Building Semantic Causal Models to Predict Treatment Adherence for Tuberculosis Patients in Sub-Saharan Africa

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Abstract. Poor adherence to prescribed treatment is a major factor contributing to tuberculosis patients developing drug resistance and failing treatment. Treatment adherence behaviour is influenced by diverse personal, cultural and socio-economic factors that vary between regions and communities. Decision network models can potentially be used to predict treatment adherence behaviour. However, determining the network structure (identifying the factors and their causal relations) and the conditional probabilities is a challenging task. To resolve the former we developed an ontology supported by current scientific literature to categorise and clarify the similarity and granularity of factors.

Keywords: Ontology · Decision network · Tuberculosis treatment adherence · Tuberculosis treatment failure

1 Introduction

Tuberculosis (TB) treatment failure is a significant challenge facing TB control programmes in sub-Saharan African countries resulting in increased rates of drug resistance, morbidity and mortality [1, 2]. Poor treatment adherence is an important predictor of TB treatment failure [3]. Treatment adherence is defined as the extent to which a patient adheres to an appropriate treatment guideline that includes medicine adherence behaviour, following a prescribed diet, and/or executing lifestyle changes [4]. Refusal or inability to follow a prescribed treatment guideline is termed non-adherence [5].

The importance of treatment adherence behaviour has prompted public health researchers to call for the transformation of intervention programmes, by introducing a more patient centred approach to complement the current programmatic approach of

M. Huhn and L. Williams (Eds.): FHIES 2014/SEHC 2014, LNCS 9062, pp. 81–95, 2017.
DOI: 10.1007/978-3-319-63194-3_6

many treatment programs [4]. Patient-centred approaches include an understanding of existing behaviour and perceptions of target groups [4], how patient behaviour affects treatment compliance and how the social characteristics of patients affect their response to treatment [6]. TB treatment adherence behaviour (TAB) is a complex social phenomenon [3] with no general agreement on the similarity, granularity and the degree of influence of different factors [4, 3]. In addition, the diverse personal, cultural and socio-economic factors vary between countries, communities and social groups [3]. It is therefore challenging to identify distinguishing characteristics of potential treatment defaulters [4] in specific communities.

A decision network (DN) is a potentially useful modelling paradigm to model the complex factors and relationships that influence TAB. DN models are based on Bayesian networks (BN) which are used to represent vague and probabilistic causal relations between different variables [7, 8]. A DN can potentially be used to predict TAB and may be used as the basis for decision support tools to help TB programme coordinators identify and/or predict potential treatment default behaviour. Developing such networks for TAB requires significant modelling effort, including the identification of influencing factors, formalizing these factors to form the network's structure, determination of the weighting for the conditional probabilities, and consolidating evidence for learning the network. Expert knowledge and primary data sources are also required, particularly when dealing with unstructured data [9].

Ontologies can be useful to consolidate and represent categorical knowledge from an unstructured source of data. An ontology has been defined as an explicit specification of a conceptualization [10] and is a method that has already been used successfully to represent common knowledge in the public health domain [11, 12]. Ontologies have significant capability for structuring and classifying concepts and providing connections and relationships between concepts in an application domain [13].

This study describes an ontology for representing, consolidating and structuring the factors influencing the adherence behaviour of TB patients. The ontology categorises the factors and represents their effect on adherence behaviour and, crucially, enables the linking of factors to clinical studies that provide evidence for their predictive value. Furthermore, we show how the ontology can be used to construct a decision network model for particular TB communities.

The rest of the paper is structured as follows: Sect. 2 outlines previous work, Sect. 3 presents the ontology while Sect. 4 demonstrates its use in constructing decision networks. Section 5 concludes with a summary and pointers for future work.

2 Previous Work

Mathematical models have been used previously to model adherence behaviour. A machine-learning method was used to identify predictors for treatment adherence for heart failure patients [14]. A support vector machine was used for classification and analysis of the data collected directly from the patients. The study identified, among others, gender, age, education, and monthly income as predictors for medication adherence. The study stopped short of predicting medication adherence in heart failure patients and instead identified and analysed the variables that could affect medication adherence. The investigators were not able to draw any inferences with respect to the causal relationship between these predictors.

