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Standardizing Representation of Medication in LMICs: Case of Malawi and RxNORM

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Abstract. Background: Sharing medication data between different health systems is essential for continuity of care. To provide common and consistent representation of medication data across disparate health systems, the National Library of Medicine (NLM) developed RxNORM; a normalized naming system for generic and branded drugs that facilitates semantic interoperation between different drug terminologies. RxNORM has become the standard vocabulary for representing medicines in the United States.
Objective: To assess the extent to which RxNORM concepts can be used to accurately represent essential medicine from a setting outside the United States.
Methods: To assess the coverage of RxNORM for medicine outside the United States, we used the 2015 Malawi Essential Medicines (MEML-2015) list as a test case. Terms from the list were transcribed electronically for easy processing and matched to RxNORM concepts using exact and partial matching algorithms. Results from the electronic matching were manually verified for correctness. All terms that could not be matched using the algorithms were manually searched for in RxNORM to ensure accurate classification as a term without a corresponding RxNORM concept.
Results: Of the 603 unique MEML-2015 medicines, 63% could be accurately represented by active RxNORM concepts. Anti-infectives were the class of medicines with the most unmatched medicines. Four other classes of medicine had complete coverage by RxNORM concepts.
Conclusion: A significant number of essential medicines could not be accurately represented using RxNORM concepts. A framework for adding such medicine as RxNORM concepts while maintaining continuous integration with periodical RxNORM updates is needed.

Keywords: RxNORM, Semantic interoperability, low-resource settings.

1 Introduction

Since the early 2000's, there has been an unprecedented increase in the use of electronic medical record (EMR) systems. By 2014, 75% of American hospitals had adopted a basic EMR in comparison to only 15% in 2010 [1]. This increase in EMR adoption has among other things highlighted the difficulties in sharing medical information electronically between different systems due to various reasons such as different representations of information [2]. Different systems encode information in different ways leading to ambiguity in meaning and interpretation. This introduces a significant barrier to the exchange and aggregation of data from various systems for continuity of patient care, planning, quality improvement and research.

To reduce the ambiguity in the meaning and interpretation of medical information, lists of terms have been explicitly enumerated where each term has an unambiguous and non-redundant definition [3]. A list of terms that has been enumerated in this manner is called a controlled vocabulary. Often, vocabularies

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contain terms from a single domain. An example of this is the Logical Observation Identifiers Names and Codes (LOINC) vocabulary which contains names of various laboratory tests. Each laboratory test in LOINC has a unique identifier which when used consistently describes the same test, thereby ensuring the same interpretation and meaning.

When a vocabulary has been widely accepted and adopted for encoding information in a domain, it is called a standard vocabulary for that specific use case. For example, LOINC is a standard vocabulary for encoding laboratory test orders. The Systematized Nomenclature of Medicine, Clinical Terms (SNOMED CT) is another standard vocabulary that is widely used for encoding diseases, symptoms, signs, specimen types, procedures and other things. To provide common and consistent representation of medication data across disparate health systems in the United States, the National Library of Medicine (NLM) developed RxNORM; a normalized naming system for generic and branded drugs that facilitates semantic interoperation between different drug terminologies [4]. The ability to map drugs across various drug terminologies and the accompanying meaningful use regulations have made RxNORM a standard for drug knowledge representation in the United States [5].

Various studies have been conducted to assess the coverage of RxNORM for medicine used in the United States ambulatory setting. One such study showed that at least 97% of electronic prescriptions could be accurately represented by an RxNORM identifier [6]. A similar study by O'Neil and Bell found that RxNORM provides concepts covering almost all ambulatory e-prescriptions [7]. However, these studies were conducted in the United States health setting. Little is known about how well RxNORM covers drugs used outside this setting.

