registry of Navarre (REMA) that collects the Minimum Basic Data Set (MBDS) at discharge from public and private hospitals[30].

– Congenital Anomalies and Hereditary Diseases Registry of Navarre (RACEHNA),

of the Medical Genetics Service of Navarre's Hospital[31].

– Early detection of inborn metabolic errors[32].

– Mortality statistics of Navarre[33].

– Navarre's Cancer Registry.

– Notifiable Diseases Registry.

– Electronic clinical records in Primary Care (ECRPC).

Navarre neither has an Orphan Drugs Registry nor an informative system of compassionate-use drugs but after this analysis, the incorporation of new sources that were already used by other regions was considered. These data sources are:

– Hospital drugstore and prescriptions (electronic prescription) registries.

– Chronic Renal Patients Registry of Navarre[34].

Moreover, during the implementation period of RERNA the importance of taking into consideration new cases that might be provided by other data sources is becoming evident, such as:

– Temporary Work Disability Registry of Navarre (RITA)[35,36].

– Assistance databases of the Hospital Care Services of Navarre.

Data collection and evaluation. Data is obtained from administrative databases of Navarre´s Health Service, patients' clinical records and from private health centres of Navarre.

The process by which data registered in RERNA is collected and evaluated includes the following phases: extraction of cases from the different data sources (depending on the correspondent codes and according to the list of diseases agreed by SpainRDR); elimination of duplicates; diagnosis validation and check-up of vital status.

Study of implementation of a computerized management system. An important part of the implementation of RERNA is related to the data management system that gathers the data and requires a high security level. For that purpose, a preliminary study to assess the software needs was performed. Among other tasks, the need of integration of several healthcare information systems of Navarre was defined in order to obtain data of RD, patients and cases, applying crossing and validation rules for dumping data to RERNA. Those rules specify how the information exchange between different sources is to be performed, the validation of demographic data and the detection of duplicate cases.

DISCUSSION

Thanks to the SpainRDR project, by which the Spanish Rare Diseases Registries Network was established, RERNA was implemented at the same time and following the same methodology than other regional population-based RDR in Spain[37]. Currently, RERNA is adapting to the ReeR's structure, which was created by the MSSSI at the end of 2015 and after Spain-RDR was concluded.

After the first review of data sources for RERNA, 8 out of 12 sources proposed by the different network nodes were identified[28]. Later, 2 data sources were included in that list and also, the prescriptions and the hospital drugstores databases were chosen as alternative sources to the orphan drugs and the compassionate-use drugs registries, which are used by other Spanish Regions. Moreover, in Navarre the Temporary Disability Registry,

a data source not identified by other nodes, is being exploited[36] and the possibility of incorporating the Spanish Disabled People Database, that has already been used by the Region of Murcia, is being evaluated[38].

Other data sources proposed by the Network but, that were not identified by any of the Spanish Regions, were the databases of patients associations. In Navarre we are starting to work accordingly: we have proceeded contacting some regional associations in order to standardize the necessary data for this purpose, as well as preparing the drafting of the informed consent forms for the affected people, which are essential for associations to provide the information to RERNA.

There are many RDR worldwide, but only a few of them are population-based and the majority of them are specific for one RD or for a concrete group of diseases[39]. Veneto Region's RDR (Italy) deserves to be highlighted; it was created in 2000[19], and it was the only regional registry established in Italy before the publication of the Ministerial Decree of 2001 by which the Italian Rare Diseases National Registry (Registro Nazionale Malattie Rare) was established. This national registry achieved total coverage of Italian territory in 2011[40].

Among European registries, the Italian strategy is the closest one to the strategy used by the Spanish RDR, although the methodology differs significantly between them[41]. In both cases, registries of the different regions of the country nourish the national registry. In the case of Italy, it was national legislation that prompted the gradual creation of regional registries whereas in Spain all the regional registries started almost at the same time, prompted by the SpainRDR project, even though they did not have national legislation at the beginning and each region has had to create their own.

In addition, both the Italian and Spanish strategies raise the importance of compiling information from multiple data sources, while acknowledging that not all regional registries manage to achieve this objective. In the specific case of Navarre, besides adding new data sources to RERNA, extending the study period as long as possible in order to detect the highest number of prevalent cases, and thus improve the sensibility of RERNA, has also been observed as a very important aspect.

In Europe, there is another registry of national scope that collects information on RD in general (and not of specific diseases or groups of diseases) and which its implementation methodology was completely different: the French national registry for RD, known as CEMARA (CEntres MAladies RAres). This registry is based on a solid network of 131 centres with experience that electronically collect their patients with RD. This network was established thanks to the first French national plan for RD (2005-2008), although currently the registered patients come from 62 of those centres[41,42,43]. Something similar could be achieved in Spain if a certain system was established: one for Centres, Services and Reference Units (CSUR) that treat patients affected by RD, and that could register the cases they diagnose or the ones they monitor.