A cost-benefit mathematical modelling approach was used for describing treatment adherence for diabetic patients [15]. A synthesis of several psychological theories of medication compliance was used to produce a model that was tested using diabetic treatment adherence cases. The test was carried out at both population and individual levels, and it proved that a detailed "mechanistic" mathematical representation of medication adherence is possible and useful for the public health domain. This study however did not consider the structuring of the factors and did not draw any causal relationships between them.

A Bayesian network was used to identify and analyse non-compliance in glaucoma patients and to examine factors that motivate their poor adherence [16]. A model was developed to identify poor compliers by discriminating between low-compliance and moderate- or high-compliance patients.

Ontologies have been used to represent common knowledge in the bio-medical and public health domains. This includes disease representation and epidemiology [17, 11], heterogeneous information and system integration [12, 18], bio-medical information structuring [19, 20], and healthcare service support [21, 22]. An ontology was developed to model TB care pathways to help clinical officers access and retrieve the best available evidence from underlying medical databases [21]. An ontology was also used to classify the terminology used to describe standard laboratory test codes using TB as a case study [20]. A generic and extensible framework that can be used to assess patient adherence and persistence rates from production EMR data was developed in [23]. The framework used an ontology to represent different drugs and patient classification information.

3 An Ontology for Factors Influencing Adherence Behaviour

3.1 Categorising TB Treatment Adherence Influencing Factors

An ontology to categorize and represent the factors that influence treatment adherence behaviour of TB patients was developed. An extensive survey of the literature was first undertaken to compile a comprehensive list of factors affecting TAB in sub-Saharan Africa. Three qualitative review papers and fourteen case-based papers that dealt with the categorisation and consolidation of TAB casual factors were reviewed and provided background knowledge of the factors and their categories. The qualitative review papers provided common aspects of factors classification, while the other papers identified the various factors that influence TAB in sub-Saharan African countries.

The classifications presented in the review papers were done in order to better understand the factors [3, 24] and for proposing interventions [4]. This reveals earlier attempts to consolidate and categorise the factors to support intervention and decision-making in TB control. These papers presented similar models for the categories, but the description of the categories and the identified factors vary. The major categories identified across the three papers are: personal/patient-centred, clinical/therapy, health-care system, structural/economic, disease factor, social, health service, and condition related factors. The three papers reviewed include most of the categories with particular focus on factors that are peculiar to sub-Saharan Africa.

3.2 Ontology Development

The ontology was developed in the Ontology Web Language (OWL) using the Protégé tool[1]. The ontology categorises the factors, their effects on TAB and supporting evidence for the inclusion of the factor. The main classes in the ontology are the `InfluencingFactor` and `Evidence` classes. These classes have subclasses and are linked by object properties that define their relationships (see Figs. 1 and 2 below).

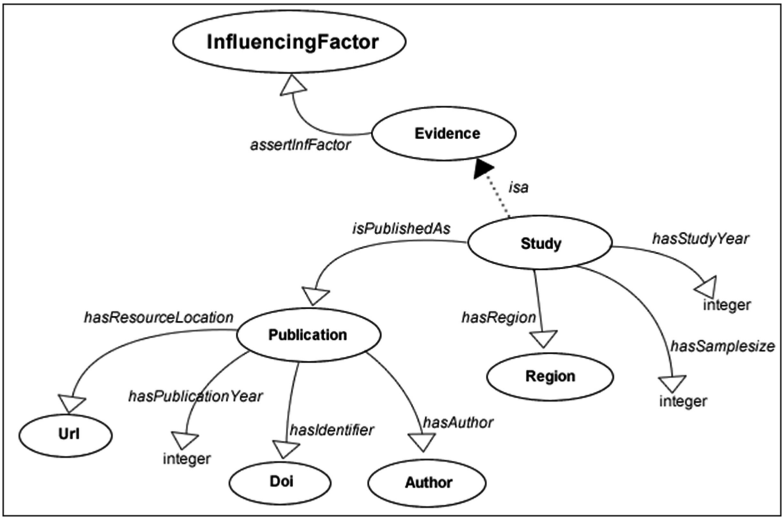

Fig. 1. Key concepts of the influencing factors ontology

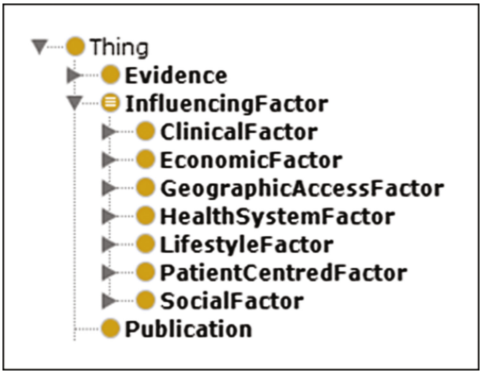

Fig. 2. High level classes of the ontology

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1 http://protege.stanford.edu/.

