results of this analysis. Discarded Type 1 records, which represent true duplicates, were 1 908, corresponding to 1.7% of the total valid records. Therefore the cleaned database was made of 110,841 records.

The quality of the data collected by the RNMR has been assessed with respect to completeness and consistency of procedures. Table III summarizes the results of this control for each variable of the common data set. While completeness analysis was based on the observation of the database records, the assessment of consistency of procedures summarizes the discrepancies emerged during the preparation of the first RNMR report. The variables characterizing case and diagnosis showed a very limited number of missing values and a remarkable improvement could be observed, during time, in the completeness of recording of the centre making diagnosis. It is often the case with registries, that the date of death of patients is not collected systematically and timely by registry data providers. Although some records reported live cases with unrealistic age, there was no criterion that the RNMR could use to spot all records that did not update this information regularly.

The date of disease onset is largely and persistently incomplete. An analysis of the records showed that missing data were mostly associated with some RRs. Indeed, while it is difficult to define the date of the symptoms onset in the case of patients affected by a rare diseases since a long time, or when the first signs or symptoms of a rare diseases are unspecific, some RRs do not collect this data. The completeness of data regarding the use of orphan drugs was assessed as follows. At first, the diseases were identified, for which an indication of use of orphan drugs was given; then, making reference to all the records of each of the diseases so identified, the fraction of records with missing values was calculated. This analysis indicated that, in the whole database, treatments were indicated for 56 conditions and that incomplete records (i.e. records which do not show the indication of a drug nor the explicit indication of no drug use) represented 14.9%. The lack of this data showed a marked decrease with time, indicating the steady improvement in its collection. Table 3 also summarizes the observations regarding the accuracy of the minimum set of data collected by RNMR.

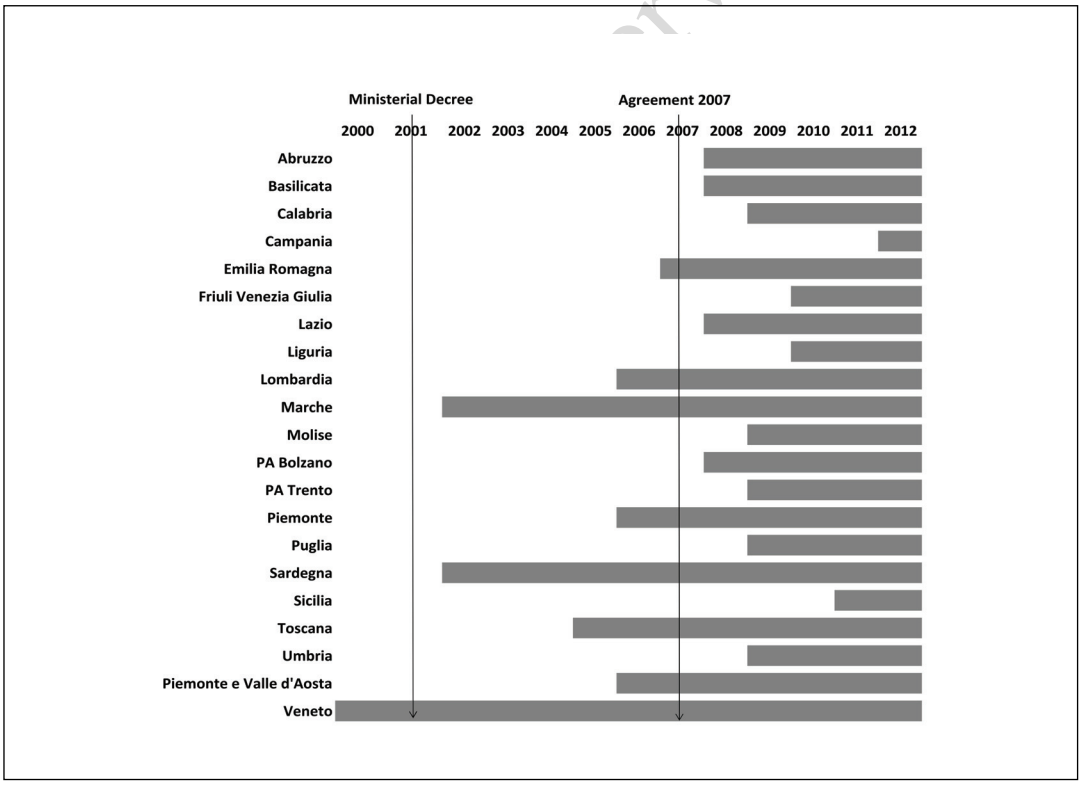

Figure 1 - Establishment of regional RD registries in Italy.
The year indicated refers to the year of institution of the registry.