RxNORM was developed by the NLM primarily for use in the United States. Therefore, while RxNORM has a large collection of drug products, its focus on the United States market could limit its coverage of products that are either not approved for use in the United States or are infrequently used in the United States. In addition, prevalence rates of diseases vary from country to country affecting the level of demand for certain medicines. Due to varying levels of demand, some countries will have a wide variety of drugs to treat some conditions while others will have fewer options. This is a result of both the demand for those drugs and the number of pharmaceutical companies operating in those countries or regions. Therefore, it is reasonable to expect that some drugs will not be present in RxNORM.

Furthermore, a drug can be produced by one or more manufacturers usually with different brand names and packaging. Since not all pharmaceutical companies operate at a global scale, it is highly likely that drug names used in various regions of the world will be different and that common and well-known brand names in one part of the world would be unavailable and unknown in other parts. Therefore, differences in drug formulary are to be expected across various regions and countries.

Lastly, before any drug can be used in the United States, the Food and Drug administration (FDA) must first approve it [8]. The same is true in most countries and being approved in one country does not guarantee that the same will happen in other countries. The ramifications of this is that different countries may have different list of medicines approved for use. With these factors in mind, any use of RxNORM in health settings outside of the United States must first assess the extent to which RxNORM meets their use case and consider how best they can handle any potential deficiencies.

This research measures the extent to which RxNORM covers drug formulary used in a health setting outside the United States namely, Malawi and proposes a framework for closing the gap where some drug formulary cannot be coded with the standard RxNORM vocabulary.

2 Methods

2.1 Materials

Drugs that are used to treat the most common and prevalent health conditions in an area are called essential medicine [9]. Essential medicines are often the most frequently used and address most of the health needs in an area. The World Health Organization (WHO) encourages countries to have a fixed, periodically reviewed list of these drugs and to ensure that there is a steady supply of drugs on this list. As such, an essential medicines list is a perfect yardstick for measuring coverage of a drug vocabulary for a given setting or use case. We therefore chose the Malawi Essential Medicines List (MEML) as our test case for assessing the coverage of RxNORM for a low-resource health setting outside the United States.

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We used the 2015 release of the MEML, henceforth referred to as MEML-2015, to conduct the initial coverage assessment of RxNORM [10]. The MEML-2015 has 696 drugs classified into 31 categories based on the ailments that they are used to treat. Some drugs are used to treat multiple ailments and are repeated between and within ailment categories. We removed these duplicate MEML-2015 drug entries to ensure accuracy in measuring the coverage of RxNORM. All drugs were listed using their generic names which prescribers from both public and private hospitals are encouraged to use [10].

The initial coverage assessment was conducted using the October 2017 release of RxNORM. We used the full release version of RxNORM to ensure that we did not miss any RxNORM concepts that had been deprecated due to discontinued use in the United States health setting.

2.2 Data pre-processing

All the drugs from the publicly available MEML-2015 PDF document were transcribed into an easily manipulatable form. During this process, fractional dose strengths were simplified to their lowest forms. For example, Promethazine HCL 5mg/5ml elixir and Azithromycin 200mg/5ml suspension were simplified to Promethazine HCL 1mg/ml elixir and Azithromycin 40mg/ml suspension respectively. We did not however change the dose strength unit for each of the drugs.

Furthermore, we matched the dose forms for the MEML-2015 drugs to those specified in the RxNORM documentation [11]. For example, implant was changed to drug implant and eye ointment to ophthalmic ointment. This was done to comply with pre-defined RxNORM dose forms. All syrups and elixirs were also changed to oral solution as stipulated in the RxNORM documentation [12].

2.3 Granularity of Terms Matching

To calculate the coverage of the MEML-2015 list by RxNORM, we matched terms from the MEML-2015 to concepts in RxNORM. RxNORM lists drugs at various levels of granularity. A fully specified drug has the active ingredients, dose strength and dose form which includes the route of administration [13]. For example, 50 milligrams of Ibuprofen in its fully specified form is listed as a concept with the name “Ibuprofen 50 MG Oral Tablet”. Specific brand names can also be added to RxNORM concepts if they exist. This introduces variation in the way the drug is represented such that the same 50 milligrams of Ibuprofen drug can be linked to more than one concept name as follows: “Advil 50 MG Oral Tablet”, “Ibuprofen 50 MG Oral Tablet”, “Ibuprofen 50 MG Oral Tablet [Advil]”. This poses a problem for matching using names as it is not always the case that all these different names are listed in RxNORM.