Influencing Factors Ontology: Classes Description

The Influencing Factor Class: `InfluencingFactor`
A factor is a characteristic or a group of characteristics of a TB patient that has been identified as influencing treatment adherence and is informed by research studies performed on one or more communities. To create the ontology, categories from the literature were refactored into seven comprehensive and unique categories to eliminate conceptual overlaps.

We identified unique factor categories from the literature that can be distinctly represented in the ontology. These are the patient centred, clinical, economic, social, health system, geographical access, and lifestyle related categories. Figure 2 shows these categories in Protégé. The ontology presently contains twenty-eight unique factors that are commonly identified as predictors of TAB in sub-Saharan Africa.

A hierarchical structure was used to represent the factors in the ontology. This made it possible to represent granularities of the factors. Figure 3 below shows the structure for the patient centred category as an example of the structure representing the `InfluencingFactor` class in the ontology.

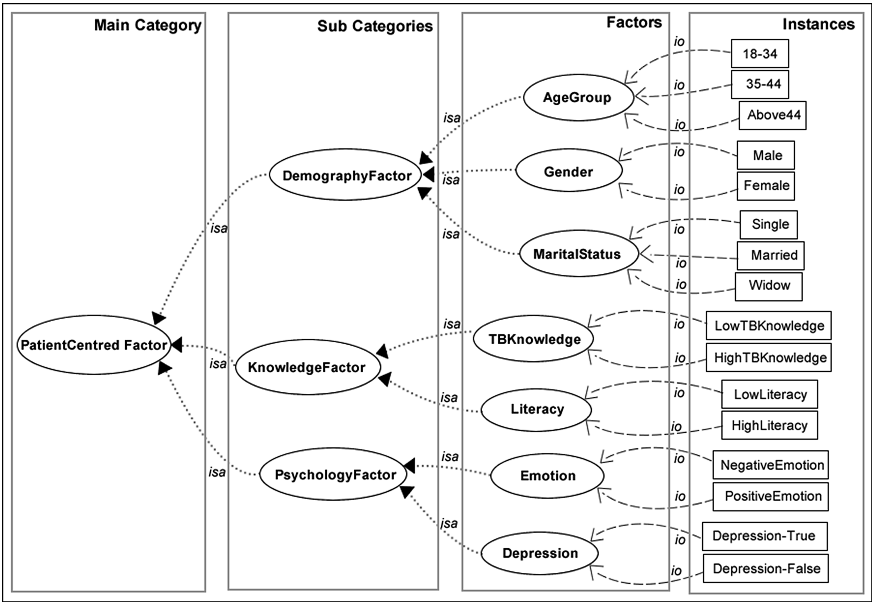

Fig. 3. Example of hierarchical CCF class ontology

The Evidence Class: `Evidence`
`Evidence` is formal or informal knowledge that provides supporting information for a TB patient's characteristic or group of characteristics as having influence on TAB. `Evidence` includes expert knowledge from review papers and scientific studies carried out on TB patients.

The Study Class: `Study`
This is a type of `Evidence` that is (an empirical) scientific study/research carried out in a region on some population (sample of patients) in a particular year or period. A `Study` is described with sets of attributes, which include the year of the study, the study region, and information about the scientific publication that reports the findings of the study. The `Study` class is defined as a sub-type of the `Evidence` class.

The Publication Class: `Publication`
A `Publication` represents any published document that is produced from a study. It has attributes such as the name of the author(s), year of publication, URL of the online location of the document, the digital object identifier (doi) for the document.

The Region Class: `Region`
A `Region` refers to the place where the study was carried out (study location), it may be the town, city, province or country of the study. The `Region` class is related to the `Study` class and is limited to countries in this paper. It will be expanded, in future work, into a spatial ontology, using the "`partOf`" relation to connectspatial entities (city, district, province, country).

