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Let's not Miss the Opportunity to Improve Rare Disease Reporting Through ICD-11 Implementation

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Abstract
The identification of rare diseases in health data is crucial for their epidemiological definition. Beyond the existing terminology system ORPHAcodes, we describe the possibilities of the 11th revision of the International Classification of Diseases. We analyzed the linkages of ORPHAcodes to ICD-11 items with only 376 items lacking unique representation in ICD-11. ICD-11 can be used to identify most rare diseases in administrative data.

Keywords: Rare diseases; Classification; Terminology; Administrative data

Introduction

Rare diseases (RD) are defined differently in different parts of the world, but the basic parameter for defining rarity is most often the epidemiological characteristic of prevalence. In order to determine prevalence RD have to be identified in the collected data.

In Europe, the definition of a rare disease is "one affecting fewer than 5 out of 10,000 members of the general population", while it must be a serious, chronic and often life-threatening condition [1-4].

An important information resource in the field of rare diseases is Orphanet, a multilingual information portal on rare diseases and orphan drugs [5].

Rare disorders defined in Orphanet nomenclature (ORPHAcodes) are cross-referenced with other international terminologies, classifications, and reference databases (including OMIM, ICD-10, ICD-11, SNOMED-CT, MedDRA, UMLS, MeSH, and GARD), in order to enable interoperability between different clinical information systems [6].

The content of Orphanet is published and regularly updated on Orphanet portal, where a full-text search system and an interactive presentation of rare disease classification hierarchies are available. Its full content can be downloaded at Orphadata as the Orphanet Nomenclature Pack, available in nine languages including Czech.

Based on Orphanet database and knowledge resources several projects expanding the original work took place in recent years: 1) Joint European project RD-ACTION in 2014-2020 with the main objectives to support the development and sustainability of the Orphanet database and ensure an appropriate codification of RD in health information systems, 2) European project RD-CODE in 2019-2021 with objectives to develop rules and structured

documentation for ORPHAcoding needs and pilot implementations in target European countries (Czech Republic, Malta, Romania, Spain, Italy/Veneto Region), 3) European projects OD4RD and OD4RD2 in 2022-2025 with main objective to contribute to the generation of standardized, interoperable data on RD diagnosis, through maintenance of the Orphanet nomenclature of RD.

Materials and Methods

In addition to specific rare disease data collections, rare disease cases can also be found in existing administrative data sources.

Administrative health data refers to the information that is collected within the health-care system for reasons other than clinical care. It may include claims for reimbursement, records of health services provided, medical procedures carried out, prescribed medication and information about conditions for which the health care service was provided.

Different coding systems are used in particular administrative databases to identify disease or health condition. Examples of existing coding systems with the ability to capture rare diseases are: ICD-10 (International Classification of Diseases, 10th Revision) and derived modifications [Classification and coding system supplemented by a terminology layer], ICD-11 (International Classification of Diseases, 11th Revision) [Classification, terminology and coding system], MedDRA (Medical Dictionary for Regulatory Activities)[Medical terminology dictionary], MeSH (Medical Subject Headings) [Controlled vocabulary for literature indexing], OMIM (Online Mendelian Inheritance in Men) [Catalogue of human genes and phenotypes], ORPHAcodes [Terminology and coding system], SNOMED CT (Systemized Nomenclature of Medicine, Clinical Terms) [Terminology and ontology].

However, the main classification/coding system used in general administrative data collections for the purpose of standardized Health status information is the ICD-10. In some countries the ICD-10 or modified ICD-10 coding schemes are enriched by specialised clinical terminologies. A good example is Alpha-ID system in Germany. The Alpha-ID is a sequential and stable identification number, which is allocated to each entry in the alphabetical index of ICD-10.

11th revision of ICD is the result of an unprecedented collaboration with clinicians, statisticians, coders, classification and IT experts from around the world, to ensure interoperability and comparability of digital health data. ICD-11 provides access to 17,000 diagnostic categories, with over 100,000 medical diagnostic index terms [7]. World Health Assembly adopted ICD-11 in May 2019, and it came into effect on 1st January 2022 [8].