In this study, we considered a MEML-2015 drug to have matched an RxNORM concept if they had the same active ingredient, dose strength and dose form. For example, if both RxNORM and MEML-2015 had an entry for Acyclovir 200mg tablet, it was counted as a match. However, if MEML-2015 had Acyclovir 200mg tablet and RxNORM had Acyclovir 200mg capsule, it was counted as a mismatch because of the different dose form. The same criteria also applied to dose strength such that “Ibuprofen 50 MG Tablet” was not considered equivalent to “Ibuprofen 25 MG Tablet” even though 2 tablets of 25 MG Ibuprofen theoretically are equivalent to 50 MG Ibuprofen. This was done to ensure that individual products can be accurately represented.

Our matching criteria was not stringent on the route of administration because the MEML-2015 did not always explicitly specify the route of administration especially for oral products. We therefore made exceptions for dose forms such as tablets, capsules, suspensions and solutions that were not listed with an explicit route of administration by considering oral products with similar active ingredients, dose strengths and dose forms as matches. However, in the cases where the MEML-2015 made explicit mention of the route of administration, the same constraint was placed on the matching such that “Hydrocortisone 1% topical ointment” in MEML-2015 and “Hydrocortisone 1% ointment” in RxNORM were treated as a mismatch. Furthermore, for suspensions and solutions that were clearly labelled as injections, we did not consider oral products with similar active ingredients, dose strengths and dose forms as matches.

All MEML-2015 terms were first matched electronically and then verified manually. The manual verification process ensured that all terms were correctly matched. All false matches between MEML-2015 terms and RxNORM concepts were corrected. Furthermore, MEML-2015 terms that were unmatched were manually searched in RxNORM to ensure that they had no corresponding RxNORM

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concept that could accurately represent the term. Once the matching and verification was complete, we calculated the coverage of RxNORM for the MEML-2015 by getting the proportion of MEML-2015 terms that were matched with RxNORM.

3 Results

The MEML-2015 has 603 unique drug entries. Out of these, 380 drugs were matched to current concepts in RxNORM representing a coverage percentage of 63%. A further 29 drugs matched with RxNORM concepts that have been retired and are no longer recommended for use. The remaining 194 drugs could not be matched to pre-existing concepts in RxNORM. The drugs that could not be matched to RxNORM concepts came from 27 MEML-2015 categories. Of these categories with unmatched terms, Anti-infective medicines (43) had the highest count of unmatched drugs followed by dermatological medicines (24). Four MEML-2015 categories namely: Anti-migraine medicines, diuretics, peritoneal dialysis solutions, and medicines for arthritis had all their drugs matched with a concept in RxNORM. The complete breakdown of the counts of matched and unmatched drugs per MEML-2015 categories is provided in Table 1.

Table 1. A summary of the categories of the Malawi Essential Medicines List and the RxNORM concepts that matched to drugs in each category. Some drugs are repeated between and within categories.

Category	Matched	Obsolete	Unmatched	Total
Anaesthetics	26	1	15	42
Medicines for Pain and Palliative Care	29	3	4	36
Antiallergics and medicines used in Anaphylaxis	7	0	3	10
Antidotes and other medicines used in poisonings	8	0	2	10
Anticonvulsants/Antiepileptics	8	0	2	10
An-ti-infective medicines	87	6	43	136
Anti--migraine medicines	6	0	0	6
Antineoplastic and immunosuppressant medicines	28	1	6	35
Antiparkinsonism medicines	2	1	2	5
Medicines affecting the blood	9	1	4	14
Blood products and plasma substitutes	6	0	6	12
Cardiovascular medicines	37	0	10	47
Dermatological medicines (Topical)	16	1	24	41
Diagnostic agents	9	0	15	24
Disinfectants and Antiseptics	1	0	3	4
Diuretics	6	0	0	6
Gastrointestinal medicines	15	2	7	24