Class Relationships in the Ontology

Evidence → Influencing-factor: `assertInfFactor`
The relationship between the `Evidence` and `InfluencingFactor` classes is an assertion. A TAB influencing factor is asserted by some evidence or some evidence asserts some TAB influencing factors. For example, a `Study`, which is an `Evidence`, asserts that `Male` gender is an `InfluencingFactor`. The relationship is represented by the `assertInfFactor` object property, an abbreviation for assert-influencing-factor with the inverse property `infFactorAssertedBy`. The `assertInfFactor` object property has 3 sub properties that qualify the type of influence that is asserted. These are:

- Assert-Positive-Influencing-Factor: The property states that the `Evidence` confirms a significant positive `Influencingfactor`. Positive influence implies that the factor motivates good TAB. For example, `Study-001` ***`assertPosInfFactor`*** `HighIncome`
- Assert-Negative-Influencing-Factor: The property states that the `Evidence` confirms a significant negative `Influencingfactor`. Negative influence implies that the factor motivates poor TAB. For example, `Study-002` ***`assertNegInfFactor`*** `AlcoholAbuse`
- Assert-Neutral-Influencing-Factor: The property states that the `Evidence` confirms a neutral `Influencingfactor`. Neutral influence implies a non-significant or unknown influence of the factor. For example, `Study-010` ***`assertNeuInfFactor`*** `GoodExercise`

The above primitives provide further expressivity for modellers to qualify asserted factors, but this is not enforced, i.e. the `assertInfFactor` relation may still be used if the modeller wishes not to qualify the influence of a factor.

Study-evidence → Publication: `isPublishedAs`
The `isPublishedAs` relationship exists between a `Study` and a `Publication` that shows whether the study has been published as a research document. The relationship is represented with the `isPublishedAs` object property. For instance

```
SouthAfrica-001 isPublishedAs CharacteristicsOfAnti-
    tuberculosisMedicationAdherenceInSouthAfrica.
```

This relationship allows modellers to discover those influencing factors that are supported by published studies. The publication also serves as a reference for factors discovered by specific studies.

Study-evidence → Region: `hasRegion`
This relationship provides location information of the `Evidence`. This is very important for modellers to be able to link the assertions of factors to the region where the study is carried out. The relationship is represented by "`hasRegion`". Modellers can use the region of the study to look for factors that are within a particular region and base their models on factors asserted by studies in that region or in regions with profiles similar to their own.

3.3 Usage of the TAB Influencing Factor Ontology

Reasoning with the Evidence
The main purpose of the ontology is to specify a wide range of potential influencing factors, supported by published scientific studies. The modeller will then explore the ontology either by navigation or querying to discover and select potential factors that are appropriate for a specific community.

For instance, influencing factors can be selected based on the number of positive or negative influences that are asserted by previous studies. This provides an opportunity to fine tune the influencing factors' selected by modellers. For example, alcohol abuse may be a stronger negative influencing factor than unemployment as asserted by previous studies presented in the ontology. Lists of influencing factors can be generated and refined by location, number of supporting studies, year that the study was carried out, or cohort (sample) size.

Consider a scenario where a modeller wishes to find a set of potential influencing factors based on studies carried out on Ethiopian communities after 2009. First, the ontology is queried for influencing factors that have been asserted by any study. This is done by using the inverse of `assertInfFactor` object property. This query is shown in the Manchester OWL Syntax [25] below.

```
Class ExampleClass:
EquivalentTo: Factor and (infFactorAssertedBy some
              Evidence)
```

The query is then refined to reflect the study related assertions only and narrowed down by the region of the study.

```
Class ExampleClass:
EquivalentTo: InfluencingFactor and (infFactorAssertedBy some (Study and hasRegion
              value Ethiopia))
```

Study size and year are two other constraints that can be used to restrict evidence. A modeller may intend to set a minimum sample size and only consider factors that are asserted by recent studies. A complete query for selecting factors that are identified by published studies carried out in Ethiopia from 2009 till date, which has a sample size not less than 500 patients is shown below:

```
Class ExampleClass:
EquivalentTo: InfluencingFactor and (infFactorAssertedBy some (Study and ((hasRegion value Ethiopia)
      and (hasSampleSize some integer [>= 500])
      and (hasYear some integer [>=2009]) and (isPublishedAs some Publication))))
```

All the queries described above can be executed via the DL query tab in the Protégé tool.