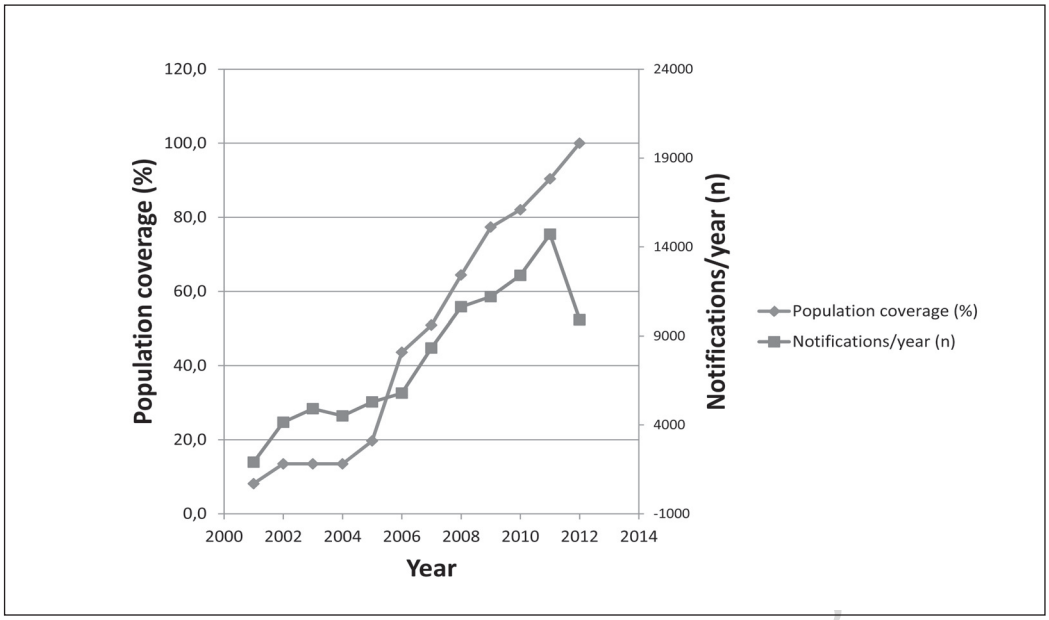

Figure 2 - Nominal population coverage of the RNMR and notification flow.
The year indicated refers to the institution of the regional registry. Notifications reported for the year 2012 refer to the first half of the year.

Table III - Completeness and accuracy of the common dataset.

Common data set	Completeness (% missing)[a]			Accuracy
	Whole database (110,841 records)	Calendar years 2010-2011 (27,114 records)	Calendar year 2012 (6 months) (9,913 records)	
Gender	0.0	0.0	0.0	Data is collected consistently among data sources according to usual identification procedures
Date of birth	0.0	0.0	0.0	Data is collected consistently among data sources according to usual identification procedures
Region of residence	0.1	0.1	0.0	Data is collected consistently among data sources according to usual identification procedures
Diagnosis	0.0	0.0	0.0	Diagnoses are controlled and validated by the RRsb and their accuracy rely on the selection criteria for the centres to become FDC of the RD network
Date of diagnosis	1.0	--	--	Inconsistencies among regions on the identification of the relevant diagnostic event and diagnostic centre.
Centre of RD diagnosis	11.9	1.2	0.4	Inconsistencies among regions on the identification of the relevant diagnostic event and diagnostic centre. A centre may change name following reorganisation.
Vital status	ND	ND	ND [c]	Uncertainties in this variable depend on the fact that the data sources of RRs[b] may not be fully aware of the reason why patients are lost to follow up. In the future, date of decease will be collected from death registries: this will result in a systematic and precise, although delayed, appraisal of this condition.
Date of decease	ND	ND	ND	Expectedly good (when reported). In the future, date of decease will be collected from death registries: this will result in a systematic and precise, although delayed, appraisal of this condition.
Date of disease onset	46.4	57.1	81.4	Uncertainties in this variable depend on i) lack of patient's recollection; ii) gradual appearance of unspecific symptoms over a long period. Symptoms could also not set on due to effective treatment following early diagnosis (e.g. following neonatal screening)
Orphan drug used	14.9	10.7	4.6	The name of the active substance is communicated, but no standard catalogue or coding is used.

[a] Data completeness is measured as the proportion (%) of records without the indication of the value of the variable; calendar years refer to the date of diagnosis; [b] Regional registry; [c] ND = not determined

Preliminary results after the start of activity with full nominal coverage of the national territory

Altogether, the valid records which are stored at present into RNMR are 110.841. This number corresponds to the overall diagnoses communicated to RNMR up to 30 June 2012 by RRs which have started their collection at different dates between 2000 and the end of 2011. The records referred to diagnoses made in the first 6 months of 2012, with RRs covering all the national territory, were 9,913. Although these features prevent, at present, any sound epidemiological estimate of rare diseases in Italy, some observations on the composition of the rare diseases notifications communicated to RNMR, may be of interest. Table IV shows the distribution, across the ICD 9-CM Chapters, of the diagnoses notified to the RNMR. The RDs under this surveillance system include conditions named individually and with group denominations. Altogether, the records reported at least one case of 485 conditions. All groups and subgroups mentioned in the MD were represented, making up 58,942 records, including 7,328 records of 137 pathologies mentioned as examples. Besides these, 296 individual RDs were represented with 51,899 records. Of these records, about 50% were made up by 15 most frequent diseases: achalasia, amyotrophic lateral sclerosis, behçet disease, bullous pemphigoid, chronic inflammatory demyelinating polyneuropathy, down syndrome, hereditary hemorrhagic telangiectasia, idiopathic central precocious puberty, keratoconus, Klinefelter syndrome, Lambert-Eaton syndrome, Marfan syndrome, mixed cryoglobulinemia, pemphigus, Turner syndrome. Twenty-nine diseases were represented with one record only.