ICD-11 includes detailed and frequently used information and combinations. However, it is not restricted to these coumpounds; an infinite number of meaningful code combinations can be created. All entities in the ICD-11 are rendered in the Foundation, which is an acyclic graph (meaning no entity can ever be its own descendant as or parent) of all entities and their relationship trees. Unlike in previous revisions ICDs, the Foundation may have multiple inheritances, where a single term may have one or more, sometimes many more, parents [9].

As a part of the ICD revision, collaboration with Orphanet resulted in including all rare disease terminology in the terminology layer of ICD-11. The ongoing WHO - Orphanet collaboration was set to enable regular updates of rare diseases content in the ICD-11 [10].

There are several possibilities of identification RD in ICD-11.

Diseases or health conditions that are more common, where greater public health importance requires statistical outputs, have their own ICD-11 for Mortality and Morbidity Statistics (MMS) code (e.g. CA25.0 Classical cystic fibrosis).

All rare diseases, although it may not have its own MMS code, can be identified in the ICD-11 terminology layer, referred to as it's Foundation with a Uniform Resource Identifier (URI) assigned to each entity and are therefore identifiable in the data. The highly detailed identification allows subsequent aggregation into general categories for statistical outputs.

A rare condition can also be captured by combining multiple ICD-11 codes or URIs. A disease that does not individually meet the prevalence criteria for rarity can be classified as a rare disease when additional case-specific

information is captured via code combination. For example, an uncommon cancer can be considered rare when detailed information about its localization, histopathology, or other specific clinical parameters is provided.

ORPHAcodes are updated continuously in the database, while the official release of Orphanet Nomeclature Pack in July is valid for following year. ICD-11 releases are published in February valid for following year. The publication of each system releases differ which can be one of the reasons for the difference RD listing in ICD-11. An ongoing effort is underway to facilitate the timely updating cycles with Orphanet.

ICD-11 offers multilingual web-based digital tools for conversion of text based clinical information into coded health data [9].

Results

ICD-11 includes nearly 5,500 rare diseases and their synonyms in the Foundation and aggregated under the same nonspecific ICD-11 code [11].

Based on the Orphanet Terminology Pack, we analyzed the number of ORPHAcodes rare disease terminology concepts (version available for download from 1 July 2023) in relation to ICD-11 (release 2024-01).

The ORPHAcodes system contains a total of 11,136 concepts in the current Nomenclature pack. Of these, 1,230 have the property 'OBSOLETE' or 'NON RARE IN EUROPE', these concepts should not be used for active coding of rare diseases in Europe. A further 3,308 have the level 'group of disorders' or 'subtype of disorder' in ORPHAcodes (see in Table 1).

Table 1. Distribution of 9,906 active ORPHAcodes terminology concepts by level of detail

Level of detail	**Number of items**
Disorders	6,598
Groups of disorders	2,264
Subtypes of disorders	1,044
Total	**9,906**

Table 2 shows further breakdown of the 6,598 rare diseases identified by the ORPHAcode mapped to ICD-11 MMS categories.

Table 2. ORPHAcodes terminology concepts mapped to ICD-11 MMS according to the type of linkage

BTNT (ORPHAcode is broader than the targeted code used to represent it)	225
E (Exact mapping: the two concepts are equivalent)	1,367
NTBT (ORPHAcode is narrower than the targeted code used to represent it)	3,618
Total aligned rare diseases	**5,210**

In 376 cases is the rare disease defined in ORPHAcodes not separately identifiable using ICD-11.

A closer breakdown of the 3,618 ORPHAcodes terminology concepts that are classifiable in the ICD-11 MMS but do not have their own unique identification in it shows that in most cases the ICD-11 Foundation terminology layer provides the unique identification (3,242 cases).

Conclusions

Compared to ICD-10, ICD-11 identifies almost all rare disease entities. Rare disease reporting through ICD-11 can standardize rare disease data (in terms of quality and completeness) and enable linkage to comprehensive clinical information on episodes of care, comorbidities, and other health status factors (signs, symptoms, phenotype, ICD-11 terminology features, such as extension codes). By achieving standardization, it can improve diagnosis, treatment, and quality of life of patients with rare diseases.

List of Abbreviations: Not applicable.

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