STRENGTHS AND LIMITATIONS

This paper aims to show the methodology used by the Spain-RDR project for the implementation of a Spanish population-based RDR. One of the great strengths of this project is, on one hand, that it has managed to create, almost in a simultaneous way, registries in every Spanish Region, agreeing on a common methodology; and, on the other hand, it has facilitated the standardization and inclusion in the network of some more specific registries.

Thus, SpainRDR Network gathered and coordinated the information of the national patients registry, that of regional population-based registries, and that of more specific registries of different territorial areas that were implemented by medical societies, scientific researchers, patients associations, pharmaceutical industry, etc. The methodology described is highly innovative because it combines two strategies: patient registries (mainly focused on research) and population-based registries (focused on epidemiological aspects and socio-sanitary management). In this way, it gives a significant added value to other previously developed proposals such as the Italian and French models, which are mainly focused on clinical aspects. Moreover, the list of RD proposed to be followed is the most ambitious one until now, even though it is not as exhaustive and specific as the Orphanet directory.

Among this project's limitations could be its traceability, both for treated patients in different health centers and for used codes in the different HIS, so to avoid duplicate cases. Furthermore, the availability to access the identified information sources in which possible cases can be detected is not the same in all regions, neither in number of sources nor concerning data collecting phases. And all of which substantially limits the comparability. Patients' traceability is not a limitation in Navarre because for a long time the clinical record number has been unified in all the public healthcare network, in addition 97% of the resident population has the IHC available with a Personal Identification Code of Navarre and another Personal Identification Code of the Navarre Healthcare Service (CIP-SNS), which is assigned a few days after birth. They all collect both the MBDS and other HIS, which are RERNA sources.

Additionally, trying to estimate the prevalence of RD only using administrative databases can generate incorrect indicators because the information that is gathered can be biased: some nonspecific codes, coding errors, discarded diagnosis or the fragmentary population coverage that the source might present, among many other reasons[44,45].

In order to try to alleviate these limitations: on one side, it would be necessary to extend the period of data collection and the sources for case identification as much as possible to avoid an underestimation of the figures; and, on the other side, it is important to validate the information of the identified cases not to overestimate them, because the lack of specificity of the diseases classifications used by Spanish HIS[5] and the possible mistakes when coding diseases make it possible to find redundant and false-positive cases[46,47]. These issues are being addressed and the work has already begun in order to improve the quality of RERNA: data is being included prospectively and retrospectively (the current period under study is 2000-2017), the data sources that nourish the registry have been expanded[18,36] and continuous validation studies of the identified cases, by groups of diseases, are being performed; they are being held in two different ways[48,49,50,51,52]:

1) Crossing the patients identified in RERNA with those collected by other specific registries that collect only validated cases.

2) Reviewing the clinical diagnosis of the implicated patients, in collaboration with the correspondent specialized health care services.

These jobs are very important for RERNA to be able to give specific information and valid indicators, and are in line with the guidelines currently set by the ReeR[27]. Besides, validation studies allow determining sensibility and positive predictive value of the different data sources for each checked code[53].

In this sense, an important advantage of RERNA regarding other regional RDR is that Navarre has 2 specific registries, that are not implanted at national level and that also have a long track record in their field: the Navarre's Cancer Registry, a valuable tool for collecting rare tumours[54]; and the Congenital Anomalies and Hereditary Diseases Registry of Navarre, that includes genetic syndromes diagnosed during childhood, almost all of them with low prevalence and, thus, "rare"[18,31]. However, the early detection program of congenital metabolic disorders, which is already implanted at national level but, in a heterogeneous way, identifies in Navarre cases of the 7 endocrine-metabolic diseases agreed in 2014 for the whole country[55,56], although until 2016 only phenylketonuria and congenital hypothyroidism were screened[32]; while in other Spanish Regions their Newborn Screening Programs include even more than twenty congenital errors of metabolism, all of them included in the group of the RD[57,58,59].

CONCLUSIONS

Population-based registries of RD are fundamental to study and quantify these types of diseases since the classification and coding systems used in the current health information systems are very nonspecific. The analysis and data crossing among several information sources is paramount to maximize the ability to detect cases (sensibility). Given the low prevalence of these diseases, a high rate of false positives among the identified cases greatly affects the estimate of epidemiological indicators.

The confirmation of specialists (both in regional hospitals and CSUR) and the availability of other RD specific registries, hospital or population-based, enable the validation of the cases revealed through massive quests in the HIS, since the rest of the cases will have to be revised one at a time for their future integration in the RDR.

The code and specific descriptors for RD implemented in the HIS, as well as training the involved professionals in coding, would all help to improve the existing HIS's specificity and sensibility, as identification sources of RD cases.

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