Table IV - Distribution, across the ICD 9-CM Chapters, of diseases notified to RNMR up to 30 June 2012.

	ICD 9-CM Chapters	Percent records
1.	Infectious and parasitic diseases	0.1
2.	Neoplasms	5.0
3.	Endocrine, nutritional, and metabolic diseases, and immunity disorders	17.4
4.	Diseases of the blood and blood-forming organs	16.6
6.	Diseases of the central nervous system and sense organs	26.0
7.	Diseases of the circulatory system	4.3
9.	Diseases of the digestive system	1.3
10.	Diseases of the genitourinary system	0.6
12.	Diseases of the skin and subcutaneous tissue	3.3
13.	Diseases of the musculoskeletal system and connective tissue	5.5
14.	Congenital anomalies	19.7
15.	Certain conditions originating in the perinatal period	0.1
16.	Symptoms, signs, and ill-defined conditions	0.0
	Total	100

Discussion

The European Commission Communication: "Rare diseases: Europe's challenge"[2] and the subsequent Council Recommendation[7] emphasize the strategic importance of Patient Registries in the field of RD.

The national network of Centres, identified at regional and interregional level, and of Regional/Interregional Registries dedicated to RD, was successfully implemented in Italy following the MD and the agreements between the Government and the Italian regions. To date, the Italian RNMR is a surveillance system, with the the main objective of producing epidemiologic evidence on RD in Italy, and of supporting policy making and HS planning. This role of the RNMR has been confirmed by the draft National Plan on RD, recently proposed for public consultation by the Ministry of Health[13]. Considering the complexity of building such registries in a devolved system of responsibility for healthcare delivery, substantial efforts were necessary in various steps of RNMR development, especially at regional level where the supporting infrastructures had to be established.

The strong legal base, its integration in the public health service and its connection with the dedicated national RD patient protection policy ensures the registry stability, comprehensiveness and population coverage. However, the need to cope with different levels of local resources, the slow responsiveness and limited flexibility typical of institutional processes as well as the need to rely on quality and comparable data made the implementation of the RNMR a slow and stepwise process, which is far from being concluded. The common data set agreed among the central and regional health authorities, is indeed the result of a selection of data, the collection of which could be sustainable, made comparable and be used to provide information coherent with the national scope of the RNMR, as distinct from the regional level responsibilities.

During the gradual establishment of the Regional RD registries, which achieved nominal completion during 2011, a steadily increasing flow of data on RD patients was established from the RRs to the RNMR. Moreover, we could observe also a continuously increasing involvement of the operators of the RD registry system. To achieve this result, an important role was played by the dedicated training courses in the regions which do not have a proprietary Rare Diseases Registry, conducted in a systematic way by the experts of the RNMR.

The preparation of the first Report on the RNMR activity[9], in collaboration with the RRs, turned to be a powerful tool to review the operation of this complex system and to highlight the need for a number of critical improvements. The collection of the vital status and death date should be undertaken systematically. To this aim, the

RNMR is seeking access to the national database of death records. Moreover, the inconsistencies in the collection of the disease onset date and the adoption of improved definitions of the diagnostic event relevant to determine the date of diagnosis and the centre making diagnosis are being discussed. Finally a more accurate list of active substances is to be adopted. The procedures used to validate records and to control data completeness also should be better distributed between the RNMR and the RRs to make the data flow a smooth process.

The actual coverage of the population depends on the quality and functions of the information systems developed at regional or interregional level. The different lengths of periods of operation of the RRs (ranging from about 1 to more than 10 years) result in different effectiveness of the registration process and only some regions collect data on RD patients using multiple data sources. Therefore, with the progressive improvement of RRs operations, the heterogeneity of the case reporting completeness will become less and less relevant. However, this issue has to be assessed and addressed appropriately.

At present, therefore, the data currently stored in the RNMR represents the baseline for a continuous improvement of the national and RRs and to start a validation process through the comparison of the RNMR results with studies in other population groups. For an overall improvement of the Italian RD surveillance system, CNMR is promoting collaborations with National statistical services, clinicians, patient associations and other data sources. Moreover, additional opportunities for improvement will come from the participation of CNMR and other experts of the Italian RD network in other European and global initiatives, such as the European Platform for rare disease registries (EPIRARE: www.epirare.eu), the International Rare Disease Research Consortium, (IRDiRC: www.irdirc.org) and the Integrated Platform connecting databases, registries, biobanks and clinical bioinformatics for Rare Disease research (RD-Connect:www.rd-connect.eu.

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