Complex Class Creation from the Influencing Factor Ontology
Although the ontology is reasonably comprehensive, it can still be extended. The factor category can be extended either by creating a new main category or sub classes to the existing categories. Querying the factors and creating equivalent classes for the result of the queries can form new factor categories. This is important for creating classes that will be used for the construction of a DN in the event that the classes represented in the ontology do not match the community of interest.

For example, assuming we need to create a new class called "Personal Attitude" to represent groups of factors that are associated with TB patient's behaviour. This class will consist of some patient demographic information and some social related factors. The principle behind this derived class is that each patient has their normal daily attitude that contributes to their treatment adherence decision. The primary factors for this derived class are gender, age-group, emotion, depression, and stigma. The class is defined as:

```
Class Personal Attitude:
  EquivalentTo: Gender and MaritalStatus and
      AgeGroup and Emotion and Depression and
      Stigma
```

4 Construction of DN Model with the Ontology

The influencing factor ontology provides support for the construction of a DN model for TB adherence behaviour (TAB) for a specific community. A DN consists of two aspects, i.e. the network structure and the conditional probability table (CPT). The structure is composed of nodes and the arcs that represent the relationships between nodes. In this section we describe how the ontology can be used to develop the structure of an appropriate belief network (Bayesian network).

Firstly, a list of nodes and their respective states are generated from the ontology. Then, these nodes are linked with arcs to form a belief (Bayesian) network. The belief network is modified into a DN by adding decision and utility nodes. Lastly, CPT tables are added to each nodes based on the occurrence probability and influence weighting of each of the factors represented in the network.

4.1 Decision Model Development Methodology

An example case study is described below to explain the method for constructing the DN model. It demonstrates how modellers can use the ontology to construct a DN model for a specific TB community in sub-Saharan Africa.

Defining the Example Case
Suppose that a modeller wishes to develop a TAB DN for South Africa. By exploring the ontology, the modeller discovers a paper by Naidoo *et al.* [26]. The modeller discovered that five of the influencing factors identified by the paper are represented in the ontology. The factors, which are gender, age group, alcohol abuse, comorbidity and poverty level are useful and adequate to model a DN for his/her TB community. This is because the paper affirms that poor TAB are influenced by:

- Gender: Being a male patient
- Age-group: Patient with age above 34 years
- Alcohol abuse: Patients who abuse alcohol
- Comorbidity: Patient undertaking treatment for more than one chronic disease
- Poverty level: Patient with medium and high poverty level

The modeller decides to use these factors for modelling and testing an initial DN for his/her TB community. The modeller must select the relevant classes from the ontology and these will be automatically transformed into an appropriate belief network structure.

Selection of Relevant Classes (Factors)
The ontology was queried to select the list of influencing factors that are required to compose the list of the root nodes and their states. This was carried out by applying a query to identify the influencing factors identified by the study which was published as [26].

```
Class CaseStudy:
EquivalentTo: InfluencingFactor and (infFactorAssert-
      edBy some (Study and ((hasRegion value SouthAf-
      rica)  and  (isPublishedAs  value  PredictorsOf-
      TuberculosisAndAntiretroviralMedicationNon-
      adherenceInPublicPrimaryCarePatientsInSouthAf-
      rica-ACrossSectionalStudy))))
```

With the above query, the five influencing factor classes and their instances asserted by [26] are selected.

Transformation of Ontology Primitives into Belief Network Primitives
The TAB ontology is designed such that classes and instances in the ontology can be directly mapped to primitives in a belief network. The mapping is shown in Fig. 4 below.

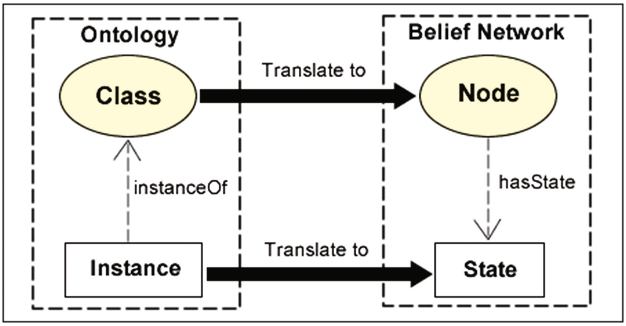

Fig. 4. Transformation of ontology primitives into belief network primitives

The selected factors from the ontology are transformed into nodes, and their respective instances translate into node states. In our example case, the five nodes generated are the root nodes of the belief network. For instance Age-group node and its three discrete states is a direct translation of the "`AgeGroup`" class and the instances "`18-34`", "`35-44`" and "`Above 44`". Table 1 below shows the influencing factor classes and their corresponding instances. The classes are needed to construct the root nodes to be linked to the hypothesis node (TAB).