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Hormones, other endocrine medicines and Contraceptives	20	3	8	31
Immunologicals	1	1	15	17
Muscle relaxants (peripherally acting) and cholinesterase inhibitors	4	0	1	5
Ophthalmological preparations	33	2	9	44
Obstetric medicines	12	0	4	16
Peritoneal dialysis solutions	0	2	0	2
Medicines for mental and behavioural disorders	28	1	4	33
Medicines acting on the Respiratory Tract	3	0	7	10
Solutions correcting water electrolytes and acid--based disturbances	8	0	5	13
Vitamins and minerals	10	3	2	15
Ear, Nose and throat medicines in Children	14	0	5	19
Specific Medicines for Neonatal Care	1	1	1	3
Medicines for Arthritis	2	0	0	2
Medicines used to treat Nutritional Disorders	11	4	9	24
Total	447	33	216	696

4 Discussion

The initial coverage assessment of Malawi essential medicines by RxNORM raised several interesting points. To begin with, the category with the most missing drugs was Anti-infective medicines. This was not so surprising as this was the largest category of medicines in the MEML-2015. While most of the drugs have common active ingredients, we found that MEML-2015 items often differed with RxNORM concepts in dose strength. We were not able to identify why this was the case.

We also found that several concepts that could be used to describe entries in the MEML-2015 have over time been retired in RxNORM. These retired concepts accounted for 6.9% of all the concepts to which MEML concepts were mapped to. This proportion is comparable to 8.1% replacement rate that O'Neil & Bell found in their study [7]. However, unlike that study, we were not able to find replacements for those concepts. This suggests that overtime the coverage of RxNORM for any given drug list can either increase or decrease. It is therefore necessary that coverage assessments be performed regularly to ensure that RxNORM still covers most drugs used in a given setting.

Furthermore, our assessment also identified some inconsistencies in dose form specifications in RxNORM. The technical documentation for RxNORM specifies a predetermined list of permissible dose forms. However, when conducting the matching we encountered dose forms that are not part of the dose form specification such as gas and pessaries. This was mostly a result of bringing together information from various drug terminologies and maintaining the concept names and dose forms from the original terminologies.

We also observed that the MEML-2015 lacked specificity with regards to routes of administration as alluded to in our methods section. This led us to make assumptions that while sensible may not always be true. This was a limitation of our study design.

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5 Future Work and Conclusions

Our initial assessment of the coverage of RxNORM for Malawi Essential medicine showed that not all drugs used in Malawi are available as concepts in RxNORM. The 63% coverage found is significantly smaller in comparison to similar studies conducted in United States health setting. To this end, we propose to improve the coverage by adding all drugs approved for use in Malawi to RxNORM. In Malawi, all drugs must be approved for use by the Pharmacy, Medicines and Poisons Board (PMPB) before they are made available to consumers [14]. By adding all PMPB approved medicine to RxNORM, we hypothesise that the coverage of medicine used in this setting will improve.

To the best of our knowledge, the only external tool that facilitates updating RxNORM by other people outside of RxNORM maintenance team was developed by the OHDSI collaborative [15]. This tool consists of several scripts that add new concepts to RxNORM. However, this tool may not be ideal for several reasons. To begin with, the output from this set of scripts is a new data model that is different from the original RxNORM schema. The change in data schemas makes it difficult to incorporate the monthly updates from RxNORM which are important for transactional EHR systems. Second, scripts do not provide an intuitive workflow for users that may not be familiar with the command line interface. An interactive graphical user interface is better suited for this work and would cater to the needs of people from various backgrounds. We therefore propose to build an application that will allow batch searching of RxNORM and facilitate addition of new concepts to RxNORM using a graphical user interface.

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