Generating the Decision Network
While the (factor) nodes and states are dynamically generated from the ontology, the central TAB, and decision and utility nodes are static. All factor nodes become parent nodes of the TAB node, to form a Naïve Bayes network structure.

Figure 5 below shows the diagram of the DN model for the case study. The DN model consists of a TAB belief network. The influencing factors are modelled as root nodes. The TAB node is the hypothesis node; its states are the patient's TAB that determines the patient's decision to take the drugs. The "Take Drugs" node is a

Table 1. Selected influencing factors for the DN model

Class/Node	Instance/State
Gender	Male
	Female
AgeGroup	18–34
	35–44
	Above44
PovertyLevel	LowPoverty
	MediumPoverty
	HighPoverty
HIVComorbidity	Comorbidity-True
	Comorbidity-False
AlcoholAbuse	AlcoholAbuse-True
	AlcoholAbuse-False

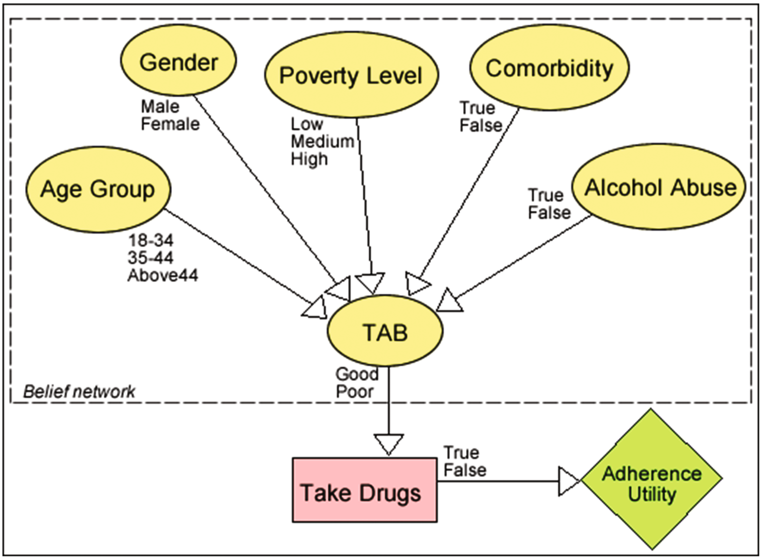

Fig. 5. Example case decision network model

decision node that is influenced by the TAB state of the patient. Adherence utility node measures the adherence risk of TB patients

With the structure in place, the modeller can do further customisation of the network, including refinement of the CPTs and adding additional nodes. While default CPTs are generated along with the structure, these must be repopulated by the modeller to adequately represent the target community, based on a combination of expert knowledge and data obtained from the target community. While the ontology provides some indication of the weighting of the influencing relation (negative, neutral or positive) determining CPT values is currently not addressed by the ontology and is left for future work.

Automation of the DN Construction with Tools
As described above an appropriate DN can be automatically generated from the ontology. An initial prototype was implemented in Java to automate the construction of the belief network model. Queries to extract classes and instances from the ontology were written in SPARQL and implemented using the Java Jena API[2].

The Jena API provided a platform for automating the transformation of the classes into node lists and the dependency information required to construct the network structure. The Bayesian network tool (BNJ) [27] was then used to generate an initial BN structure. Further customisation is carried out manually using the Hugin Expert[3] Bayesian network tool

5 Conclusions and Future Work

This paper presents an ontology to capture and consolidate knowledge about influencing factors for TB adherence behaviour. Furthermore, it shows how the ontology can be used to generate an appropriate decision network for a particular community. While Bayesian networks have been used previously to model adherence, to our knowledge, this is the first approach to use an ontology to generate the initial network structure. An important feature of the ontology is the integration of literature and scientific studies to support the inclusion of various factors. The ontology covers both the breadth and the depth of factors in sub-Saharan Africa as reported by key scientific review papers.

The ontology can be used by modellers to generate DNs for specific communities. Modellers may easily discover and select classes and their instances from the ontology which can be used to create the nodes and states of a belief network. A mechanism is proposed for direct translation from the ontology structure to the BN structure, to ease DN model construction. User specified influencing factor classes are translated into nodes while instances are converted into the states.

The expected impact of the study is to facilitate wider usage of decision support tools for TB patient management in low resource countries of sub-Saharan Africa. A decision network tool can be used by healthcare workers in identifying potential defaulters by generating risk indices for TB patients in a particular community. Allocation of resources, most especially scarce healthcare worker time, can be optimised based on risk levels in particular communities. This will help simplify TB patient monitoring and follow up services.

This study is a first step towards automating decision network construction with limited expert knowledge of TAB. Prior to this study, knowledge about TAB influencing factors were encapsulated in scientific publications and difficult to harmonise. The study

[2] https://jena.apache.org/.

[3] http://www.hugin.com/.

made successful attempt to harmonise the influencing factors from scientific publication and presented them as structured knowledge useful for predicting TAB amongst other possible uses.

The proposed ontology serves as a repository of TAB knowledge useful in high TB prevalence region like sub-Saharan Africa to support patient management. The repository of knowledge is very important to support public health decision making. It provides a possibility to share and reuse knowledge about influencing factors of TAB. The study is an important step towards providing a global repository of harmonised knowledge about TAB influencing factors.

However, there is the need for strengthening of the ontology for DN construction that is useful for prediction. This will involve the refinement of the ontology structure and the determination of the accuracy of input evidence in the ontology. There is also the need to improve the usefulness of the DN through the strengthening of the input information and the complexity of the network to represent patient's TAB in reality. The improved DN will be evaluated on usefulness to predict patient's TAB

Future work includes strengthening the `Evidence` class in the ontology, introduction of influence weighting for CPT generation, modelling spatial relation for `Region` class, and populating the ontology with more evidence from sub-Saharan African and other regions as well. Furthermore, TAB influencing factor ontology will also be presented as a web-service where users can query for influencing factors that represents their community of interest.

Development of complex DN models using the ontology is another direction to further explore. The TAB DN model will be developed to enhance its usefulness for patient management support. Lastly, our proposed method can be developed into a platform for predicting TB patient's behaviour in relation to treatment.

Acknowledgement. This work, including support for the Health Architecture Laboratory (HeAL) project as well as for DM, CS and AP and a PhD scholarship to KO, was funded by grants from the Rockefeller Foundation (Establishing a Health Enterprise Architecture Lab, a research laboratory focused on the application of enterprise architecture and health informatics to resource-limited settings, Grant Number: 2010 THS 347) and the International Development Research Centre (IDRC) (Health Enterprise Architecture Laboratory (HeAL), Grant Number: 106452-001). CS was additionally funded for aspects of this work by a grant from the Delegation of the European Union to South Africa to the South African Medical Research Council (SANTE 2007 147-790; Drug resistance surveillance and treatment monitoring network for the public sector HIV antiretroviral treatment programme in the Free State). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. WHO: Global tuberculosis report 2013, p. 145. World Health Organization, Geneva, Switzerland (2013)
2. Gandhi, N.R., Nunn, P., Dheda, K., Schaaf, H.S., Zignol, M., van Soolingen, D., Jensen, P., Bayona, J.: Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet **375**(9728), 1830–1843 (2010)

3. Munro, S.A., Lewin, S.A., Smith, H.J., Engel, M.E., Fretheim, A., Volmink, J.: Patient adherence to tuberculosis treatment: a systematic review of qualitative research. Plos Med. **4**(7), 1230–1245 (2007)
4. Sabaté, E.: Organization WH: Adherence to Long-term Therapies: Evidence for Action: World Health Organization (2003)
5. CDC: Self-Study Modules on Tuberculosis: Patient Adherence to Tuberculosis Treatment. In. Edited by Prevention CfDCa, pp. 1–123. Centers for Disease Control and Prevention, Atlanta, Georgia (1999)
6. Mushlin, A.I., Appel, F.A.: Diagnosing potential noncompliance: physicians' ability in a behavioral dimension of medical care. Arch. Intern. Med. **137**(3), 318–321 (1977)
7. Costa, P.C., Laskey, K.B.: PR-OWL: a framework for probabilistic ontologies. Front. Artif. Intell. Appl. **150**, 237 (2006)
8. Laskey, K.B., Costa, P.C., Janssen, T.: Probabilistic ontologies for knowledge fusion. In: 11th International Conference on Information Fusion, pp. 1–8. IEEE (2008)
9. Rajput, Q.N., Haider, S.: Use of Bayesian network in information extraction from unstructured data sources. Int. J. Inf. Technol. **5**(4), 207–213 (2009)
10. Gruber, T.R.: Toward principles for the design of ontologies used for knowledge sharing. Int. J. Hum.-Comput. S.t **43**(5–6), 907–928 (1995)
11. Malhotra, A., Younesi, E., Gundel, M., Muller, B., Heneka, M.T., Hofmann-Apitius, M.: ADO: a disease ontology representing the domain knowledge specific to Alzheimer's disease. Alzheimer's & Dementia: J. Alzheimer's Assoc. **10**(2) (2013)
12. Alonso-Calvo, R., Maojo, V., Billhardt, H., Martin-Sanchez, F., Garcia-Remesal, M., Perez-Rey, D.: An agent- and ontology-based system for integrating public gene, protein, and disease databases. J. Biomed. Inform. **40**(1), 17–29 (2007)
13. Noy, N., McGuinness, D.: Ontology Development 101: A Guide to Creating Your First Ontology (2001)
14. Son, Y.J., Kim, H.G., Kim, E.H., Choi, S., Lee, S.K.: Application of support vector machine for prediction of medication adherence in heart failure patients. Healthcare Inform. Res. **16**(4), 253–259 (2010)
15. Dinh, T., Alperin, P.: A behavior-driven mathematical model of medication compliance. In: The 33rd Annual Meeting of the Society for Medical Decision Making. Society for Medical Decision Making (2011)
16. Nordmann, J.-P., Baudouin, C., Renard, J.-P., Denis, P., Regnault, A., Berdeaux, G.: Identification of noncompliant glaucoma patients using Bayesian networks and the eye-drop satisfaction questionnaire. Clin. Ophthalmol **4**, 1489–1496 (2010)
17. Cowell, L., Smith, B.: Infectious disease ontology. In: Sintchenko, V. (ed.) Infectious Disease Informatics, pp. 373–395. Springer, New York (2010)
18. Koum, G., Yekel, A., Ndifon, B., Etang, J., Simard, F.: Design of a two-level adaptive multi-agent system for malaria vectors driven by an ontology. BMC Med. Inform. Decis. Mak. **7**(1), 1–10 (2007)
19. Baker, P.G., Goble, C.A., Bechhofer, S., Paton, N.W., Stevens, R., Brass, A.: An ontology for bioinformatics applications. Bioinformatics **15**(6), 510–520 (1999)
20. Eilbeck, K., Jacobs, J., McGarvey, S., Vinion, C., Staes, C.: Exploring the use of ontologies and automated reasoning to manage selection of reportable condition lab tests from LOINC (2013)
21. Kostkova, P., Kumar, A., Roy, A., Madle, G., Carson, E.: Ontological Principles of Disease Management from Public Health Perspective: A Tuberculosis Case Study. City University, London (2005)

22. Dieng-Kuntz, R., Minier, D., Ruzicka, M., Corby, F., Corby, O., Alamarguy, L.: Building and using a medical ontology for knowledge management and cooperative work in a health care network. Comput. Biol. Med. **36**(7–8), 871–892 (2006)
23. Mabotuwana, T., Warren, J.: A framework for assessing adherence and persistence to long-term medication. Stud. Health Technol. Inform. **150**, 547–551 (2009)
24. Jin, J.J., Sklar, G.E., Min Sen Oh, V., Chuen Li, V.: Factors affecting therapeutic compliance: A review from the patient's perspective. Ther. Clin. Risk Manag. **4**(1), 269–286 (2008)
25. Horridge, M., Drummond, N., Goodwin, J., Rector, A.L., Stevens, R., Wang, H.: The Manchester OWL syntax. In: OWLed (2006)
26. Naidoo, P., Peltzer, K., Louw, J., Matseke, G., Mchunu, G., Tutshana, B.: Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study. BMC Public Health **13**(1), 396 (2013)
27. Moodley, D., Simonis, I., Tapamo, J.R.: An architecture for managing knowledge and system dynamism in the worldwide sensor web. Int. J. Semant. Web Inf. Syst. **8**(1), 64–88 (2012)